THE HARRIET LANE HANDBOOK

THE JOHNS HOPKINS HOSPITAL

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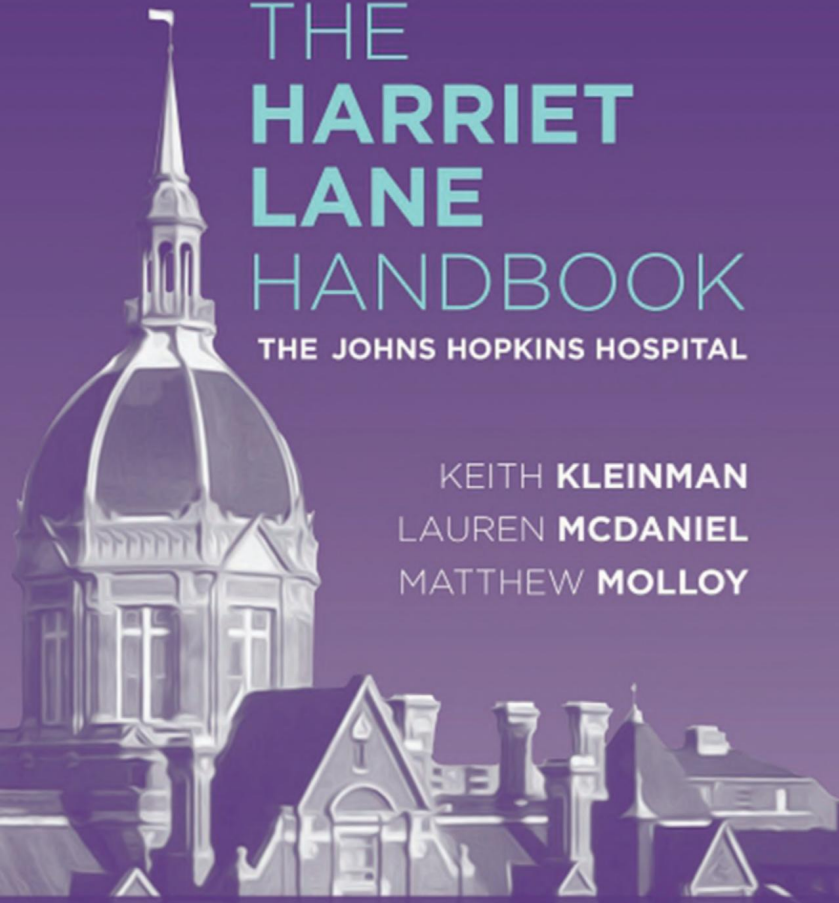

TWENTY-SECOND EDITION

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PEDIATRIC PARAMETERS AND EQUIPMENT

	Premie	Newborn	6 mo	1 yr	2-3 yr	4-6 yr	7-10 yr	11-15 yr	>16 yr
WT (kg)	2.5-3.5	3.5-4	6-8	10	13-16	20-25	25-35	40-50	>50
BAG VALVE MASK	Infant	Infant	Small child	Small child	Child	Child	Child/small adult	Adult	Adult
NASAL AIRWAY (Fr)	12	12	14-16	14-16	14-18	14-18	16-20	18-22	22-36
ORAL AIRWAY	Infant 50 mm	Small 60 mm	Small 60 mm	Small 60 mm	Small 70 mm	Small 70-80 mm	Med 80-90 mm	Med 90 mm	Med 90 mm
BLADE	MIL 0	MIL 0	MIL 1	MIL 1, MAC 2	MIL 1, MAC 2	MIL 2, MAC 3	MIL 2, MAC 3	MIL 2, MAC 3	MIL 2, MAC 3
ETT	2.5-3.0	3.0-3.5	3.5-4.0	4.0-4.5	4.5-5.0	5.0-5.5	5.5-6.0	6.0-6.5	7.0-8.0
LMA	1	1	1.5	2	2	2.5	2.5-3	3	4
GLIDESCOPE	1	1 or 2	2	2	3	3	3	3 or 4	3 or 4
IV CATH (ga)	22-24	22-24	20-24	20-24	18-22	18-22	18-22	18-20	16-20
CVL (Fr)	3	3-4	4	4-5	4-5	5	5	7	7
NGT/OGT (Fr)	5	5-8	8	10	10-12	12-14	12-14	14-18	14-18
CHEST TUBE (Fr)	10-12	10-12	12-18	16-20	16-24	20-28	20-32	28-38	28-42
FOLEY (Fr)	6	8	8	8	8	8	8	10	12

ESTIMATED BLOOD PRESSURE BY AGE

Measurement	50th %	5th %
Systolic BP	90 + (age × 2)	60 (neonate); 70 (1 mo-1 yr) 70 + (age × 2) (for 2-10 yr) <90 (>10 yr)
MAP	55 + (age × 1.5)	40 + (age × 1.5)

NORMAL VITAL SIGNS BY AGE

Age	Heart Rate (beats/min)	Blood Pressure (mmHg)	Respiratory Rate (breaths/min)
Premie	120-170	55-75/35-45 (gestational age approximates normal MAP)	40-70
0-3 mo	110-160	65-85/45-55	30-60
3-6 mo	100-150	70-90/50-65	30-45
6-12 mo	90-130	80-100/55-65	25-40
1-3 yr	80-125	90-105/55-70	20-30
3-6 yr	70-115	95-110/60-75	20-25
6-12 yr	60-100	100-120/60-75	14-22
>12 yr	60-100	100-120/70-80	12-18

ENDOTRACHEAL TUBE FORMULAS

Uncuffed ETT size: age (years)/4 + 4; Cuffed ETT size: age (years)/4 + 3
ETT depth (from lip to mid-trachea): ETT internal diameter (size) × 3

GLASGOW COMA SCALE

Activity	Score	Child/Adult	Score	Infant
Eye opening	4	Spontaneous	4	Spontaneous
	3	To speech	3	To speech/sound
	2	To pain	2	To painful stimuli
	1	None	1	None
Verbal	5	Oriented	5	Coos/babbles
	4	Confused	4	Irritable cry
	3	Inappropriate	3	Cries to pain
	2	Incomprehensible	2	Moans to pain
	1	None	1	None
Motor	6	Obeys commands	6	Normal spontaneous movement
	5	Localizes to pain	5	Withdraws to touch
	4	Withdraws to pain	4	Withdraws to pain
	3	Abnormal flexion	3	Abnormal flexion (decorticate)
	2	Abnormal extension	2	Abnormal extension (decerebrate)
	1	None	1	None (flaccid)

Adapted from Hunt EA, Nelson-McMillan K, McNamara L. The Johns Hopkins Children's Center Kids Kard, 2016.

RESUSCITATION MEDICATIONS

Adenosine Supraventricular tachycardia	**0.1 mg/kg IV/IO RAPID BOLUS (over 1-2 sec), Flush with 10 mL normal saline** May repeat at 0.2 mg/kg IV/IO, then 0.3 mg/kg IV/IO after 2 min Max first dose 6 mg, max subsequent dose 12 mg Administer using a 3-way stopcock attached to a 10 ml NS flush
Amiodarone Ventricular tachycardia Ventricular fibrillation	**5 mg/kg IV/IO** No Pulse: Push Undiluted Pulse: Dilute and give over 20-60 minutes Max first dose 300 mg, max subsequent dose 150 mg Only give max of 3 IV push doses Monitor for hypotension Strongly consider pretreating with IV calcium in patients with a pulse to prevent hypotension
Atropine Bradycardia (increased vagal tone) Primary AV block	**0.02 mg/kg IV/IO/IM, 0.04–0.06 mg/kg ETT** Max single dose 0.5 mg Repeat in 5 minutes if needed (up to twice) to max total dose 1 mg
Calcium chloride (10%) Hypocalcemia	**20 mg/kg IV/IO** Max dose 1 gram
Calcium Gluconate (10%)	**60 mg/kg IV/IO** Max dose 3 grams
Dextrose	**Weight-Based Dosing: 0.5–1 gram/kg** **Volume-Based Dosing ("Rule of 50"):** **<5 kg: 10% dextrose 5-10 mL/kg IV/IO** **5-44 kg: 25% dextrose 2-4 mL/kg IV/IO** **≥45 kg: 50% dextrose 1-2 mL/kg IV/IO** **Max single dose 50 grams = 100 mL**
Epinephrine Pulseless arrest Bradycardia (symptomatic) Anaphylaxis	**0.01 mg/kg IV/IO every 3–5 min (max single dose 1 mg)** **0.1 mg/kg ETT every 3–5 min (max single dose 2.5 mg)** **Anaphylaxis:** **0.01 mg/kg IM (1 mg/mL) in thigh every 5-15 min PRN; max single dose 0.5 mg** **Standardized/Autoinjector:** **<7.5 kg: no autoinjector, see above** **7.5 to <15 kg: 0.1 mg IM** **15 to <30 kg: 0.15 mg IM** **≥30 kg: 0.3 mg IM**
Hydrocortisone Adrenal Crisis/ Insufficiency	**2 mg/kg IV/IM/IO** Max dose 100 mg
Insulin (Regular or Aspart) Hyperkalemia	**0.1 units/kg IV/IO with 0.5 gram/kg of dextrose** Max dose 10 units
Lidocaine Antiarrhythmic	**1 mg/kg IV/IO** (ETT dose is 2-3x IV dose) Max single dose 100 mg May repeat in 10-15 min x2
Magnesium sulfate Torsades de pointes Hypomagnesemia	**50 mg/kg IV/IO** No Pulse: Push Pulse: Give over 20-60 minutes Max single dose 2 grams Monitor for hypotension/bradycardia
Naloxone Opioid overdose Coma	**Respiratory Depression: 0.001-0.005 mg/kg/dose IV/IO/IM/Subcut (max 0.1 mg first dose, may titrate to effect)** **Full Reversal/Arrest Dose: 0.1 mg/kg IV/IO/IM/Subcut (max dose 2 mg)** ETT dose 2–3 times IV dose, IN dose 2-4 mg. May give every 2 min PRN
Sodium Bicarbonate (8.4% = 1 mEq/mL) Administer only with clear indication: Metabolic acidosis Hyperkalemia Tricyclic antidepressant overdose	**1 mEq/kg IV/IO** Dilute 8.4% sodium bicarbonate 1 : 1 with sterile water for patients <10 kg to a final concentration of 4.2% = 0.5 mEq/mL Hyperkalemia: Max single dose 50 mEq

ETT Meds (NAVEL: naloxone, atropine, vasopressin, epinephrine, lidocaine)—dilute meds to 5 mL with NS, follow with positive-pressure ventilation.

Adapted from Hunt EA, Nelson-McMillan K, McNamara L. The Johns Hopkins Children's Center Kids Kard, 2018 and the American Heart Association, PALS Pocket Card, 2015.

IV INFUSIONS* $6 \times \frac{\text{Desired dose (mCg/kg/min)}}{\text{Desired rate (mL/hr)}} \times \text{Wt (kg)} = \frac{\text{mg drug}}{\text{100 mL fluid}}$

Medication	Dose (mCg/kg/min)	Dilution in 100 mL in a Compatible IV Fluid	IV Infusion Rate
Alprostadil (prostaglandin E_1)	0.05–0.1	0.3 mg/kg	1 mL/hr = 0.05 mCg/kg/min
Amiodarone	5–15	6 mg/kg	1 mL/hr = 1 mCg/kg/min
DOPamine	5–20	6 mg/kg	1 mL/hr = 1 mCg/kg/min
DOBUTamine	2–20	6 mg/kg	1 mL/hr = 1 mCg/kg/min
EPINEPHrine	0.1-1	0.6 mg/kg	1 mL/hr = 0.1 mCg/kg/min
Lidocaine, post resuscitation	20–50	6 mg/kg	1 mL/hr = 1 mCg/kg/min
Phenylephrine	0.1–2, up to 5 in severe circumstances	0.3 mg/kg	1 mL/hr = 0.05 mCg/kg/min
Terbutaline	0.1–4 (up to 10 has been used)	0.6 mg/kg	1 mL/hr = 0.1 mCg/kg/min
Vasopressin (pressor)	0.17–8 milliunits/kg/min	6 units/kg	1 mL/hr = 1 milliunit/kg/min

*Standardized concentrations are recommended when available. For additional information, see Larsen GY, Park HB et. al. Standard drug concentrations and smart-pump technology reduce continuous-medication-infusion errors in pediatric patients. Pediatrics. 2005;116(1):e21-e25.

Special thanks to Lisa Hutchins, Clinical Pharmacy Specialist, for her expert guidance with IV infusion and resuscitation medication guidelines.

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TWENTY-SECOND
EDITION

A MANUAL FOR PEDIATRIC HOUSE OFFICERS

THE HARRIET LANE HANDBOOK

THE HARRIET LANE HOUSE STAFF AT
THE CHARLOTTE R. BLOOMBERG CHILDREN'S CENTER OF
THE JOHNS HOPKINS HOSPITAL

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To our families

Michael and Debbie Kleinman, you have always been there for guidance and support and have allowed me to follow my dreams. Mary Buckley Kleinman, thank you for being such a loving and devoted wife; you push me to be better every day. Dr. Kimberly Erica Kleinman, you are such a wonderful sister whom I have always looked up to. Camper Whitney Kleinman, you are beautiful in every way. Ina Zun, you were the perfect grandmother and the reason that I am a doctor; I miss you every day.

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To our patients and their families

We will never forget the lessons you have taught us and the trust you place in us.

To our residents

We are inspired by your brilliance, boldness, and dedication to caring for children.

To the wonderful pediatricians and educators who trained us

Especially Nicole Shilkofski, Janet Serwint, George Dover, Tina Cheng

In loving memory of Dr. Michael Burke

Preface

"Why this child? Why this disease? Why now?"

—Barton Childs, MD

The Harriet Lane Handbook was first developed in 1953 after Harrison Spencer (chief resident in 1950–1951) suggested that residents should write a pocket-sized "pearl book." As recounted by Henry Seidel, the first editor of *The Harriet Lane Handbook,* "Six of us began without funds and without [the] supervision of our elders, meeting sporadically around a table in the library of the Harriet Lane Home." The product of their efforts was a concise yet comprehensive handbook that became an indispensable tool for the residents of the Harriet Lane Home. Ultimately, Robert Cooke (department chief, 1956–1974) realized the potential of the Handbook, and, with his backing, the fifth edition was published for widespread distribution by Year Book. Since that time, the handbook has been regularly updated and rigorously revised to reflect the most up-to-date information and available clinical guidelines. It has grown from a humble Hopkins resident "pearl book" to become a nationally and internationally respected clinical resource. Now translated into many languages, the handbook is still intended as an easy-to-use manual to help pediatricians provide current and comprehensive pediatric care.

Today, *The Harriet Lane Handbook* continues to be updated and revised *by* house officers *for* house officers. Recognizing the limit to what can be included in a pocket guide, additional information has been placed online and for use via mobile applications. The online-only content includes references, expanded text, and additional tables, figures, and images.

In addition to including the most up-to-date guidelines, practice parameters, and references, we will highlight some of the most important improvements in the twenty-second edition of *The Harriet Lane Handbook:*

The Emergency Management and Trauma, Burn, and Common Critical Care Emergencies chapters have been reorganized. The **Emergency and Critical Care Management** chapter now focuses on the medical management of common critical care emergencies, while the management of trauma, including burns, has been consolidated into the **Traumatic Injuries** chapter.

The Development, Behavior, and Mental Health chapter has been separated into two chapters with expanded content: **Behavior, Development, and Developmental Disability** and **Psychiatry**, reflecting the growing need for pediatricians to understand mental and behavioral health.

The **Genetics** chapter has been reorganized to present categories of metabolic disease in easily referenced tables and to provide an organization to different patterns and etiologies of dysmorphology.

The **Hematology** chapter has been restructured with much of the text re-organized and expanded into tables and figures, including a new algorithmic approach to anemia. Content on the management of transfusion reactions has been added.

The **Immunoprophylaxis** chapter includes a new section on vaccine hesitancy.

The **Nutrition and Growth** chapter now includes expanded content on the management of overweight and obese children, definitions of various degrees of malnutrition, information on refeeding syndrome, and a table with instructions on the preparation of fortified formula. Enteral formulas have been reorganized based on clinical indications.

The **Radiology** chapter has been reorganized with all-new images and more focused content.

The **Rheumatology** chapter has been refocused for the general pediatrician and includes a section on the primary care management of rheumatologic diseases.

The Harriet Lane Handbook, designed for pediatric house staff, was made possible by the extraordinary efforts of this year's Johns Hopkins Harriet Lane Pediatric Residency Program senior resident class. It has been an honor to watch these fine doctors mature and refine their skills since internship. They have balanced their busy work schedules and personal lives while authoring the chapters that follow. We are grateful to each of them, along with their faculty advisors, who selflessly dedicated their time to improve the quality and content of this publication. The high quality of this handbook is representative of our residents, who are the heart and soul of our department.

Chapter		Resident	Faculty Advisor
1	Emergency and Critical Care Management	Kelsey Stayer, MD Lisa Hutchins, PharmD	Justin M. Jeffers, MD, MEHP Nicole Shilkofski, MD, MEd
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The Formulary is complete, concise, and up-to-date thanks to the tireless efforts of Carlton K.K. Lee, PharmD, MPH. With each edition, he carefully updates, revises, and improves the section. His herculean efforts make the Formulary one of the most useful and cited pediatric drug reference texts available.

We are grateful and humbled to have the opportunity to build on the great work of the preceding editors: Drs. Henry Seidel, Harrison Spencer, William Friedman, Robert Haslam, Jerry Winkelstein, Herbert Swick, Dennis Headings, Kenneth Schuberth, Basil Zitelli, Jeffery Biller, Andrew Yeager, Cynthia Cole, Peter Rowe, Mary Greene, Kevin Johnson, Michael Barone, George Siberry, Robert Iannone, Veronica Gunn, Christian Nechyba, Jason Robertson, Nicole Shilkofski, Jason Custer, Rachel Rau, Megan Tschudy, Kristin Arcara, Jamie Flerlage, Branden Engorn, Helen Hughes, and Lauren Kahl. Many of these previous editors continue to make important contributions to the education of the Harriet Lane house staff, none more than Dr. Nicole Shilkofski, our current residency program director. We are constantly impressed by her enthusiasm for education and her advocacy for the residents. As recent editors, Drs. Helen Hughes and Lauren Kahl also have been instrumental in helping us to navigate this process. We hope to live up to the legacy of these many outstanding clinicians, educators, and mentors.

An undertaking of this magnitude could not have been accomplished without the support and dedication of some extraordinary people. First, we would like to thank Dr. Janet Serwint, our residency program director during our first two years of residency. Thank you for entrusting us with the opportunity to serve as Chief Residents and *Harriet Lane Handbook* editors. We would also like to offer special thanks to Kathy Mainhart, an invaluable asset to our program. Without her guidance, we would all be lost. Thank you to Dequira Jones and Carly Hyde, the newest additions to our program staff. We are so appreciative of your support this past year. And last but certainly not least, thank you to our Department Director, Dr. Tina Cheng. We are so grateful for your mentorship and guidance—we are honored to help shape the Children's Center in your vision.

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Contents

Chapter 1

Emergency and Critical Care Management

Kelsey Stayer, MD and Lisa Hutchins, PharmD

This chapter is presented in accordance with the universal acronym **C-A-B** (circulation, airway, breathing) to emphasize the reduction of "no blood flow" time.[1-3] However, given the high prevalence of asphyxial cardiac arrest in the pediatric population, ventilation remains fundamental to the resuscitation of the critically ill child.[4] This chapter serves to function as a guide to caring for "sick" children, spanning the principles of resuscitation and stabilization, as well as management of the most common pediatric medical emergencies.

I. APPROACH TO THE UNRESPONSIVE CHILD

A. Circulation[1-3,5-10]

1. Assessment
   a. **Pulse:** Spend no more than **10 seconds** assessing pulse. Assess brachial pulse in infants, carotid or femoral pulse in children.
   b. **Perfusion:** Check for pallor, mottling, or cyanosis. Capillary refill time >2 seconds is delayed and <1 to 2 seconds or "flash" may indicate warm shock.
   c. **Rate:** Bradycardia **<60 beats/min** with **poor perfusion** requires immediate cardiopulmonary resuscitation (CPR). Tachycardia **>220 beats/min** suggests pathologic tachyarrhythmia.
   d. **Rhythm:** Attach patient to defibrillator or continuous electrocardiography. In arrest, check rhythm every 2 minutes with minimal interruptions in chest compressions (e.g., during compressor change).
   e. **Blood pressure (BP):** Hypotension in a pediatric patient is a **late** manifestation of circulatory compromise.
   f. **Urine output:** Normal output is 1.5 to 2 mL/kg/h in infants and young children and 1 mL/kg/h in older children.
2. Management: Initiate CPR immediately if patient is pulseless or bradycardic (<60 beats/min) with poor perfusion.
   a. **Chest compressions:** See Box 1.1 for an outline of the five components of **high-quality CPR.**
   b. **Monitoring:** Continuous capnography and invasive hemodynamic monitoring may guide effectiveness of chest compressions.
      (1) Target **end-tidal CO_2** ($EtCO_2$) **>20 mmHg.** If consistently less than, improve compressions and assess for excessive ventilation.
      (2) Abrupt and sustained rise in $EtCO_2$ is often observed just prior to clinical return of spontaneous circulation (ROSC).

BOX 1.1

FIVE COMPONENTS OF HIGH-QUALITY CARDIOPULMONARY RESUSCITATION

- "Push fast": Target rate of **100–120 compressions/min**
- "Push hard": Target depth of **at least ⅓ anteroposterior diameter of chest**
  - Place step stool at side of bed to assist compressor
  - Slide backboard under patient or place on hard surface
  - Use the compression technique that achieves the best results
    - Consider two-handed, one-handed, two-finger, or two-thumb-encircling hands techniques
  - Aim for 1 fingerbreadth below intermammary line in infants, 2 fingerbreadths in prepubertal children, and the lower half of the sternum in adolescents
- Allow full chest recoil between compressions
- **Minimize interruptions** in chest compressions
  - Rotate compressor every 2 min or sooner if fatigued
  - Check cardiac rhythm at time of compressor change
- Avoid excessive ventilation
  - If no advanced airway (endotracheal tube, laryngeal mask airway, tracheostomy) secured, perform **30:2 compression-ventilation ratio** (with single rescuer or for any adolescent/adult) or **15:2 ratio** (in an infant/child only if 2 rescuers present)
  - If advanced airway secured, give **one breath every 6–8 sec** with continuous compressions
  - Ventilation volume should produce no more than minimal, visible chest rise

(3) If a patient has an indwelling arterial catheter, assess waveform for feedback to evaluate chest compressions. Target **diastolic BP >25 mmHg** in infants and **>30 mmHg** in children.

c. **Defibrillation:** Shockable arrest rhythms include **ventricular fibrillation** and **pulseless ventricular tachycardia.** Nonshockable arrest rhythms include asystole, pulseless electrical activity, and bradycardia with poor perfusion.
   (1) Use age- and size-appropriate pads as recommended per manufacturer.
   (2) Initial shock dose is **2 J/kg**, second dose is **4 J/kg**, subsequent doses are ≥**4 J/kg** (**maximum 10 J/kg or adult maximum dose**).

d. **Cardioversion:** A synchronized electrical shock delivered for hemodynamically **unstable** patients with **tachyarrhythmias** (i.e., supraventricular tachycardia, atrial flutter, ventricular tachycardia) and **palpable pulses**.
   (1) Initial dose is **0.5 to 1 J/kg**. Increase to **2 J/kg** if ineffective, repeating doses if necessary. Reevaluate diagnosis if rhythm does not convert to sinus.
   (2) Consultation with a pediatric cardiologist is recommended for elective cardioversion for stable patients with tachyarrhythmias.

e. **Resuscitation**
   (1) **Access:** Place intraosseous access immediately if in arrest or if intravenous (IV) access difficult.

(a) If previously established, central access is preferred for drug administration.
(b) Endotracheal tube (ETT) drug administration is acceptable if required. Lidocaine, epinephrine, atropine, and naloxone (LEAN) and vasopressin can be administered via endotracheal route.

(2) **Pharmacotherapy:** See Table 1.1 detailing medications for pediatric resuscitation. If actual body weight is unavailable, use length-based habitus-modified (e.g., Mercy method, PAWPER tape) estimation methods, parental estimates, or length-based (e.g., Broselow tape) estimation methods, in order of accuracy.

(3) **Fluids:** Administer isotonic crystalloid for treatment of shock even if BP is normal.
(a) Administer up to 60 mL/kg of isotonic crystalloid in 20 mL/kg increments in non-neonates during the first 20 minutes until perfusion improves. Frequently reassess for hepatomegaly, pulmonary crackles, and respiratory distress.
(b) Special consideration for **cardiogenic shock:**
(i) Administer an initial fluid bolus of 5 to 10 mL/kg over 10 to 20 minutes if cardiac insufficiency suspected or unknown (consider in neonate).
(ii) Be prepared to support oxygenation and ventilation in case of pulmonary edema.
(c) Special consideration for **septic shock**: Specific goals of therapy include $ScvO_2$ (central venous saturation) ≥70%, adequate BP, normalized heart rate (HR), and appropriate end-organ perfusion.

f. **Extracorporeal-CPR** (**E-CPR):** Rapid deployment of venoarterial (VA) or venovenous (VV) extracorporeal membrane oxygenation (ECMO) to artificially provide oxygenation, ventilation, and circulation as a means of CPR for in-hospital arrest refractory to conventional interventions. Contraindications are limited but may include extremes of prematurity or low birth weight, lethal chromosomal abnormalities, uncontrollable hemorrhage, or irreversible brain damage. Should not be offered if likely to be futile.

B. Airway and Breathing[1,7,11-17]

1. Assessment
a. **Airway patency:** Perform head tilt and chin lift or jaw thrust to open airway. Avoid overextension in infants.
b. **Spontaneous respirations:** Assess spontaneous patient effort.
(1) If breathing regularly, place patient in **recovery position** (turn onto side).
(2) If the patient has a palpable pulse but inadequate breathing, **provide a 1-second breath every 3 to 5 seconds.**
c. **Adequacy of respiration:** Evaluate for symmetric chest rise. Auscultate for equal breath sounds with good aeration.

TABLE 1.1

PEDIATRIC RESUSCITATION MEDICATIONS[5,7,11,17]

Medication	Indication	Dosing	Mechanism	Side Effects
Adenosine	SVT secondary to AV node reentry or accessory pathways	Initial: 0.1 mg/kg IV (max 6 mg) Sec: 0.2 mg/kg IV (max 12 mg) Third: 0.3 mg/kg IV (max 12 mg) Wait 2 min between doses Administer with three-way stopcock rapid push/flush technique	Purine nucleoside blocks AV node conduction	Brief period of asystole (10–15 sec)
Amiodarone	Shock-refractory VF or pVF, stable SVT, unstable VT	5 mg/kg (max 300 mg) IV/IO No pulse: Push undiluted dose Pulse: Dilute and run over 20–60 min Repeat dosing: 5 mg/kg (up to max 150 mg) up to 15 mg/kg total Infusion: 5–15 mCg/kg/min (max 20 mg/kg/day or 2200 mg/day)	Potassium-channel blockade suppresses AV node, prolongs QT and QRS	Risk of polymorphic VT, hypotension, decreased cardiac contractility
Atropine	Bradycardia from increased vagal tone, cholinergic drug toxicity, second- and third-degree AV block	0.02 mg/kg IV/IO/IM (min 0.1 mg/dose, max 0.5 mg/dose; larger doses may be needed for organophosphate poisoning) or 0.04–0.06 mg/kg ET Repeat dosing: may repeat once after 5 min	Cholinergic blockade accelerates atrial pacemakers, enhances AV conduction	Tachycardia, risk of myocardial ischemia, paradoxical bradycardia with lower than minimal dosing
Calcium chloride	Hypocalcemia, hyperkalemia, hypermagnesemia, calcium channel blocker overdose	20 mg/kg (max 1 g) IV/IO Administer over 10–20 sec in arrest Consider calcium gluconate in nonarrest if access is peripheral only	Binds myocardial troponin to increase cardiac contractility	Risk of myocardial necrosis
Dextrose	Documented hypoglycemia	0.5–1 g/kg IV/IO Newborn: 5–10 mL/kg $D_{10}W$ Infants, children: 2–4 mL/kg $D_{25}W$ Adolescents: 1–2 mL/kg $D_{50}W$	Restores energy metabolite	Risk of poor neurologic outcomes in setting of hyperglycemia

Epinephrine	Asystole, PEA, VT, pVT, diastolic hypotension, bradycardia	Bolus: 0.01 mg/kg IV/IO (0.1 mg/mL; max 1 mg) or 0.1 mg/kg ET (1 mg/mL; max 2.5 mg) Repeat dosing: Bolus every 3–5 min as needed Infusion: 0.1–1 mCg/kg/min	α-Agonism increases heart rate and cardiac contractility	Tachycardia, ectopy, tachyarrhythmias, hypertension
Lidocaine	Shock-refractory VF or pVT (second-line after amiodarone)	Bolus: 1 mg/kg (max 100 mg) IV/IO, 2–3 mg/kg ET Repeat dosing: 1 mg/kg (max 100 mg) every 10–15 min up to 3–5 mg/kg in first hr Infusion: 20–50 mCg/kg/min	Sodium-channel blockade shortens the duration of the action potential	Myocardial depression, altered mental status, seizures, muscle twitching
Magnesium sulfate	Torsades de pointes, hypomagnesemia	50 mg/kg (max 2 g) IV/IO No pulse: Push dose Pulse: Run over 20–60 min	Calcium antagonist depresses abnormal secondary depolarizations and AV node conduction	Hypotension, bradycardia
Naloxone	Opioid overdose	Full reversal: 0.1 mg/kg/dose (max 2 mg/dose) IV/IO/IM, 0.2 mg/kg to 1 mg/kg/dose ET, or 2–4 mg IN Repeat dosing: every 2–3 min as needed	Opioid antagonist reverses opioid-induced respiratory depression, sedation, analgesia and hypotension	Rapid withdrawal, agitation, pain, pulmonary edema
Procainamide	Stable SVT, atrial flutter, atrial fibrillation, VT	Load: 15 mg/kg IV/IO, run over 30–60 min Infusion: 20-80 mCg/kg/min (Max 2 g/24 hr)	Sodium-channel blockade prolongs effective refractory period, depresses conduction velocity	Proarrhythmic, polymorphic VT, hypotension
Sodium bicarbonate	Routine use in arrest is **not** recommended; hyperkalemia, arrhythmias in tricyclic overdose	1 mEq/kg IV/IO Hyperkalemia: Max single dose 50 mEq	Buffers acidosis by binding hydrogen ions to improve myocardial function, reduce SVR and inhibit defibrillation	May impair tissue oxygen delivery, hypokalemia, hypocalcemia, hypernatremia, impaired cardiac function

AV, Atrioventricular; *$D_{10}W$*, dextrose 10% in water; *ET*, endotracheal; *HR*, heart rate; *ICP*, intracranial pressure; *IM*, intramuscular; *IO*, intraosseous; *IV*, intravenous; *IN*, intranasal; *mCg*, microgram; *PEA*, pulseless electrical activity; *pVF*, pulseless ventricular fibrillation; *pVT*, pulseless ventricular tachycardia; *SVR*, systemic vascular resistance; *SVT*, supraventricular tachycardia; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

d. **Distress:** Recognize tachypnea, grunting, flaring, retractions, stridor, or wheeze. Infants may exhibit head bobbing.

2. Securing airway
   a. **Bag-mask ventilation** (BVM): May be used indefinitely if ventilating effectively.
      (1) Avoid pushing mask down, which can obstruct airway. Bring face into mask.
      (2) Consider **oropharyngeal** airway in the **unconscious** patient with obstruction. Correct size will extend from corner of mouth to mandibular angle.
      (3) Consider **nasopharyngeal** airway in the **conscious** (gag reflex intact) or unconscious patient with obstruction. Correct size will extend from tip of nose to tragus of ear.
      (4) Cricoid pressure (Sellick maneuver) may be used to minimize gastric inflation and aspiration. Avoid excess pressure leading to tracheal obstruction.
   b. **Laryngeal mask airway** (LMA)**:** Supraglottic airway placed blindly. Useful to emergently secure access to a difficult airway.
      (1) Use manufacturer-specific weight-based mask size estimation systems or the combined width of the patient's index, middle, and ring fingers to estimate mask size.
      (2) Continuous chest compressions can be performed once LMA is placed.
   c. **Endotracheal intubation:** Rapid sequence intubation is indicated in patients presenting with (presumed) full stomach. Immediately sequential sedation and neuromuscular blockade help to avert the need for positive pressure ventilation, minimizing aspiration risk.
      (1) **Preparation:** Always have a secondary plan to manage the airway if intubation is unsuccessful.
         (a) **Preoxygenation**: Deliver 100% oxygen via a nonrebreather mask for at least 3 minutes. Children have higher oxygen consumption than adults and can rapidly become hypoxemic.
         (b) **Equipment:** Collect monitoring, suctioning, and oxygen delivery equipment.
            (i) If available, quantitative **$EtCO_2$** is recommended as primary method to confirm ventilation.
            (ii) Place suction catheter at head of bed. Set suction device from **−80 mmHg to −120 mmHg.**
            (iii) Consider nasogastric tube for stomach decompression. See Chapter 4 for placement.
         (c) **Airway supplies:** Both cuffed and uncuffed ETTs are acceptable. Cuffed tubes may decrease risk of aspiration.
            (i) If available, use a length-based estimator (e.g., Broselow tape) of ETT size and laryngoscope blade size.
            (ii) To estimate age-based ETT size (internal diameter) for patients 2 to 10 years:

Cuffed ETT (mm) = (age in years/4) + 3.5
Uncuffed ETT (mm) = (age in years/4) + 4.0

(iii) To approximate depth of insertion:

Depth (mm) = ETT size (mm) ×3

(iv) Choose laryngoscope blade type and size based on patient age and airway.
(v) Straight (i.e., Miller) blades are typically reserved for children <2 years age or difficult airways.
[1] Miller #00-1 for premature to 2 months age
[2] Miller #1 for 3 months to 3 years age
[3] Miller #2 for >3 years age
(vi) Curved (i.e., Mac) laryngoscope blades are often more effective for children >2 years age.
[1] Mac #2 for >2 years age
[2] Mac #3 for >8 years age

(d) **Pharmacology:** See Table 1.2 for rapid sequence intubation medications.
(e) **Positioning:** Place patient in "sniffing" position with neck slightly extended to align the airway.
(i) Infants and toddlers may require towel roll beneath **shoulders** due to large occiput.
(ii) Children and adolescents may require towel roll beneath **neck.**

(2) **Procedure:** Advanced airways should be placed by experienced healthcare providers with appropriate training.
(a) Confirm placement by detecting $EtCO_2$, observing chest wall movement, auscultating for symmetric breath sounds, and monitoring oxygen saturation. Evaluate placement via chest radiograph.

(3) **Failure:** Acute respiratory failure in an intubated patient may signify **D**isplacement of the ETT, **O**bstruction, **P**neumothorax, or **E**quipment failure (**DOPE**).

d. **Surgical airway:** Consider needle or surgical cricothyrotomy if BVM, endotracheal intubation, and LMA fail. If available, consult emergently with difficult airway specialists (pediatric anesthesiologist, intensivist, and/or otolaryngologist).

3. Oxygenation and Ventilation
a. Oxygen delivery systems:
(1) Low-flow systems (e.g., nasal cannula, simple face mask) **do not meet** the inspiratory flow demand of the patient. Delivery of set fraction of inspired oxygen (FiO_2) is difficult due to room air mixing.
(2) High-flow systems (e.g., nonrebreather, oxygen hood) **do meet** the inspiratory flow demand of the patient. Measurable FiO_2 is delivered.

TABLE 1.2

RAPID SEQUENCE INTUBATION MEDICATIONS[11,15-17,20]

Medication	Benefit	Indication	Dosing	Side Effects
1. Adjuncts				
Atropine	Prevent bradycardia associated with laryngoscope insertion, decrease oral secretions	Bradycardia in any patient, infants <1 year, children 1–5 years receiving succinylcholine, children >5 years receiving a second dose of succinylcholine	0.02 mg/kg IV/IO/IM (max 0.5 mg)	Tachycardia, pupil dilation
Glycopyrrolate	Decrease oral secretions, may cause less tachycardia than atropine, preserves pupillary exam in trauma	Hypersalivation	0.004–0.01 mg/kg IV/IM/IO (max 0.1 mg)	Tachycardia
Lidocaine	Blunts rise in ICP associated with laryngoscopy	Elevated ICP, shock, arrhythmia, and status asthmaticus	1 mg/kg IV/IO (max 100 mg)	Myocardial depression, altered mental status, seizures, muscle twitching
2. Induction Agents				
Etomidate (sedative)	Minimal cardiovascular side effects, minimally decreases ICP	Multitrauma patient at risk for increased ICP and hypotension Caution in patients with adrenal suppression; avoid in septic shock	0.3 mg/kg IV/IO	Suppresses adrenal corticosteroid synthesis, vomiting, myoclonus, lowers seizure threshold
Fentanyl (analgesic, sedative)	Minimal cardiovascular effect	Shock	1–5 mCg/kg slow IV/IM push (max 100 mCg)	Chest wall rigidity, bradycardia, respiratory depression
Ketamine (sedative, analgesic)	Catecholamine release causes bronchodilation, abates bradycardia associated with laryngoscope insertion, increases HR and SVR, produces a "dissociative amnesia"	Status asthmaticus, shock and hypotensive patients Caution in patients at risk for elevated ICP or glaucoma history	1–2 mg/kg IV/IO (max 150 mg) 4–6 mg/kg IM	Vomiting, laryngospasm, hypersalivation, emergence reactions (hallucinations)

Midazolam (sedative, amnestic, anxiolytic)	Minimal cardiovascular effect	Mild shock	0.05–0.3 mg/kg IV/IM/IO (max 10 mg)	Dose-dependent respiratory depression, hypotension
Propofol (sedative)	Ultra-short acting	Role in RSI unclear Avoid in shock or patients who require maintenance of CPP	1 mg/kg IV initial bolus, then 0.5 mg/kg boluses every 3 min as needed	Hypotension, myocardial depression, metabolic acidosis; may cause paradoxical hypertension in children
3. Neuromuscular blockade				
Succinylcholine (depolarizing)	Shortest acting neuromuscular blockade agent, reversible with acetylcholinesterase inhibitor	Role limited due to adverse events Contraindicated in neuromuscular disease, myopathies, spinal cord injury, crush injury, burns, renal insufficiency	IV: ≤2 years: 2 mg/kg >2 years: 1 mg/kg (30–60 sec onset, 4–6 min duration) IM: 3–4 mg/kg (3–4 min onset, 10–30 min duration) Max dose: 150 mg/dose IV/IM	Hyperkalemia, trigger of malignant hyperthermia, masseter spasm, bradycardia, muscle fasciculations, increased intracranial, intraocular, and intragastric pressure
Rocuronium (nondepolarizing)	Minimal cardiovascular effect, reversible with sugammadex	Caution in patients with difficult airway	1.2 mg/kg IV/IM/IO (30–60 sec onset, 30–40 min duration) Max dose: 100 mg	Prolonged duration in hepatic failure
Vecuronium (nondepolarizing)	Minimal cardiovascular effect, reversible with sugammadex	Caution in patients with difficult airway	0.15–0.2 mg/kg IV/IO (1–3 min onset, 30–40 min duration) Max dose: 10 mg	Prolonged duration in hepatic failure

CPP, Cerebral perfusion pressure; *HR*, heart rate; *ICP*, intracranial pressure; *IM*, intramuscular; *IV*, intravenous; *IO*, intraosseous; *mCg*, microgram; *SVR*, systemic vascular resistance; *RSI*, rapid sequence intubation.

(3) High-flow nasal cannula **(HFNC)**:
(a) High-flow, noninvasive respiratory support provides a heated and humidified air-oxygen mixture that may improve gas exchange by providing airway-distending pressure.
(b) Optimal and maximal flow rates are unknown. Consensus supports a maximum flow rate of up to **2 L/kg/min** or 12 L/min for infants and toddlers, 30 L/min for children, and up to 50 L/min for adolescents and adults.

b. Noninvasive positive pressure ventilation **(NIPPV)**:
(1) **CPAP:** Delivery of a continuous, distending positive airway pressure independent of patient inspiratory effort.
(2) **BiPAP:** Pressure-limited ventilatory mode in which the clinician sets an inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP).
(a) EPAP is started at 4 to 5 cmH_2O and increased to a maximum of 8 to 12 cmH_2O.
(b) Set 4 to 6 cmH_2O of pressure support, or the difference between IPAP and EPAP.
(c) Consider setting a "backup rate," or respiratory rate just shy of the spontaneous respiratory rate to be delivered in case of apnea.

c. Mechanical Ventilation:
(1) **Parameters:**
(a) Rate: Number of mechanical breaths delivered per minute.
(b) FiO_2: Fraction of oxygen in inspired gas.
(c) PIP: Peak inspiratory pressure attained during respiratory cycle.
(d) Positive end-expiratory pressure (PEEP): Distending pressure that increases functional residual capacity (FRC), or volume of gas at the end of exhalation.
(e) Mean airway pressure (P_{aw}): Average airway pressure over entire respiratory cycle, which correlates to mean alveolar volume.
(f) Tidal volume (V_T): Volume of gas delivered during inspiration.
(g) Time: May indicate a function of time spent in inspiration (T_i), in high pressure (T_{high}), or in low pressure (T_{low}).
(2) **Modes of Ventilation:**
(a) **Controlled Ventilation:** Ventilation is completely mechanical with no spontaneous ventilation efforts expected from the patient.
(i) Pressure-controlled ventilation **(PCV)**: A preset respiratory rate and T_i delivers a pressure-limited breath (the set pressure is maintained during inspiration). V_T is determined by the preset pressure as well as lung compliance and resistance.
(ii) Volume-controlled ventilation **(VCV)**: A preset respiratory rate and T_i delivers a preset V_T.

(b) Intermittent mandatory ventilation **(IMV)**: Allows the patient to breathe spontaneously between a preset number of (mandatory) mechanical breaths.
  (i) Synchronized IMV **(SIMV)**: If patient initiates spontaneous breath, mandatory breath is synchronized with patient effort rather than spaced evenly over each minute.
  (ii) If spontaneous breathing rate is less than mandatory rate, some mandatory breaths will be delivered in the absence of patient effort.
  (iii) Delivered breaths may be volume regulated or pressure limited.

(c) Airway-pressure-release ventilation **(APRV)**: Most of the respiratory cycle is spent at a high distending pressure (a functionally high CPAP phase) with intermittent, short release to a low pressure for a brief ventilation phase. Spontaneous breathing can be superimposed at any point in the cycle.

(d) **Support ventilation:** Mechanical breaths support patient-initiated breaths, but no mandatory breaths are provided.
  (i) Pressure support **(PS)**: Delivers a preset amount of pressure to assist spontaneous respiratory effort.
  (ii) Often used in combination with other modes of ventilation to support spontaneous breaths greater than preset respiratory rates.

(e) High-frequency oscillatory ventilation **(HFOV)**: Gas flow pressurizes the system to the preset P_{aw} while a piston moves backwards and forwards to force and withdraw a small V_T (that approximates anatomic dead space) into the lungs at rates exceeding normal respiratory rates.

(3) **Management:** The three subdivisions of mechanical ventilatory support are the acute (lung recruitment), maintenance (lung recovery), and weaning phases.

(a) **Acute:** See Table 1.3 for ventilation parameter initial settings and titration effects.

(b) **Maintenance:** To avoid volutrauma, barotrauma, or oxygen toxicity, maintain V_T at 4-6 mL/kg, PIP < 35 cmH_2O, and FiO_2 ≤ 60%.

(c) **Weaning:**
  (i) Assess daily for clinical signs of readiness, such as spontaneous breathing efforts.
  (ii) Standard indices indicating readiness include: FiO_2 <50%, PEEP of 5 cmH_2O, PIP <20 cmH_2O, normalized rate for age, and absence of hypercapnia or acidosis.
  (iii) The general approach combines gradual weaning of parameters and reliance on pressure-support modes.

(d) **Extubation:**
  (i) Provide humidified inspired oxygen after extubation.

TABLE 1.3

MECHANICAL VENTILATION PARAMETER SETTINGS AND EFFECTS[11,14,17]

Parameter	Initial Setting	Effect of ↑ on $PaCO_2$	Effect of ↑ on PaO_2
PIP	≤28 cmH_2O or ≤29–32 cmH_2O for reduced chest wall compliance	↓↓	↑
PEEP	3–5 cmH_2O	↑	↑↑
V_T	5–8 mL/kg or 3–6 mL/kg for poorly compliant lungs	↓↓	↑
Rate	Normal rate for age	↓↓	Minimal ↑
I:E ratio	(33%) 1:2 (67%)	No change	↑
FiO_2	<50% and/or to maintain PaO_2 between 80 and 100 mmHg and SpO2 ≥95%	No change	↑↑
High-Frequency Ventilation Parameters			
Amplitude (ΔP)	Set to produce a visible wiggling motion to the level of the lower abdomen	↓	No change
Frequency (Hz)	Range from 3–20 Hz (180–1200 breaths per min)	↑↑	↓
P_{aw}	5 cmH_2O > than P_{aw} of previous conventional ventilation	Minimal ↓	↑

FiO_2, Fraction of inspired oxygen; *I:E*, inspiratory to expiratory; *Hz*, hertz; *P_{aw}*, mean airway pressure; *$PaCO_2$*, partial pressure of carbon dioxide (arterial); *PaO_2*, partial pressure of oxygen (arterial); *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure; *V_T*, tidal volume.

(ii) In case of uncuffed tube or the absence of an air leak at delivered pressure <30 cmH_2O, consider 24 hours of dexamethasone (airway edema dosing) to prevent postextubation stridor.

II. MANAGEMENT OF SHOCK[3,5,7,11]

A. Definition: Physiologic state characterized by inadequate oxygen and nutrient delivery to meet tissue demands

1. **Compensated**: Perfusion to vital organs is maintained by compensatory mechanisms.
   a. Tachycardia is often the first and most sensitive vital sign change.
   b. Blood flow is redirected from nonvital organs and tissues to vital organs by a selective increase in systemic vascular resistance (SVR), resulting in reduced peripheral perfusion and decreased urine volume.
   c. Cardiac contractility increases to maintain cardiac output.
   d. Increased venous smooth muscle tone improves preload and stroke volume.
2. **Decompensated**: Perfusion to vital organs is compromised. Denoted by **hypotension**, poor perfusion, oliguria/anuria, and altered mental status.

B. Etiology: Categorized into four basic types:

1. **Hypovolemic**: inadequate fluid intake, increased fluid losses (hemorrhage, gastroenteritis, burns). Assess for tachycardia, narrow pulse pressure, delayed capillary refill, cool extremities.
2. **Cardiogenic**: congenital heart disease, myocarditis, cardiomyopathy, arrhythmia. Assess for increased respiratory effort from pulmonary edema, hepatomegaly, jugular venous distension, and cyanosis.
3. **Distributive**: sepsis, anaphylaxis, neurogenic (e.g., high cervical spine injury)
   a. Assess for tachycardia, fever, and petechial, purpuric, or urticarial rash.
   b. Warm septic shock is characterized by bounding peripheral pulses, flash capillary refill, and wide pulse pressure.
   c. Cold septic shock is characterized by decreased peripheral pulses, delayed capillary refill, and narrow pulse pressure.
   d. Neurogenic shock is characterized by hypotension with a wide pulse pressure, normal HR or bradycardia, and hypothermia.
4. **Obstructive**: tension pneumothorax, cardiac tamponade, pulmonary embolism, ductal-dependent congenital cardiac abnormalities
   a. Early clinical presentation is indistinguishable from hypovolemic shock. Progression of shock leads to signs and symptoms similar to cardiogenic shock.
   b. Cardiac tamponade is characterized by muffled heart sounds and pulsus paradoxus.
   c. Ductal-dependent lesions may be characterized by higher preductal versus postductal BP or arterial oxygen saturation.

C. Management

1. Administer 100% supplemental oxygen initially regardless of oxygen saturation to optimize oxygen delivery. Once perfusion restored, titrate as able to avoid adverse effects from hyperoxia.
2. See Table 1.4 for type- and etiology-specific pathophysiology and management of shock.
3. See Table 1.5 for vasoactive agents to support cardiac output. Vasoactive agents affect SVR (vasodilators and vasoconstrictors), cardiac contractility (inotropes), or HR (chronotropes). Some agents increase blood flow via contractility and vasodilation (inodilators) or increase perfusion pressure via contractility and vasoconstriction (inoconstrictors).

III. MANAGEMENT OF COMMON EMERGENCIES

A. Anaphylaxis[18]

1. **Definition**: Rapid-onset (minutes to hours) usually immunoglobulin E (IgE)-mediated systemic allergic reaction involving multiple organ systems, including two or more of the following:
   a. **Cutaneous/mucosal** (80% to 90%): flushing, urticaria, pruritis, angioedema

TABLE 1.4

PATHOPHYSIOLOGY AND MANAGEMENT OF SHOCK[3,5]

Type	HR	Preload	Contractility	SVR	Management
Hypovolemic	↑	↓↓	Normal or ↑	↑	Rapid administration of isotonic crystalloids Replace blood loss with 10 mL/kg PRBCs boluses Consider colloids if response is poor to crystalloids and loss of protein-containing fluids is suspected
Distributive	↑ or ↓	Normal or ↓	Normal or ↓	±	Administer isotonic crystalloids to expand intravascular volume Support with vasopressors if fluid-refractory
Septic	↑	↓↓	Normal or ↓	↓	**Within 1st hour:** Administer isotonic crystalloid boluses, broad-spectrum antibiotics, and consider stress-dose hydrocortisone **Warm:** Support with norepinephrine or high-dose dopamine **Cold:** Support with epinephrine or dopamine
Neurogenic	Normal or ↓	↓↓	±	↓↓	Position patient flat or head-down Administer a trial of isotonic crystalloid therapy If fluid-refractory, support with norepinephrine or epinephrine Maintain normothermia
Cardiogenic	±	↑	↓↓	↑	Consider cautious administration (10–20 min) of isotonic crystalloid (5–10 mL/kg); stop if fluid overload develops Support with inodilator milrinone Decrease metabolic demand with oxygen therapy, ventilatory support and antipyretics
Obstructive	↑	±	Normal	↑	Correct underlying cause Start prostaglandin E_1 if ductal-dependent lesion suspected Consider initial fluid challenge with isotonic crystalloid (10–20 mL/kg)

HR, Heart rate; *PRBCs*, packed red blood cells; *SVR*, systemic vascular resistance

TABLE 1.5

MEDICATIONS TO SUPPORT CARDIAC OUTPUT[5,7,11]

Medication	Dose	Mechanism	Comments
Dobutamine	2–20 mCg/kg/min	Selective β_1 agonist	Inotrope May predispose to arrhythmia Indicated for normotensive, poorly perfused shock
Dopamine	5–20 mCg/kg/min	Direct dopamine receptor agonist, indirect β and α agonist (stimulates norepinephrine release), direct α agonist at high dose (>15 mCg/kg/min)	Low to moderate dose: inotrope, chronotrope, splanchnic vasodilator High dose: vasopressor Indicated for shock with poor contractility and/or low SVR and cold septic shock if epinephrine unavailable
Epinephrine	0.1–1 mCg/kg/min	β_1 and β_2 agonist at low dose (<0.3 mCg/kg/min), α_1 agonist at high dose (>0.3 mCg/kg/min)	Low dose: inotrope, chronotrope, vasodilator High dose: vasopressor Indicated for hypotensive shock with marked circulatory instability and cold septic shock
Milrinone	Loading: 50 mCg/kg over 15 min, then 0.25–0.75 mCg/kg/min	Type III phosphodiesterase-inhibitor	Inodilator Improves cardiac output with little effect on heart rate Indicated for normotensive shock with myocardial dysfunction and cold septic shock refractory to epinephrine
Norepinephrine	0.05–2.5 mCg/kg/min	α_1 and β_1 agonist	Vasoconstrictor, mild inotrope Indicated for shock with low SVR (warm septic, anaphylactic, spinal) and cold shock refractory to epinephrine if diastolic BP low
Phenylephrine	Loading: 5–20 mCg/kg/dose (max 500 mCg), then 0.1–0.5 mCg/kg/min	Pure α_1 agonist	Vasoconstrictor
Vasopressin (ADH)	0.17–8 mUnits/kg/min	Vasopressin receptor agonist	Vasoconstrictor Consider for cardiac arrest, refractory hypotension in septic shock and GI hemorrhage

ADH, Antidiuretic hormone; *BP*, blood pressure; *cGMP*, cyclic guanosine monophosphate; *GI*, gastrointestinal; *mCg*, microgram; *NO*, nitric oxide; *SVR*, systemic vascular resistance.

b. **Respiratory** (70%): laryngeal edema, bronchospasm, dyspnea, wheezing, stridor, hypoxemia
c. **Gastrointestinal** (45%): vomiting, diarrhea, nausea, crampy abdominal pain
d. **Circulatory** (45%): tachycardia, hypotension, syncope

2. Management:
   a. **Stop exposure** to precipitating antigen.
   b. While performing A-B-Cs, immediately give intramuscular **(IM) epinephrine** into midanterolateral thigh.
      (1) For child, administer **0.01 mg/kg of 1 mg/mL solution** up to a max dose of 1 mg/dose. For adult-sized patients, first administer **0.2 to 0.5 mg of 1 mg/mL solution**, increasing as necessary up to max single dose of 1 mg.
      (2) Autoinjector dosing: 7.5 to <15 kg use **0.1 mg**, 15 to <30 kg use **0.15 mg**, ≥30 kg use **0.3 mg.**
      (3) Repeat dosing every 5 to 15 minutes as needed.
   c. Provide oxygen and ventilatory assistance. Consider early endotracheal intubation.
   d. Obtain IV access. For management of shock, resuscitate with 20 mL/kg isotonic crystalloid fluid boluses and vasoactive agents as needed.
   e. Place patient in Trendelenburg position (head 30 degrees below feet).
   f. Consider adjuvant pharmacologic agents:
      (1) **Histamine receptor antagonist:** Diphenhydramine (H1-antagonism) and ranitidine/famotidine (H2-antagonism)
      (2) **Corticosteroid:** Methylprednisolone or dexamethasone
      (3) **Inhaled β_2 agonist:** Albuterol
   g. Symptoms may recur ("biphasic anaphylaxis") up to 72 hours after initial recovery.
      (1) Observe for a minimum of 4 to 10 hours for late-phase symptoms.
      (2) Discharge with an epinephrine autoinjector and an anaphylaxis action plan.

B. Upper Airway Obstruction

1. Epiglottitis[19-20]
   a. **Definition:** Life-threatening, rapidly progressive inflammation (usually infectious) of the supraglottic region.
      (1) Most often affects children between 1 and 7 years, but may occur at any age.
      (2) May be caused by infection, thermal injury, caustic ingestion, or foreign body.
      (3) Most common infectious organisms include *Haemophilus influenzae* (unvaccinated), *Streptococcus pneumoniae,* group A streptococci, and *Staphylococcus aureus.*
      (4) Patients often present febrile, toxic-appearing, and tripoding in respiratory distress. Drooling, dysphagia and inspiratory stridor are common. Barky cough is absent.

b. **Management:** Avoid *any agitation* of the child prior to securing airway to prevent impending complete obstruction.
   (1) Allow child to assume a position of comfort. Unobtrusively provide blow-by oxygen. Monitor with pulse oximetry.
   (2) To secure airway, emergently consult difficult airway personnel (pediatric anesthesiologist, intensivist, and/or otolaryngologist).
      (a) If unstable (unresponsive, cyanotic, bradycardic), emergently intubate.
      (b) If stable with high suspicion, escort patient to OR for laryngoscopy and intubation under general anesthesia. Equipment for tracheotomy should be readily available.
      (c) If stable with moderate or low suspicion, obtain lateral neck radiograph to assess for "thumb sign" of an inflamed epiglottis.
   (3) Initiate broad-spectrum antibiotic therapy (e.g., vancomycin and Ceftriaxone).

2. **Croup**[21-22]
   a. **Definition:** Common infectious inflammation of the subglottic area.
      (1) Most common in infants aged 6 to 36 months.
      (2) 75% of infections are caused by parainfluenza virus.
      (3) Patients present with fever, barking cough, inspiratory stridor, and increased work of breathing, often worse at night.
   b. Management:
      (1) Administer oxygen to children with hypoxemia or severe respiratory distress. Consider humidified air, although current consensus suggests it is ineffective for mild to moderate disease.
      (2) If **no stridor at rest**, give dexamethasone. Consider nebulized budesonide in patients vomiting or who lack IV access.
      (3) If **stridor at rest**, give dexamethasone and nebulized racemic epinephrine. Observe for 2 to 4 hours given short duration of action of nebulized epinephrine.
      (4) Indications for hospitalization include >1 racemic epinephrine nebulization required, atypical age (<6 months), severe respiratory distress, or dehydration.
      (5) Consider heliox (helium and oxygen mixture) to improve turbulent airflow in moderate to severe croup, although benefit is controversial.

3. Foreign body aspiration[1,20,23]
   a. **Definition:** Acute airway obstruction from aspiration of an organic (e.g., nuts, seeds, grapes, hot dogs) or inorganic (e.g., coins, pins, beads, balloons, small toy parts) foreign body.
      (1) Male children younger than 3 years of age are most susceptible.
      (2) Patients (<40%) present with classic triad of paroxysmal cough, wheezing, and decreased air entry. Other manifestations include cyanosis, fever, stridor, and persistent pneumonia or notably may be asymptomatic.

(3) The most common location is the right main bronchus (45% to 57%), then left main bronchus (18% to 40%), and trachea (10% to 17%).

b. **Management:** Care is taken to avoid converting a partial airway obstruction into complete obstruction.

(1) If **not** breathing (no cough or sound):

(a) Infant: Deliver repeated cycles of 5 back blows followed by 5 chest compressions until object is expelled or victim becomes unresponsive.

(b) Child: Perform subdiaphragmatic abdominal thrusts (Heimlich maneuver) until object is expelled or victim becomes unresponsive.

(c) Patients should be taken to the OR for emergent removal under direct laryngoscopy and bronchoscopy.

(2) If **breathing** (forcefully coughing, phonating):

(a) Obtain posteroranterior chest (including neck) radiograph to screen for radiopaque body or mediastinal shift. Consider inspiratory and expiratory films (or bilateral lateral decubitus in young patients) to assess for air trapping. A normal chest radiograph does not rule out foreign body.

(b) If clinical concern is high, consider urgent bronchoscopy or laryngoscopy.

(3) If patient becomes **unresponsive:** initiate CPR immediately.

(a) After 30 chest compressions, open airway and remove foreign body if visible. Do **not** perform blind sweep.

(b) Attempt to give two breaths and continue with cycles of chest compressions and ventilations until object expelled.

C. Status Asthmaticus[24-28]

1. **Definition**: Inflammatory airflow obstruction secondary to triad of airway edema, bronchoconstriction, and hyperresponsiveness.
2. **Examination**: Assess breathlessness, speech, alertness, respiratory rate, accessory muscle use, wheezing, HR, pulsus paradoxus, peak expiratory flow, SpO_2, and pCO_2.
3. **Management**:
   a. Provide oxygen to achieve SpO_2 ≥90%. If hypoxemia not readily corrected with supplemental oxygen, consider pneumothorax, pneumonia, methemoglobinemia, or other process.
   b. See Table 1.6 for pharmacologic agents used in acute asthma exacerbations.
   c. Ventilation interventions:
      (1) Normalizing pCO_2 can be a sign of impending respiratory failure.
      (2) NIPPV (e.g., BiPAP) may be used in patients with impending respiratory failure to avoid intubation but requires a cooperative patient with spontaneous respirations.

TABLE 1.6

STATUS ASTHMATICUS MEDICATIONS[24-28]

Medication	Dose	Comments
Short-acting β_2 agonist		
Albuterol	**Mild to Moderate:** Administer up to 3 doses in the first hour MDI: 4–8 puffs (90 mCg/puff) q20 min–4 hr Nebulizer: 0.15 mg/kg (min 2.5 mg, max 5 mg) q20 min–4 hr **Severe:** Continuous nebulization: 0.5 mg/kg/hr (max 30 mg/hr)	Inhaler (with spacer) is preferred delivery method given equal or greater efficacy, fewer side effects, and shorter length of stay
Anticholinergics		
Ipratropium bromide	Administer q20 min for 3 doses with albuterol MDI: 4–8 puffs (17 mCg/puff) Nebulizer: 0.25–0.5 mg	No additional benefit shown in inpatient setting
Systemic corticosteroids		
Dexamethasone	**Mild to Moderate:** 0.6 mg/kg/day PO/IV/IM for 1–2 days (max 16 mg/day)	Equally as efficacious as prednisone or prednisolone with fewer side effects, better compliance and palatability
Prednisone, Prednisolone	**Mild to Severe:** 2 mg/kg/day PO for 5–7 days (max 60 mg/day)	Taper if course ≥7 days or bounce back from recent exacerbation
Methylprednisolone	**Severe:** Loading: 2 mg/kg IV (max 60 mg) Maintenance: 2 mg/kg/day IV divided q6–12hr (max <12 years 60 mg/day, ≥12 years 80 mg/day)	No known advantage in severe exacerbations for higher dosing or IV administration over oral therapy, provided normal GI transit and absorption
Injected β_2 agonist		
Epinephrine	0.01 mg/kg of 1 mg/mL IM (max 1 mg) q15–20 min for up to 3 doses	Consider for severe exacerbation with minimal air entry Consider quickly accessed autoinjector
Terbutaline	SC: 0.01 mg/kg (max 0.25 mg/dose) q20 min for up to 3 doses, then as needed q2–6 hr IV load: 2–10 mCg/kg IV IV continuous: 0.1–0.4 mCg/kg/min (doses as high as 10 mCg/kg/min have been used)	Consider for severe exacerbation with minimal air entry IV administration may decrease the need for mechanical ventilation
Adjunct therapies		
Magnesium sulfate	25–75 mg/kg/dose IV (max 2 g), infuse over 20 min	Smooth muscle relaxant May cause hypotension; consider simultaneous fluid bolus Reduces hospitalization rates in severe exacerbations

Continued

TABLE 1.6—CONT'D

Medication	Dose	Comments
Ketamine	1–2 mg/kg IV bolus followed by 1 mg/kg/h infusion, titrated to affect	Used as a sympathomimetic adjuvant in effort to avoid endotracheal intubation Preferred induction-sedative agent for endotracheal intubation in asthma
Aminophylline	6 mg/kg IV bolus over 20 min followed by 0.5–1.2 mg/kg/h infusion (age-dependent, see formulary)	Use limited to severe exacerbations refractory to traditional interventions May improve lung function and oxygen saturation but is associated with greater length of stay and time to symptom improvement
Heliox	Optimal helium-oxygen ratio unknown, most commonly 70:30 or 80:20 mixture	Low density gas that promotes laminar airflow and improves β_2 agonist delivery to distal airways Useful in severe or very severe exacerbations
Inhaled anesthetics (e.g., halothane, isoflurane, sevoflurane)	Consultation with pediatric anesthetist recommended	Rescue therapy for intubated patients with life-threatening exacerbation Associated with prolonged length of stay and increased cost Isoflurane may cause hypotension Sevoflurane may cause renal tubular injury, hepatotoxicity, neuropathy

GI, Gastrointestinal; *IM*, intramuscular; *IV*, intravenous; *mCg*, microgram; *MDI*, metered-dose inhaler; *SC*, subcutaneous.

(3) Intubation should be approached cautiously given the risk of worsening air-trapping and difficulty in managing the transition from extremely negative to positive pressure ventilation.
   (a) Indications include severe airway obstruction, markedly increased work of breathing, refractory hypoxemia, and impending respiratory arrest.
   (b) Ventilation strategies include slower rates with prolonged expiratory phase, minimal end-expiratory pressures, and short inspiratory times to minimize hyperinflation and air trapping.

(4) Consider inhaled anesthetics or ECMO as rescue therapies.

D. Pulmonary Hypertensive Crisis[11,29]

1. Definition:
   a. Pulmonary hypertension (PH) is defined as resting elevated mean pulmonary artery pressure (PAP) **≥25 mmHg** in children >3 months of age.

b. A **pulmonary hypertensive crisis** is a sudden increase in PAP and pulmonary vascular resistance (PVR) that causes acute right-sided heart failure.
   (1) May be triggered by pain, anxiety, tracheal suctioning, hypoxia, acidosis, or respiratory illness. Most commonly described after cardiac surgery or in the setting of rapid withdrawal of PH-specific therapies.
   (2) Patients present with systemic hypotension, oxygen desaturation (if atrial or ventricular communication present), and decreased $EtCO_2$ on capnography (reduced pulmonary blood flow).
   (3) Assess for increased intensity of systolic murmur (worsening tricuspid regurgitation) and increased hepatomegaly.

2. **Management:** Timely consultation with providers with expertise in managing PH is recommended.
   a. Implement efforts to keep patient calm. Consider opiates, sedatives, and neuromuscular blockade to reduce stress response, especially postoperatively. Avoid agents that decrease SVR.
   b. Administer supplemental oxygen to treat hypoxemia or as an adjunct to pulmonary vasodilators.
   c. Avoid acute hypercarbia and acidosis, which abruptly increase PVR. Consider brief hyperventilation or sodium bicarbonate infusions.
   d. Diuretics treat congestive symptoms. Avoid excessive reduction in intravascular volume leading to decreased cardiac output.
   e. NIPPV may improve oxygenation, treat hypoventilation, and reduce work of breathing. Weigh benefits against increasing patient anxiety and delaying mechanical ventilation.
   f. PH-specific pharmacologic therapies aim to induce pulmonary vasodilation, support the right ventricle, and maintain cardiac output.
      (1) **Inhaled pulmonary vasodilators:** Nitric oxide
         (a) Indicated to reduce need for ECMO in patients with an oxygen index >25.
         (b) Rapid withdrawal of low doses may cause rebound PH. Gradually decrease dose when weaning.
         (c) Monitor for methemoglobinemia.
      (2) **Phosphodiesterase type-5 inhibitors:** Sildenafil, tadalafil
         (a) Often used to prevent rebound PH associated with cessation of nitric oxide.
         (b) Monitor for acute hypotension or hypoxemia secondary to increased alveolar-arterial gradient.
      (3) **Synthetic prostacyclin analogs:** Epoprostenol (Flolan), treprostinil, iloprost
      (4) **Endothelin receptor antagonist:** Bosentan
   g. Consider ECMO or emergent atrial septostomy in case of failed medical management.

E. Hypertensive Crisis[11,30]

1. Definition:
   a. For normal BP values based on age and height, see Chapter 7.
   b. **Hypertensive emergency:** Acutely elevated BP (usually significantly >99th percentile for age and gender) with evidence of end-organ damage.
      (1) Most commonly secondary to renal disease, catecholamine-producing tumors, endocrine syndromes, toxidromes, medication withdrawal, or elevated intracranial pressure (ICP).
      (2) Presents with encephalopathy (e.g., headaches, vomiting, seizures, altered mental status), vision disturbance, congestive heart failure (e.g., dyspnea, peripheral edema, gallop rhythm), and acute kidney injury.
   c. **Hypertensive urgency:** Acutely elevated BP (usually >5 mmHg greater than the 99th percentile for age and gender) without evidence of end-organ damage.
      (1) Most commonly primary hypertension in children >7 years age, followed by renal disease.
      (2) Present with minor complaints (e.g., headaches, nausea).
2. Management:
   a. Rule out increased ICP before instituting antihypertensive treatment given critical need to maintain cerebral perfusion.
   b. Goal is to reduce BP by **≤25%** in the **first 8 hours,** then gradual normalization over the next **24 to 48 hours.**
   c. See Table 1.7 for hypertensive emergency and urgency medications.

F. Hypercyanotic Crisis ("Tet spell")[20,31]

1. **Definition**: Cyanotic emergency secondary to an acute worsening of a preexisting right ventricular outflow tract obstruction (e.g., in a patient with tetralogy of Fallot) that prevents pulmonary blood flow and induces a right-to-left intracardiac shunt.
   a. Peak incidence occurs between 2 and 4 months of age.
   b. Usually occurs in the morning after crying, feeding, or defecation.
   c. Patients present with extreme cyanosis, hyperpnea, tachypnea, and agitation.
2. **Management:** Follow stepwise approach, escalating if spell is not broken.
   a. Make every effort to calm the child. Allow parent to comfort. Consider oral sucrose analgesia (e.g., Sweet-Ease).
   b. Bring knees to chest in infants or encourage squatting in older children to increase SVR and decrease shunting.
   c. Administer 100% oxygen **if patient tolerates**, although effect is limited given absence of effective pulmonary blood flow.
   d. For stepwise pharmacologic abortive management, see Table 1.8.
   e. Consider isotonic crystalloid resuscitation (5 to 10 mL/kg boluses) to ensure adequate preload if patient is dehydrated.

TABLE 1.7

HYPERTENSIVE CRISIS MEDICATIONS[11,30]

Drug	Dose	Pharmacokinetics	Mechanism	Side Effects
PARENTERAL THERAPY				
Esmolol	Bolus: 100–500 mCg/kg Infusion: 100–500 mCg/kg/min (max 1000 mCg/kg/min)	Onset: Immediate Duration: 10–30 min	β_1 blocker	Bradycardia, bronchospasm (at high doses)
Hydralazine	0.1–0.2 mg/kg/dose IV/IM (max 2 mg/kg/dose or 20 mg) q4–6 hr PRN	Onset: 5–30 min Duration: 2–6 hr	Direct arteriole vasodilator	Reflex tachycardia, flushing, lupus-like syndrome
Labetalol	Bolus: 0.2–1 mg/kg (max 40 mg) Infusion: 0.4–1 mg/kg/hr (max 3 mg/kg/hr)	Onset: 2–5 min Duration: 2–6 hr	β_1, β_2, and α_1 blocker	Hyperkalemia, bronchospasm; caution in liver failure due to prolonged duration of action
Nicardipine	Start at 0.5–1 mCg/kg/min (max 5 mCg/kg/min or 15 mg/hr)	Onset: 1–2 min Duration: 2–4 hr	Calcium channel blocker	Reflex tachycardia
Nitroprusside	0.3–4 mCg/kg/min (max 10 mCg/kg/min)	Onset: 30 sec to 2 min Duration: 1–10 min	Arterial and venous vasodilation via NO	Cyanide toxicity
ENTERAL THERAPY				
Captopril	0.3–0.5 mg/kg (max 6 mg/kg/day or 450 mg/24h)	Onset: 15–30 min Duration: 2–6 hr	ACE inhibitor; lowers blood pressure without causing tachycardia	Hyperkalemia, neutropenia, angioedema, cough; contraindicated in bilateral renal artery stenosis or solitary kidney
Clonidine	2–10 mCg/kg/dose q6–8 hr (max 25 mCg/kg/24 hr up to 0.9 mg/24 hr)	Onset: 30–60 min Duration: 6–10 hr	Peripheral vasodilator	Bradycardia, rebound hypertension
Nifedipine	0.1–0.25 mg/kg/dose q4–6 hr PO/SL (max 10 mg/dose, 1–2 mg/kg/24 hr)	Onset: 15–30 min Duration: 4–6 hr	Calcium channel blocker	Precipitous hypotension, reflex tachycardia

ACE, Angiotensin-converting enzyme; *IM*, intramuscular; *IV*, intravenous; *mCg*, microgram; *NO*, nitric oxide; *PO*, oral; *PRN*, as needed; *SL*, sublingual

TABLE 1.8

HYPERCYANOTIC CRISIS ABORTIVE MEDICATIONS[20,31]

Medication	Dose	Comment
Ketamine	1–2 mg/kg IM or IV, administer IV dose over 60 sec	Sedating, increases SVR
Morphine	0.05–0.2 mg/kg IM, SC or IV; do *not* wait for IV access	Calms agitation, suppresses hyperpnea Monitor for respiratory depression
Phenylephrine	5–20 mCg/kg IV bolus	α Agonist, increases SVR
Propranolol	0.15–0.25 mg/kg, via slow IV push Max initial dose 1 mg	β Blockade decreases heart rate, promoting ventricular filling Monitor for hypotension

IM, Intramuscular; *IV*, intravenous; *SC*, subcutaneous; *SVR*, systemic vascular resistance.

f. Treat acidosis with sodium bicarbonate.
g. For refractory spells, consider general anesthesia and emergent surgery for palliation with a systemic to pulmonary shunt or full repair.

G. Altered Level of Consciousness[20,32]

1. **Definition**: A spectrum of impaired consciousness spanning confusion, disorientation, agitation, stupor, lethargy, and coma.
   a. Fluctuations in level of consciousness are common and progression may occur rapidly.
   b. **Coma**: Refers to an unarousable state.
   c. **Lethargy**: Refers to a depressed consciousness resembling sleep from which a patient can be aroused but immediately returns to depressed state.
   d. **Stupor**: Refers to a state of depressed responses to external stimuli but not totally asleep.
   e. Standard descriptors of level of responsiveness include:
      (1) The **Glasgow Coma Scale** (and modified scale for infants): See Table 1.9 to score level of responsiveness.
      (2) **AVPU** mnemonic: Graded as **A** if alert, **V** if responsive to verbal stimulation, **P** if responsive to painful stimulation, or **U** if unresponsive.
   f. Broad differential considerations include **D**rugs, **I**nfection, **M**etabolic, and **S**tructural causes (DIMS).
   g. See Table 1.10 for common etiologies and targeted work-up recommendations.
2. **Management:** Stabilize initially. Further management is aimed at correcting underlying etiology.
   a. Airway, Breathing, Circulation:
      (1) Administer supplemental oxygen to patients presenting with seizure or with signs of shock, regardless of pulse oximetry reading.
      (2) Intubation is indicated in patients unable to protect their airway.
      (3) Consider delaying administration of atropine unless necessary secondary to the loss of pupillary light reflex.

TABLE 1.9

COMA SCALES[20]

Grading	Glasgow Coma Scale	Modified Coma Scale for Infants
EYE OPENING		
4	Spontaneous	Spontaneous
3	To speech	To speech
2	To pain	To pain
1	None	None
VERBAL		
5	Oriented	Coos or babbles
4	Confused	Irritable
3	Inappropriate words	Cries to pain
2	Nonspecific sounds	Moans to pain
1	None	None
MOTOR		
6	Follows commands	Normal, spontaneous movements
5	Localizes pain	Withdraws to touch
4	Withdraws to pain	Withdraws to pain
3	Abnormal flexion	Abnormal flexion
2	Abnormal extension	Abnormal extension
1	None	None

Data from Shaw KN, Bachur RG. *Fleisher & Ludwig's Textbook of Pediatric Emergency Medicine.* 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2016.

(4) Avoid hypercarbia, maintaining $PaCO_2$ in normal range. Prophylactic hyperventilation is not recommended.

b. **Dextrose:** Correct hypoglycemia immediately with a 5 to 10 mL/kg bolus of 10% dextrose or 2 to 4 mL/kg of 25% dextrose. After bolus, start a continuous infusion of dextrose-containing fluids to avoid recurrent hypoglycemia.

c. **Imaging:** Request emergency head computed tomography (CT) if patient stable for transport. Consult with neurosurgical team if indicated.

d. **Hyponatremia**: Often asymptomatic unless sodium decreases rapidly or becomes severe (i.e., <125 mmol/L).

(1) Treat **symptomatic** hyponatremia immediately with a 3 to 5 mL/kg bolus of 3% hypertonic saline over 15 to 30 minutes until seizure activity ceases or serum sodium level is >125 mmol/L.

(2) See Chapter 11 for subsequent, slow correction of asymptomatic hyponatremia.

e. **Infection:** If presentation concerning for severe sepsis, treat empirically with broad-spectrum antibiotics (e.g., ceftriaxone and vancomycin) within the first hour. Include antiviral therapy (e.g., acyclovir) if viral encephalitis is suspected. Lumbar puncture should be performed only if there is no clinical suspicion of increased ICP and the patient is stable.

TABLE 1.10

ETIOLOGIES AND TARGETED EVALUATION OF ALTERED LEVEL OF CONSCIOUSNESS

Category	Etiologies	Work-up
Drugs	Opiates (e.g., oxycodone, fentanyl, heroin) Sympathomimetics (e.g., cocaine, MDMA) Anticholinergics (e.g., diphenhydramine, TCAs) Cholinergics (e.g., organophosphates) Serotonin syndrome (e.g., SSRIs, dextromethorphan)	Urine toxicology screen Acetaminophen level ASA level Ethanol level ECG Blood gas Serum chemistry
Infection	Systemic sepsis Meningitis Encephalitis Abscess	Blood culture Complete blood count Urine analysis and culture CSF analysis and culture (if indicated)
Metabolic	Hypoglycemia Electrolyte abnormalities (e.g., hypernatremia/hyponatremia) Uremic encephalopathy Hyperammonemic encephalopathy Diabetic ketoacidosis Inborn error of metabolism Hepatic failure Renal failure	Blood gas Lactate Glucose Electrolytes Liver enzymes Renal function Ammonia Serum amino acids Urine organic acids Acylcarnitine profile Coagulation studies Serum/urine osmolarity
Structural	Space-occupying lesions (e.g., tumor, blood, abscess, cyst, cerebral edema secondary to trauma) Obstructions to cerebral blood flow (e.g., thrombus, vasculitis)	Head CT or MRI
Other	Anoxia Hypothermia/hyperthermia Seizure/postictal state Psychiatric/psychogenic	EEG

ASA, Acetylsalicylic acid (aspirin); *CSF*, cerebral spinal fluid; *CT*, computed tomography; *ECG*, electrocardiogram; *EEG*, electroencephalogram; *MDMA*, 3,4-Methylenedioxymethamphetamine (ecstasy); *MRI*, magnetic resonance imaging; *SSRI*, selective serotonin reuptake inhibitor; *TCAs*, tricyclic antidepressants.

Data from Krmpotic K. A clinical approach to altered level of consciousness in the pediatric patient. *Austin Pediatr.* 2016;3(5):1046.

f. **Ingestion**: General management includes decreasing absorption, altering metabolism, and enhancing elimination.
   (1) Contact the regional poison control center for specific treatment recommendations.
   (2) See Chapter 3 for toxicology management.

g. **Naloxone:** Administer opioid antagonist (full reversal: 0.1 mg/kg/dose IV/IM/subcutaneous [SC], max 2 mg/dose) if opioid ingestion

is suspected. Repeat dosing every 2 to 3 minutes. Short duration of action may necessitate multiple doses.

h. **Thiamine:** Consider administration prior to hypertonic glucose for patients with eating disorders, chronic disease, or alcoholism to prevent Wernicke encephalopathy.

i. If patient is an infant or toddler, consider evaluation for inborn error of metabolism, hepatic failure, renal failure, or nonaccidental trauma.

H. Status Epilepticus[33-34]

1. **Definition**: Prolonged seizure (clinical or electrographic) or recurrent seizure activity without return to baseline lasting **5 minutes** or more.
   a. Common acute etiologies: febrile seizures, metabolic disturbances, sepsis, head trauma, stroke/hemorrhage, drug toxicity, inadequate antiepileptic therapy, hypoxia, hypertensive encephalopathy, autoimmune encephalitis
   b. Common chronic etiologies: preexisting epilepsy, tumor, stroke, inborn error of metabolism, ethanol abuse
2. **Management:** Timely administration of anticonvulsant therapy is associated with a greater likelihood of seizure termination and better neurologic outcomes. See Table 1.11 for timed evaluation and treatment outline.

TABLE 1.11

STATUS EPILEPTICUS TREATMENT GUIDELINE[33-34]

IMMEDIATE APPROACH (0–5 min)

Management:

Protect airway, intubate if needed

Assess vitals

Bedside fingerstick blood glucose

Establish peripheral IV access: administer emergent AED, fluid resuscitation, nutrient resuscitation (thiamine, dextrose)

Labs: laboratory blood glucose, CBC, BMP, calcium, magnesium, antiseizure medication drug levels

Medication	Dose	Comment
Diazepam (Valium)	0.15–0.5 mg/kg IV (max 10 mg/dose) 2–5 years: 0.5 mg/kg PR (max 20 mg/dose) 6–11 years: 0.3 mg/kg PR (max 20 mg/dose) ≥12 years: 0.2 mg/kg PR (max 20 mg/dose) May repeat dose once in 5 min	Monitor for hypotension, respiratory depression
Lorazepam (Ativan)	0.1 mg/kg IV (max 4 mg/dose) May repeat dose once in 5–10 min	Monitor for hypotension, respiratory depression
Midazolam (Versed)	0.2 mg/kg IM/IN 0.5 mg/kg buccal Max: 10 mg all forms Single dose recommended	Monitor for hypotension, respiratory depression

Continued

TABLE 1.11—CONT'D

URGENT APPROACH (5–15 min)

Management:
Secondary AED control therapy
Initiate vasopressor support if indicated
Neurological examination
CT if indicated
Labs: Liver function tests, coagulation studies, toxicology screen, inborn error of metabolism screening
Neurologic consultation

Medication	Dose	Comment
Fosphenytoin	20 mg PE/kg IV/IM (max 1500 mg PE/24 hr) May give additional 5 mg PE/kg repeat dose	Monitor for arrhythmia, hypotension
Levetiracetam (Keppra)	20–60 mg/kg IV (max 4500 mg/dose)	Minimal drug interactions Not hepatically metabolized
Phenytoin	20 mg/kg IV (max 1500 mg/24 hr) May give additional 5–10 mg/kg repeat dose	Monitor for arrhythmia, hypotension, purple glove syndrome
Phenobarbital	15–20 mg/kg IV (max 1000 mg) May give additional 5–10 mg/kg repeat dose	Monitor for hypotension, respiratory depression
Valproic Acid	20–40 mg/kg IV May give additional 20 mg/kg repeat dose (max 3000 mg/dose)	Use with caution in TBI Monitor for hyperammonemia, pancreatitis, hepatotoxicity, thrombocytopenia

REFRACTORY APPROACH (15–60 min)

Management:
Refractory AED control therapy
Continuous EEG monitoring if indicated
MRI if indicated
Lumbar puncture if indicated
Consider broad-spectrum antibiotics and antivirals if indicated
Intracranial pressure monitoring if indicated
Urinary catheter

Medication	Dose	Comment
Midazolam (continuous infusion)	Load: 0.2 mg/kg Infusion: 0.05–2 mg/kg/hr Breakthrough: 0.1–0.2 mg/kg bolus	Tachyphylaxis with prolonged use Monitor for respiratory depression, hypotension
Pentobarbital	Load: 5–15 mg/kg Infusion: 0.5–5 mg/kg/hr Breakthrough: 5 mg/kg bolus	Monitor for hypotension, respiratory depression, cardiac depression, paralytic ileus
Propofol	Load: 1–2 mg/kg Infusion: 20–65 mCg/kg/min Breakthrough: 1 mg/kg bolus	Monitor for hypotension, respiratory depression, cardiac failure, rhabdomyolysis, metabolic acidosis, renal failure, hypertriglyceridemia, pancreatitis (propofol related infusion syndrome)

AED, Antiepileptic drug; *BMP*, basic metabolic panel; *CBC*, complete blood count; *CT*, computed tomography; *EEG*, electroencephalogram; *IM*, intramuscular; *IN*, intranasal; *IV*, intravenous; *mCg*, microgram; *PE*, phenytoin equivalent; *PR*, per rectum;*TBI*, traumatic brain injury

I. Increased Intracranial Pressure[35-37]

1. **Definition:** An increase in the volume of an intracranial component (brain, blood, or cerebrospinal fluid) within the fixed volume of the skull that exceeds the limits of compensation, generally accepted as a sustained increase **≥20 mmHg.**
   a. Intricately related to cerebral perfusion via the following equation:
      Cerebral perfusion pressure (CPP) =
      Mean arterial pressure (MAP)–ICP
   b. Most commonly caused by brain trauma, tumors, or intracranial infections.
   c. Patients present with headache, diplopia, nausea, vomiting, or decreased level of consciousness.
   d. Assess for signs of trauma, ataxia, pupillary asymmetry, papilledema, cranial nerve dysfunction, bulging fontanelle, or abnormal posturing.
      (1) Foramen magnum herniation: hypertension, bradycardia, irregular respirations (Cushing triad)
      (2) Transtentorial herniation: ipsilateral papillary dilation, contralateral hemiparesis
   e. Evaluation may include infectious studies, electrolytes, toxicology screen, and stat CT head. Lumbar puncture is contraindicated due to herniation risk if cause is obstructive.
2. **Management:** Adequate CPP (**>40 mmHg**) is critical to overcome the resistance of increased ICP.
   a. Stabilize initially as per resuscitation guidelines.
      (1) Maintain normal oxygenation and ventilation to treat increased metabolic demand and avoid hypercarbia-related cerebral vasodilation.
      (2) Consider hyperventilation ($EtCO_2$ target between 25 and 30) for patients with **active** evidence of herniation. Prophylactic hyperventilation is otherwise not recommended.
      (3) Support MAP with adequate isotonic fluid resuscitation and vasoactive agents.
   b. Consultation with neurosurgical team is recommended and required immediately if evidence of herniation is present.
   c. Administer **mannitol** (0.25 to 1 g/kg) and/or **hypertonic saline** (5 to 10 mL/kg of 3% hypertonic saline) in case of acute neurologic deterioration or cerebral herniation.
      (1) Continuous infusions of 3% hypertonic saline (0.5 to 1.5 mL/kg/h) may be titrated as necessary to maintain ICP less than 20 mmHg.
      (2) Rapid osmotic diuresis from mannitol may cause hypovolemia and hypotension, especially in polytrauma patients.
   d. Request **noncontrast head CT** to evaluate for emergent surgical pathology.
   e. Treat acute seizure activity given the associated increased cerebral metabolic rate and subsequent increased cerebral blood flow. Consider prophylactic antiseizure therapy (e.g., phenytoin, levetiracetam), if transport or delayed definitive care is anticipated.

f. Sedation and analgesia prevent increases in ICP related to pain and agitation, although benefit is balanced with risk of hypotension and alteration of neurologic exam.
g. Avoid secondary brain injury by maintaining neuroprotective parameters: Maintain head midline and elevated at 30 degrees, normoglycemia, normonatremia, normothermia, and correct acidosis.
h. If elevated ICP is refractory to medical management, consider draining an existing ventriculoperitoneal shunt or acute neurosurgical intervention (external ventricular drain or decompressive craniectomy).
i. For elevated ICP refractory to medical and surgical management, consider barbiturate coma.

IV. CRITICAL CARE REFERENCE DATA

1. Minute ventilation (V_E):

$$V_E = \text{Respiratory rate} \times \text{Tidal volume } (V_T)$$

2. Alveolar gas equation:

$$P_AO_2 = [FiO_2 (P_{atm} - PH_2O)] - (P_aCO_2/R)$$

   a. P_AO_2 = Alveolar partial pressure of oxygen
   b. FiO_2 = Inspired fraction of oxygen (0.21 at room air)
   c. P_{atm} = Atmospheric pressure (760 mmHg at sea level; adjust for high altitude)
   d. PH_2O = Water vapor pressure (47 mmHg)
   e. P_aCO_2 = Arteriolar partial pressure of carbon dioxide (measured via arterial blood gas)
   f. R = Respiratory quotient (0.8; CO_2 produced/O_2 consumed)

3. Alveolar-arterial oxygen gradient (A-a gradient):

$$\text{A–a gradient} = P_AO_2 - P_aO_2$$

   a. P_AO_2 = Alveolar partial pressure of oxygen (estimated from alveolar gas equation)
   b. P_aO_2 = Arteriolar partial pressure of oxygen (measured via arterial blood gas)
   c. Normal gradient is 20 to 65 mmHg on 100% oxygen or 5 to 20 mmHg on room air
   d. The A-a gradient is increased in hypoventilation, diffusion limitations, pulmonary blood-flow shunts and ventilation/blood flow (V/Q) mismatch.

4. Oxygenation index (OI):

$$OI = P_{aw} \times FiO_2 \times 100 / P_aO_2$$

   a. P_{aw} (mmHg) = Mean airway pressure
   b. OI >40 in hypoxemic respiratory failure is historically considered an indication for extracorporeal life support.

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Chapter 2

Traumatic Injuries

Nymisha Chilukuri, MD

See additional content on Expert Consult

I. COMPONENTS OF THE TRAUMA ASSESSMENT

A. Primary Survey

1. The primary survey includes assessment of ABCDE (airway, breathing, circulation, disability, exposure/exsanguination). This includes intravenous (IV) access, preferably two large-bore catheters.
2. **NOTE:** The Advanced Trauma Life Support algorithm developed by the American College of Surgeons continues to support the ABC sequence in the primary survey. For nontraumatic cardiorespiratory arrest, the circulation, airway, and breathing (CAB) sequence is currently in use by the American Heart Association as part of the Pediatric Advanced Life Support algorithm (see Chapter 1).

B. Secondary Survey (**Fig. 2.1**)

II. HEAD AND NECK TRAUMA

A. Head Imaging

1. The PECARN algorithm (Fig. 2.2) is often used to assess risk for clinically important traumatic brain injury.[1]
2. If signs of traumatic brain injury on computed tomography (CT), consider consultation by pediatric neurosurgery/trauma surgeon.

B. Cervical Spine and Neck Imaging

1. There are currently no unified protocols or clinical guidelines for pediatric cervical spine clearance after blunt trauma.
2. Based on PECARN C-Spine criteria,[2] consider obtaining imaging if any of the following are present in a patient ≤16 years old:
   a. Altered mental status
   b. Focal neurologic deficits
   c. Complaint of neck pain
   d. Torticollis
   e. Substantial injury to the torso
   f. Predisposing condition
   g. High-risk motor vehicle crash
   h. Diving accident
3. Note, many institutions alternatively use NEXUS criteria for clinical c-spine clearance. This is validated in children ≥8 years old[3] and includes #1, 2, and 3 of PECARN c-spine plus presence of intoxication or painful, distracting injury.[4,5]

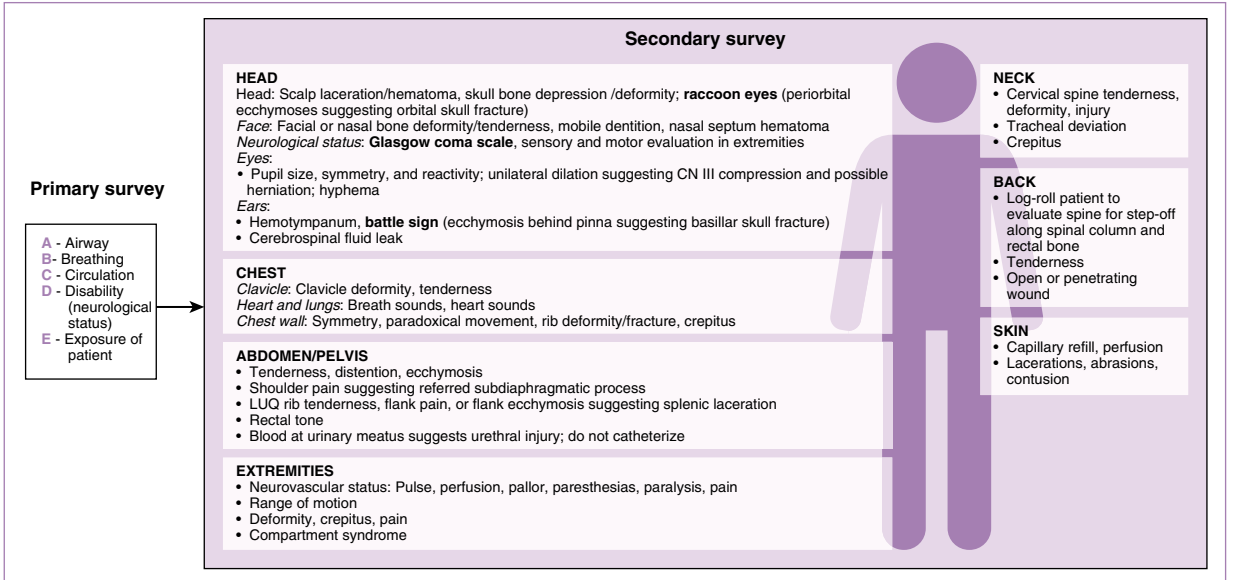


FIGURE 2.1
Trauma primary and secondary survey.

FIGURE 2.2

Recommended algorithm for obtaining head computed tomography in children after head trauma by age. (*From Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study.* The Lancet. *2009;374(9696):1160–1170.*)

4. Recent guidelines by the Pediatric Cervical Spine Clearance Working Group Algorithm[6] additionally highlight the following factors:
   a. In patients ≤3 years old, consider plain radiographs, if c-spine cannot be cleared clinically.
   b. Clinical clearance can be done regardless of mechanism of injury if a child is ≥3 years and is asymptomatic with normal mental status and normal physical examination.
   c. Clinical clearance CANNOT be performed if the child is observed to have or reports persistent neck pain, or if there is abnormal head posture or difficulty in neck movement.

C. Specific Imaging Studies

1. C-spine x-ray (XR) with minimum of two views (lateral, anteroposterior, and/or odontoid views) (90% sensitivity in identifying bony cervical spine injury).[7]
2. Consider further cross-section imaging for further evaluation of vertebral cervical fracture.[8]
3. Consider magnetic resonance imaging (MRI) scan for further evaluation of ligamentous and cord cervical spine injury.[9,10]
4. Spinal cord injury without radiographic abnormality (SCIWORA): Neurologic symptoms persist with no radiographic abnormality. Of note, recent research found that MRI revealed abnormal features only in those patients with complete neurologic deficits and may lack sensitivity with abnormal features associated with partial or temporary neurologic deficits.[11,12]
5. If signs of spinal column or vascular injury on imaging, consider consultation by trauma, spine, and/or neck surgeon.

III. CONCUSSION

A. Concussion Evaluation

1. The Acute Concussion Evaluation (ACE) can be used in multiple settings (see Section XI. Resources), including the clinic and emergency department (ED).[13–15]
2. Patients should be referred to a concussion specialist if symptoms persist greater than 10 to 14 days, if they worsen, or if a patient has a history of multiple concussions.

B. Return-to-school and Return-to-play Guidelines (**Table 2.1**)

1. Overarching goal is to allow healing from first injury in an attempt to prevent "second impact syndrome": Diffuse cerebral swelling in the setting of a second concussion that occurred while still symptomatic from an earlier concussion. This is a rare but potentially fatal complication of concussions.
2. Consider providing the ACE Care Plan for parent and child guidance (see Section XI. Resources).
3. Brain rest: Although evidence-based guidelines for brain rest following concussion are limited, current research suggests that extreme rest (i.e., bed rest) can hinder recovery from concussions.[16] Other studies

TABLE 2.1

RETURN-TO-PLAY AND RETURN-TO-SCHOOL[15]

Return-to-Play Guidelines	Return-to-School Guidelines
BRIEF GUIDELINES Each step should last a minimum of 24 hr. Move to the next level of activity only if no symptoms are experienced. If symptoms return, patients should stop activities and notify a health professional. After evaluation, once the patient has not had symptoms for minimum 24 hr, patients should resume play at the previous tolerated step of the return to play guidelines.	**BRIEF GUIDELINES[41]** If symptoms affect concentration or if unable to tolerate stimulation for more than 30 min without symptoms, consider remaining at home with light mental activities (watching TV, light reading, and interaction with the family), so long as they do not provoke symptoms. Minimize computer use, texting, and video games. If able to tolerate stimulation for minimum of 30–45 min without symptoms, consider returning to learning with modifications. Providers should provide school notes.
Step 1: No physical activity Step 2: Low levels of physical activity Examples: Walking, light jogging, light stationary biking, light weightlifting (lower weight with higher repetitions, no bench, no squat) Step 3: Moderate levels of physical activity with body/head movement Examples: Moderate jogging, brief running, moderate-intensity stationary biking, moderate-intensity weightlifting (reduced time and/or reduced weight from typical routine) Step 4: Heavy noncontact physical activity Examples: Sprinting/running, high-intensity stationary biking, regular weightlifting routine, noncontact sport-specific drills (in three planes of movement) Step 5: Full contact in controlled practice Step 6: Full contact in game play	**SUGGESTED SCHOOL MODIFICATIONS:** Shortened school days Frequent breaks during classes Extra time to complete coursework/assignments and tests Decreased homework load No significant classroom or standardized testing at this time Consider 504 Plan and/or Individualized Education Plan (IEP)

have found that some degree of cognitive rest can be beneficial and that patients presenting with signs of injury following concussion (e.g., loss of consciousness, posttraumatic amnesia) are more likely to benefit from rest following concussion than those patients presenting with symptoms alone (somatic, cognitive, affective, and sleep-related symptoms).[17]

4. For further guidelines, please discuss with concussion specialist.

IV. THORACIC AND ABDOMINAL TRAUMA EVALUATION[18]

A. Physical Exam

"Seat belt sign" is a significant predictive factor for surgical abdominal injury after blunt trauma (sensitivity 70.6%, specificity 82.4%).[19]

B. Laboratory Studies to Consider

Type and cross-match, complete blood cell count (CBC; low hemoglobin indicates possible hemorrhage; however, this is a late sign), electrolytes,

liver function tests (high AST/ALT indicate liver injury), lipase (high level indicates pancreatic injury), and urinalysis (hematuria indicates possible renal/bladder injury).

C. Imaging Studies to Consider

1. Chest radiograph
   a. Look for rib fracture, pneumothorax and/or hemothorax, pulmonary contusion, pneumomediastinum.
   b. Consider chest CT with IV contrast, if recommended by radiologist and/or trauma surgeon.
2. Pelvis radiograph
   a. Look for pelvis fracture.
   b. Consider pelvis CT if recommended by radiologist and/or trauma surgeon.
3. Abdominal/pelvis CT with IV contrast
   a. This is the "gold standard" for intra-abdominal injury diagnosis; however, radiographs should be obtained first if there is concern for additional injuries that would compromise clinical stability.
   b. For blunt abdominal trauma, routine oral contrast is not indicated, whereas IV contrast can help to identify visceral, vascular, or bowel injury.[20]
   c. For penetrating abdominal trauma, triple contrast (oral, rectal, IV) CT to identify peritoneal penetration or intra-abdominal organ injury in stable stab wound victims.[21]
   d. Look for duodenal hematoma, hemoperitoneum, bladder injury, solid organ hemorrhage (e.g., spleen and/or liver).
   e. If gross hematuria or urinalysis with greater than 50 RBC/hpf, consider genitourinary tract trauma and consider CT abdomen and pelvis with and without IV contrast (CT urography) and CT cystogram, in consultation with radiology/urologist/trauma surgeon.
4. Extended focused assessment with sonography for trauma (eFAST)
   a. Can help to identify intra-abdominal free fluid and parenchymal injury (sensitivity 50%, specificity 85%).[22]
   b. eFAST with bilateral anterior lung views is highly sensitive for pneumothorax.
   c. Consider performing if qualified personnel available.
5. If any workup is positive for thoracic or abdominal trauma, immediate consultation with nearest pediatric trauma center/surgeon is indicated.

V. ORTHOPEDIC/LONG BONE TRAUMA

A. Physical Exam

1. Look for swelling, ecchymosis, or deformity. Look for breaks in the skin (abrasions, lacerations) overlying the apex of the fracture suggestive of open fracture.
2. Bleeding
   a. Consider arterial bleed if absent pulses and cool extremity with bleeding.
   b. Consider venous bleed if persistent pulse with bleeding.

3. Compartment syndrome: Tense, swollen area at site of injury, pain, paresthesia, paresis, pallor, pulselessness (if unable to palpate pulse, consider using vascular ultrasound with Doppler).
4. If signs/symptoms of compartment syndrome or open fracture, consultation with a pediatric orthopedic surgeon is recommended.

B. Imaging

1. Children's bones are less densely calcified, have thickened periosteum, and have a growth plate, all of which increase their vulnerability to fractures.
2. Obtain radiographs if bony point tenderness or deformity, decreased sensation, decreased range of motion, or overlying skin discoloration.
3. Radiographs with anterior-posterior and lateral views ± oblique and including areas above and below the suspected area of injury are recommended.

C. Fractures Unique to Children

1. Physeal or Salter-Harris fractures[18]: Fractures involving growth plates (see Chapter 26).
2. Plastic fractures: Pliability of bones in response to compressive and transverse forces.
   a. Torus or buckle fracture: Compression injury with buckled cortex
   b. Greenstick fracture: Fracture on one side of the diaphysis with cortex intact on other side of diaphysis
   c. Bowing or bending fractures
3. Avulsion fractures: Tendon or ligament dislodging a bone fragment. These are more common among adolescents participating in sports.

D. Fractures Requiring Urgent Orthopedic Surgeon Consultation

1. Open fractures
2. Unacceptably displaced fractures
3. Fractures with associated neurovascular compromise (consider emergent reduction to improve neurovascular status if orthopedic surgery is not available on-site)
4. Significant growth plate or joint injuries
5. Complete or displaced fractures of the long bones of the extremities
6. Pelvic fractures (other than minor avulsions)
7. Spinal fractures
8. Dislocations of major joints other than the shoulder

E. Fractures That Are Appropriate to Manage Acutely With Outpatient Referral to Orthopedics (**Table 2.2**)

VI. DENTAL TRAUMA

A. Components of a Tooth (**Fig. 2.3**)

B. Differences Between Primary and Permanent Teeth (**Fig. 2.4**)

1. Primary teeth appear 6 months to 3 years of age, are relatively smaller, whiter, front teeth have a smooth biting surface.

TABLE 2.2

COMMON PEDIATRIC ORTHOPEDIC INJURIES AND MANAGEMENT

Injury	ED Management	Follow-up
Clavicle fracture without tenting or displacement (if present, orthopedic surgery consultation required)	Sling	Primary care provider in 2 weeks
Acromioclavicular joint separation	Sling	Orthopedics in 1 week
Proximal humerus fracture WITHOUT deformity, displacement, neurovascular injury	Sling	Orthopedics within 1 week
Distal radius or ulna fracture WITHOUT deformity, displacement, neurovascular injury	Volar splint	Orthopedics within 1 week
Salter-Harris Type 1—Distal radius	Volar splint	Orthopedics within 1 week
Salter-Harris Type 1—Distal fibula	Posterior splint, crutches	Orthopedics within 1 week

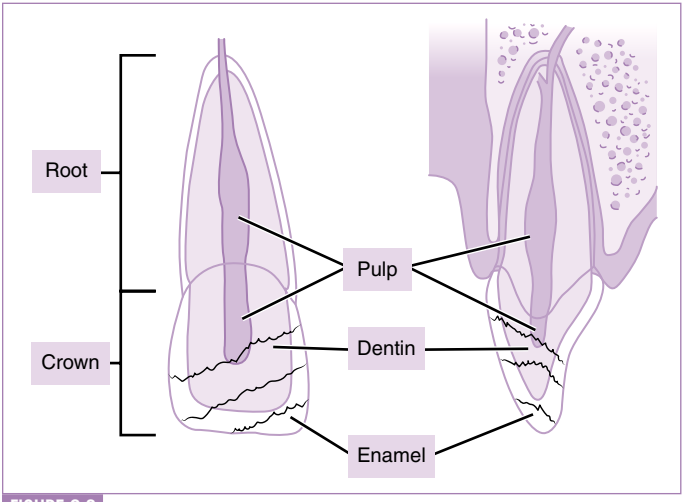


FIGURE 2.3
Normal anatomy of a tooth. (*Modified from Textbook of Pediatric Emergency Medicine.*[18])

2. Permanent teeth appear 6 years to 21 years of age, relatively larger, front teeth have a ridged biting surface.

C. Dental Injuries

1. Avulsion
   a. An avulsion injury involves complete displacement of the tooth from the alveolar socket.[23]
   b. If a primary tooth, outpatient dental follow-up is appropriate.
   c. If a permanent tooth, this is a dental emergency!

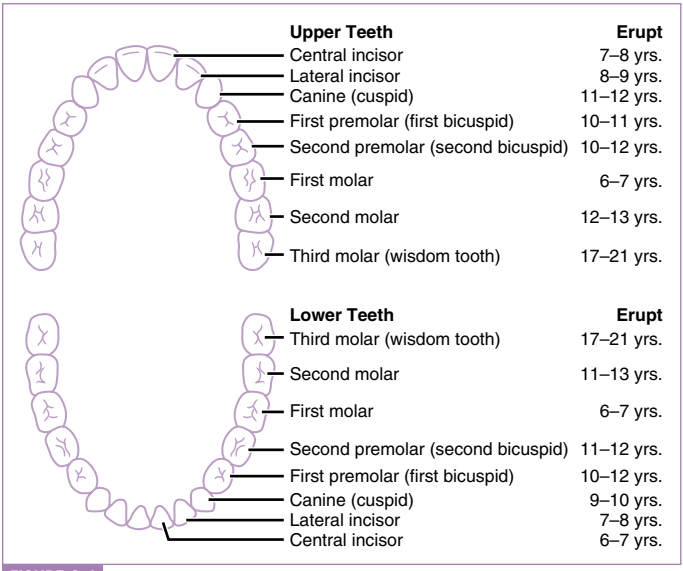


FIGURE 2.4

Development from primary to permanent teeth by location. (*Modified from American Dental Association.* www.mouthhealthy.org)

d. **Most important: Immediate reimplantation should occur within 60 minutes to maximize tooth viability. Without a tooth present, the periodontal ligament can degenerate.**

e. Method:
   (1) Pick up the avulsed tooth by the crown and avoid touching the root to prevent injury to the periodontal ligament.
   (2) Wash the tooth briefly with saline or Hanks Balanced Salt Solution (HBSS).
   (3) Administer local lidocaine into the gum if time permitting.
   (4) Insert the root into the alveolar socket with concave part facing the tongue.
   (5) Ask the patient to bite on gauze to hold it in position.
   (6) **Refer to a dentist emergently for splinting.**

f. Reimplantation should always be attempted. If reimplantation is not possible, place the tooth in a container in osmolality balanced media (e.g., HBSS, cold milk) and **refer to a dentist emergently for reimplantation and splinting.**

2. Luxation

a. Luxation injuries result from physical displacement of tooth within the alveolar socket, tearing of the periodontal ligament with possible injury to the alveolar bone.[24]

TABLE 2.3

TOOTH FRACTURE TYPES AND FOLLOW-UP RECOMMENDATIONS[24,25]

Fracture Type	Follow-up recommendations
Enamel Fracture	Dental evaluation outpatient for possible binding of tooth fragment, if available
Enamel-Dentin Fracture	Dental evaluation 48–72 hr to place a dressing of calcium hydroxide to prevent injury to the pulp
Enamel-Dentin-Pulp Fracture	Immediate dental evaluation within 48 hr
Alveolar Ridge Fracture	Emergent dental evaluation

   b. Primary tooth: If tooth is loose, there is an increased risk of aspiration, and the tooth may be extracted with firm pressure with gauze. If tooth is not loose, may need repositioning and splinting. In both situations, refer to a dentist for evaluation within 48 hours.
   c. Permanent tooth: Immediate dental evaluation required if significant tooth mobility; otherwise, outpatient evaluation within 48 hours is appropriate.
3. Subluxation
   a. Subluxation is characterized by tooth injury with minor mobility without displacement.
   b. Regardless of whether permanent or primary tooth, outpatient dental follow-up, ideally within 48 hours, is needed to rule out root fracture.
4. Tooth fracture:
   a. Classify the fracture per involvement of enamel, dentin, and pulp.[25]
   b. For management guidelines: Table 2.3.

D. Anticipatory Guidance Following Dental Trauma

1. Avoid contact sports
2. Analgesics as needed for pain control (e.g., acetaminophen, ibuprofen, cold compresses)
3. Soft diet
4. Use a soft toothbrush, if able to brush teeth
5. Regular follow-up with a dentist

VII. OPHTHALMOLOGIC TRAUMA[26]

A. Chemical Injury to the Eye[18]

1. Determine if substance is an acid or alkali. Alkali solutions tend to be more damaging because they penetrate more deeply.
2. Obtain a baseline pH by touching Litmus paper to the conjunctiva.
3. Retract eye lids as much as possible and irrigate immediately with normal saline or lactated Ringer solution. This can be performed at the eyewash station or with a standard bag of fluid with tubing placed at the medial canthus. Allow the liquid to pass over the open eye to the lateral canthus.

4. Continue irrigation for a minimum of 30 minutes with minimum 1 to 2 L of solution or until pH becomes neutral (7.0 to 7.4). Additional fluid may be required.
5. Monitor conjunctival pH with Litmus paper 10 to 20 minutes after irrigation.[27]
6. Consider ophthalmologic consultation and discuss with Poison Control.

B. Ruptured Globe

1. A ruptured globe is caused by laceration or puncture of the cornea and/or sclera following trauma caused by projectile, sharp, or blunt trauma.
2. Key physical exam findings include: Teardrop shaped pupil pointing towards perforation, hyphema (hemorrhage in the anterior chamber) and/or subconjunctival hemorrhage, severe pain, decreased visual acuity, edema.
3. Stop the exam and place a rigid eye shield.
4. Elevate the head of the bed.
5. Keep patient as calm as possible and control symptoms (e.g., antiemetics and pain control) to avoid increased globe pressure and further extrusion of vitreous/aqueous humor.
6. Immediately consult ophthalmology and administer antibiotics.

C. Corneal Abrasion

1. Key physical exam findings include red eye with tearing, intense pain, resistance to eye opening, photophobia, foreign body sensation.
2. Consider application of topical anesthetic before examination. If foreign body sensation is present on your exam, evert eyelids to look for retained foreign body.
3. Apply fluorescein staining and examine with Wood lamp. Focal uptake indicates abrasion.
4. Consider ophthalmic ointment or artificial tears for lubrication and pain relief.
5. Consider ophthalmologic consultation in the ED if concern for larger corneal abrasions involving visual axis, corneal laceration, ulceration, embedded foreign body, or prolonged healing (i.e., symptoms not improving after several days).

D. Superglue to the Eye[28]

1. Trim eyelashes as needed with blunt-tip scissors.
2. Apply copious amounts of ointment, such as bacitracin ophthalmic ointment or baby shampoo, and gently massage eyelashes to break down the glue. Advise that the patient continue this as often as possible. Dissolution of glue may take several days.
3. Consider consultation with ophthalmology if several days of ointment is unsuccessful.

E. Eyelid Laceration

1. Consider consultation with ophthalmology if: Full-thickness lacerations (exposed adipose tissue), laceration through the lid margin or tarsal plate,

lacerations involving lacrimal canaliculi (medial third of the upper/lower lids), or ptosis (unequal lifting of lids with upward gaze would suggest this).
2. Some superficial lacerations that occur in the direction of a natural skin fold may not require repair.

F. Orbital Floor Fractures

1. This injury is usually caused by blunt trauma and is often referred to as a "blow out fracture," because the weakest area of the orbital bones is the orbital floor/maxillary roof.
2. Key physical exam findings include: Eyelid swelling, ecchymosis, enophthalmos of affected eye, ptosis, diplopia, anesthesia of the cheek (involvement of infraorbital nerve), decreased extraocular eye movements (especially decreased superior range of the globe due to inferior rectus entrapment).
3. Evaluate for other eye injuries (e.g., retinal trauma, ruptured globe).
4. Consider consultation with ophthalmology and plastics/otorhinolaryngology surgeon.

G. Other Instances Requiring Ophthalmologic Consultation

1. Traumatic iritis is associated with blunt trauma with painful red eye, pupillary constriction, and photophobia, often with delayed presentation of symptoms (24 to 72 hours) after trauma.
2. Sudden loss of vision could suggest retrobulbar hemorrhage or retinal detachment.

VIII. ANIMAL BITES

A. Wounds at the Highest Risk of Infection

1. Bites over hand, foot, genitalia, or joint surface
2. Bites from a cat or human
3. Wounds in an asplenic or immunocompromised patient
4. Wounds with delayed presentation to care >12 hours

B. Decision to Suture

1. Avoid closing wounds at high risk of infection (see earlier) unless for cosmetic reasons, large wounds or wounds with edges far apart where loose approximation can be helpful.
2. Wounds on head and neck can be safely sutured after copious irrigation and wound débridement if within 6 to 8 hours of injury and there are no signs of infection. Avoid skin glue due to high risk of infection.
3. In large wounds, subcutaneous dead space should be closed with a minimal number of absorbable sutures, with delayed closure in 3 to 5 days, if there is no evidence of infection.
4. Wounds that involve tendons, joints, deep fascia, or major vasculature should be evaluated by a surgeon.

C. Antibiotic Prophylaxis[29]

1. Table 2.4.

TABLE 2.4

ANTIBIOTIC MANAGEMENT OF ANIMAL AND HUMAN BITES

Type of Bite	Organisms	Treatment
Animal bite	*Staphylococcus aureus, Streptococci,* Oral Anaerobes, *Pasteurella, Capnocytophaga canimorsus*	Amoxicillin/clavulanate for 5 days TMP/SMX and clindamycin, if allergy to penicillin
Human bite	*Streptococcus viridans, S. aureus,* Oral Anaerobes, *Eikenella corrodens*	Amoxicillin/clavulanate for 5 days Clindamycin AND ciprofloxacin, if allergy to penicillin

2. Consider IV antibiotics if patient is critically ill or unable to tolerate PO intake.

D. Tetanus Postexposure Prophylaxis: See Chapter 16

E. Rabies Postexposure Prophylaxis: See Chapter 16

IX. BURNS

A. Burns That Should Prompt Consideration of Elective Intubation

1. Signs of inhalational injury (e.g., singed nasal hairs, soot at the nares, oropharyngeal erythema)
2. Early onset stridor
3. Severe burns of face and/or mouth
4. Progressive respiratory insufficiency

B. Estimation of the Surface Area of Burns

1. See Fig. 2.5.
2. Only include partial- and full-thickness burns and exclude superficial burns in the calculation of body surface area.

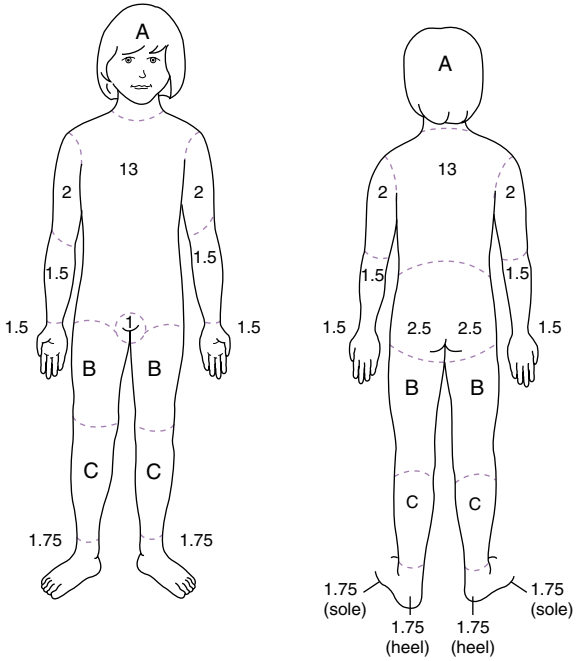
C. Estimation of the Depth of Burns (Table 2.5)

D. Fluid Resuscitation in Patients With Burns (Fig. 2.6)

1. Consider central venous access for burns greater than 25% BSA.
2. Withhold potassium from IV fluids generally for the first 48 hours because of a large release of potassium from damaged tissues.
3. Foley catheter placement is recommended to monitor urine output during fluid resuscitation phase.

E. Indications for Transfer to a Burn Center[30]

1. ≥10% partial-thickness and/or full-thickness burns
2. ≥5% full-thickness burns
3. If burn débridement is warranted (e.g., any partial-thickness burn >2 cm in diameter)
4. Respiratory involvement and/or major trauma
5. Electrical, chemical, or inhalation injury
6. Burns of critical areas, such as face, hands, feet, perineum, or joints
7. Circumferential burns



	<1 yr	1 yr	5 yr	10 yr	15 yr	Adult
A Front or back of head	9.5	8.5	6.5	5.5	4.5	3.5
B Front or back of thigh	2.75	3.25	4	4.25	4.5	4.75
C Front or back of leg	2.5	2.5	2.75	3	3.25	3.5

FIGURE 2.5
Burn assessment chart. All numbers are percentages. (*Modified from Barkin RM, Rosen P.* Emergency Pediatrics: A Guide to Ambulatory Care. *6th ed. St. Louis: Mosby; 2003.*)

8. Patient with underlying chronic illness
9. Suspicion of abuse or unsafe home environment

F. Management of Burns Not Referred to Burn Center

1. For a partial-thickness burn not requiring débridement:
   a. Clean with warm saline or mild soap and water.
   b. Apply topical antibacterial agent such as bacitracin (requires daily dressing changes) or silver-impregnated dressings (dressing can be

TABLE 2.5

BURN CLASSIFICATION

Wound Depth	Layer Involved	Clinical Findings
Superficial	Epidermis	Dry, painful, erythematous (like a sunburn)
Partial Thickness	Dermis	Moist, painful, erythematous Blistering present, blanches Disruption of nails, hair, sebaceous glands
Full Thickness	Subcutaneous, fascia, muscle, bone	Pale, charred, waxy, leathery, insensate No bleeding or blanching

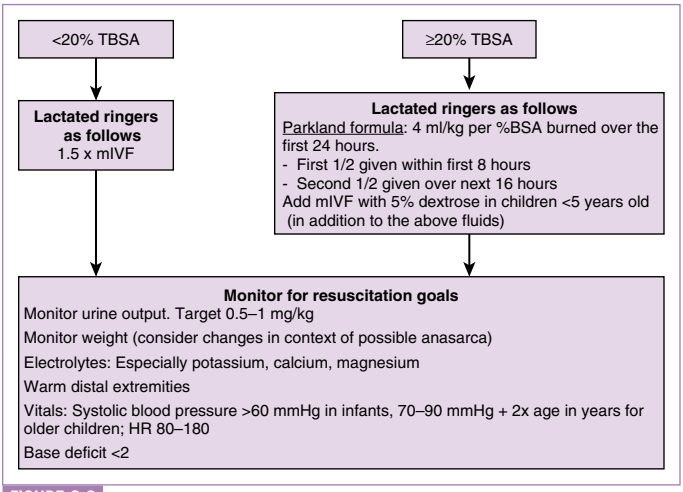


FIGURE 2.6

Formulaic fluid resuscitation for pediatric burns.[18]

left in place until follow-up) and cover with nonadherent dressing.
2. Follow-up inspections of wound should occur at 24 and 72 hours.
3. Follow-up within one week at a pediatric burn center is highly recommended.
4. Oral antibiotics are not indicated.

G. Other Special Considerations With Burns

1. Circumferential burns can increase risk of compartment syndrome.
2. Tetanus prophylaxis is warranted with burns. Refer to Chapter 16 for details.

H. Other Types of Burns

1. Household electrical burn[31]: In general, household outlets are 120 to 240 V and rarely cause serious injuries or cardiac arrhythmias.
2. High-voltage burns (>1000 V), including lightning burns:
   a. Patients are at increased risk of ventricular arrhythmias or asystole. Consider cardiac monitoring for 48 hours.[31]
   b. Patients are also at increased risk of compression spine fractures or

spinal cord injury due to tetany, as well as compartment syndrome, rhabdomyolysis, and hyperkalemia due to muscle swelling.

X. NONACCIDENTAL TRAUMA

A. Physical Abuse

1. **Red flags in history**
   a. Delay in presentation
   b. Inconsistent/incomplete/vague/changing explanations for significant injury
   c. History is inconsistent with age, pattern, or severity of the injury
   d. History is inconsistent with child's physical or developmental capabilities
   e. Different witnesses provide different explanation
2. **Concerning physical exam findings**[32]
   a. Bruises: In protected areas (chest, abdomen, back, buttocks), multiple, in various stages of healing, those that do not fit history or developmental stage of child, in unusual places (e.g., postauricular, neck, inner aspect of arms), those consistent with slap of hand or pinch.
   b. Burns: Multiple, well-demarcated, stocking/glove distribution, symmetrically burned palms/soles, buttocks and/or lower legs, mirror image burns of extremities, spared inguinal or other flexural creases, appearance of a cigarette burn.
   c. Other: Frenulum tears, loop marks from cord or cable, bites.
   d. See Figs. 2.7–2.10 (color plates) and Figs. EC 2.A-D for examples.
3. **Imaging guidelines**
   a. Skeletal survey[33–35]
      (1) In children less than 2 years of age, use skeletal survey to evaluate for bony injury. This includes frontal and lateral views of the skull, lateral views of the cervical spine and thoracolumbosacral spine, and single frontal views of the long bones, hands, feet, chest, and abdomen.

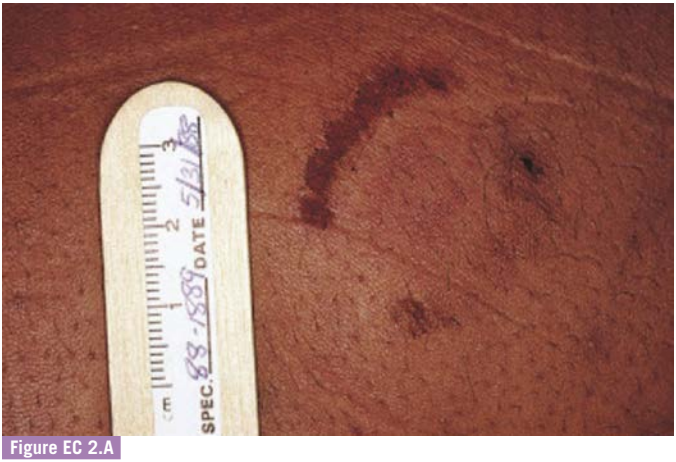


Figure EC 2.A

Bite mark outlining the dental arch. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

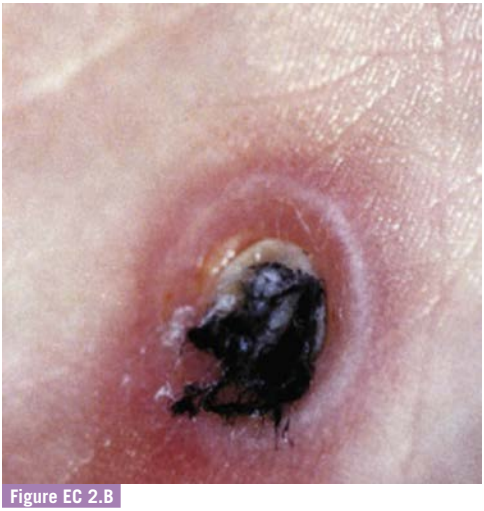


Figure EC 2.B

Cigarette burn appearing as a circular punched out lesion. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

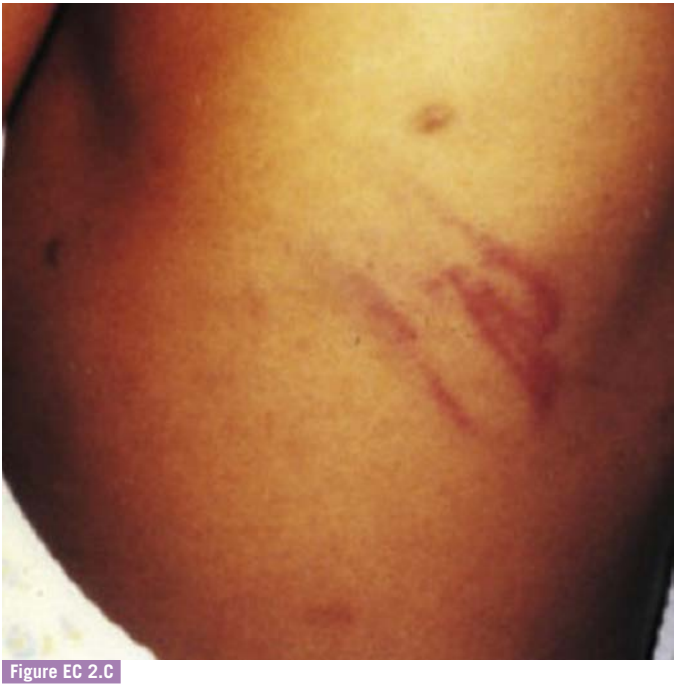


Figure EC 2.C
Loop marks from a cord or cable. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

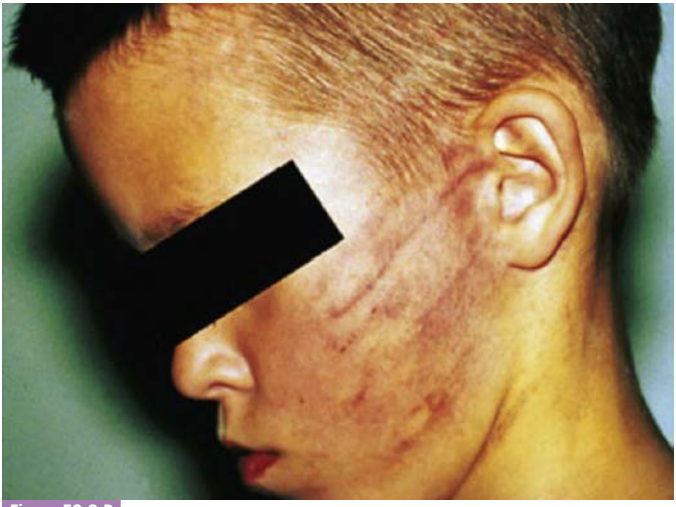


Figure EC 2.D

Multiple parallel lines equally distributed due to a slap from a hand. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

(2) In children greater than 5 years of age, targeted imaging to the area(s) of suspected injury is usually appropriate. The utility of screening with skeletal survey diminishes after 5 years of age.
(3) In children 2 to 5 years of age, decisions about type of imaging are open to clinical judgement.
(4) Do not use "babygrams" (i.e., whole-body x-rays in one image) because of the high rate of false-negatives.
(5) Follow-up skeletal survey approximately 2 weeks after the initial examination should be performed when abnormal or equivocal findings are found on initial study and when abuse is suspected on clinical grounds to identify fractures missed on initial survey.
(6) Fractures with an association with child abuse include rib fractures, metaphyseal bucket and corner fractures, spine and scapula fractures, and complex skull fractures (Fig. 2.11 and Figs. EC 2.E-G for examples).

b. Head CT without contrast if:
(1) Less than 6 months of age with suspected abuse
(2) Neurologic changes
(3) Facial injuries concerning for abuse

c. Additional imaging/consultation
(1) Ophthalmologic evaluation for retinal hemorrhages.
(2) MRI may identify lesions not detected by CT (e.g., posterior fossa injury and diffuse axonal injury).

4. **What to do if physical abuse is suspected**
a. All healthcare providers are required by law to report suspected child maltreatment to the local police and/or child welfare agency.
b. In addition, consider consultation with local child injury/abuse specialist.
c. Medical stabilization is the primary goal; prevention of further injuries is the long-term goal.
d. The professional who makes such reports is immune from any civil or criminal liability.
e. Carefully and legibly document the following:
(1) Reported and suspected history and mechanisms of injury.
(2) Any history given by the victim in his or her own words (use quotation marks).
(3) Information provided by other providers or services.
(4) Physical examination findings, including drawings of injuries and details of dimensions, color, shape, and texture. Consider early use of police crime laboratory photography to document injuries. If taking photos, start with full patient, then part of patient, then zoomed into wound, and then take a separate photo of wrist identification band.

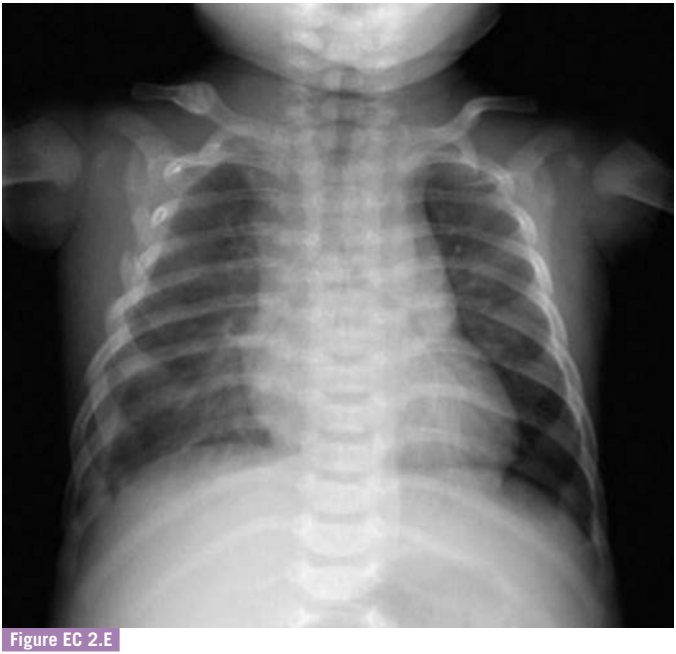


Figure EC 2.E

Healing right clavicular fracture and nine fractures of the right ribs and four fractures of the left ribs. (*Modified from Coley BD.* Caffey's Pediatric Diagnostic Imaging. *13th ed. Philadelphia: Elsevier; 2019.*)[40]

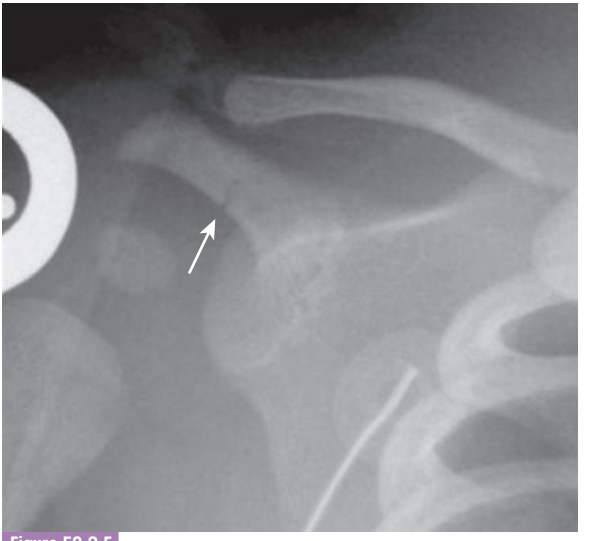


Figure EC 2.F
Right acromial fracture (arrow). (*Modified from Coley BD.* Caffey's Pediatric Diagnostic Imaging. *13th ed. Philadelphia: Elsevier; 2019.*)[40]

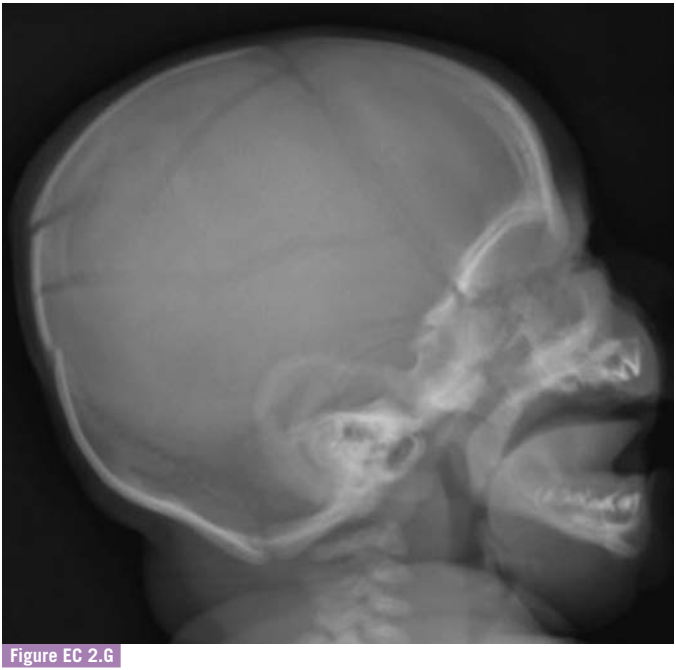


Figure EC 2.G

Bilateral parietal fractures of the skull. (*Modified from Coley BD.* Caffey's Pediatric Diagnostic Imaging. *13th ed. Philadelphia: Elsevier; 2019.*)[40]

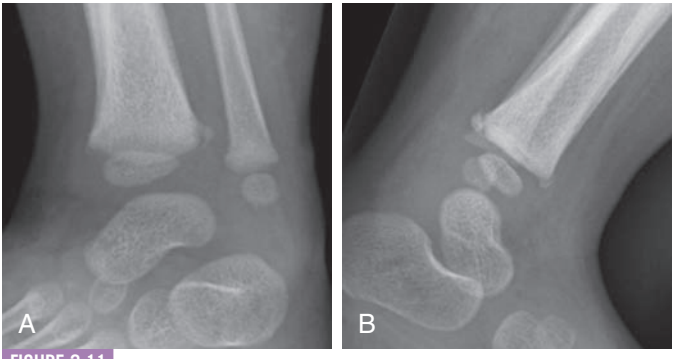


FIGURE 2.11

"Bucket-Handle Fracture" (A) and a "Corner Fracture" of the distal tibial metaphysis (B). (*Modified from Coley BD.* Caffey's Pediatric Diagnostic Imaging. *13th ed. Philadelphia: Elsevier; 2019.*)[40]

B. Sexual Abuse

1. **Physical Exam Findings**
   a. Normal genital examination does not rule out abuse; most examinations are normal in cases of abuse.[36]
   b. Table 2.6 for physical exam findings highly suggestive of sexual abuse.[37]
2. **What to do if sexual abuse is suspected**[38]
   a. If suspected sexual abuse occurred within 72 hours to a child younger than 12 years or within 120 hours to a child older than 12 years, defer interview and examination and urgently involve a multidisciplinary team with a sexual assault nurse examiner with expertise in the evaluation of sexual abuse.
   b. Nonacute examinations falling outside of the above time windows should be deferred to a child advocacy center.
   c. Genital examination should be performed by a trained forensic specialist.
   d. Evaluate the need for sexually transmitted infection (STI) testing.
3. **STI testing**
   a. Tests include: Serum human immunodeficiency virus (HIV), serum syphilis, gonorrhea (culture or NAAT from pharynx and anus in boys and girls, vagina in girls and urethra in boys), chlamydia (culture or NAAT from anus in boys and girls, vagina in girls).
   b. In adolescents, recommended for all patients.
   c. In prepubertal children, consider testing if:
      (1) Experienced penetration of the vagina or anus
      (2) Abuse by a stranger

TABLE 2.6

PHYSICAL EXAM FINDINGS SUGGESTIVE OF SEXUAL ABUSE[37]

ACUTE TRAUMA TO GENITAL/ANAL TISSUES
Acute laceration(s) or bruising of labia, penis, scrotum, or perineum, posterior fourchette or vestibule not involving the hymen
Bruising, petechiae, or abrasion on the hymen
Acute laceration of the hymen of any depth, partial or complete
Vaginal laceration
Perianal laceration with exposure of tissues below the dermis
RESIDUAL (HEALING) INJURIES TO GENITAL/ANAL TISSUES
Perianal scar
Scar of the posterior fourchette or fossa
Healed hymenal transection/complete hymen cleft—a defect in the hymen below the 3–9 o'clock location that extends to or through the base of the hymen with no hymenal tissue discernible at that location
Signs of female genital mutilation or cutting, such as loss of part or all of the prepuce (clitoral head), labia minora or majora, or vertical linear scar adjacent to the clitoris
FINDINGS DIAGNOSTIC OF SEXUAL ABUSE
Pregnancy
Semen identified in forensic specimens taken directly from the child's body

(3) Abuse by a perpetrator known to be infected with an STI or at high risk of being infected (e.g., IV drug use, men who have sex with men, people with multiple sexual encounters)
(4) Child with sibling or other relative in the household with STI
(5) Child living in an area with high rate of STI in the community
(6) Signs/symptoms of an STI
(7) Already been diagnosed with one STI

XI. RESOURCES

A. Acute Concussion Evaluation Forms for Emergency Department and Physician/Clinician Office: https://www.cdc.gov/headsup/providers/tools.html

B. Acute Concussion Evaluation Care Plans for Work and School: https://www.cdc.gov/headsup/providers/discharge-materials.html

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A complete list of references can be found online at www.expertconsult.com.

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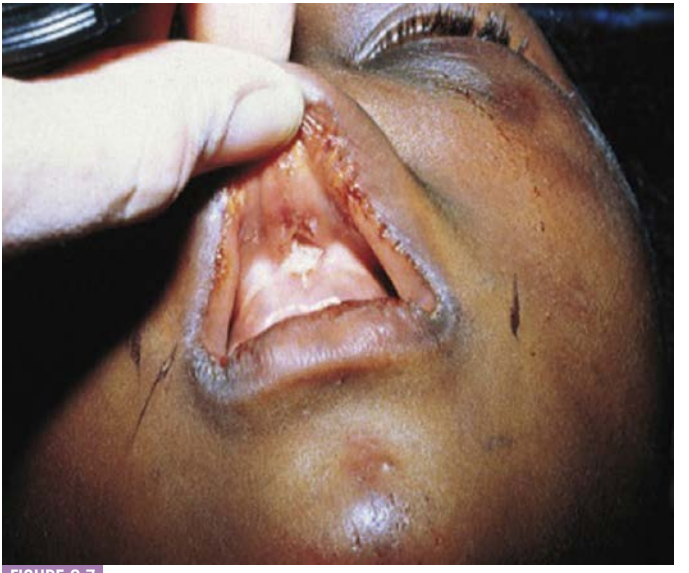

FIGURE 2.7

Frenulum tear due to direct blow to the face. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ*. Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

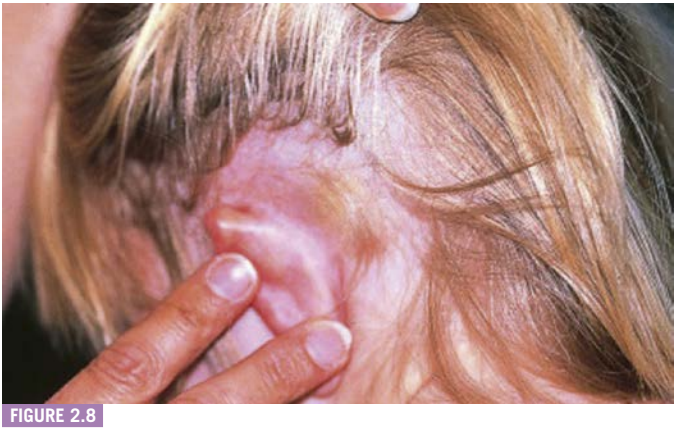

FIGURE 2.8

Postauricular bruising. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ*. Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

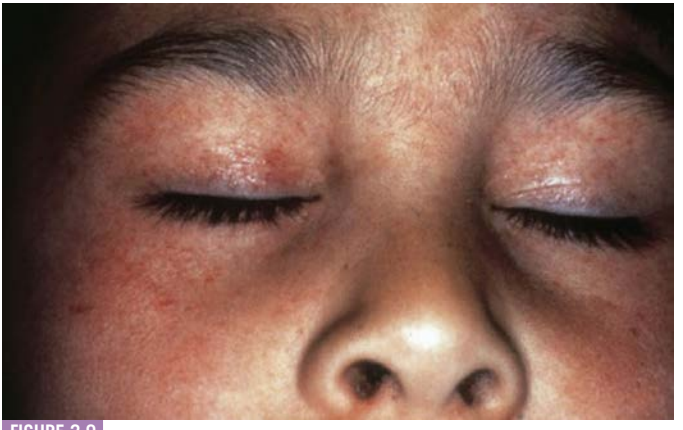

FIGURE 2.9
Petechial lesions due to choking. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

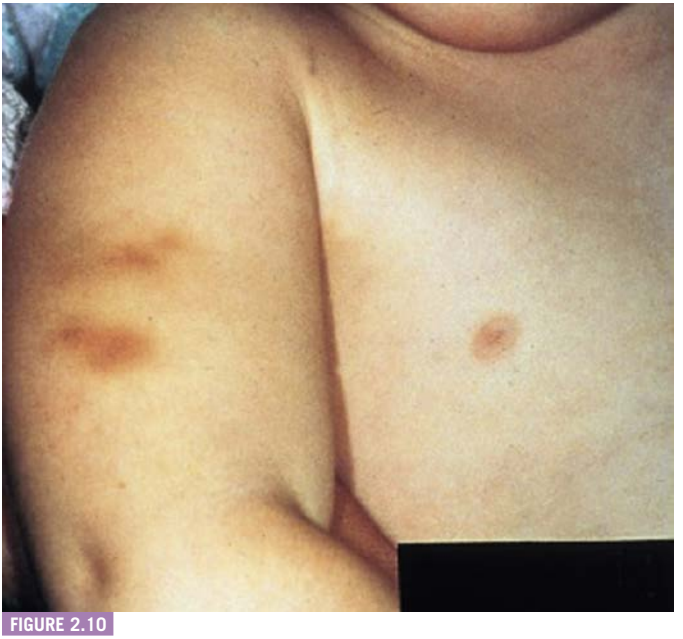

FIGURE 2.10
Pinch marks signified by two small bruises separated by clear space. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

Chapter 3

Toxicology

Maria D. Latham, MD

See additional content on Expert Consult

Whenever ingestion is suspected, contact local poison control at 1-800-222-1222.

Each year the American Association of Poison Control Centers records more than 1.2 million childhood poisoning exposures. Of these exposures, 76% occur in children younger than the age of 6 years. Exposures in young children are often unintentional, whereas adolescents are more likely to have intentional ingestions.[1]

I. INITIAL EVALUATION

A. History

1. **Exposure history**

Obtain history from witnesses and/or close contacts. Route, timing, and number of exposures (acute, chronic, or repeated ingestion), prior treatments or decontamination efforts.[2,3]

2. **Substance identification and quantity ingested**

Attempt to identify exact name of substance(s) ingested, including: product name, active ingredients, possible contaminants, expiration date, concentration, and dose. Attempt to estimate the missing volume of liquid or the number of missing pills from a container. Poison control can assist with pill identification.

3. **Environmental information**

Accessible items in the house or garage; open containers; spilled tablets; household members taking medications, visitors to the house, herbs, or other complementary medicines.[2]

B. Workup and Laboratory Investigation

1. **Electrocardiogram (ECG)**: Several medications will cause ECG changes, including QRS prolongation.
2. **Blood Tests**
   a. Individual drug levels such as acetaminophen, aspirin, and ethanol are helpful general screenings in an acute, unknown ingestion.
   b. Acetaminophen levels are especially important to test in suicidal ingestions. Acetaminophen is detected in 1/500 of all suicidal ingestions even when it is not reported as an ingested agent.[3]
   c. Venous blood gas, blood glucose, and serum electrolytes.
3. **Urine Toxicology Screens**
   a. Basic screens include amphetamines, cocaine, opiates, phencyclidine (PCP), and tetrahydrocannabinol (THC).

b. Positive results are presumptive only; must be confirmed by gas chromatography/mass spectrometry.[4]

C. Clinical Diagnostic Aids (Table EC 3.A)

II. TOXIDROMES

See Table 3.1.

III. INGESTIONS AND ANTIDOTES

See Table 3.2.

A. Decontamination

1. **Activated charcoal**[5]
   a. Most effective when used within first hour after ingestion but can be given after first hour, especially for sustained-release preparations. Should be given PO to an awake and alert patient. Nasogastric (NG) tube should be used only if a patient is intubated.
   b. Substances not absorbed by charcoal: Iron, alcohols, lithium
   c. Contraindications: Unprotected airway, caustic ingestion, disrupted gastrointestinal tract, concern for aspiration
2. **Whole bowel irrigation**
   a. Indicated for evacuation of substances not bound to activated charcoal such as iron, lead-containing foreign bodies, fatal sustained release products, drug packing.
   b. Use a polyethylene glycol electrolyte solution preparation to irrigate the bowel. Recommended rates: 9 months to 6 years (500 mL/hr), 6 to 12 years (1000 mL/hr), more than 12 years (1500 to 2000 mL/hr).

B. Enhanced Removal

1. Hemodialysis or exchange transfusions may be indicated to remove a drug/toxin.
2. Ingestions that may require enhanced removal therapies: Salicylate, lithium, methanol, ethylene glycol, metformin-associated lactic acidosis, valproate, theophylline

C. Other Considerations

1. Many ingestions managed primarily with supportive care of any associated toxic effects, such as hypotension or hyperpyrexia.
2. Seizures: First line agents are benzodiazepines. Barbiturates or propofol should be considered as second line agents. Phenytoin has no role in the treatment of toxin-induced seizures.[6]
3. Patients with severe poisoning and refractory cardiorespiratory failure after ingestion are potential extracorporeal membrane oxygenation (ECMO) candidates because the toxic effects are transient.

TABLE EC 3.A

CLINICAL DIAGNOSTIC AIDS

Clinical Sign	Intoxicant
VITAL SIGNS	
Hypothermia	Alcohol, antidepressants, barbiturates, carbamazepine, carbon monoxide, clonidine, ethanol, hypoglycemics, opioids, phenothiazines, sedative-hypnotics
Hyperpyrexia	Amphetamines, anticholinergics, antihistamines, atropinics, β-blockers, cocaine, iron, isoniazid, monoamine oxidase inhibitors (MAOIs), phencyclidine, phenothiazines, quinine, salicylates, sympathomimetics, selective serotonin reuptake inhibitors (SSRIs), theophylline, thyroxine, tricyclic antidepressants (TCAs)
Bradypnea	Acetone, alcohol, barbiturates, botulinum toxin, clonidine, ethanol, ibuprofen, opioids, nicotine, sedative-hypnotics
Tachypnea	Amphetamines, barbiturates, carbon monoxide, cyanide, ethylene glycol, isopropanol, methanol, salicylates *Direct pulmonary insult:* Hydrocarbons, organophosphates, salicylates
Bradycardia	α-Agonists, alcohols, β-blockers, calcium channel blockers, central α_2-agonist, clonidine, cyanide, digoxin, opioids, organophosphates, plants (lily of the valley, foxglove, oleander), sedative-hypnotics
Tachycardia	Alcohol, amphetamines, anticholinergics, antihistamines, atropine, cocaine, cyclic antidepressants, cyanide, iron, phencyclidine, salicylates, sympathomimetics, theophylline, TCAs, thyroxine
Hypotension	α-Agonists, angiotensin-converting enzyme (ACE) inhibitors, barbiturates, carbon monoxide, cyanide, iron, methemoglobinemia, opioids, phenothiazine, sedative-hypnotics, TCAs *Profound hypotension:* β-blockers, calcium channel blockers, clonidine, cyclic antidepressants, digoxin, imidazolines, nitrites, quinidine, propoxyphene, theophylline
Hypertension	Amphetamines, anticholinergics, antihistamines, atropinics, clonidine, cocaine, cyclic antidepressants (early after ingestion), diet pills, ephedrine, MAOIs, nicotine, over-the-counter cold remedies, phencyclidine, phenylpropanolamine, pressors, sympathomimetics, TCAs *Delayed hypertension:* Thyroxine
Hypoxia	Oxidizing agents
NEUROMUSCULAR	
Nervous system instability	*Insidious onset:* Acetaminophen, benzocaine, opioids *Abrupt onset:* Lidocaine, monocyclic or tricyclic antidepressants, phenothiazines, theophylline *Delayed onset:* Atropine, diphenoxylate *Transient instability:* Hydrocarbons
Depression and excitation	Clonidine, imidazolines, phencyclidine
Ataxia	Alcohol, anticonvulsants, barbiturates, carbon monoxide, heavy metals, hydrocarbons, solvents, sedative-hypnotics

Continued

TABLE EC 3.A—CONT'D

CLINICAL DIAGNOSTIC AIDS

Clinical Sign	Intoxicant
Chvostek/Trousseau signs	Ethylene glycol, hydrofluoric acid–induced hypocalcemia, phosphate-induced hypocalcemia from Fleet enema
Coma	Alcohol, anesthetics, anticholinergics (antihistamines, antidepressants, phenothiazines, atropinics, over-the-counter sleep preparations), anticonvulsants, baclofen, barbiturates, benzodiazepines, bromide, carbon monoxide, chloral hydrate, clonidine, cyanide, cyclic antidepressants, γ-hydroxybutyrate (GHB), hydrocarbons, hypoglycemics, inhalants, insulin, lithium, opioids, organophosphate insecticides, phenothiazines, salicylates, sedative-hypnotics, tetrahydrozoline, theophylline
Delirium, psychosis	Alcohol, anticholinergics (including cold remedies), cocaine, heavy metals, heroin, lysergic acid diethylamide (LSD), marijuana, mescaline, methaqualone, peyote, phencyclidine, phenothiazines, steroids, sympathomimetics
Miosis	Barbiturates, clonidine, ethanol, opioids, organophosphates, phencyclidine, phenothiazines, muscarinic mushrooms
Mydriasis	Amphetamines, antidepressants, antihistamines, atropinics, barbiturates (if comatose), botulism, cocaine, glutethimide, LSD, marijuana, methanol, phencyclidine
Nystagmus	Barbiturates, carbamazepine, diphenylhydantoin, ethanol, glutethimide, MAOIs, phencyclidine (both vertical and horizontal), sedative-hypnotics
Paralysis	Botulism, heavy metals, paralytic shellfish poisoning, plants (poison hemlock)
Seizures	Ammonium fluoride, amphetamines, anticholinergics, antidepressants, antihistamines, atropine, β-blockers, boric acid, bupropion, caffeine, camphor, carbamates, carbamazepine, carbon monoxide, chlorinated insecticides, cocaine, cyclic antidepressants, diethyltoluamide, ergotamine, ethanol, GHB, *Gyromitra* mushrooms, hydrocarbons, hypoglycemics, ibuprofen, imidazolines, isoniazid, lead, lidocaine, lindane, lithium, LSD, meperidine, nicotine, opioids, organophosphate insecticides, phencyclidine, phenothiazines, phenylpropanolamine, phenytoin physostigmine, plants (water hemlock), propoxyphene, salicylates, strychnine, theophylline
CARDIOVASCULAR	
Hypoperfusion	Calcium channel blockers, iron
Wide QRS complex	TCAs
ELECTROLYTES	
Anion gap metabolic acidosis	Acetaminophen, carbon monoxide, chronic toluene, cyanide, ethylene glycol, ibuprofen, iron, isoniazid, lactate, methanol, metformin, paraldehyde, phenformin, salicylates
Electrolyte disturbances	Diuretics, salicylates, theophylline
Hypoglycemia	Alcohol, β-blockers, hypoglycemics, insulin, salicylates

TABLE EC 3.A—CONT'D

CLINICAL DIAGNOSTIC AIDS

Clinical Sign	Intoxicant
Serum osmol gap	Acetone, ethanol, ethylene glycol, isopropyl alcohol, methanol, propylene glycol
SKIN	
Cyanosis unresponsive to oxygen	Aniline dyes, benzocaine, nitrites, nitrobenzene, phenazopyridine, phenacetin
Flushing	Alcohol, antihistamines, atropinics, boric acid, carbon monoxide, cyanide, disulfiram
Jaundice	Acetaminophen, carbon tetrachloride, heavy metals (iron, phosphorus, arsenic), naphthalene, phenothiazines, plants (mushrooms, fava beans)
ODORS	
Acetone	Acetone, isopropyl alcohol, phenol, salicylates
Alcohol	Ethanol
Bitter almond	Cyanide
Garlic	Heavy metal (arsenic, phosphorus, thallium), organophosphates
Hydrocarbons	Hydrocarbons (gasoline, turpentine, etc.)
Oil of wintergreen	Salicylates
Pear	Chloral hydrate
Violets	Turpentine
RADIOLOGY	
Small opacities on radiograph	Halogenated toxins, heavy metals, iron, lithium, densely packaged products

TABLE 3.1

TOXIDROMES

Drug Class	Temp	HR	RR	BP	Pupils	Skin	Mental Status	Other Signs	Causative Agents
Anticholinergic *"Mad as a hatter, red as a beet, blind as a bat, hot as a hare, dry as a bone"*[a]	↑	↑	↑/nl	↑/nl	Dilated	Dry, flushed	Delirium, psychosis, paranoia	Urinary retention, decreased bowel sounds, thirst, garbled speech	Antihistamines, atropine, antipsychotics, phenothiazines, scopolamine, TCAs
Cholinergic *"SLUDGE, Killer B's"*[a]	nl	↓	↑ (bronchospasm)	↓/nl	Constricted	Sweaty	Depressed, confused	Salivation, lacrimation, urination, defecation, emesis. Liquid nicotine can cause fasciculations and paralysis.	Organophosphates, pesticides, nerve agents, tobacco, liquid nicotine
Opioids	↓/nl	↓ /nl	↓ (hypoventilation)	↓/nl	Constricted	No change	Sedated		Morphine, fentanyl, oxycodone, methadone
Sympathomimetics	↑/nl	↑	↑/nl	↑	Dilated	Sweaty	Agitated	At risk for seizures, coronary vasospasm	Amphetamines, cocaine
Sedative/Hypnotics *"Coma with normal vitals"*	nl	nl	↓/nl	↓/nl	Normal	No change	Depressed		Benzodiazepines, barbiturates, ethanol
Serotonergic	↑	↑	↑	↑/nl	Dilated	Flushed	Confusion	Shivering, muscle rigidity, at risk for seizures, hyperreflexia and clonus of lower extremities	SSRIs, SNRIs, MAOIs, trazadone, dextromethorphan, LSD, TCAs, MDMA (ecstasy)

[a]The "mad as a hatter" mnemonic references delirium, flushed skin, mydriasis, hyperpyrexia, and dry skin/urinary retention seen in the anticholinergic toxidrome. The "SLUDGE" mnemonic references salivation, lacrimation, urination, diaphoresis, gastrointestinal distress (including diarrhea), and emesis seen in the cholinergic toxidrome. The "Killer B's" mnemonic references bronchospasm, bronchorrhea, and bradycardia seen in the cholinergic toxidrome.

↑ refers to increased or elevated vital sign, ↓ refers to decreased or depressed vital sign, nl refers to vital sign within normal limits.

BP, Blood pressure; *HR*, heart rate; *LSD*, lysergic acid diethylamide; *MAOIs*, monoamine oxidase inhibitors; *RR*, respiratory rate; *SNRIs*, serotonin and norepinephrine reuptake inhibitors; *SSRIs*, selective serotonin reuptake inhibitors; *TCAs*, tricyclic antidepressants; *Temp*, temperature.

TABLE 3.2

COMMONLY INGESTED AGENTS

Ingested Agent	Signs and Symptoms	Antidote[a]
Acetaminophen	See Section IV	
Amphetamines	See sympathomimetics toxidrome in Table 3.1	Supportive care **Benzodiazepines** for agitation
Anticholinergics	See anticholinergic toxidrome in Table 3.1	**Physostigmine**
Anticholinesterase (insecticides, donepezil, mushrooms)	See cholinergic toxidrome in Table 3.1	**Atropine**
Antihistamines	See anticholinergic toxidrome in Table 3.1; paradoxical CNS stimulation, dizziness, seizures, prolonged QT	Supportive care
Benzodiazepines	See sedative/hypnotic toxidrome in Table 3.1	**Flumazenil**
β-Blockers	Bradycardia, hypotension, AV conduction block, bronchospasm, hypoglycemia	**Glucagon** See **insulin/dextrose** treatment in calcium channel blockers
Calcium channel blockers	Bradycardia, hypotension, AV conduction block, pulmonary edema, hyperglycemia	**Calcium chloride (10%)** **Calcium gluconate (10%)** **Glucagon** **High-Dose Insulin/Dextrose[9]:** 1 unit/kg bolus → infuse at 1–10 unit/kg/hr; give with D25W at 0.5 g/kg/hr. Monitor BG frequently.
Clonidine	Symptoms resemble an opioid toxidrome. CNS depression, coma, lethargy, hypothermia, miosis, bradycardia, profound hypotension, respiratory depression	**Naloxone**
Cocaine	See sympathomimetics toxidrome in Table 3.1	Supportive care
Detergent pods	Vomiting, sedation, aspiration, respiratory distress	Supportive care
Ecstasy	Hallucinations, teeth grinding, hyperthermia, hyponatremia, seizures	Supportive care
Ethanol	See sedative/hypnotic toxidrome in Table 3.1 Hypoglycemia in young children	Supportive care
Ethylene glycol/ methanol	Similar to ethanol; additionally, blurry or double vision (methanol), renal failure/hypocalcemia (ethylene glycol), osmol gap with severe anion gap metabolic acidosis	**Fomepizole** Ethanol (only to be used as second line agent when fomepizole unavailable; risk of inappropriate dosing, CNS depression, aspiration, and hypoglycemia). Consider dialysis.

TABLE 3.2—CONT'D

COMMONLY INGESTED AGENTS

Ingested Agent	Signs and Symptoms	Antidote[a]
Iron	Vomiting, diarrhea, hypotension, lethargy, anion gap metabolic acidosis, cardiogenic shock, renal failure	**Deferoxamine**
Lead	See Section V	
Nicotine	Vomiting and cholinergic toxidrome in Table 3.1	Supportive care
NSAIDs	Nausea, vomiting, epigastric pain, headache, gastrointestinal hemorrhage, renal failure	Supportive care
Opioids	See opioid toxidrome in Table 3.1	**Naloxone**
Organophosphates	See cholinergic toxidrome in Table 3.1	**Atropine** **Pralidoxime**
Salicylates	Gastrointestinal upset, tinnitus, tachypnea, hyperpyrexia, dizziness, lethargy, dysarthria, seizure, coma, cerebral edema	**Sodium bicarbonate** Consider dialysis
Serotonergic Agents	See serotonergic toxidrome in Table 3.1	**Benzodiazepines (first line)** Cyproheptadine
Sulfonylureas	Hypoglycemia, dizziness, agitation, confusion, tachycardia, diaphoresis	**Food (if able)** **Dextrose:** 0.5–1 g/kg (2–4 mL/kg of D25W) *After euglycemia achieved:* **Octreotide:** 1–1.25 mCg/kg SQ Q6–12 hr (max dose 50 mCg) if rebound hypoglycemia
Synthetic cannabinoids	Agitation, altered sensorium, tachycardia, hypertension, vomiting, mydriasis, hypokalemia	Supportive care
TCAs	Tachycardia, seizures, delirium, widened QRS possibly leading to ventricular arrhythmias, hypotension	*For wide QRS complex:* **Sodium bicarbonate:** 1–2 mEq/kg IV push, followed by D5W + 140 mEq/L $NaHCO_3$ and 20 meq/L KCl at 1.5× maintenance fluid rate with goal serum pH 7.45–7.55
Warfarin	Bleeding	**Phytonadione/Vitamin K_1**

[a]See Formulary for dosing recommendations.

BG, Blood glucose; *CNS*, central nervous system; *KCl*, potassium chloride; *$NaHCO_3$*, sodium bicarbonate; *NSAIDs*, nonsteroidal antiinflammatory drugs; *TCA*, tricyclic antidepressant.

Data from Gummin DD, Mowry JB, Spyker DA, et al. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clin Toxicol.* 2017;56(12):1213–1415.

IV. ACETAMINOPHEN OVERDOSE[7]

NAPQI metabolite is hepatotoxic.

A. Four Phases of Intoxication

1. **Phase 1 (first 24 hours):** Nonspecific symptoms such as nausea, malaise, vomiting.
2. **Phase 2 (24 to 72 hours):** Above symptoms resolve; right upper quadrant pain, hepatomegaly, and increasing transaminases develop.
3. **Phase 3 (72 to 96 hours):** Return of nonspecific symptoms as well as evidence of liver failure (increased prothrombin time, lactate, phosphate), renal failure, and encephalopathy.
4. **Phase 4 (4 days to 2 weeks):** Recovery or death.

B. Treatment Criteria

1. **Serum acetaminophen** concentration above the possible toxicity line on the Rumack-Matthew nomogram after single acute ingestion (Fig. 3.1).
2. **History of ingesting more than 200 mg/kg or 10 g** (whichever is less) and serum concentration not available or time of ingestion not known.
3. **If time of ingestion is unknown or multiple/chronic ingestion,** check acetaminophen level and AST. Treat if either is elevated.

C. Antidote: *N*-Acetylcysteine (See Formulary)

1. **PO:** 140 mg/kg loading dose followed by 70 mg/kg Q4 hours for 17 doses (18 total doses including loading dose).
2. **Intravenous (IV):** 150 mg/kg *N*-acetylcysteine IV loading dose over 60 minutes, followed by 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours for a total infusion time of 21 hours. Some patients may require more than 21 hours of *N*-acetylcysteine administration.
3. **Liver failure:** Continue the 100 mg/kg over 16 hours infusion until resolution of encephalopathy, AST less than 1000 units/L, and INR less than 2.

V. LEAD POISONING[8]

A. Definition:

Centers for Disease Control and Prevention (CDC) defines a reference level of 5 mCg/dL to identify children with elevated blood lead levels (BLLs).

B. Sources of Exposure:

Paint, dust, soil, drinking water, cosmetics, cookware, toys, and caregivers with occupations and/or hobbies using lead-containing materials or substances.

C. Overview of Symptoms by Blood Lead Level:

1. **BLL ≥40 mCg/dL:** Irritability, vomiting, abdominal pain, constipation, anorexia
2. **BLL ≥70 mCg/dL:** Lethargy, seizure, and coma. **Note:** Children may be asymptomatic with lead levels greater than 100 mCg/dL.

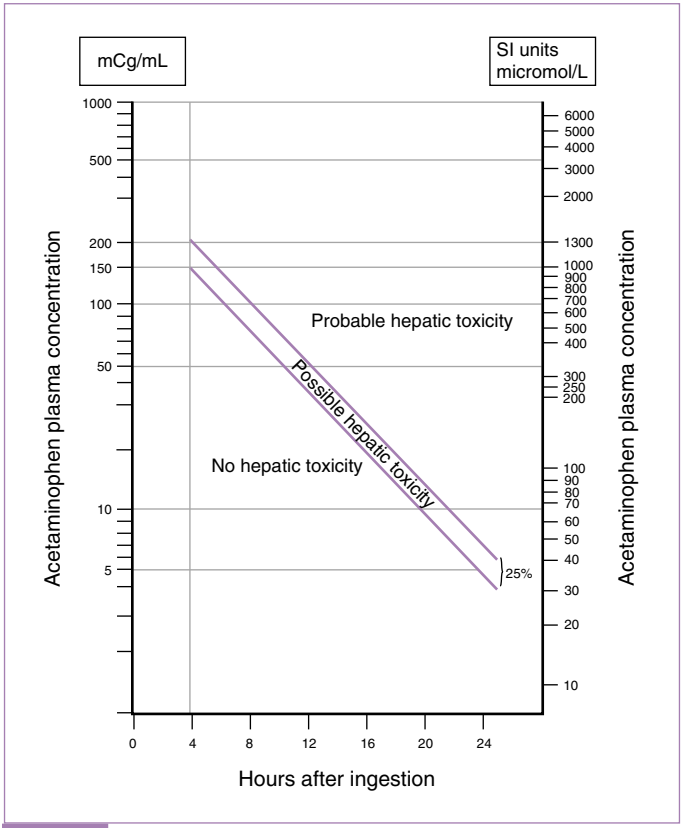

FIGURE. 3.1

Rumack-Matthew nomogram. Semilogarithmic plot of plasma acetaminophen levels versus time. This nomogram is valid for use after single acute ingestions of acetaminophen. The need for treatment cannot be extrapolated based on a level before 4 hr. (Data from Pediatrics 55:871, 1975 and Micromedex.)

D. Management

1. See Tables 3.3 and 3.4 for general management and repeat testing guidelines.
2. Chelation therapy[2]
   a. Asymptomatic children with BLL 45 to 69 mCg/dL
      Succimer: 1050 mg/m^2/day PO divided Q8 hours × 5 days, then 700 mg/m^2/day divided Q12 hours × 14 days. See Formulary for more details.

TABLE 3.3

MANAGEMENT OF LEAD POISONING[8]

Blood Lead Levels (BLL)	Recommended Guidelines *See Table 3.4 for Repeat Testing Guidelines.*
5–9 mCg/dL	1. Obtain detailed environmental exposure history to assess for possible sources. 2. Provide education about reducing environmental lead exposure and reducing dietary lead absorption[a]
10–19 mCg/dL	1. As above for BLL 5–9 mCg/dL 2. Consider iron studies. 3. Environmental investigation may be available based on local resources.
20–44 mCg/dL	1. As above for BLL 5–9 mCg/dL 2. Environmental investigation 3. Iron level, complete blood cell count (CBC), abdominal radiography with bowel decontamination if indicated 4. Complete exam including neurodevelopmental assessment
45–69 mCg/dL	1. As above for BLL 20–44 mCg/dL 2. Administer oral chelation therapy, consider hospitalization
≥70 mCg/dL	1. Hospitalize and commence chelation therapy 2. Contact local poison control

[a]Iron, calcium, and vitamin C help to minimize absorption of lead.

TABLE 3.4

REPEAT BLOOD LEAD TESTING GUIDELINES[8]

If Screening BLL is: (mCg/dL)	Time Frame of Confirmation of Screening BLL	Follow-Up Testing (After Confirmatory Testing)	Later Follow-Up Testing After BLL Declining
≥5–9	1–3 months	3 months	6–9 months
10–19	1 week–1 month[a]	1–3 months	3–6 months
20–24	1 week–1 month[a]	1–3 months	1–3 months
25–44	1 week–1 month[a]	2 weeks–1 month	1 month
45–59	48 hr	*Repeat testing as soon as possible after chelation therapy*	
60–69	24 hr		
≥70	Urgently		

[a]Per provider discretion.

BLL, Blood lead level.

b. Asymptomatic children with BLL ≥70 mCg/dL
   (1) **Succimer:** Per above dosing.
   (2) **Edetate (EDTA) calcium disodium:** 1000 mg/m^2 (max dose 2 to 3 g) as 24-hour IV infusion × 5 days. Begin two hours after first dose of succimer. Monitor renal function closely.

Warning: Do not mistake edetate disodium for edetate calcium disodium. Edetate *calcium* disodium is the correct medicine used for the treatment of lead poisoning.

c. Symptomatic children (e.g., lead encephalopathy, seizure)
   (1) **Dimercaprol (BAL):** 450 mg/m^2/day IM divided Q4 hours × 3 to 5 days (number of days based on clinical course). Do not give to patients with peanut allergy. Do not use concomitantly with iron, as BAL-iron complex is a potent emetic. Use with caution in patients with G6PD deficiency, as it may cause hemolysis.
   (2) **Edetate (EDTA) calcium disodium:** 1500 mg/m^2 (maximum dose 2 to 3 g) as 24-hour IV continuous infusion × 5 days. Begin four hours after first dose of BAL.

VI. WEB RESOURCES

- American Association of Poison Control Centers: http://www.aapcc.org/
- American Academy of Clinical Toxicology: http://www.clintox.org/index.cfm
- Centers for Disease Control and Prevention, Section on Environmental Health: http://www.cdc.gov/nceh

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 4

Procedures

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I. GENERAL GUIDELINES

A. Consent

Before performing any procedure, it is crucial to obtain informed consent from the parent or guardian by explaining the procedure, the indications, any risks involved, and any alternatives. Obtaining consent should not impede life-saving, emergency procedures.

B. Risks

1. All invasive procedures involve pain, risk for infection and bleeding, and potential injury to neighboring structures.
2. Sedation and analgesia should be planned in advance, and the risks of such explained to the parent and/or patient as appropriate. (See Chapter 6 and the AAP Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures.[1])
3. Universal precautions and proper sterile technique should be followed for all patient contact that exposes the healthcare provider to bodily fluids.

C. Documentation

It is important that the physician performing the procedure document the informed consent process. Include the date, time, additional personnel present (if applicable), brief summary of the consent conversation, the diagnosis, recommended procedure, specific risks and benefits, and alternative treatments. It is equally important to document if a patient refuses a procedure and that the risks associated with refusal were discussed.

D. Attending to the Needs of a Fearful Child

Children represent a vulnerable population in that they often lack the capacity to understand why a potentially uncomfortable procedure is being performed. All efforts should be made to provide information about the procedure to the child at an age-appropriate level. Utilize Child Life Specialists as able. When possible, allow the child to touch unfamiliar objects in the examination room to desensitize them and enhance trust. Address the child's fears. Toddlers often fear separation from the parent. Older children often fear pain. Adolescents often worry about embarrassment sustained by expressing anxiety or fear. Encourage active parent participation and presence. Allow all children a degree of basic autonomy such as selecting the postprocedure bandage color.

II. ULTRASOUND FOR PROCEDURES

A. Introduction to Ultrasound

Ultrasound has become an increasingly important bedside diagnostic and procedural aid, and it can improve visualization of subcutaneous structures during procedures.

B. Ultrasound Basics

1. **Probe Selection**
   a. Linear transducers use higher frequencies to produce higher resolution images and are primarily used for procedures in pediatrics. A wide area of contact at the skin surface facilitates needle placement in procedures.
   b. Curvilinear transducers use low to midrange frequencies and permit deep structure visualization. Though they provide a wide area of skin contact to facilitate procedures near concave and convex surfaces, larger curvilinear probes are difficult to use in small children.
   c. There are a variety of other probes (phased-array, microconvex) that generate sector shaped images but are predominantly used for diagnostic purposes.
2. **Image Optimization**
   a. Ensure adequate contact by using enough ultrasound gel and applying comfortable pressure on the skin.
   b. Gain: Measure of image brightness which is used for optimizing images and reducing artifact.
   c. Frequency: Increase to improve image resolution of shallow structures. Decrease to improve imaging of deep structures.
   d. Depth: Adjust to visualize structure of interest and at least a centimeter of tissue below that structure.

III. NEUROLOGIC PROCEDURES: LUMBAR PUNCTURE[2,3]

A. Indications:

Examination of spinal fluid for suspected infection, inflammatory disorder, or malignancy, instillation of intrathecal chemotherapy, or measurement of opening pressure.

B. Complications:

Local pain, infection, bleeding, spinal fluid leak, hematoma, spinal headache, and acquired epidermal spinal cord tumor (caused by implantation of epidermal material into the spinal canal if no stylet is used on skin entry).

C. Cautions and Contraindications:

1. Increased intracranial pressure (ICP): Before lumbar puncture (LP), perform a funduscopic examination. Presence of papilledema, retinal hemorrhage, or clinical suspicion of increased ICP should prompt further evaluation and may be a contraindication to the procedure. A sudden drop in spinal canal fluid pressure by rapid release of cerebrospinal fluid (CSF) may cause fatal herniation. Computed tomography (CT)

may be indicated before LP if there is suspected intracranial bleeding, focal mass lesion, or increased ICP. A normal CT scan does not rule out increased ICP but usually excludes conditions that may put the patient at risk for herniation. Decision to obtain CT should not delay appropriate antibiotic therapy, if indicated.
2. Bleeding diathesis: Platelet count greater than 50,000/mm^3 is desirable before LP, and correction of any clotting factor deficiencies can minimize the risk for bleeding and subsequent cord or nerve root compression.
3. Overlying skin infection may result in inoculation of CSF with organisms.
4. LP should be deferred in unstable patients, and appropriate therapy should be initiated, including antibiotics, if indicated.

D. Procedure:

1. Apply local anesthetic cream if sufficient time is available.
2. Position child (Fig. 4.1) in either the sitting position or lateral recumbent position, with hips, knees, and neck flexed. Keep shoulders and hips aligned to avoid rotating the spine. *Do not* compromise a small infant's cardiorespiratory status with positioning.
3. Locate the desired intervertebral space (either L3 to L4 or L4 to L5) by drawing an imaginary line between the top of the iliac crests. Alternatively, ultrasound can be used to mark the intervertebral space (see Section XI, Online Content).
4. Prepare the skin in a sterile fashion. Drape conservatively to make monitoring the infant possible. Use a 20- to 22-G spinal needle with stylet (1.5, 2.5, or 3.5 inch depending on the size of the child). A smaller-gauge needle will decrease the incidence of spinal headache and CSF leak.
5. Overlying skin and interspinous tissue can be anesthetized with 1% lidocaine using a 25G needle.
6. Puncture the skin in the midline just caudad to the palpated spinous process, angling slightly cephalad toward the umbilicus. Advance several millimeters at a time, and withdraw stylet frequently to check for CSF flow. **Needle may be advanced without the stylet once it is completely through the skin.** In small infants, one may *not* feel a change in resistance or "pop" as the dura is penetrated.
7. If resistance is met initially and the needle cannot be advanced, withdraw needle to just under the skin surface and redirect the angle of the needle slightly.
8. Send CSF for appropriate studies. In general, send the first tube for culture and Gram stain, the second tube for measurement of glucose and protein levels, and the last tube for cell count and differential. Additional tubes can be collected for viral cultures, polymerase chain reaction (PCR), or CSF metabolic studies, if indicated. If subarachnoid hemorrhage or traumatic tap is suspected, send the first and fourth tubes for cell count, and ask the laboratory to examine the CSF for xanthochromia.

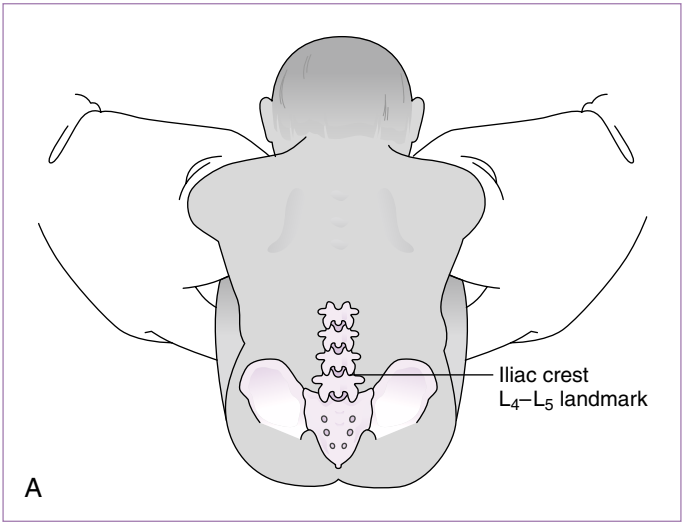

FIGURE 4.1
Lumbar puncture site. (A) Infant placed in sitting position. (B) Infant placed in lateral (recumbent) position. (*From Dieckmann R, Fiser D, Selbst S.* Pediatric Emergency and Critical Care Procedures. *St. Louis: Mosby; 1997.*)

9. Accurate measurement of CSF pressure can be made only with the patient lying quietly on his or her side in an unflexed position. It is not a reliable measurement in the sitting position. Once the free flow of spinal fluid is obtained, attach the manometer and measure CSF pressure. Opening pressure is recorded when the CSF level is steady.

E. A video on lumbar punctures is available on the *New England Journal of Medicine's* website.

IV. OTOLARYNGOLOGIC PROCEDURES

A. Cerumen Impaction Removal[4,5]

1. **Indications**: Symptomatic (decreased hearing, pain) and/or assessment of the ear. Clinicians should *not* routinely disimpact asymptomatic patients whose ears can be adequately assessed.
2. **Complications**: Allergic reaction to cerumenolytics, trauma, earache, dizziness, nystagmus, retention of water, tympanic membrane perforation.
3. **Procedures:**
   a. **Cerumenolytics**
      (1) There is no high-quality evidence suggesting that one cerumenolytic is more effective than another. Water and saline are equally as effective as cerumenolytics. There is no difference in efficacy between oil-based and water-based treatments.
      (2) Avoid hydrogen peroxide; may exacerbate cerumen impaction.
      (3) Apply 5 to 10 eardrops twice daily for no longer than 4 days. Keep the head tilted for several minutes for cerumenolytic retention.
   b. **Irrigation**
      (1) Direct visualization is not necessary.
      (2) Irrigation of the ear canal with a large syringe containing lukewarm water is equally effective as a commercial mechanical jet irrigator.[5]
      (3) Place a small bucket (e.g., emesis bin) under the patient's ear to collect water.
      (4) Straighten the ear as much as possible by lifting the auricle up and posteriorly. Gently apply a continuous stream upwards in the canal.
      (5) **Note** that irrigation is contraindicated in patients with tympanostomy tubes or perforated tympanic membranes, and for removing vegetables/legumes (increases swelling) and button batteries (enhances current flow).
   c. **Manual Removal/Instrumentation**
      (1) Most useful for cerumen removal in the outer one-third of the ear.
      (2) Direct visualization is essential, and may render manual removal impossible in an uncooperative patient.
      (3) Tools include curettes (plastic or metal), spoons, alligator forceps. Do not attempt to break through the cerumen. Advance the loop of the curette behind the cerumen and retrieve.
   d. **A video on cerumen removal is available on the *New England Journal of Medicine's* website.**

B. Foreign Body Removal from Ear[6]

1. **Indications**: Retained foreign body in the external auditory canal.

2. **Contraindications**: Urgent referral to an otolaryngologist **prior** to attempted removal is indicated if object is a button battery or penetrating the ear canal (e.g., pencil, cotton-tipped swab).
3. **Complications**: External auditory canal trauma (most common), perforation of the tympanic membrane, retained foreign object.
4. **Procedure:**
   a. Insects should be killed with mineral oil, ethanol, or lidocaine prior to attempted removal.
   b. Irrigation is useful for hard objects resistant to grasping that are nonocclusive.
   c. Instrumentation is most successful for irregularly shaped objects that are graspable.
   d. Refer to otolaryngology if removal is unsuccessful.
5. **A video on removal of foreign bodies from the ear and nose is available on the *New England Journal of Medicine's* website.**

C. Foreign Body Removal from Nose[6,7]

1. **Indications**: Retained foreign body in the nasal cavity. Button batteries and magnets attached to the nasal septum require urgent removal.
2. **Contraindications**: Most nasal foreign bodies do not require subspecialty referral. Consider otolaryngology referral for posterior objects, button batteries, and unsuccessful initial attempts.
3. **Complications**: Epistaxis, perforation of cribriform plate, retained foreign object.
4. **Procedure**: Lidocaine or any vasoconstrictor (e.g., crushed ice) may be used to minimize bleeding and edema.
   a. **Self-Removal**: The easiest and least invasive method. Typically, only effective for patients older than 3 years. Instruct the patient to occlude the unobstructed nostril and blow his/her nose.
   b. **Parent Kiss**: Provides up to a 60% successful removal rate.
      (1) Instruct the caregiver to place his/her lips around the patient's lips (similar to a "mouth-to-mouth" resuscitation breath) and occlude the uninvolved nostril with one finger.
      (2) Quickly and forcefully exhale one puff into the child's mouth. This maneuver often expels the foreign body.
   c. **High-Flow Oxygen**: Best for foreign bodies that *completely* occlude the anterior nasal cavity. Place suction tubing into the unobstructed nostril while the child's mouth is closed. Deliver 10 to 15 L/min of oxygen flow through the tubing.
   d. **Instrumentation**: Best for foreign bodies that are *nonocclusive*.
      (1) Equipment: alligator forceps, right-angle hook, Foley catheter (5 to 8 Fr), irrigating devices
      (2) Use alligator forceps to extract compressible objects that have rough surfaces.
      (3) Use a right-angle hook for smooth objects that cannot be easily grasped.

(4) Use a Foley catheter for small round objects (e.g., marble). Lubricate the catheter, advance the uninflated catheter past the object, inflate the catheter balloon, and withdraw the catheter and the object.

D. Management of Epistaxis[6,8]

1. **Indications**: Simple nosebleed. Most cases of epistaxis in children have a benign etiology. Referral to an otolaryngologist is only indicated for uncontrollable bleeding, posterior epistaxis, hemodynamic instability, or anatomic abnormalities (e.g., tumors, polyps). See Chapter 14 for management of epistaxis in patients with hemophilia, von Willebrand disease, immune thrombocytopenia, or other bleeding disorders.
2. **Complications**: Persistent bleeding, swallowing blood, toxic shock syndrome (from packing material), septal hematomas/abscesses from traumatic packing.
3. **Procedure**: The child should sit upright and bent forward at the waist to minimize swallowing blood.
   a. **Direct compression**: Instruct the child or parent to compress the nasal alae together for a minimum of 5 to 10 minutes. Most simple bleeds will clot after 5 to 10 minutes.
   b. **Topical vasoconstriction**: Use oxymetazoline-soaked cotton pledgets or gauze. Phenylephrine is associated with morbidity when used topically and should be avoided in patients younger than 6 years of age. However, if bleeding is refractory to other interventions, the minimum dose of phenylephrine needed to cease bleeding should be used. Use a squirt bottle or apply the vasoconstrictor on a piece of cotton, applying direct pressure on the nose for 5 to 10 minutes.
   c. **Nasal packing**
      (1) Apply topical anesthetic (4% lidocaine or tetracaine) on a cotton pledget and insert into the nasal cavity.
      (2) Rub antibiotic ointment into a quarter-inch × 72-inch gauze ribbon. Using a nasal speculum or forceps, pack the nasal cavity by grasping the gauze ribbon approximately 6 inches from its end and placing the packing as far back as possible. Ensure that the free end protrudes from the nose and secure with tape.
      (3) Maintain packing for 72 hours and prescribe antistaphylococcal antibiotic for 7 to 10 days to minimize risk of toxic shock syndrome. If bleeding persists after 72 hours, packing should be replaced and the child referred to an otolaryngologist.

V. CARDIOVASCULAR PROCEDURES

A. Vagal Maneuvers for Supraventricular Tachycardia (SVT)[9,10,11]

1. **Indications**: Supraventricular tachycardia, 2:1 atrioventricular (AV) block, evaluation of cardiac murmurs.

2. **Contraindications**: Carotid sinus massage is to be avoided in patients with prior stroke within the past 3 months or any history of ventricular arrhythmia.
3. **Complications**: Typically transient (resolve within seconds to minutes) and include prolonged sinus pause, hypertension (increased intrathoracic pressure), hypotension (decreased venous return/decrease in intrathoracic pressure on exhalation).
4. **Procedure:**
   a. **Cold stimulus to the face**: Briefly place an icepack or washcloth soaked in ice water on the forehead or bridge of the nose. The ice should not be applied for longer than 30 seconds to avoid frostbite.
   b. **Valsalva maneuver**: Place the patient in supine position and instruct to exhale forcefully against a closed glottis. The strain should be maintained for 10 to 15 seconds before resuming normal breathing.
   c. **Modified Valsalva maneuver**: Greater success rate at restoring sinus rhythm than standard Valsalva. Place the patient in a semi-recumbent position (45-degree angle), and apply standard Valsalva strain. Immediately reposition supine with 15 seconds of passive leg raise at a 45-degree angle.
   d. **Carotid sinus massage**: Place the patient in a supine position with neck extension. Apply steady pressure for 5 to 10 seconds to **one** carotid sinus (inferior to the angle of the mandible where pulsation is detected). If unsuccessful, wait 1 to 2 minutes and repeat on the contralateral side.

B. Heelstick and Fingerstick[12]

1. **Indications:** Blood sampling in infants, obtaining point of care whole blood samples such as serum glucose
2. **Complications:** Infection, bleeding, osteomyelitis.
3. **Procedure:**
   a. Warm heel or finger.
   b. Clean with alcohol.
   c. Using a lancet puncture heel on the lateral aspect, avoiding the posterior area, or finger on the distal palmar lateral pad.
   d. Wipe away the first drop of blood, and then collect the sample using a capillary tube or container.
   e. Alternate between squeezing blood from the leg toward the heel (or from the hand toward the finger) and then releasing the pressure for several seconds.

C. Peripheral Intravenous Access

1. **Indications:** Blood sampling and access to peripheral venous circulation to deliver fluid, medications, or blood products.
2. **Complications:** Thrombosis, infection.
3. **Procedure:**
   a. Apply tourniquet around the extremity proximal to chosen site.
   b. Prepare site with alcohol or chlorhexidine.

c. Insert IV catheter, bevel up, at an angle almost parallel to the skin, advancing until a *flash* of blood is seen in the catheter hub. Advance the plastic catheter only, remove the needle, and secure the catheter.
d. After removing tourniquet, attach a syringe and apply gentle negative pressure to withdraw blood for serum sampling. Then, attach T connector filled with saline to the catheter, flush with normal saline (NS) to ensure patency of the IV line.

4. **Ultrasound-Guided Procedure:**
   a. With linear ultrasound probe, identify a vein that does not appear to be prohibitively tortuous or stenotic. Perform this by sliding the probe along the course of the vessel and identifying its direction and branching. The saphenous veins in the calves, veins in the forearms, antecubital areas, inside of the upper arms, and external jugular veins are areas where ultrasound guidance can help. An ideal vessel appears less than 1 cm below the skin surface. Deeper vessels are prone to through-and-through perforation of the vessel. Infiltration around deeper vessels is also a risk, as a shorter length of catheter resides in the vessel after insertion.
   b. Prepare the site, and in the case of limb vessels, place a tourniquet proximal to the insertion site.
   c. Under ultrasound visualization, insert the needle into the skin at a shallow (usually <30 degrees) angle to the skin at the midline of the probe near where it contacts the skin. With the probe visualizing the vessel transversely, slowly advance the needle and follow the tip of the needle by sliding the probe away from you. Advance the ultrasound probe until the needle punctures the vessel wall.
   d. Proceed with cannulation of the vessel and secure the intravenous catheter per standard procedure.
5. **Infiltration and Extravasation**[13]: Common injury secondary to fluid infusion into subcutaneous tissues around the venipuncture site. Typically occurs due to puncture of the vein or if the catheter slips out of the vein. The difference between infiltration and extravasation is the type of fluid that has leaked (nonvesicant vs. vesicant). Infiltrations are generally benign, although they can still inflict damage via exertion of mechanical forces on surrounding structures. Extravasation due to a vesicant can cause blistering and burns, leading to necrosis of the tissue. To determine if infiltration/extravasation has occurred, firmly occlude the vein 1 to 2 inches proximal to the insertion site. Continued infusion without resistance indicates infiltration. Immediately stop the infusion. Refer to institutional policy for guidelines regarding application of medication (e.g., hyaluronidase, phentolamine, nitroglycerin ointment). Elevate the affected limb to reduce swelling; apply a warm compress for 10 to 15 minutes; encourage movement of the affected arm. Reevaluate the site every 8 hours.
6. **A video on peripheral IV placement is available on the *New England Journal of Medicine's* website.**

7. **A video on ultrasound-guided peripheral IV placement is available on the *New England Journal of Medicine's* website.**

D. External Jugular Puncture and Catheterization (see Section XI, Online Content)

E. Radial Artery Puncture and Catheterization[2,3]

1. **Indications:** Arterial blood sampling or frequent blood gas and continuous blood pressure monitoring in an intensive care setting.
2. **Complications:** Infection, bleeding, occlusion of artery by hematoma or thrombosis, ischemia if ulnar circulation is inadequate.
3. **Procedure:**
   a. Before the procedure, test adequacy of ulnar blood flow with the Allen test: Clench the hand while simultaneously compressing ulnar and radial arteries. The hand will blanch. Release pressure from the ulnar artery, and observe the flushing response. Procedure is safe to perform if the entire hand flushes.
   b. Locate the radial pulse. It is optional to infiltrate the area over the point of maximal impulse with lidocaine. Avoid infusion into the vessel by aspirating before infusing. Prepare the site in a sterile fashion.
   c. Puncture: Insert a butterfly needle attached to a syringe at a 30- to 60-degree angle over the point of maximal impulse. Blood should flow freely into the syringe in a pulsatile fashion. Suction may be required for plastic tubes. Once the sample is obtained, apply firm, constant pressure for 5 minutes and then place a pressure dressing on the puncture site.
   d. Catheter placement: Secure the patient's hand to an arm board. Leave the fingers exposed to observe any color changes. Prepare the wrist with sterile technique and infiltrate over the point of maximal impulse with 1% lidocaine. Insert an IV catheter with its needle at a 30-degree angle to the horizontal until a flash of blood is seen in the catheter hub. Advance the plastic catheter and remove the needle. Alternatively, pass the needle and catheter through the artery to transfix it, and then withdraw the needle. Very slowly, withdraw the catheter until free flow of blood is noted, then advance the catheter and secure in place using sutures or tape. Seldinger technique (Fig. 4.2) using a guidewire can also be used. Apply a sterile dressing and infuse heparinized isotonic fluid (per institutional protocol) at a minimum of 1 mL/hr. A pressure transducer may be attached to monitor blood pressure.
   e. Suggested size of arterial catheters based on weight:
      (1) Infant (<10 kg): 24 G or 2.5 Fr, 2.5 cm
      (2) Child (10 to 40 kg): 22 G or 2.4 Fr, 2.5 cm
      (3) Adolescent (>40 kg): 20 G
4. **Ultrasound-Guided Procedure**
   a. Use the linear probe. After the sterile field has been prepped, apply gel to the probe and place within a sterile cover. Place the ultrasound probe transverse to the artery on the radial, posterior tibial, or

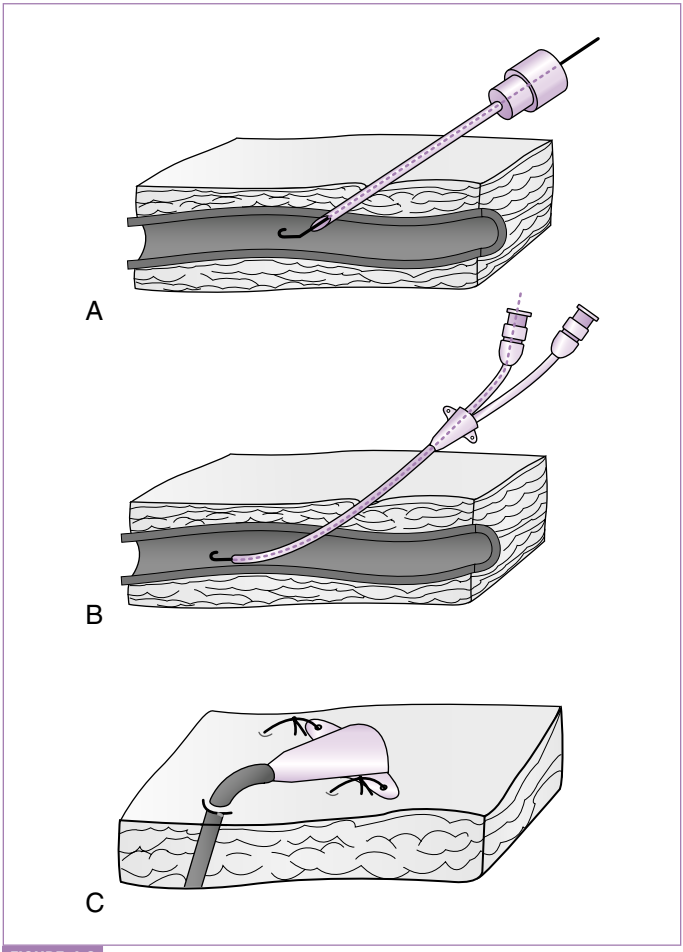

FIGURE 4.2
Seldinger technique. (A) Guidewire is placed through introducer needle into lumen of vein. (B) Catheter is advanced into vein lumen along guidewire. (C) Hub of catheter is secured to skin with suture. (*Modified from Fuhrman B, Zimmerman J.* Pediatric Critical Care. *4th ed. Philadelphia: Mosby; 2011.*)

dorsalis pedis pulse. Identify the artery, which will appear pulsatile with some compression. Once the artery has been identified, center the probe over the vessel (Fig. 4.3). Insert the needle into the skin at a 45-degree angle at the midline of the probe near where it contacts the skin. With the probe visualizing the vessel transversely, slowly

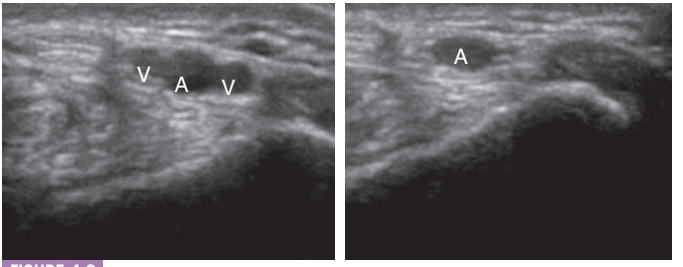

FIGURE 4.3
Ultrasound transverse view of radial artery. In the left image, the radial artery is seen in cross section with veins on either side. On the right image, pressure has been applied and the veins are collapsed while the artery remains patent. *A,* Artery; *V,* vein. (*From Weiner MM, Geldard P, Mittnacht AJC. Ultrasound guided vascular access: a comprehensive review.* J Cardiothorac Vasc Anesth. *2013;27(2):345–360.*)

advance the needle and follow the tip of the needle by sliding the probe away. Advance the ultrasound probe until the needle punctures the vessel wall. Proceed with the rest of the procedure after vessel puncture, as described previously.

5. **Videos on arterial puncture and radial artery catheterization are available on the *New England Journal of Medicine's* website.**
6. **A video on ultrasound-guided radial artery catheterization is available on the *New England Journal of Medicine's* website.**

F. Posterior Tibial and Dorsalis Pedis Artery Puncture

1. **Indications:** Arterial blood sampling when radial artery puncture is unsuccessful or inaccessible.
2. **Complications:** Infection, bleeding, ischemia if circulation is inadequate.
3. **Procedure:**
   a. Posterior tibial artery: Puncture the artery posterior to medial malleolus while holding the foot in dorsiflexion.
   b. Dorsalis pedis artery: Puncture the artery at dorsal midfoot between first and second toes while holding the foot in plantar flexion.

G. Intraosseous (IO) Access[2,3] (Fig. 4.4)

1. **Indications:** Obtain emergency access in children during life-threatening situations. This is very useful during cardiopulmonary arrest, shock, burns, and life-threatening status epilepticus. Any crystalloid, blood product, or drug that may be infused into a peripheral vein may also be infused into the IO space. The IO needle should be removed once adequate vascular access has been established. Insertion of IO needle into fractured bones should be avoided.
2. **Complications:**
   a. Complications are rare, particularly with the correct technique. Frequency of complications increases with prolonged infusions.

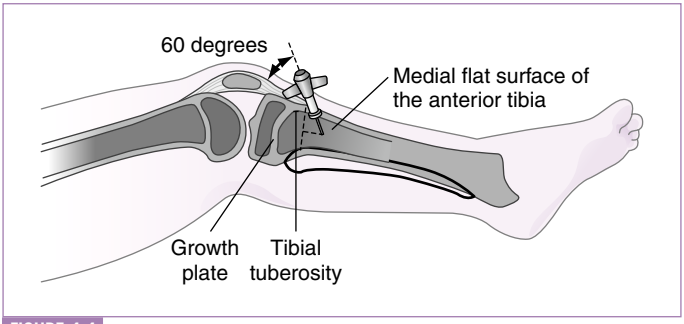

FIGURE 4.4

Intraosseous needle placement using standard anterior tibial approach. Insertion point is in the midline on medial flat surface of anterior tibia, 1 to 3 cm (2 fingerbreadths) below tibial tuberosity. (*From Dieckmann R, Fiser D, Selbst S.* Pediatric Emergency and Critical Care Procedures. *St. Louis: Mosby; 1997.*)

b. Complications include extravasation of fluid from incomplete or through and through cortex penetration, infection, bleeding, osteomyelitis, compartment syndrome, fat embolism, fracture, epiphyseal injury.

3. **Sites of entry (in order of preference):**
   a. Anteromedial surface of the proximal tibia, 2 cm below and 1 to 2 cm medial to the tibial tuberosity on the flat part of the bone.
   b. Distal femur 3 cm above the lateral condyle in the midline.
   c. Medial surface of the distal tibia 1 to 2 cm above the medial malleolus (may be a more effective site in older children).
   d. Proximal humerus, 2 cm below the acromion process into the greater tubercle with the arm held in adduction and internal rotation.
   e. Anterosuperior iliac spine at a 90-degree angle to the long axis of the body.
4. **Procedure:**
   a. Prepare the selected site in a sterile fashion.
   b. If the child is conscious, anesthetize the puncture site down to the periosteum with 1% lidocaine (optional in emergency situations).
   c. Choose between a manual IO or drill-powered IO insertion device:
      (1) For manual IO needle: Insert a 15- to 18-gauge IO needle perpendicular to the skin at an angle away from the epiphyseal plate, and advance to the periosteum. With a boring rotary motion, penetrate through the cortex until there is a decrease in resistance, indicating that you have reached the marrow. The needle should stand firmly without support. Secure the needle carefully.
      (2) For drill-powered IO needle: Enter skin with the needle perpendicular to the skin, as with the manual needle, and press the needle until you meet the periosteum. Then apply easy pressure

while gently depressing the drill trigger until you feel a decrease in resistance. Remove the drill while holding the needle steady to ensure stability prior to securing the needle. Use an EZ-IO AD for patients greater than 40 kg, and use EZ-IO PD for patients greater than 6 kg and less than 40 kg.

d. Remove the stylet and attempt to aspirate marrow. (Note that it is not necessary to aspirate marrow.) Flush with crystalloid solution. Observe for fluid extravasation. Marrow can be sent to determine glucose levels, chemistries, blood types and cross-matches, hemoglobin levels, blood gas analyses, and cultures.
e. Attach standard IV tubing. Increased pressure (through pressure bag or push) may be necessary for infusion. There is a high risk for obstruction if continuous high-pressure fluids are not flushed through the IO needle.

5. **A video on IO catheter placement is available on the *New England Journal of Medicine's* website.**

H. Umbilical Artery and Umbilical Vein Catheterization[2]

1. **Indications:** Vascular access (via umbilical vein [UV]), blood pressure monitoring (via umbilical artery [UA]), or blood gas monitoring (via UA) in critically ill neonates.
2. **Complications:** Infection, bleeding, hemorrhage, perforation of vessel, thrombosis with distal embolization, ischemia or infarction of lower extremities, bowel, or kidney, arrhythmia if catheter is in the heart, air embolus.
3. **Contraindications:** Omphalitis, peritonitis, possible/confirmed necrotizing enterocolitis, intestinal hypoperfusion.
4. **Line placement:**
   a. Umbilical arterial catheter (UAC) line: Low line vs. high line.
      (1) Low line: Tip of catheter should lie just above the aortic bifurcation between L3 and L5. This avoids renal and mesenteric arteries near L1, possibly decreasing the incidence of thrombosis or ischemia.
      (2) High line: Tip of catheter should be above the diaphragm between T6 and T9. A high line may be recommended in infants weighing less than 750 g, in whom a low line could easily slip out.
   b. Umbilical venous catheter (UVC) lines should be placed in the inferior vena cava above the level of the ductus venosus and the hepatic veins and below the level of the right atrium.
   c. Catheter length: Determine the length of catheter required using either a standardized graph based on shoulder-umbilical length or the following birth weight (BW) regression formula:
      (1) UAC Low Line (cm) = BW (kg) × 7
      (2) UAC High Line (cm) = (3 × BW (kg)) + 9
      (3) UVC Length (cm) = 0.5 × UAC high line (cm) + 1.
5. **Procedure for UAC line** (Fig. 4.5):

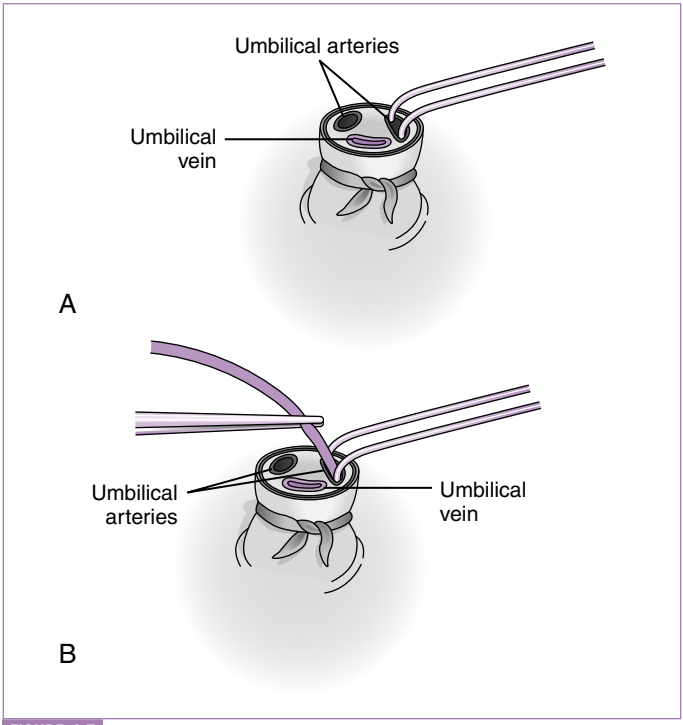

FIGURE 4.5

Placement of umbilical arterial catheter. (A) Dilating lumen of umbilical artery. (B) Insertion of umbilical artery catheter. (*From Dieckmann R, Fiser D, Selbst S*. Pediatric Emergency and Critical Care Procedures. *St. Louis: Mosby; 1997*.)

a. Determine the length of the catheter to be inserted for either high (T6 to T9) or low (L3 to L5) position.
b. Restrain infant. Maintain the infant's temperature during the procedure. Prepare and drape the umbilical cord and adjacent skin using sterile technique.
c. Flush the catheter with sterile saline solution before insertion. Ensure that there are no air bubbles in the catheter or attached syringe.
d. Place sterile umbilical tape around the base of the cord. Cut through the cord horizontally about 1.5 to 2 cm from the skin; tighten the umbilical tape to prevent bleeding.
e. Identify the one large, thin-walled UV and two smaller, thick-walled arteries. Use one tip of open, curved forceps to gently probe and dilate one artery. Then use both points of closed forceps, and dilate artery by allowing forceps to open gently.

f. Grasp the catheter 1 cm from its tip with toothless forceps and insert the catheter into the lumen of the artery. Aim the tip toward the feet and gently advance the catheter to the desired distance. *Do not force.* If resistance is encountered, try loosening umbilical tape, applying steady and gentle pressure, or manipulating the angle of the umbilical cord to the skin. Often the catheter cannot be advanced because of the creation of a "false luminal tract." There should be good blood return when the catheter enters the iliac artery.
g. Confirm catheter tip position with x-ray or ultrasound. Secure catheter with a suture through the cord, a marker tape, and a tape bridge. The catheter may be pulled back but *not* advanced once the sterile field is broken.
h. Observe for complications: Blanching or cyanosis of lower extremities, perforation, thrombosis, embolism, or infection. If any complications occur, the catheter should be removed.
i. Use isotonic fluids containing heparin per institutional policy. Never use hypoosmolar fluids in the UA.

6. **Procedure for UVC line** (see Fig. 4.5):
   a. Determine the desired length and follow steps "a" through "d" for UA catheter placement.
   b. Isolate the thin-walled UV, clear thrombi with forceps, and insert catheter, aiming the tip toward the right shoulder. Gently advance the catheter to the desired distance. *Do not force.* If resistance is encountered, try loosening the umbilical tape, applying steady and gentle pressure, or manipulating the angle of the umbilical cord to the skin. Resistance is commonly met at the abdominal wall and again at the portal system. *Do not* infuse anything into the liver.
   c. Confirm catheter tip position with x-ray or ultrasound. Secure catheter with a suture through the cord, a marker tape, and a tape bridge. The catheter may be pulled back but *not* advanced once the sterile field is broken.
7. **A video on UVC/UAC line placement is available on the *New England Journal of Medicine's* website.**

VI. PULMONARY PROCEDURES

A. Use of Metered-Dose Inhalers and Spacer[6]

1. **Indications**: Delivery of medication to distal airways in the lungs.
2. **Complications**: Failure of medication delivery. **Note** that there are risks associated with the medication rather than the delivery method.
3. **Procedure:**
   a. Shake the inhaler, remove the cap, and attach it to the spacer device.
   b. Instruct the child to exhale completely.
   c. Place the mouthpiece of the spacer into the patient's mouth, and instruct the child to make a complete seal with the lips. Alternatively, a spacer with a mask can be placed over the child's mouth if they are unable to make a seal with their lips.

d. Spray 1 puff from the inhaler into the spacer and instruct the patient to breathe slowly and deeply, holding the breath for 10 seconds.
e. Wait 1 minute and repeat as indicated.

B. Needle Cricothyrotomy[6,14]

1. **Indications**: When an emergency airway is required and the clinician is unable to use bag-mask ventilation or secure an orotracheal or nasotracheal airway. Common indications include facial fractures, blood or vomitus in the airway, airway obstruction (e.g., foreign body, tumor, edema from trauma).
2. **Contraindications**: No absolute contraindications. Relative contraindications include unable to locate landmarks, laryngotracheal damage, coagulopathy, bleeding dyscrasia.
3. **Complications**: Bleeding, hypoxia, pneumothorax, esophageal laceration, vocal cord injury, posterior tracheal wall perforation, infection.
4. **Procedure:**
   a. Immobilize the larynx with the nondominant hand and identify the cricothyroid membrane. This is located by palpating the laryngeal prominence at midline of the thyroid cartilage and then moving distally 1 to 2 cm to a small depression. This depression overlies the cricothyroid membrane.
   b. Insert a 12 to 14-gauge *angiocatheter* caudally at a 30- to 45-degree angle through the cricothyroid membrane while aspirating the needle as it is inserted.
   c. Attach the needle to an oxygen source that can deliver roughly 30 psi. Alternatively, a bag-valve device can be connected using a 7.0 endotracheal tube adapter and a 3 mL syringe with plunger removed.
   d. Intermittent ventilation can be achieved by cutting a small hole in the oxygen tubing, and covering the hole in the tubing. Allow for expiration by uncovering the hole for 4 to 10 seconds.

C. Needle Thoracostomy[2,15]

1. **Indications:** Evacuation of a pneumothorax, hemothorax, chylothorax, large pleural effusion, or empyema for diagnostic or therapeutic purposes.
2. **Complications:** Infection, bleeding, pneumothorax, hemothorax, pulmonary contusion or laceration, puncture of diaphragm, spleen, or liver, or bronchopleural fistula.
3. **Procedure:**
   a. Prepare and drape the skin as clean as possible, with goal of sterility.
   b. Insert a large-bore angiocatheter (14- to 22-gauge based on patient size and likely depth of the chest wall) into the anterior second intercostal space in the midclavicular line. Insert needle over superior aspect of rib margin to avoid neurovascular structures. If the angiocatheter permits, a 3- to 10-mL syringe with 1 to 2 mL of saline can be connected to it. Aspirating the syringe while inserting the IV will pull air bubbles through the saline if an air collection exists. A rush of bubbles signifies successful access.

c. When pleural space is entered, withdraw needle and attach catheter to a three-way stopcock and syringe, and aspirate air. The stopcock is used to stop air flow through the catheter when sufficient evacuation has been performed.
d. Subsequent insertion of a chest tube is often necessary for ongoing release of air. It is advised not to completely evacuate chest prior to placement of chest tube to avoid pleural injury.

4. **A video on needle decompression of spontaneous pneumothorax is available on the *New England Journal of Medicine's* website.**

VII. GASTROINTESTINAL PROCEDURES

A. Nasogastric Tube Placement[6,16]

1. **Indications**: Enteral nutrition, administration of medications, treatment of ileus or obstruction, gastric decompression.
2. **Contraindications**: Esophageal stricture, esophageal varices, severe midface trauma (cribriform plate disruption), bleeding diatheses, alkaline ingestion.
3. **Complications**: Malposition, coiling of tube, esophageal perforation, pneumothorax.
4. **Procedure:**
   a. Approximate the length of 6- to 10-Fr tube insertion by positioning the tube from the nares or mouth to the ear, then to the mid-xyphoid-umbilicus. Mark this length on the tube with marker.
   b. The patient should be sitting as upright as possible. The head should be tilted toward the chest.
   c. Lubricate the tube and insert the tube through the nose. Advance the tube to the length mark, asking the patient to swallow while the tube is inserted. It may be helpful to provide a cup of water with a straw.
   d. Confirm placement of the tube with a radiograph of the lower chest/upper abdomen. Ensure that the tube is located distal to the carina, crosses the diaphragm, and rests in a central position in the gastric region. The tube should not cross the midline. Additional confirmation can be obtained by testing the pH of aspirated contents. A of pH 1 to 4 confirms proper positioning. Alternatively, insert a small amount of air (20 to 30 mL) through the tube while listening to the gastric area with a stethoscope.
   e. Secure the tube.

B. Gastrostomy Tube Replacement[6,17]

1. **Indications**: Dislodged, blocked, or replacement of gastrostomy tube (G-tube) or gastrostomy button.
2. **Complications**: Perforation, bleeding, pneumoperitoneum, creation of "false track" particularly if tube is newly placed. **Note** that misplacement and associated complications are rare for children with a mature G-tube track undergoing tube replacement in a pediatric emergency room.

3. **Procedure:**
   a. Deflate balloon completely with a syringe and pull the tube out steadily.
   b. Insert new tube in the stoma and inflate balloon fully with water. Gently tug on the tube to assess whether the balloon is inflated. Secure the tube.
   c. Confirm intragastric placement by aspirating gastric contents.
   d. If replacement tube is not immediately available, a Foley catheter of similar size may be placed using the method above to maintain tract patency.
   e. If the G-tube track is too constricted for placement of G-tube, consider upsizing with Foley catheter serial dilation.
4. **A video on gastrostomy tube exchange is available on the *New England Journal of Medicine's* website.**

VIII. GENITOURINARY PROCEDURES

A. Urinary Bladder Catheterization[3,6,18]

1. **Indications:** To obtain urine for urinalysis and sterile culture, to accurately monitor hydration status, and bladder decompression.
2. **Complications:** Hematuria, infection, trauma to urethra or bladder, intravesical knot of catheter (rarely occurs).
3. **Contraindications:** Pelvic fractures, known trauma to the urethra, or blood at the meatus.
4. **Catheter Selection**: 5 Fr for children younger than 6 months; 8 Fr for children between 6 months and adolescence; 10 Fr for adolescents.
5. **Procedure:**
   a. For collection of urinalysis and/or urine culture, the infant/child should not have voided within 1 hour of procedure.
   b. Prepare the urethral opening using sterile technique.
   c. In males, apply gentle traction to the penis to straighten the urethra. In uncircumcised male infants, expose the meatus with gentle retraction of the foreskin. The foreskin has to be retracted only far enough to visualize the meatus.
   d. In girls, the urethral orifice may be difficult to visualize, but it is usually immediately superoanterior to the vaginal orifice.
   e. Gently insert a lubricated catheter into the urethra. Slowly advance catheter until resistance is met at the external sphincter. Continued pressure will overcome this resistance, and the catheter will enter the bladder. Only a few centimeters of advancement are required to reach the bladder in girls. In boys, insert a few centimeters longer than the shaft of the penis.
   f. Carefully remove the catheter once specimen is obtained, and cleanse skin of iodine.
   g. If indwelling Foley catheter is inserted, inflate balloon with sterile water or saline as indicated on bulb, then connect catheter to drainage tubing attached to urine drainage bag. Secure catheter tubing to inner thigh.

6. **Videos on catheterization of the male urethra and catheterization of the female urethra are available on the *New England Journal of Medicine's* website.**

B. Suprapubic Bladder Aspiration[2]

1. **Indications:** To obtain urine in a sterile manner for urinalysis and culture in children younger than 2 years (avoid in children with genitourinary tract anomalies, coagulopathy, or intestinal obstruction). This bypasses distal urethra, thereby minimizing risk for contamination.
2. **Complications:** Infection (cellulitis), hematuria (usually microscopic), intestinal perforation.
3. **Procedure** (Fig. 4.6):
   a. Anterior rectal pressure in girls or gentle penile pressure in boys may be used to prevent urination during the procedure. Child should not have voided within 1 hour of procedure.
   b. Restrain child in the supine, frog leg position. Prepare suprapubic area in a sterile fashion.
   c. The site for puncture is 1 to 2 cm above the symphysis pubis in the midline. Use a syringe with a 22-gauge, 1-inch needle, and puncture at a 10- to 20-degree angle to the perpendicular, aiming slightly caudad.
   d. Ultrasound guidance:
      (1) Ultrasound can be used to visualize the urinary bladder for this procedure as follows: Use the curvilinear or linear probe. Apply the probe in transverse position in the midline of the lower abdomen, positioning it to locate the bladder. The bladder is a midline structure with a dark center and bright margins. The shape of the bladder is usually rounded; however, it can appear spherical, pyramidal, or even cuboidal (Fig. 4.7).
      (2) The bladder may be empty as well with no dark cavity. If no clear structure, give fluids and reassess in 30 minutes. This technique can also be used in the evaluation of anuric patients, to differentiate between decreased urine production and urinary retention. This is also useful in the case of patients with a urinary catheter as the catheter is usually visible. If it is visualized and the bladder also has urine around it, the catheter is likely malfunctioning.
      (3) Aspiration can be performed after marking the site with ultrasound, proceeding with preparing and draping the patient and proceeding to puncture.
   e. **Gently exert suction as the needle is advanced until urine enters syringe.** The needle should not be advanced more than 3 cm. Aspirate urine with gentle suction.
   f. Remove needle, cleanse skin of iodine, and apply a sterile bandage.
4. **A video of suprapubic bladder aspiration is available on the *New England Journal of Medicine's* website.**

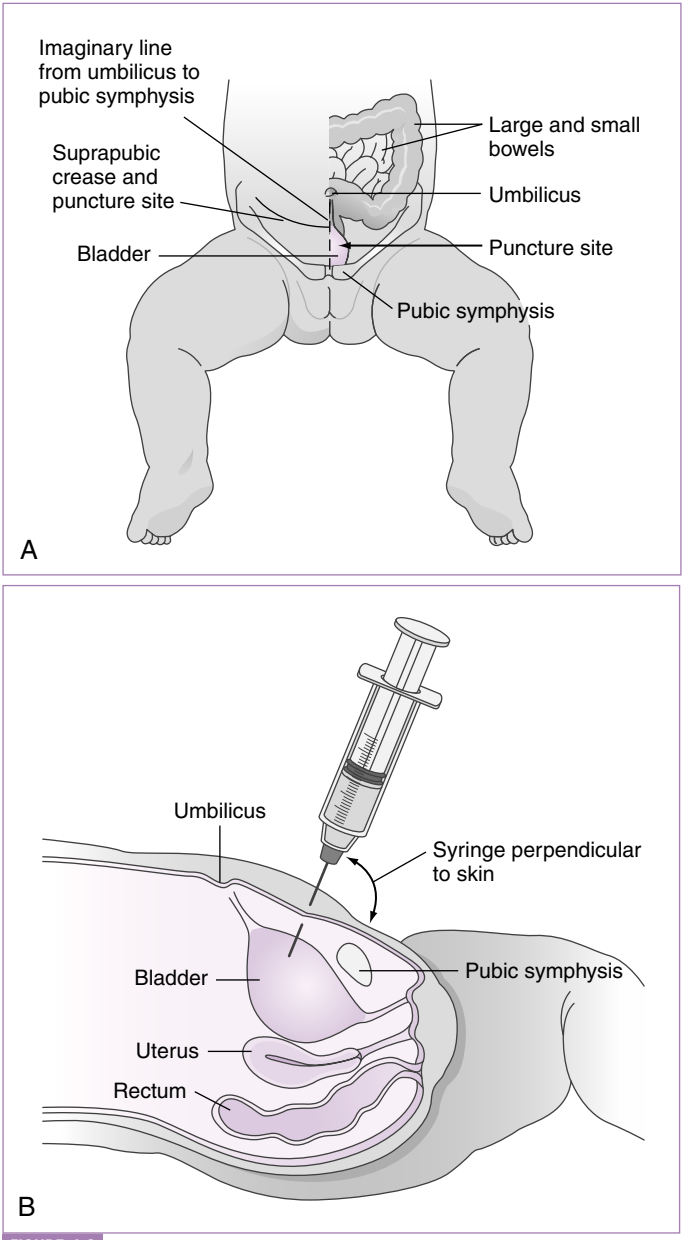

FIGURE 4.6

Landmarks for suprapubic bladder aspiration. (*Modified from Dieckmann R, Fiser D, Selbst S.* Pediatric Emergency and Critical Care Procedures. *St. Louis: Mosby; 1997.*)

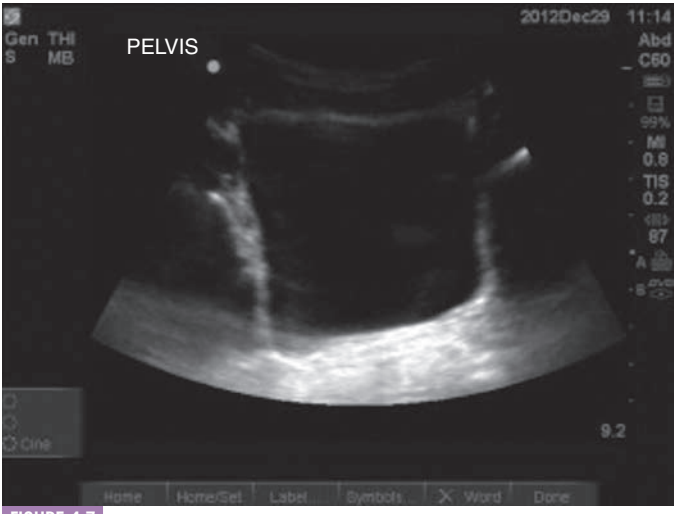

FIGURE 4.7
Ultrasound of bladder. In this transverse midline view of the pelvis the bladder appears black (anechoic) and cuboid in the midline. This is the typical appearance of a full bladder on ultrasound, although the shape may vary. (*From Leeson K, Leeson B. Pediatric ultrasound: applications in the emergency department.* Emerg Med Clin North Am. *2013;31(3):809–829.*)

IX. MUSCULOSKELETAL PROCEDURES

A. Basic Splinting[2]

1. **Indications:** To provide short-term stabilization of limb injuries while accommodating swelling associated with acute injuries.
2. **Complications:** Pressure sores, dermatitis, neurovascular impairment.
3. **Procedure:**
   a. Determine style of splint needed (see Section IX.B).
   b. Measure and cut fiberglass or plaster to appropriate length. If using plaster, upper-extremity splints require 8 to 10 layers and lower-extremity splints require 12 to 14 layers.
   c. Pad extremity with copious cotton roll padding, taking care to overlap each turn by 50%. In prepackaged fiberglass splints, additional padding is not generally required. Bony prominences may require additional padding. Place cotton between digits if they are in a splint.
   d. Immerse plaster slabs into room temperature water until bubbling stops. Smooth out wet plaster slab, avoiding any wrinkles. Fiberglass splints will harden when exposed to air; however, application of a small amount of room temperature water can accelerate this process.
   e. Position splint over extremity and mold to desired contour. Wrap with an elastic bandage to hold molded splint onto extremity in position of

function. Continue to hold desired form of splint upon extremity until fully hardened.

f. **NOTE:** Plaster becomes warm while drying. Using warm water will decrease drying time. This may result in inadequate time to mold splint. Turn edge of the splint back on itself to produce a smooth surface. Take care to cover the sharp edges of fiberglass.

g. Use crutches or slings as indicated.

h. The need for orthopedic referral should be individually assessed.

i. Emergent orthopedic referral may be required, including when there is concern for neurovascular compromise or compartment syndrome of the affected extremity.

4. **Postsplint Care:**
   a. Standard rest, ice, and elevation of affected extremity should be performed.
   b. Avoid weight bearing on splinted extremity.
   c. Do not get splint wet. Splints can be wrapped in water-resistant items such as a plastic bag or a specially designed splint bag to allow for showering. Use a hair dryer in instances where the splint has accidentally gotten wet.
   d. Do not stick items such as a pen or clothes hanger to scratch inside the splint.
   e. If areas in or distal to the splint develop numbness, tingling, increased pain, turn blue or pale, or become swollen, patient should loosen the elastic bandage of the splint. Instruct to seek immediate medical care if this does not quickly (<30 minutes) resolve these symptoms.
5. **A video on basic splinting techniques is available on the *New England Journal of Medicine's* website.**

B. Selected Splints and Indications (Fig. 4.8)

1. **Long Arm Posterior Splint**
   a. Indications: Immobilization of elbow and forearm injuries.
   b. Procedure: Elbow flexed at 90 degrees, forearm in neutral position, slight dorsiflexion of the wrist. Splint extends from palmar crease of the hand to mid upper arm along the ulnar side of the forearm and the posterior aspect of the humerus. Width should be semicircumferential.
2. **Sugar Tong Forearm Splint**
   a. Indications: For distal radius and wrist fractures; to immobilize the elbow and minimize pronation and supination.
   b. Procedure: Elbow flexed at 90 degrees, forearm in neutral position, and slight dorsiflexion of the wrist. Splint extends from palmar crease along volar aspect of forearm, around elbow, and dorsally to the metacarpals. Fingers and thumb remain free. Width should support arm on both sides but not overlap.
3. **Ulnar Gutter Splint**
   a. Indications: Nonrotated fourth or fifth (boxer) metacarpal metaphyseal fracture with less than 20 degrees of angulation, uncomplicated fourth and fifth phalangeal fracture.

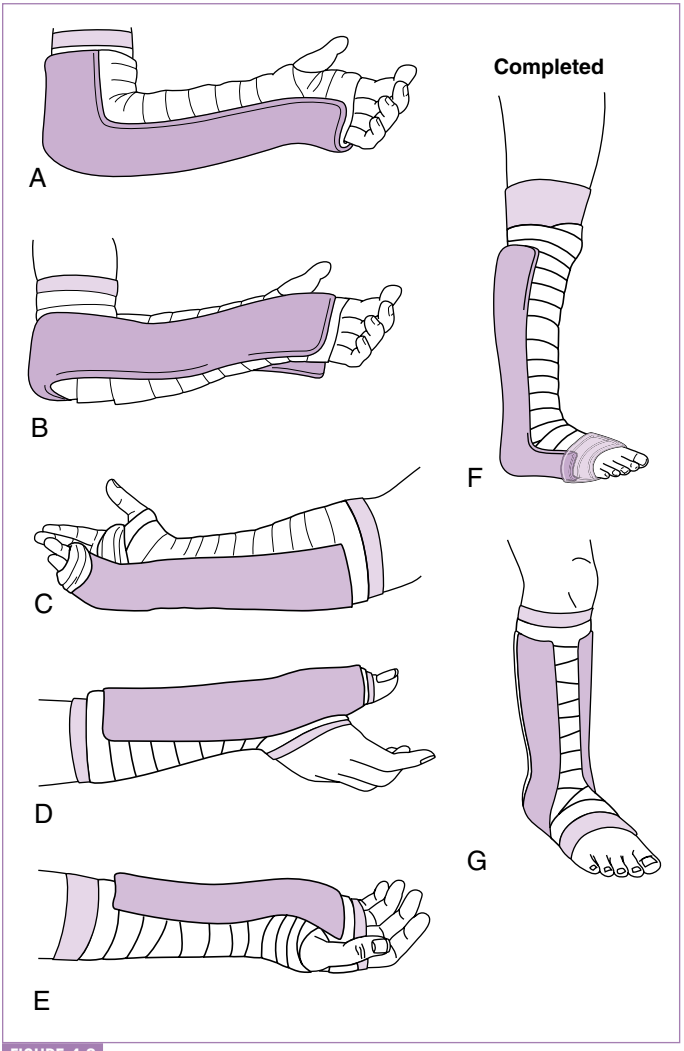

FIGURE 4.8

Selected splint types. Light purple layer is stockinette, white layer is cotton roll, dark purple layer is the splint. (A) Long arm posterior splint. (B) Sugar tong forearm splint. (C) Ulnar gutter splint. (D). Thumb spica splint. (E) Volar splint. (F) Posterior ankle splint. (G) Ankle stirrup splint.

b. Assess for malrotation, displacement (especially Salter I type fracture), angulation, and joint stability before splinting.
c. Procedure: Elbow in neutral position, wrist in slight dorsiflexion, metacarpophalangeal (MP) joint at 60 to 90 degrees, interphalangeal (IP) joint at 20 degrees. Apply splint in U shape from the tip of the fifth digit to 3 cm distal to the volar crease of the elbow. Splint should be wide enough to enclose the fourth and fifth digits.

4. **Thumb Spica Splint**
   a. Indications: Nonrotated, nonangulated, nonarticular fractures of the thumb metacarpal or phalanx, ulnar collateral ligament injury (gamekeeper's or skier's thumb), scaphoid fracture or suspected scaphoid fracture (pain in anatomic snuff box).
   b. Procedure: Wrist in slight dorsiflexion, thumb in some flexion and abduction, IP joint in slight flexion. Apply splint in U shape along radial side of forearm extending from tip of thumb to mid-forearm. Mold the splint along the long axis of the thumb so that thumb position is maintained. This will result in a spiral configuration along the forearm with maintained apposition of the index finger and thumb.
5. **Volar Splint**
   a. Indications: Wrist immobilization for wrist sprains, strains, or certain fractures.
   b. Procedure: Wrist in slight dorsiflexion. Apply splint on palmar surface from the MP joint to 2 to 3 cm distal to the volar crease of the elbow. It is useful to curve the splint to allow the MP joint to rest at an 80- to 90-degree angle.
6. **Posterior Ankle Splint**
   a. Indications: Immobilization of ankle sprains and fractures of the foot, ankle, and distal fibula.
   b. Procedure: Place patient in prone position with ipsilateral knee flexed at 90 degrees and affected ankle held in flexion at 90 degrees. Splint should extend from base of toes to upper portion of the calf. Width should match that of the foot. An ankle stirrup (sugar tong) splint can be added to increase stability for ankle fractures.
7. **Ankle Stirrup Splint**
   a. Indications: Immobilization of the ankle.
   b. Procedure: Ankle held in flexion at 90 degrees. Splint extends in U-shaped fashion from fibular head underneath the ankle to just below the knee. Width should be one half of the narrowest circumference of the lower leg and not overlapping. May be used alone or in combination with (placed after) posterior ankle splint.

C. Radial Head Subluxation (Nursemaid's Elbow) Reduction[19]

1. **Presentation:** Commonly occurs in children aged 1 to 4 years with a history of inability to use an arm after it was pulled. Child presents with affected arm held at the side in pronation, with elbow slightly flexed.

2. **Caution:** Rule out a fracture clinically before doing procedure. Consider radiograph if mechanism of injury or history is atypical or if exam is concerning for fracture (swelling, bruising, tenderness, etc.).
3. **Procedure:**
   a. Two most common techniques include hyperpronation (HP) and traditional supination-flexion (SF) maneuvers. Recent meta-analyses of randomized trials evaluating the two techniques favor HP for both efficacy and pain tolerance.
   b. Support the elbow with one hand, and place your thumb laterally over the radial head at the elbow applying pressure medially. With your other hand, grasp the child's hand in a handshake position or at the wrist. The child's thumb should point downward.
   c. HP method: Forcefully pronate the wrist. You may feel a click as reduction occurs.
   d. SF method: Quickly and deliberately supinate and externally rotate the forearm, and simultaneously flex the elbow.
   e. Most children will begin to use the arm within 15 minutes, some immediately after reduction. If reduction occurs after a prolonged period of subluxation, it may take the child longer to recover use of the arm. In this case, the arm should be immobilized with a posterior splint.
   f. If procedure is unsuccessful, consider obtaining a radiograph. Maneuver may be repeated if needed.
4. **A video on reduction of nursemaid's elbow is available on the *New England Journal of Medicine's* website.**

D. Finger/Toe Dislocation Reduction[2]

1. **Indications:** IP and MP/metatarsophalangeal dislocations.
2. **Complications:** Fracture of phalanges, entrapment of neurovascular structures.
3. **Cautions:** Volar dislocations and dorsal dislocations with interposition of the volar plate or entrapment of the metacarpal/metatarsal head often cannot be performed using closed reduction.
4. **Procedure:**
   a. Evaluate for neurovascular compromise in the affected digit. Perform radiographs to evaluate for possible fracture.
   b. Consider procedural sedation or a digital block prior to procedure.
   c. Grasp the digit proximal to fracture to allow for stabilization.
   d. Grasp the tip of the distal digit and apply longitudinal traction, with the joint typically slipping into place.
   e. Alternatively, grasp the distal phalanx and mildly hyperextend to accentuate the deformity while applying longitudinal traction.
   f. After reduction, again evaluate neurovascular status and obtain radiographs to ensure proper position and to further evaluate for fracture.
   g. Immobilize the joint using a padded splint using full extension for distal IP joints and 20 to 30 degrees of flexion for proximal IP joints.

E. Knee Arthrocentesis[2]

1. **Indications:** Evaluation of fluid for the diagnosis of disease, including infectious, inflammatory, and crystalline disease, and removal of fluid for relief of pain and/or functional limitation.
2. **Contraindications:** Bleeding diathesis, local fracture, overlying skin infection.
3. **Complications:** Pain, bleeding, infection.
4. **Procedure:**
   a. Place child supine on exam table with knee in slight flexion, with use of a padded roll underneath the knee for support, if unable to slightly flex.
   b. The lateral or medial approach can be made, with the lateral approach preferred to avoid the vastus medialis muscle.
   c. The puncture point should be at the posterior margin of the patella in both cases.
   d. Prepare the overlying skin in a sterile fashion, and once cleaned, numb the area using 1% lidocaine with a small-gauge needle. Then, using an 18-gauge needle attached to a syringe, puncture the skin at a 10- to 20-degree downward angle, and advance under continuous syringe suction until fluid is withdrawn, indicating entry into the joint space.
   e. In large effusions, several syringes may be needed for complete fluid removal if so desired, and the needle may have to be redirected to access pockets of fluid.
   f. Upon completion, withdraw the needle and cover the wound with a sterile gauze dressing.
   g. Synovial fluid can then be sent for studies as indicated.
5. **A video on knee arthrocentesis is available on the *New England Journal of Medicine's* website.**

F. Hematoma Blocks[20]

1. **Indications:** Analgesia for closed fracture of the extremity that requires manipulation or closed reduction. It is an alternative when procedural sedation is not possible or is impractical.
2. **Contraindications:** Allergic reactions to local anesthetic agents, open fracture, cellulitis overlying fracture site, presence of a neurovascular deficit or vascular deficit.
3. **Complications:** Rare, but include compartment syndrome, local anesthetic toxicity (circumoral and tongue numbness, dizziness, tinnitus, and visual disturbances), and osteomyelitis.
4. **Procedure:**
   a. Perform using aseptic technique.
   b. Draw up the local anesthetic solution into a syringe with a 22- or 23-gauge, 2-inch-long needle. Bupivacaine, for postprocedure analgesia, is desired and can be used alone or mixed with lidocaine in a 50:50 ratio. (See Chapter 6 for dosage maximum.)
   c. Place a wheal of 1% lidocaine subcutaneously over the fracture site. Allow 1 to 2 minutes for the anesthetic to take effect.

d. Slowly insert and advance the needle attached to the local anesthetic solution through the skin wheal and aimed at the fracture site. C-arm fluoroscopy can aid fracture/hematoma localization. Slowly advance the needle.
   (1) Aspirate with the syringe to **ensure there is no free flow of blood**, which indicates that the needle is within a blood vessel**.** If there is free blood flow, do not inject the local anesthetic solution.
   (2) A flash, without flow, of blood indicates entry of the tip of the needle into the hematoma.
   (3) Redirect needle if you strike bone or if no flash of blood is returned.
e. Once flash, without flow, is obtained, slowly inject the local anesthetic solution into the hematoma.
f. Reposition the needle to different areas within the hematoma and inject small amounts of the local anesthetic into each area. This technique distributes the local anesthetic solution to increase the efficacy of the hematoma block and minimizes the risk of intravascular injection of the entire dose of local anesthetic.
g. Withdraw the needle, apply a bandage to the skin puncture site, and await analgesia.

X. SKIN/DERMATOLOGIC PROCEDURES

A. Immunization and Medication Administration[3]

NOTE: Please see Chapters 16 and 30 for relevant vaccines and medications and their appropriate administration routes.

1. **Subcutaneous Injections**
   a. **Indications**: Immunizations and medications.
   b. **Complications**: Bleeding, infection, allergic reaction, lipohypertrophy or lipoatrophy after repeated injections.
   c. **Procedure:**
      (1) Locate injection site: Upper outer arm or outer aspect of upper thigh.
      (2) Cleanse skin with alcohol.
      (3) Insert 0.5-inch, 25- or 27-gauge needle into subcutaneous layer at a 45-degree angle to the skin. Aspirate for blood, if none present, inject medication/immunization.
2. **Intramuscular (IM) Injections**
   a. **Indications**: Immunizations and other medications.
   b. **Complications**: Bleeding, infection, allergic reaction, nerve injury.
   c. **Cautions**
      (1) Avoid IM injections in a child with a bleeding disorder or thrombocytopenia.
      (2) Maximum volume to be injected is 0.5 mL in a small infant, 1 mL in an older infant, 2 mL in a school-aged child, and 3 mL in an adolescent.

d. **Procedure**
   (1) Locate injection site: Anterolateral upper thigh in smaller child or outer aspect of upper arm (deltoid) in older one. The dorsal gluteal region is less commonly used because of risk for nerve or vascular injury. To find the ventral gluteal site, form a triangle by placing your index finger on the anterior iliac spine and your middle finger on the most superior aspect of the iliac crest. The injection should occur in the middle of the triangle formed by the two fingers and the iliac crest.
   (2) Cleanse skin with alcohol.
   (3) Pinch muscle with free hand, and insert 1-inch, 23- or 25-gauge needle until hub is flush with skin surface. For deltoid and ventral gluteal muscles, needle should be perpendicular to skin. For anterolateral thigh, needle should be at a 45-degree angle to the long axis of the thigh. Aspirate for blood; if none present, inject medication.

B. Basic Laceration Repair[2]

1. **Wound Irrigation**[21,22]: Numerous studies, including a large Cochrane review, conclude that there is no difference in the infection rates of wounds irrigated with either tap water or sterile NS. The volume of irrigation depends on the location and size of the wound; 100 mL/1 cm of laceration is a good approximation for relatively uncontaminated wounds.
2. **Suturing:**
   a. **Basic Suturing Technique** (Fig. 4.9):
      (1) Simple interrupted: Basic closure of most uncomplicated wounds.
      (2) Horizontal mattress: Provides eversion of wound edges.
      (3) Vertical mattress: For added strength in areas of thick skin or areas of skin movement; provides eversion of wound edges.
      (4) Running intradermal: For cosmetic closures.
      (5) Deep dermal: For bringing together deeper portions of wounds with dissolving sutures to allow improved approximation and closure of superficial surfaces.
   b. **Procedure:**
      (1) See Tables 4.1–4.3 for sutures material, size, and time for removal.[23]
      (2) **NOTE:** Lacerations of the face, lips, hands, genitalia, mouth, or periorbital area may require consultation with a specialist. Ideally, lacerations at increased risk for infection (areas with poor blood supply, contaminated, or crush injury) should be sutured within 6 hours of injury. Clean wounds in cosmetically important areas may be closed up to 24 hours after injury in the absence of significant contamination or devitalization. In general, bite wounds should not be sutured except in areas

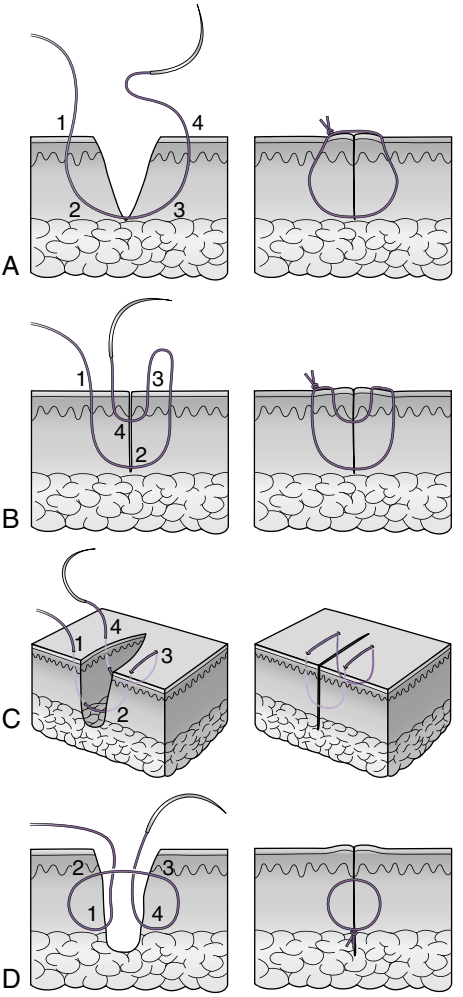

FIGURE 4.9

A–D, Suture techniques. (A) Simple interrupted. (B) Vertical mattress. (C) Horizontal mattress. (D) Deep dermal. (*Modified from Srivastava D, Taylor RS. Suturing technique and other closure materials. In: Robinson JK, Hanke CW, Siegel DM, et al., eds.* Surgery of the Skin. *3rd ed. Elsevier: Philadelphia, PA; 2015:193–213.*)

of high cosmetic importance (face) or if significant gaping is present. These wounds can be closed loosely to aid in healing by secondary intention. The longer sutures are left in place, the greater potential for scarring and infection. Sutures in

TABLE 4.1

GUIDELINES FOR SUTURE MATERIAL, SIZE, AND REMOVAL[23]

Body Region	Nonabsorbable	Absorbable	Duration (Days)
Scalp	5–0 or 4–0	4–0	5–7
Face	6–0	5–0	3–5
Eyelid	7–0 or 6–0	—	3–5
Eyebrow	6–0 or 5–0	5–0	3–5
Trunk	5–0 or 4–0	3–0	5–7
Extremities	5–0 or 4–0	4–0	7–10
Joint surface	4–0	—	10–14
Hand	5–0	5–0	7
Foot sole	4–0 or 3–0	4–0	7–10

TABLE 4.2

CHARACTERISTICS OF COMMON ABSORBABLE SUTURES[23]

Material	Type	Tensile Strength	Absorption Time (Weeks)	Uses
Vicryl	Braided	75% at 14 days 50% at 21 days 5% at 30 days	8–10	Subcutaneous closure, vessel ligature
Vicryl rapide	Braided	50% at 5 days 0 at 14 days	6	Mucosa, dermis
Surgical gut plain	Twisted	Poor at 7–10 days	6–8	Subcutaneous closure
Surgical gut chromic	Twisted	Poor at 21–23 days	8–10	Subcutaneous closure
Monocryl	Monofilament	60%–70% at 7 days 30%–40% at 14 days	13–17	Subcuticular

TABLE 4.3

CHARACTERISTICS OF COMMON NONABSORBABLE SUTURES[23]

Material	Type	Tensile Strength
NYLON (USED FOR SKIN CLOSURE)		
Ethilon	Monofilament	20% per year
Dermalon	Monofilament	20% per year
Surgilon	Braided	Good
Nurolon	Braided	Good
POLYPROLENE (USED FOR SCALP, EYEBROWS)		
Prolene	Monofilament	Permanent
Surgilene	Monofilament	Permanent

cosmetically sensitive areas should be removed as soon as possible. Sutures in high tension areas (e.g., extensor surfaces) should stay in longer.

(3) Prepare child for procedure with appropriate sedation, analgesia, and restraint. Utilize Child Life or age-appropriate distraction.

(4) Anesthetize the wound with topical anesthetic or with lidocaine mixed with bicarbonate (with or without epinephrine) by injecting the anesthetic into the subcutaneous tissues (see Chapter 6).
(5) Forcefully irrigate the wound as per above. This is the most important step in preventing infection.
(6) Prepare and drape the patient for a sterile procedure.
(7) Débride the wound when indicated. Probe for foreign bodies as indicated. Consider obtaining a radiograph if a radiopaque foreign body is suspected.
(8) Select suture type for percutaneous closure (see Tables 4.1–4.3).
(9) Match layers of injured tissues. Carefully match the depth of the bite taken on each side of the wound when suturing. Take equal bites from both wound edges. Apply slight thumb pressure on the wound edge as the needle is entering the opposite side. Pull the sutures to approximate wound edges but not too tightly, to avoid tissue necrosis. In delicate areas, sutures should be approximately 2 mm apart and 2 mm from the wound edge. Larger bites are acceptable where cosmesis is less important.[2]
(10) When suturing is complete, apply topical antibiotic and sterile dressing. If laceration is in proximity of a joint, splinting of the affected area to limit mobility often speeds healing and prevents wound dehiscence.
(11) Check wounds at 48 to 72 hours in cases where wounds are of questionable viability, if wound was packed, or for patients prescribed prophylactic antibiotics. Change dressing at checkup.
(12) For hand lacerations, close skin only; do not use subcutaneous stitches. Elevate and immobilize the hand. Consider consulting a hand or plastics specialist.
(13) Consider the need for tetanus prophylaxis (see Chapter 16).

c. **A video on basic laceration repair is available on the *New England Journal of Medicine's* website**

3. **Skin Staples**
   a. **Indications:**
      (1) Best for scalp, trunk, extremity lacerations.
      (2) More rapid application than sutures, but can be more painful to remove.
      (3) Lower rates of wound infection.
   b. **Contraindications:**
      (1) Not for areas that require meticulous cosmesis.
      (2) Avoid in patients who require magnetic resonance imaging (MRI) or CT.
   c. **Procedure:**
      (1) Apply topical anesthetic, as above. Injection of lidocaine is not routinely used when using staples.
      (2) Clean and irrigate wound, as with suturing.

(3) Appose wound edges, press stapler firmly against skin at center of apposed edges, and staple.
(4) Apply antibiotic ointment and sterile bandage.
(5) Left in place for the same length of time as sutures (see Table 4.1).
(6) To remove, use dedicated staple remover.

4. **Tissue Adhesives**[24]
   a. **Indications:**
      (1) For use with superficial lacerations with clean edges.
      (2) Excellent cosmetic results, ease of application, and reduced patient anxiety.
      (3) Lower rates of wound infection.
   b. **Contraindications:**
      (1) Not for use in areas under large amounts of tension (e.g., hands, joints).
      (2) Use caution with areas near the eye or over areas with hair such as the eyebrow.
   c. **Procedure:**
      (1) Use pressure to achieve hemostasis and clean the wound as explained previously.
      (2) Hold together wound edges.
      (3) Apply adhesive dropwise along the wound surface, avoiding applying adhesive to the inside of the wound. Hold in place for 20 to 30 seconds.
      (4) If the wound is misaligned, remove the adhesive with forceps and reapply. Petroleum jelly or similar substance can aid in removal of skin adhesive.
      (5) Adhesive will slough off after 7 to 10 days.
      (6) Antibiotic ointments or other creams/lotions should not be applied to the adhesive, as this can cause premature loosening of the glue and subsequent wound dehiscence.

C. Incision and Drainage (I&D) of Abscess[2]

1. **Indications:** Diagnostic and therapeutic drainage of soft tissue abscess.
2. **Complications:** Inadequate abscess drainage, local tissue injury, pain, scar formation, and, in rare cases, fistula formation. Consider specialized surgical evaluation for abscesses in cosmetically or anatomically sensitive areas such as the face, breast, or the anogenital region.
3. **Ultrasound Identification:** Ultrasound imaging can be used to differentiate cellulitis from abscess.
   a. Use a linear probe, place the probe over the area of interest, and scan it systematically such that the entire area of interest is examined.
   b. Cellulitis characteristics on ultrasound:
      (1) Increased edema; tissue may appear slightly darker, and will have distorted, indistinct margins.
      (2) Areas may have a “cobblestone” appearance caused by edema (Fig. 4.10).

c. Abscess characteristics on ultrasound:
   (1) Dark fluid collection distinct from surrounding tissue (see Fig. 4.10).
   (2) Often round or oval in shape.
   (3) Doppler can help to distinguish between lymph nodes and fluid collections.

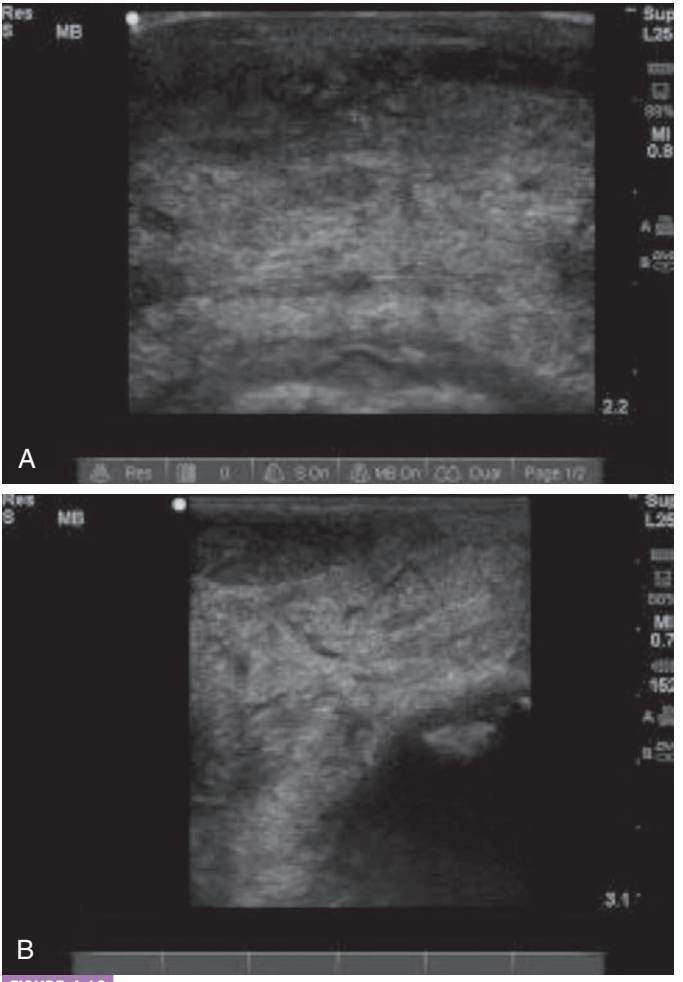

FIGURE 4.10
Ultrasound characteristics of soft tissue cellulitis and abscess. (A) Cellulitis characterized by bright (hyperechoic) tissue due to edema and inflammation in the tissue. (B) This image demonstrates the classic "cobblestone" appearance which is a later ultrasound finding in cellulitis.

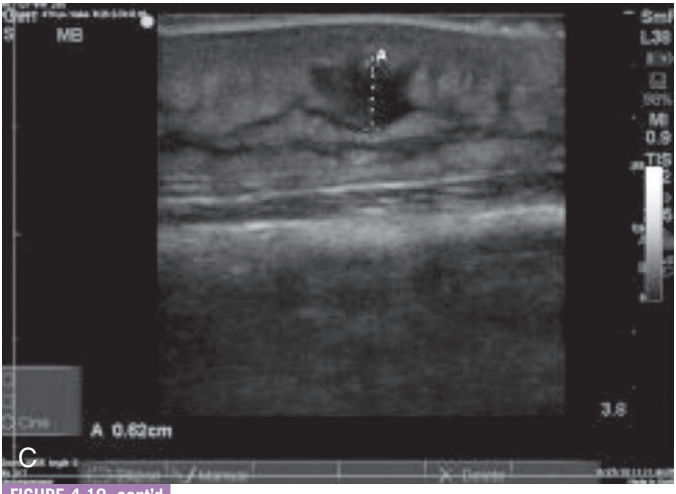

FIGURE 4.10, cont'd

(C) A black (anechoic) rounded structure is noted in the soft tissue, which is characteristic of a soft tissue abscess. Some abscesses may appear dark gray depending on the characteristics of the fluid within the abscess. (*From Leeson K, Leeson B. Pediatric ultrasound: applications in the emergency department.* Emerg Med Clin North Am. *2013;31(3):809–829.*)

4. **Procedure:**
   a. Consider procedural sedation based upon the child's expected tolerance of the procedure and the location/size/complexity of the abscess.
   b. Apply topical anesthetic cream to the abscess to numb superficial epidermis (see Chapter 6).
   c. Prepare the overlying skin in a sterile fashion, and once cleaned, numb the area using 1% lidocaine and a small gauge needle, performing first a circumferential field block of the abscess area followed by direct injection to the planned incision site.
   d. Incise the skin over the abscess down to the superficial fascia using a scalpel blade, cutting parallel to the natural crease of the skin, if present.
   e. Using a hemostat, bluntly widen and undermine the incision to break up any septations or loculated fluid collections. Vigorously irrigate the wound using sterile saline to improve removal of purulent material.
   f. If desired, introduce a sterile packing strip into the wound using a hemostat, making sure to fill in an outside-to-inside pattern without overfilling.

g. Leave a 2- to 3-cm tail outside the wound to facilitate removal and cover the wound with an absorbent dressing. Packing material should be removed in 1 to 2 days with a minimum of daily dressing changes until healed.
h. Consider starting antibiotics that cover staphylococcus and streptococcal species per local guidelines and resistance patterns.

5. **A video on I & D of Abscesses is available on the *New England Journal of Medicine's* website.**

D. Soft Tissue Aspiration[25]

1. **Indications:** Cellulitis that is unresponsive to initial standard therapy, recurrent cellulitis or abscesses, immunocompromised patients in whom organism recovery is necessary and may affect antimicrobial therapy.
2. **Complications:** Pain, infection, bleeding.
3. **Procedure:**
   a. Select site to aspirate at the point of maximal inflammation (more likely to increase recovery of causative agent than leading edge of erythema or center).
   b. Cleanse area in a sterile fashion.
   c. Local anesthesia with 1% lidocaine is optional.
   d. Fill tuberculin syringe with 0.1 to 0.2 mL of *nonbacteriostatic* sterile saline, and attach to needle.
   e. Using 18- or 20-gauge needle (22-gauge for facial cellulitis), advance to appropriate depth, inject saline, aspirate fluid, and apply negative pressure while withdrawing needle.
   f. Send fluid from aspiration for Gram stain and cultures. If no fluid is obtained, needle can be streaked on agar plate. Consider acid-fast bacillus (AFB) and fungal stains in immunocompromised patients.

E. Tuberculin Skin Test Placement[26]

1. **Indications**: Concern for exposure to tuberculosis.
2. **Contraindications**: History of severe reactions to prior placements (e.g., necrosis, anaphylactic shock, ulcerations). **Note** that there is no contraindication for any other individuals including infants, children, pregnant women, or persons who have been vaccinated with bacille Calmette-Guérin (BCG). Note that although a tuberculin skin test (TST) may be placed on the same day as a receiving a live vaccine, a TST must otherwise be placed 4 to 6 weeks after administration of a live vaccine (if not placed that same day).
3. **Complications**: Soreness, necrosis.
4. **Procedure**: Inject 0.1 mL of tuberculin purified protein derivative (PPD) with a tuberculin syringe (bevel up) into the forearm at a 5- to 15-degree angle. The bevel should be visible just below the skin surface. The injection should produce a pale elevation of the skin 6 to 10 mm in diameter.

5. **Follow-Up**: A TST should be read between 48 and 72 hours after administration. The reaction is measured across the forearm (perpendicular to the long axis) in millimeters of induration (palpable, raised, hardened area or swelling). Do not measure erythema.
6. **Interpretation**: see Chapter 17.

F. Tick Removal[27]

1. **Indications**: Visualization of tick. Urgent removal is essential, as the risk of Lyme disease transmission significantly increases after 24 hours of attachment with the risk highest at 48 to 72 hours.
2. **Complications**: Retention of tick fragments (particularly mouthparts), infection, granuloma formation.
3. **Procedure**: Only the use of blunt, medium-tipped, angled forceps or protected fingers have been shown to result in effective removal of ticks.
   a. Use blunt forceps to grasp the tick at the skin surface. Lift up firmly, applying steady pressure and without a twisting motion. Take care to not squeeze the body of the tick, because its fluid may leak infectious material.
   b. Apply antiseptic solution to the attachment site and provide patients with signs and symptoms of both local and systemic illness.

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A complete list of references can be found online at www.expertconsult.com.

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XI. ONLINE CONTENT

A. Ultrasound-Guided Lumbar Puncture

1. Use the linear probe. Before preparing the patient, obtain a transverse view of the spine perpendicular to its axis. In the transverse view, identify the anatomic midline by locating the spinous process. The periosteum of the spinous process will appear as a hyperechoic, rounded structure with dark, posterior shadowing. Center the spinous process in the middle of the probe and mark a line in a cephalad-caudad direction on the patient's back to identify the midline (Fig. EC 4.A).
2. Rotate the probe 90 degrees to obtain a longitudinal view (probe parallel to the spine). Identify the vertebral bodies and an intervertebral space above or below L4. Mark a line on either side of the skin correlating with the space (Fig. EC 4.B).
3. The intersection of the marks identifies the area to be punctured. The crosshairs formed by the marks should leave the actual insertion site clean (Fig. EC 4.C).
4. The procedure should progress with no further movement of the patient. Preparation and draping should proceed from this point toward completion of the procedure.

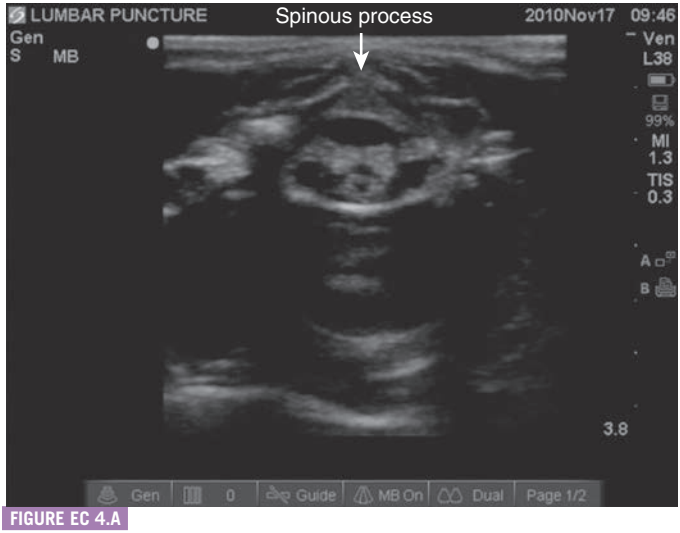

FIGURE EC 4.A

Transverse ultrasound view of the lumbar spine. The spinous process is labeled in this ultrasound image of the lumbar spine, marking the anatomic midline for a lumbar puncture. A marking line should be drawn in the cephalad-caudad direction on the skin over the spinous processes. (*From Marin J. Novel applications in pediatric emergency ultrasound*. Clin Pediatr Emerg Med. *2011;12[1]:53–64.*)

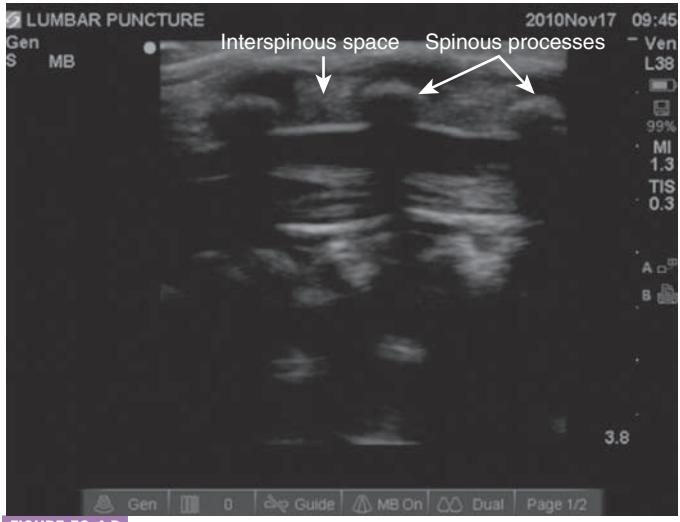

FIGURE EC 4.B

Longitudinal ultrasound view of the spine. The spinous processes are visualized as hyperechoic (bright) lines with posterior shadowing. In between the rounded spinous process is the interspinous space, which should be marked with a line for the procedure. (*From Marin J. Novel applications in pediatric emergency ultrasound.* Clin Pediatr Emerg Med. *2011;12[1]:53–64.*)

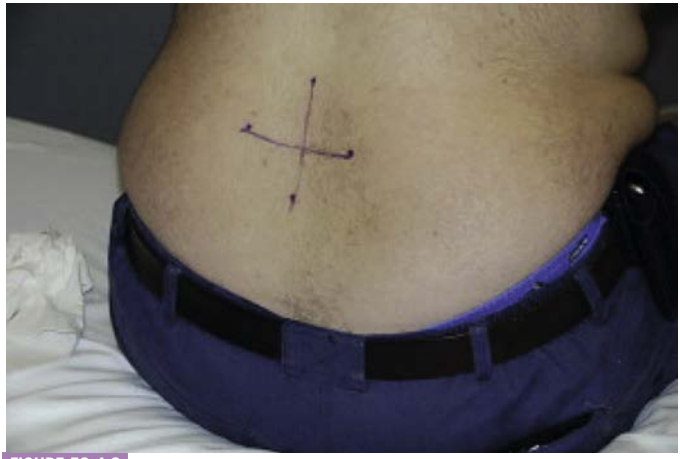

FIGURE EC 4.C

Lumbar area marked for lumbar puncture. The lines from ultrasound markings should make a cross as seen in this image. Ideally there will be an area free of marking in the center where the actual puncture site will be. (*From Strony R. Ultrasound-assisted lumbar puncture in obese patients.* Crit Care Clin. *2010;26[4]:661–664.*)

B. External Jugular Puncture and Catheterization[2]

1. **Indications:** Blood sampling in patients with inadequate peripheral vascular access or during resuscitation.
2. **Complications:** Infection, bleeding, pneumothorax.
3. **Procedure:** (Fig. EC 4.D)
   a. Restrain patient securely with head turned 45 degrees to the contralateral side of cannulation. Position with towel roll under shoulders or with head over side of bed to extend neck and accentuate the posterior margin of the sternocleidomastoid muscle on the side of venipuncture. Place patient in the 15- to 20-degree Trendelenburg position.
   b. Prepare area in a sterile fashion.
   c. The external jugular vein will distend if its most proximal segment is occluded or if the child cries. The vein runs from the angle of the mandible to the posterior border of the lower third of the sternocleidomastoid muscle.

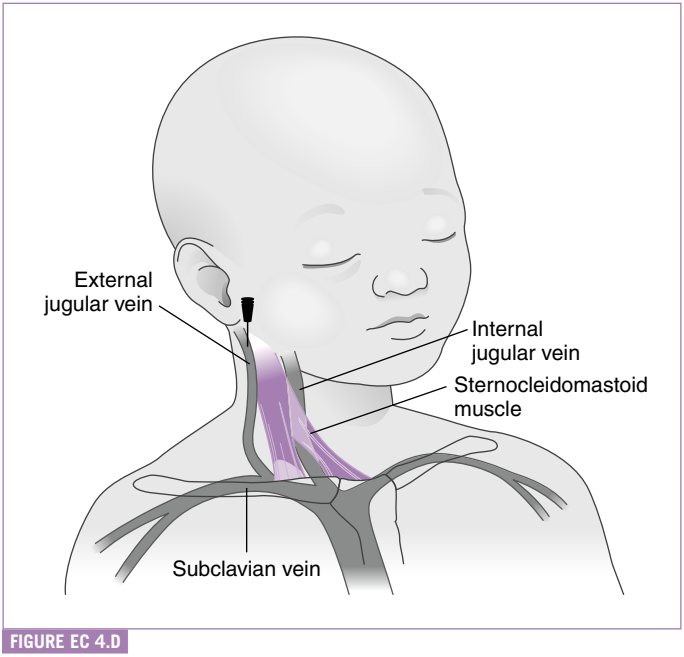

FIGURE EC 4.D

External jugular catheterization. (*From Dieckmann R, Fiser D, Selbst S.* Illustrated Textbook of Pediatric Emergency and Critical Care Procedures. *St. Louis, MO: Mosby; 1997.*)

d. With continuous negative suction on the syringe, insert the needle at approximately a 30-degree angle to the skin. Continue as with any peripheral venipuncture.
e. Apply a sterile dressing, and put pressure on the puncture site for 5 minutes.
f. Enter the vein at the point where it crosses the sternocleidomastoid muscle.
g. Proceed with peripheral catheter placement as described previously.

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Chapter 5

Adolescent Medicine

Christine Krueger, MD and Harita Shah, MD

See additional content on Expert Consult

I. ADOLESCENT HEALTH MAINTENANCE

A. Confidentiality

Begin integrating one-on-one time with the provider and patient into adolescent visits as early as age 11 to provide teens with regular opportunities to discuss concerns and sensitive topics in an open manner.[1] Adolescents are concerned about the confidentiality of their interactions with healthcare providers.[2,3] Providers should be aware of barriers to confidentiality related to consent laws and billing/explanation of benefits by insurance companies.[4]

1. **Consent laws:** All states and the District of Columbia allow minors to consent to sexually transmitted infection (STI) services (diagnosis and treatment), although some states have a minimum age to consent. Laws surrounding consent to HIV testing and treatment, contraception, abortion, and other healthcare services vary by state. Current information on consent laws by state can be found at the Guttmacher Institute's website (https://www.guttmacher.org/state-policy/explore/overview-minors-consent-law).[5]
2. **Breach of confidentiality:** Confidentiality must be breached if the adolescent is at risk of harming themselves or others (e.g., suicidal or homicidal ideation). Cases of child abuse or neglect must be reported to child protective services. The definition of statutory rape and reporting laws vary by state, with minimum age to consent to sexual activity ranging from 16 to 18 years old. Current information on reporting laws by state can be found at the Rape, Abuse & Incest National Network's website (https://rainn.org/public-policy-action).[6]

B. History Elements Unique to the Adolescent Patient

1. **Psychosocial development**[7]: Progression through adolescence is characterized by cognitive, psychosocial, and emotional developments, which help adolescents to establish their identity and autonomy. See Table EC 5.A for detailed psychosocial development by age.
2. **HEADSS assessment**[8–10]: A screening tool for psychosocial factors, which impact adolescent mental, physical, and sexual health (Box 5.1).
3. **Screening, brief intervention, and referral to treatment (SBIRT)** for substance use[11]:
   a. **S**creening: If adolescent has used any alcohol, marijuana, or other drugs in the past 12 months, administer CRAFFT questionnaire (Box 5.2). If not, administer only the "Car" question (Have you ever ridden in a car with a driver who had used alcohol or drugs?).

BOX 5.1

HE²ADS³ (MODIFIED HEADSS) ASSESSMENT[8]

(H)OME: Household composition, family dynamics and relationships, living and sleeping arrangements, recent changes, any periods of homelessness, running away from home

(E)DUCATION/**E**MPLOYMENT, (**E)**ATING: School performance, attendance, suspensions; attitude toward school; favorite, most difficult, best subjects; special educational needs; goals for the future; after-school job or other work history; body image and dieting

(A)CTIVITIES: Friendships with same or opposite sex, ages of friends, best friend, dating, recreational activities, physical activity, sports participation, hobbies, and interests

(D)RUGS: Personal use of tobacco, alcohol, illicit drugs, anabolic steroids; peer substance use; family substance use and attitudes; if personal use, determine frequency, quantity, binge, injury with use; consider use of **CRAFFT** questionnaire (Box 5.2)

(S)EXUALITY: Sexual orientation, gender identity, and relationship(s) should be explored with open-ended questions. If the adolescent is sexually active, discuss age of first sexual act, number of lifetime and current partners, ages of partners, knowledge of contraception and sexually transmitted infection/human immunodeficiency virus (STI/HIV) prevention, reproductive life plan, prior testing for STI/HIV, prior pregnancies and/or abortions, and history of nonconsensual intimate physical contact or sex. See Box EC 5.A for the "Five Ps" of the sexual history

(S)UICIDE/DEPRESSION: Feelings about self, both positive and negative; history of depression or other mental health problems; sleep problems (difficulty getting to sleep, early waking); changes in appetite or weight; anhedonia; irritability; anxiety; current or prior suicidal thoughts or attempts; other self-harming or injurious behavior; screen for depression using the Patient Health Questionnaire (PHQ-2)

(S)AFETY: Feeling unsafe at home, at school, or in the community; bullying; guns in the home; weapon carrying, what kinds of weapons; fighting; arrests; gang membership; seatbelt use

BOX 5.2

CRAFFT QUESTIONNAIRE[10]

C—Have you ever ridden in a **C**AR driven by someone (or yourself) who was "high" or had been using alcohol or drugs?

R—Do you ever use alcohol or drugs to **R**ELAX, feel better about yourself, or fit in?

A—Do you ever use alcohol/drugs while you are **A**LONE?

F—Do your family or **F**RIENDS ever tell you that you should cut down on your drinking or drug use?

F—Do you ever **F**ORGET things you did while using alcohol or drugs?

T—Have you gotten into **T**ROUBLE while you were using alcohol or drugs?

NOTE: Answering yes to two or more questions is a positive screen

From Gephart H: Rating scales, questionnaires, and behavior checklists. In *ADHD Complex: Practicing Mental Health in Primary Care.* Philadelphia, Elsevier, 2019, pp 1-7.

b. **B**rief **I**ntervention: Stratify risk based on responses to screening questions.
   (1) Low risk (abstinent): Reinforce decisions with praise and provide anticipatory guidance regarding riding in a car with a driver under the influence.
   (2) Yes to "Car" question: Counsel and encourage safety plan.
   (3) Moderate risk (CRAFFT negative): Advise cessation of substance use, educate regarding health risks of continued use, and praise personal attributes.
   (4) High risk (CRAFFT ≥2): Conduct in-depth assessment using motivational enhancement techniques, conduct brief negotiated interview, or refer as appropriate.

c. **R**eferral to **T**reatment: Further evaluation by a specialist in mental health/addiction can guide referral to an appropriate level of care.

4. **Social media**[12]: Explore how social media is used and for what quantity of time.
   a. Benefits: Communication and engagement.
   b. Risks of excessive/inappropriate use: Impaired sleep, attention, and learning; obesity; depression; viewing of unsuitable content; decrease in caregiver-child interactions; compromised privacy; meeting high-risk sexual partners or sexual predators, sexting, and cyberbullying.
      (1) Guidance for teens and families: https://www.brightfutures.org/development/adolescence/social-media.html
      (2) AAP Family Media Use Plan: www.healthychildren.org/MediaUsePlan
5. **Menstrual history:** Age of menarche, last menstrual period (LMP), frequency/regularity and duration of menstrual cycle, reproductive life plan, condom use, and contraceptive use.

C. Physical Examination Elements Unique to the Adolescent[13,14]

1. **Dentition and gums:** Caries, enamel defects from tobacco use, and enamel erosion from induced vomiting.
2. **Skin:** Acne (see Chapter 8 for treatment guidelines), atypical nevi, acanthosis nigricans, rashes, evidence of cutting, piercings, and tattoos.
3. **Thyroid:** Size, nodules.
4. **Breasts:** Sexual maturity rating for females, masses (most commonly fibrocystic changes and fibroadenomas in females, or gynecomastia in males), breast asymmetry (common occurrence in adolescence; more pronounced between Tanner pubertal stages 2 and 4).
   a. Normal female breast development: See Fig. 5.1.
   b. Physiologic gynecomastia in males:
      (1) Epidemiology: Generally, occurs in middle to late stages of puberty (usually peaks in Tanner pubertal stage 3); occurs in 50% of boys (50% unilateral, 50% bilateral).
      (2) Etiology: Breast growth stimulated by estradiol.
      (3) Clinical course: Regression usually occurs over a 2-year period.

TABLE EC 5.A

PSYCHOSOCIAL DEVELOPMENT OF ADOLESCENTS

Task	Early Adolescence (10–13 years)	Middle Adolescence (14–16 years)	Late Adolescence (>17 years)
Independence	Less interest in parental activities Wide mood swings	Peak of parental conflicts	Reacceptance of parental advice and values
Body image	Preoccupation with self and pubertal changes Uncertainty about appearance	General acceptance of body Concern over making body more attractive	Acceptance of pubertal changes
Peers	Intense relationships with same-sex friend(s)	Peak of peer involvement Conformity with peer values Increased sexual activity and experimentation	Peer group less important More time spent in sharing intimate relationships
Identity	Increased cognition Increased fantasy world Increasing sexual attractions Idealistic vocational goals Increased need for privacy Lack of impulse control	Increased scope of feelings Increased intellectual ability Feeling of omnipotence Risk-taking behavior Emerging sexual identity	Practical, realistic vocational goals Refinement of moral, religious, and sexual values Ability to compromise and to set limits Sexual identity becomes more secure

From Joffe A. Introduction to adolescent medicine. In: McMillan JA, DeAngelis CD, Feigan RD, et al., eds. *Oski's Pediatrics Principles and Practice.* 4th ed. Philadelphia: Lippincott Williams, & Wilkins; 2006.

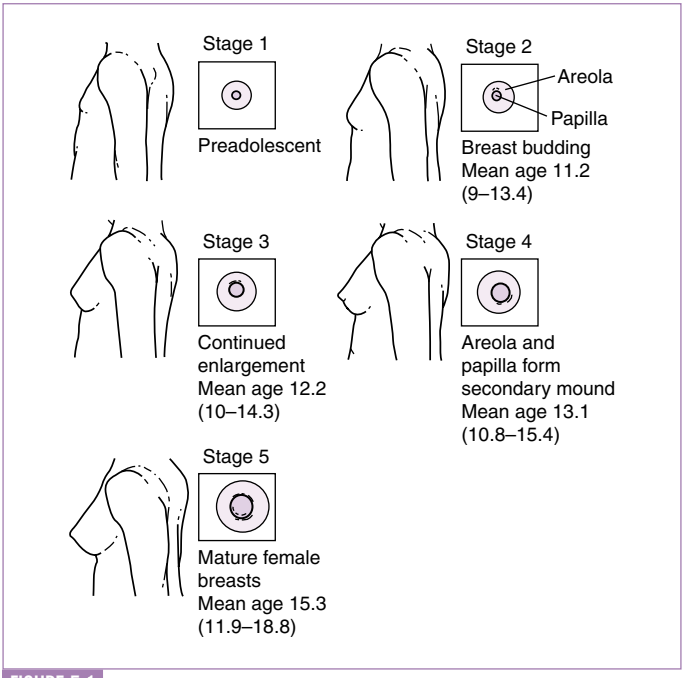


FIGURE 5.1

Tanner stages of breast development in females. (Modified from Johnson TR, Moore WM. *Children Are Different: Developmental Physiology.* 2nd ed. Columbus, OH: Ross Laboratories; 1978. Mean age and range [2 standard deviations around mean] from Joffe A. Introduction to adolescent medicine. In: McMillan JA, DeAngelis CD, Feigin RD, et al., eds. *Oski's Pediatrics: Principles and Practice.* 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:549–550.)

(4) Physical examination: Firm glandular tissue in a concentric mass beneath the areola/nipple is consistent with physiologic gynecomastia. A testicular examination should also be performed.
(5) Differential diagnosis: Nonphysiologic gynecomastia. Common causes include medication or substance use, primary or secondary hypogonadism, cirrhosis, hyperthyroidism, tumors, and pseudogynecomastia (excess adipose tissue on exam).
(6) Red flags: Symptom duration over 2 years, nipple discharge, skin changes, breast masses, and coincident testicular abnormalities.
(7) Treatment: Often no treatment is necessary. Severe or nonregressing cases may warrant referral to pediatric surgeon, endocrinologist, or oncologist, depending on suspected etiology.

TABLE 5.1

TANNER STAGES OF GENITAL DEVELOPMENT (MALE)

Tanner Stage	Comment (±2 Standard Deviations Around Mean Age)
1	Pre-pubertal
2	Enlargement of scrotum and testes[a]; skin of scrotum reddens and changes in texture; little or no enlargement of penis; mean age 11.4 years (9.5–13.8 years)
3	Enlargement of penis, first mainly in length; further growth of testes and scrotum; mean age 12.9 years (10.8–14.9 years)
4	Increased size of penis with growth in breadth and development of glans; further enlargement of testes and scrotum and increased darkening of scrotal skin; mean age 13.8 years (11.7–15.8 years)
5	Genitalia adult in size and shape; mean age 14.9 years (13–17.3 years)

[a]Testicular volume of greater than 4 mL or a long axis of greater than 2.5 cm is evidence that pubertal testicular growth has begun.

Data from Joffe A. Introduction to adolescent medicine. In: McMillan JA, DeAngelis CD, Feigin RD, et al, eds. *Oski's Pediatrics: Principles and Practice.* 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:546–557.

TABLE 5.2

TANNER STAGES OF PUBIC HAIR

Tanner Stage	Appearance
1	No hair
2	Sparse, downy hair at base of symphysis pubis
3	Sparse, coarse hair across symphysis pubis
4	Adult hair quality, fills in pubic triangle, no spread to thighs
5	Adult quality and distribution including spread to medial thighs

Data from Alario AJ, Birnkrant JD. Sexual maturation and tanner staging. *Practical Guide to the Care of the Pediatric Patient.* 2nd ed. St. Louis: Mosby; 2007:798–800.

5. **Genitalia:** For both male and female genital examinations, a chaperone should be present, an explanation should occur before the examination, and findings should be discussed.
   a. **Male**[15]:
      (1) Normal male genital development: Table 5.1.
      (2) Normal pubic hair development: Table 5.2.
      (3) Assess for signs of STIs (rashes, warts, ulcers, erosions, discharge), inguinal hernias, masses, hydroceles, and varicoceles. If there are symptoms of proctitis with history of receptive anal intercourse (e.g., rectal pain, rectal bleeding, or tenesmus), a digital rectal examination should be performed.
   b. **Female**[16,17]:
      (1) Normal pubic hair development: see Table 5.2.
      (2) External examination: Assess for signs of STIs (rashes, warts, ulcers, erosions, discharge), discharge suggestive of candidiasis or bacterial vaginosis, and evidence of trauma.

(3) Pelvic examination: Speculum exams are not routinely recommended for healthy asymptomatic women under 21 years of age. Indications for bimanual exam or speculum exam include: vaginal discharge with lower abdominal or pelvic pain (assess cervix for mucopurulent discharge, friability, large ectropion, foreign body, or cervical motion tenderness), menstrual disorders (amenorrhea, abnormal vaginal bleeding, or dysmenorrhea refractory to medical therapy), and Pap smear (see Section I.D.6).

(4) For suspected or reported sexual abuse or rape, refer to a specialized center if not appropriately trained and equipped to document evidence of trauma and collect forensic specimens.

Note: See Chapter 10 for information about precocious and delayed puberty.

D. Screening Laboratory Tests and Procedures

A lack of evidence has led to variability in guidelines for topics such as screening for dyslipidemia, iron-deficiency anemia, diabetes, and tuberculosis. The recommendations that follow are largely based on the AAP, CDC, U.S. Preventive Services Task Force (USPSTF), and the American College of Obstetricians and Gynecologists (ACOG).[1,18–20]

1. **Immunizations:** See Chapter 16.
2. **Cholesterol screening:** All children should undergo cholesterol screening once between ages 9 and 11 years and once between ages 17 and 21 years.
3. **Diabetes screening:** Consider screening for type 2 diabetes with hemoglobin A1c, fasting plasma glucose, or oral glucose tolerance test in children who have a BMI greater than 85% for age and sex with other risk factors such as family history.[21]
4. Consider selective screening for tuberculosis, anemia, and vision and hearing abnormalities if patient screens positive on risk screening questions.
5. **STI screening:** See Section II.
6. **Papanicolaou (Pap) smear cervical cancer screening:** Cytologic evaluation should be used. Human papilloma virus (HPV) testing is only recommended for routine screening above age 30. Recommended screening intervals and follow-up depend on age, medical history, and result of previous Pap smear, as presented in Table 5.3.

II. SEXUAL HEALTH

A. Sexually Transmitted Infection Screening Guidelines by Sexual Behavior[18,22,23]

1. **All adolescents over age 13:** The CDC recommends universal screening for HIV (via HIV 1/2 antigen/antibody test) at least once using an opt-out approach, or more frequently based on risk factors.

TABLE 5.3

GUIDELINES FOR PAPANICOLAOU (PAP) SMEAR SCREENING AND FOLLOW-UP

Immune Status	Recommended Timing of Pap Screening	Recommended Follow-Up Based on Pap Result	
Immunocompetent	Age 21	Normal	Repeat Papanicolaou (Pap) smear every 3 years
		Atypical squamous cells of undetermined significance (ASC-US)	Repeat Pap smear in 1 year
		Low-grade squamous intraepithelial lesion (LSIL)	Repeat Pap smear in 1 year
		High-grade squamous intraepithelial lesion (HSIL)	Gynecology referral for colposcopy
		Atypical squamous cells, cannot rule out HSIL (ASC-H)	Gynecology referral for colposcopy
Immunosuppressed	Age 21	Normal	Repeat Pap smear every year
		Abnormal	Gynecology referral
HIV+	Within 1 year of HIV diagnosis, or if perinatally acquired, within 1 year of onset of sexual activity	Normal	Repeat Pap smear every year. If three consecutive Pap smears are normal, space Pap interval to every 3 years.
		Abnormal	Gynecology referral

Data from American College of Obstetricians and Gynecologists. Committee on Practice Bulletins—Gynecology. Practice Bulletin No. 168: Cervical Cancer Screening and Prevention. *Obstet Gynecol.* 2016;128(4):e111–e130.

2. **Heterosexual with one lifetime partner:**
   a. **Male:** Screen once with HIV 1/2 antigen/antibody test; gonorrhea and chlamydia urine nucleic acid amplification test (NAAT) in high prevalence clinical settings (e.g., adolescent clinics, correctional facilities, STI clinics). Repeat as indicated by sexual risk.
   b. **Female:** Screen once with HIV 1/2 antigen/antibody test; self- or provider-collected vaginal NAAT for gonorrhea and chlamydia (routine screening recommended in sexually active women under age 25). Repeat as indicated by sexual risk. Vaginal swab is the preferred method to screen for gonorrhea and chlamydia; self-collected specimens may have higher patient acceptability. Vaginal swabs are as sensitive and specific as cervical swabs, and both are more accurate than urine samples.[24]
3. **Heterosexual with risk factors** (new partner, multiple partners, partner with STI, intravenous drug use):
   a. **Male:** Annual HIV 1/2 antigen/antibody test, rapid plasma reagin (RPR), and gonorrhea and chlamydia urine NAAT.
   b. **Female:** Annual HIV 1/2 antigen/antibody test, RPR, and self- or provider-collected vaginal NAAT for gonorrhea, chlamydia, and trichomonas.
   c. In adolescents with a history of an STI, repeat testing is recommended 3 months after treatment given high risk of reinfection.
4. **Men who have sex with men (MSM):** Annual HIV 1/2 antigen/antibody test, RPR, and gonorrhea and chlamydia NAAT (test sites of sexual contact: pharynx, urethra, and/or rectum) are recommended. For MSM with multiple or anonymous partners, consider 3 to 6 month interval STI testing.
5. **Women who have sex with women (WSW):** Equivalent STI screening as heterosexual women, guided by sexual practices (e.g., gonorrhea and chlamydia NAAT should be done at sites of sexual contact) and risk factors.
6. **Pregnant women:** At the first visit, pregnant patients should be screened with HIV 1/2 antigen/antibody test, RPR, vaginal gonorrhea and chlamydia NAAT, and hepatitis B surface antigen test.
7. **Transgender:** Given the diversity of transgender persons regarding patterns of sexual behavior, hormone use, and surgery, clinicians should assess STI risk based on the patient's sexual behaviors and current anatomy (the latter of which should guide method of NAAT testing, if indicated).
8. **Concern for recent exposure to STI:**
   a. Fourth generation HIV 1/2 antigen/antibody tests detect acute infection within 10 to 14 days. If there is concern for acute or early HIV exposure, consider an HIV RNA nucleic acid test.[25]
   b. Screen with RPR, gonorrhea and chlamydia NAAT (method of testing as described above by sexual behavior), and vaginal trichomonas NAAT for women.
   c. Consider HSV PCR testing in individuals presenting for STI evaluation with genital lesion(s).

9. **Persons living with HIV:** Screen at least annually with RPR, gonorrhea and chlamydia NAAT (method of testing as described above by sexual behavior), and vaginal trichomonas NAAT for women. Screen more frequently if indicated by sexual risk behaviors.

B. Sexually Transmitted Infection Evaluation and Management (Table 5.4)

1. **HIV:** See Chapter 17 for information on diagnosis and treatment of HIV, pre-exposure prophylaxis (PrEP), and postexposure prophylaxis (PEP). PrEP should be initiated in the primary care setting, when possible.
2. **Syphilis**[18]
   a. Etiology: *Treponema pallidum*
   b. Early syphilis (within 1 year of initial infection)
      (1) Primary syphilis (chancre): Firm, usually painless sore(s) or ulcer(s) develop at the site of initial infection (genital, rectal, or oral). Chancres typically develop within 3 weeks of infection and heal 3 to 6 weeks after development in the absence of treatment.
      (2) Secondary syphilis: Within weeks to months after a chancre appears, patients may develop body rash involving palms and soles, mucocutaneous lesions, lymphadenopathy, constitutional symptoms, and/or early neurosyphilis (e.g., meningitis or ocular syphilis).
      (3) Early latent syphilis: Asymptomatic stage.
   c. Late syphilis (over 1 year after initial infection)
      (1) Late latent syphilis: Asymptomatic stage.
      (2) Tertiary syphilis: Organ involvement may progress to cardiovascular syphilis (e.g., aortitis), late neurosyphilis (e.g., tabes dorsalis or paresis), or gummatous syphilis.
   d. Diagnosis: Testing algorithm varies by laboratory and typically includes a nontreponemal test (RPR or Venereal Disease Research Laboratory [VDRL] test) and a treponemal test (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] test, enzyme immunoassay) for confirmation.
   e. Treatment: See Table 5.4. Clinical and serologic evaluation should be performed 6 and 12 months after treatment to ensure a fourfold reduction in nontreponemal titers or seroreversion. Monitor for Jarisch-Herxheimer reaction (fever, headache, and myalgias) within 24 hours of treatment.
   f. Partner treatment: Partners with sexual contact within 90 days of a patient's diagnosis should be treated empirically. Partners with sexual contact over 90 days prior to diagnosis should be evaluated for treatment based on CDC 2015 STD Treatment Guidelines: http://www.cdc.gov/std/tg2015/.
   g. See Chapter 17 for information on neonatal syphilis and interpretation of maternal and neonatal syphilis testing.

TABLE 5.4

SEXUALLY TRANSMITTED AND GENITOURINARY INFECTIONS: GUIDELINES FOR MANAGEMENT[a]

Infection	Clinical Diagnosis	Empiric Therapy[a]	Comments
Chlamydia Infections	Uncomplicated infection of the cervix, urethra, rectum, or pharynx	Azithromycin 1 g PO once *OR* doxycycline 100 mg PO BID for 7 days *Alt: Erythromycin OR fluoroquinolone*	Consider empirical treatment for gonorrhea secondary to common coinfection
	Chlamydia infection in pregnancy	Azithromycin 1 g PO once *Alt: Amoxicillin OR erythromycin*	Test of cure 3 weeks posttreatment in all pregnant patients
	Lymphogranuloma venereum (LGV)	Doxycycline 100 mg PO BID for 21 days *Alt: Erythromycin*	
Gonorrhea Infections	Uncomplicated infection of the cervix, urethra, rectum, or pharynx	Ceftriaxone 250 mg IM once *PLUS* azithromycin 1 g PO once *Alt for ceftriaxone: Cefixime OR gemifloxacin OR gentamicin*	Dual treatment is recommended for gonorrhea secondary to organism resistance
	Epididymitis	Ceftriaxone 250 mg IM once *PLUS* doxycycline 100 mg PO BID for 10 days	For MSM, replace doxycycline with a fluoroquinolone for 10 days
	Disseminated gonococcal infections	Ceftriaxone 1 g IV/IM daily *PLUS* azithromycin 1 g PO once *Alt for ceftriaxone: Cefotaxime*	Can switch to oral therapy 24–48 h after clinical improvement. Total course: 7 days
Pelvic Inflammatory Disease (PID)	PID warranting outpatient treatment	Ceftriaxone 250 mg IM once *PLUS* doxycycline 100 mg PO BID for 14 days ± metronidazole 500 mg PO BID for 14 days	
	PID warranting inpatient treatment	Regimen A for 14 days: (Cefotetan 2 g IV q12h *OR* cefoxitin 2 g IV q6h) *PLUS* doxycycline 100 mg IV or PO q12h Regimen B for 14 days: Clindamycin 900 mg IV q8h *PLUS* gentamicin 2 mg/kg loading dose, then 1.5 mg/kg IV q8h maintenance (or 3–5 mg/kg IV single daily dosing)	Switch to oral therapy 24 h after clinical improvement to complete 14 days of treatment with doxycycline 100 mg PO BID or clindamycin 450 mg PO QID, respectively

Syphilis	Primary, secondary, or early latent syphilis (<1 year duration)	Benzathine penicillin G 50,000 U/kg (max 2.4 million units) IM (single dose) *Alt: Doxycycline OR tetracycline*	Data is limited for penicillin alternatives. Pregnant women should be treated with penicillin G regimen appropriate for stage of syphilis
	Late latent syphilis (>1 year duration); tertiary syphilis	Benzathine penicillin G 50,000 U/kg (max 2.4 million units) IM weekly for 3 weeks *Alt: Doxycycline OR tetracycline*	
Herpes (Genital, Nonneonatal)		Acyclovir or valacyclovir	See Formulary for treatment for initial infection and recurrence

Alt, Alternative; *IM*, intramuscular; *IV*, intravenous; *MSM*, men who have sex with men; *PO*, per os.

[a]For dosing for children aged ≤8 years or weighing less than 45 kg, or for dosing of alternative regimens, please refer to the CDC Treatment Guidelines, 2015: http://www.cdc.gov/std/tg2015/. Partner notification and treatment is recommended for most sexually transmitted infections. Patients treated for a sexually transmitted infection should refrain from all sexual activity for 7 days posttreatment.

3. **Chlamydia and gonorrhea**[18]
   a. Etiology: *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
   b. Clinical manifestations: Urethritis, cervicitis, pharyngitis, proctitis, epididymitis, prostatitis. Other manifestations include:
      (1) Lymphogranuloma venereum (LGV): Lymphoproliferative reaction caused by *C. trachomatis* serovars L1 to L3 that most frequently presents as proctitis and lymphadenopathy in patients who are MSM or HIV positive.
      (2) Disseminated gonococcal infection: Bacteremic spread of *N. gonorrhoeae* results in septic arthritis or arthritis-dermatitis syndrome (polyarthralgia, tenosynovitis, and dermatitis). In addition to urogenital, rectal, and pharyngeal NAAT, workup should include blood, synovial, or CSF cultures, as applicable.
   c. Diagnosis: Site-specific NAAT, including urogenital (urine NAAT in males, urine or vaginal NAAT in females [see Section II.A.2.b]), pharyngeal, and rectal.
   d. Treatment: See Table 5.4.
   e. Partner treatment: Partners should be treated. For partners for whom providers are concerned about access to prompt clinical evaluation and treatment, expedited partner therapy may be an option depending on local and state laws.
4. **Pelvic inflammatory disease (PID):** Acute infection of the female upper genital tract.[18]
   a. Etiology: Often polymicrobial in nature, however *N. gonorrhoeae* and *C. trachomatis* are the most commonly identified pathogens, followed by *Mycoplasma genitalium.*
   b. Differential diagnosis: Endometriosis, tubo-ovarian abscess (TOA), ovarian cyst, ectopic pregnancy, acute surgical abdomen, inflammatory bowel disease (IBD), pyelonephritis, dysmenorrhea, septic/threatened abortion
   c. Workup: Pelvic and bimanual examination, gonorrhea/chlamydia and HIV testing, human chorionic gonadotropin (hCG), wet preparation, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and urinalysis/urine culture if clinically indicated. Consider a complete blood cell count (CBC) with differential and pelvic ultrasound if the patient is ill-appearing, has an adnexal mass on bimanual examination, or is not improving after antibiotics.
   d. Minimum diagnostic criteria: Uterine, adnexal, or cervical motion tenderness without other identifiable causes. One or more of the following additional criteria enhances specificity: fever (>38.3°C), mucopurulent vaginal or cervical discharge, leukocytes on saline microscopy, increased ESR or CRP, laboratory documentation of chlamydial or gonorrhea infection.
   e. Treatment: See Table 5.4.
   f. Admission criteria: Cannot exclude acute surgical abdomen, presence of TOA, pregnancy, immunodeficiency, severe illness, inability

to tolerate or follow outpatient oral regimen, failure to respond to appropriate outpatient therapy, or follow-up cannot be ensured.

5. **Trichomoniasis**[18]
   a. Etiology: *Trichomonas vaginalis*
   b. Diagnosis and treatment: See Table 5.5.
   c. Follow-up: Women treated for trichomoniasis should be retested 3 months after treatment due to high rates of reinfection.
   d. Partner treatment: Partners should be treated to prevent reinfection.
6. **Mycoplasma genitalium**[18]
   a. Etiology: *Mycoplasma genitalium*
   b. Clinical manifestations: Persistent urethritis, cervicitis, or PID despite appropriate treatment.
   c. Diagnosis: No FDA-approved diagnostic test; NAAT is available in some large medical centers and commercial laboratories.
   d. Treatment: Moxifloxacin has been used successfully; refer to latest CDC treatment guidelines.
7. **Vaginal infections, genital ulcers, and warts**
   a. Diagnostic features of vaginal infections (see Table 5.5) can assist in differentiating normal vaginal discharge from bacterial vaginosis, trichomoniasis, and yeast vaginitis.
   b. Diagnostic features of genital lesions, as well as management of warts and ulcers, are presented in Table 5.6.

C. Gender and Sexual Behavior

1. **Terminology and definitions:**
   a. **Sexual orientation**[26,27]: Sexual orientation relates to sexual attraction, identity, and behavior. It is not related to gender identity. It should be defined by the individual patient.
   b. **Gender identity:** An individual's self-awareness as male or female.
   c. **Gender expression:** The way an individual expresses their gender (e.g., clothing and speech); may differ from gender identity.
   d. **Sex assigned at birth:** Often based on phenotype (external genitals, gonads, and internal sex organs) and karyotype (XX, XY, XO, XXY, etc.); assigned at birth.
   e. **Transgender:** An individual whose gender identity differs from the sex assigned at birth.
   f. **Cisgender:** An individual whose gender identity is the same as the sex assigned at birth.
   g. **Gender nonbinary:** Gender expression by an individual that does not match masculine and feminine gender norms.
   h. **Gender dysphoria**[28]: Discomfort or distress caused by discrepancy between a person's gender identity and sex assigned at birth. DSM-V criteria recommends a diagnosis occur after 6 months of continuous incongruence. For prepubescent children, the desire to be of the other gender must be present and verbalized.
2. **Special considerations in adolescents:**
   a. Adolescents may engage in a variety of sexual activities (penile-vaginal, anal, or oral intercourse) that do not reflect their sexual orientation (e.g.,

TABLE 5.5

DIAGNOSTIC FEATURES AND MANAGEMENT OF VAGINAL INFECTIONS

	No Infection/Physiologic Leukorrhea	Vulvovaginal Candidiasis	Trichomoniasis	Bacterial Vaginosis[a]
Etiology	—	*Candida albicans* and other yeasts	*Trichomonas vaginalis*	*Gardnerella vaginalis*, anaerobic bacteria, mycoplasma
Typical symptoms	None	Vulvar itching, irritation, ↑ discharge	Malodorous frothy discharge, vulvar itching	Malodorous, ↑ discharge
Discharge Amount	Variable; usually scant	Scant to moderate	Profuse	Moderate
Discharge Color	Clear or white	White	Yellow-green	Usually white or gray
Discharge Consistency	Heterogenous	Clumped; adherent plaques	Homogenous	Homogenous, low viscosity
Vulvar/vaginal inflammation	No	Yes	Yes	No
pH of vaginal fluid[b]	Usually <4.5	Usually <4.5	Usually >5.0	Usually >4.5
Amine ("fishy") odor with 10% potassium hydroxide (KOH)	None	None	May be present	Present, positive "whiff-amine" test
Microscopy[c]	Normal epithelial cells; *Lactobacillus* predominates	Leukocytes, epithelial cells, yeast, mycelia, or pseudomycelia in 40%–80% of cases	Leukocytes; motile trichomonads seen in 50%–70% of symptomatic patients, less often if asymptomatic	Clue cells, few leukocytes; *Lactobacillus* outnumbered by profuse mixed flora (nearly always including *G. vaginalis* plus anaerobes)
Usual treatment	None	Fluconazole 150 mg PO once *OR* intravaginal azole cream	Metronidazole 2 g PO once *OR* tinidazole 2 g PO once	Metronidazole 500 mg PO BID for 7 days *OR* metronidazole gel 0.75% 5 g intravaginally daily for 5 days *OR* clindamycin cream 2% 5 g intravaginally daily for 7 days

NOTE: Refer to Formulary for dosing information.

[a]Despite more sensitive and specific laboratory tests, cost and practicality make the Amsel criteria the best in-office method to diagnose Bacterial Vaginosis. To diagnose BV, at least 3 criteria must be present: (1) Homogenous, thin, gray/white discharge; (2) Vaginal pH >4.5; (3) Positive whiff-amine test; (4) Clue cells on wet mount.

[b]pH determination is not useful if blood is present.

[c]To detect fungal elements, vaginal fluid is mixed with 10% KOH before microscopic examination; to examine for other features, fluid is mixed with saline.

From Workowski KA, Bolan GA. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR3):1–137.

TABLE 5.6

DIAGNOSTIC FEATURES AND MANAGEMENT OF GENITAL ULCERS AND WARTS

Infection	Clinical Presentation	Presumptive Diagnosis	Definitive Diagnosis	Treatment/Management of Sex Partners
Genital herpes	Grouped vesicles, painful shallow ulcers to mild clinical manifestation (redness, pain, excoriations); HSV-2 more common cause of genital lesions	Tzanck preparation with multinucleated giant cells	HSV PCR	No known cure. Prompt initiation of therapy shortens duration of first episode. For severe recurrent disease, initiate therapy at start of prodrome or within 1 day. Transmission can occur during asymptomatic periods. See Formulary for dosing of acyclovir, famciclovir, or valacyclovir.
Chancroid	Etiology: *Haemophilus ducreyi* Painful genital ulcer; tender, suppurative inguinal adenopathy	No evidence of *Treponema pallidum* (syphilis) on dark-field microscopy or serologic testing; negative HSV	Use of special media (not widely available in United States); sensitivity <80%	Single dose: Azithromycin 1 g orally *OR* ceftriaxone 250 mg IM. Partners should be examined and treated, regardless of whether symptoms are present, or if they have had sex within 10 days preceding onset of patient's symptoms. Syphilis is a common co-pathogen with chancroid.
Primary syphilis (chancre)	Indurated, well-defined, usually single painless ulcer or chancre; nontender inguinal adenopathy	Nontreponemal serologic test: VDRL, RPR, or STS	Treponemal serologic test: FTA-ABS, dark-field microscopy or direct fluorescent antibody tests of lesion exudates or tissue	Parenteral penicillin G (see Table 5.4 for preparation[s], dosage, and length of treatment). Treat presumptively for persons exposed within 3 months preceding the diagnosis of primary syphilis in a sex partner or who were exposed >90 days preceding the diagnosis and in whom serologic tests may not be immediately available or follow-up is uncertain.

Continued

TABLE 5.6—CONT'D

DIAGNOSTIC FEATURES AND MANAGEMENT OF GENITAL ULCERS AND WARTS

Infection	Clinical Presentation	Presumptive Diagnosis	Definitive Diagnosis	Treatment/Management of Sex Partners
HPV infection (genital warts)	Soft, fleshy, papillary or sessile, painless growth(s) around anus, vulvovaginal area, penis, urethra, or perineum; no inguinal adenopathy	Typical clinical presentation	Papanicolaou smear revealing typical cytologic changes	Treatment does not eradicate infection. Goal: Removal of exophytic warts. Exclude cervical dysplasia before treatment. 1. **Patient-administered therapies include:** Podofilox gel or imiquimod cream 2. **Clinician-applied therapies include:** Bichloroacetic or trichloroacetic acid, surgical removal, or cryotherapy with liquid nitrogen or cryoprobe. Podofilox, imiquimod, and podophyllin are contraindicated in pregnancy. Period of communicability unknown.

NOTE: Chancroid, lymphogranuloma venereum (LGV), and granuloma inguinale should be considered in the differential diagnosis of genital ulcers if the clinical presentation is atypical and tests for herpes and syphilis are negative.

EIA, Enzyme immunoassay; *FTA-ABS*, fluorescent treponemal antibody absorbed; *HPV*, human papillomavirus; *HSV*, herpes simplex virus; *IM*, intramuscular; *RPR*, rapid plasma reagin; *STS*, serologic test for syphilis; *TP-PA*, T. pallidum passive particle agglutination assay; *VDRL*, Venereal Disease Research Laboratory.

Modified from Workowski KA, Bolan GA. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR3):1–137.

heterosexual, homosexual, bisexual). Conversely, adolescents may self-identify with a particular sexual orientation but not be sexually active.
   b. Sexual identity emerges during adolescence. It is important to provide a safe environment for adolescents to discuss questions about their sexual identity and behavior, and ask questions about sexual activities regardless of sexual orientation.
3. **Medical interventions for gender-dysphoric or transgender patients**[29–31]:
   a. Prepubertal children: Parental support and education to create a safe environment for the child. Familial support of social transition for transgender children has been associated with better mental health outcomes.
   b. Pubertal suppression (reversible): GnRH analogue (e.g., Lupron and Supprelin) can be used to suppress endogenous hormones after onset of puberty.
   c. Gender-affirming hormone therapy (partially irreversible): Estradiol or testosterone therapy with gradual dose escalation initiated after a multidisciplinary team of medical and mental health providers has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent (generally by the age of 16 years). Treatment can be considered as early as age 13.5 to 14 years.
   d. Gender-affirming surgery (including gonadectomy, hysterectomy, mastectomy, and genital surgery): Not recommended until age of majority.

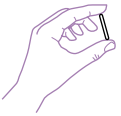
D. Contraception[32,33]

1. **Special considerations in adolescents:**
   a. Over 40% of adolescents in the United States have had sexual intercourse and over 75% of adolescent pregnancies are unplanned.[34,35]
   b. Barriers may include confidentiality concerns (e.g., fear of parental disclosure), fear of pelvic examination, and fear of medication side effects.
   c. **Long-acting reversible contraception (LARC)** methods have well-established safety and efficacy and are first-line contraceptive methods according to the ACOG and the AAP. Adherence and continuation rates of LARC methods in adolescents are superior to short-acting contraceptives. To avoid a delay in initiation, quick start method should be considered for most adolescents.[36]
   d. Providers should pay special attention to informed consent, confidentiality, parental involvement, insurance coverage, and cost. If an adolescent does not have or does not want to use their insurance coverage, refer to a clinic with Title X or other public funding (http://www.hhs.gov/opa/).
   e. Counseling should include discussion of need for barrier method to prevent STIs.
2. **Method comparison** (Fig. 5.2)[37]:
3. **Contraception selection and initiation:**
   a. **Selecting a contraceptive method:** Refer to the CDC Medical Eligibility Criteria (http://www.cdc.gov/reproductivehealth/unintendedpregnancy/usmec.htm) for relative and absolute contraindications for each

Most Effective

Reversible

Implant



0.05%

Intrauterine Device (IUD)

LNG - 0.2%
Copper T - 0.8%

How to make your method most effective

After procedure, little or nothing to do or remember.

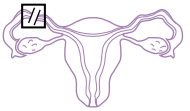
Less than 1 pregnancy per 100 women in a year

Permanent

Male Sterilization (Vasectomy)

0.15%

Female Sterilization (Abdominal, Laparoscopic, Hysteroscopic)



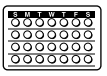
0.5%

Vasectomy and hysteroscopic sterilization: Use another method for first 3 months.

Injectable

6%

Pill



9%

Patch

9%

Ring

9%

Diaphragm

12%

Injectable: Get repeat injections on time.

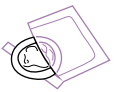
Pills: Take a pill each day.

Patch, Ring: Keep in place, change on time.

Diaphragm: Use correctly every time you have sex.

6–12 pregnancies per 100 women in a year

Male Condom

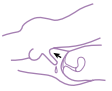


18%

Female Condom

21%

Withdrawal



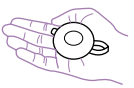
22%

Condoms, sponge, withdrawal, spermicides: Use correctly every time you have sex.

Fertility awareness -based methods: Abstain or use condoms on fertile days. Newest methods (Standard Days Method and TwoDay Method) may be the easiest to use and consequently more effective.

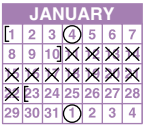
18 or more pregnancies per 100 women in a year

Sponge



24% parous women
12% nulliparous women

Fertility-Awareness Based Methods



24%

Spermicide

28%

Least Effective

CONDOMS SHOULD ALWAYS BE USED TO REDUCE THE RISK OF SEXUALLY TRANSMITTED INFECTIONS

Other Methods of Contraception

Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception.

Emergency Contraception: Emergency contraceptive pills or a copper IUD after unprotected intercourse substantially reduces risk of pregnancy.

FIGURE 5.2–CONT'D

Comparing effectiveness of family planning methods. The percentages indicate the failure rate of each contraceptive method, or the number of women who experienced an unintended pregnancy within the first year of typical use. (From Centers for Disease Control and Prevention. U.S. Selected Practice Recommendations for Contraceptive Use, 2016. *MMWR*. 2016;65[4];1–66. Available at: https://www.cdc.gov/mmwr/volumes/65/rr/rr6504a1.htm.)

hormonal contraceptive method and the CDC's Selected Practice Recommendations (http://www.cdc.gov/reproductivehealth/unintendedPregnancy/USSPR.htm) for minimum requirements to start each method.

(1) To start a hormonal method, the basic medical history should include assessment of clotting risk, blood pressure, pregnancy status, and any other pertinent medical comorbidities.

(2) Combined hormonal contraception is associated with a small increase in risk for thrombosis including deep vein thrombosis, myocardial infarction, and stroke.[38] The risk is higher in women who smoke more than 15 cigarettes a day, women over 35 years old, and women with other risk factors for cardiovascular disease.

(3) To support adherence and continuation, use a patient-centered approach, review method effectiveness, and provide anticipatory guidance regarding side effects of each method when assisting an adolescent in selecting a new contraceptive method.

b. **Quick start** (Fig. 5.3): Starting a method of contraception on the day of the visit (not waiting until a new menstrual cycle begins) should be considered for most adolescents. Can be used for all methods, including LARC, if there is reasonable certainty that the patient is not pregnant (Box 5.3). A urine pregnancy test should be performed when using this approach.[39]

4. **Specific contraceptive methods:**

Note: Contraceptive methods are described in order of effectiveness.

a. **Intrauterine device (IUD)**[36]: LARC inserted into the uterus. Safe to use among adolescents, may be inserted without difficulty in most adolescents and nulliparous women; expulsion is uncommon. Among the most effective forms of birth control. Does not increase risk of infertility; baseline fertility returns rapidly after removal. Increased risk of pelvic infection with placement, but the absolute risk of infection is low and exists only within the first 3 weeks after placement. Screening is recommended for gonorrhea and chlamydia at the time of insertion based on the CDC guidelines as age (<25 years old) is a risk factor for STIs. Insertion should not be delayed for test results; treatment can occur without IUD removal.

(1) Copper (Paragard): Hormone-free, FDA approved for 10 years of use although data supports potential efficacy for an additional 1 to 2 years.[36,40]

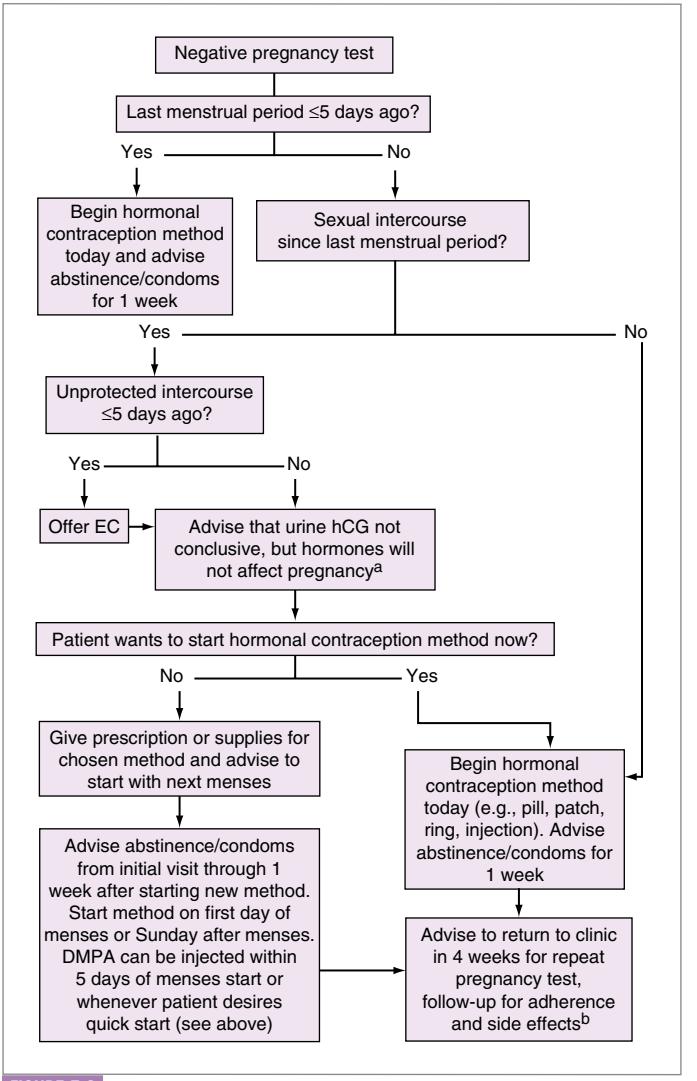


FIGURE 5.3

Algorithm for quick start initiation of contraception. *EC*, emergency contraception; *hCG*, human chorionic gonadotropin.

[a]Pregnancy tests may take 2 to 3 weeks after sex to be accurate.

[b]Consider pregnancy test at second depot medroxyprogesterone acetate (*DMPA* [Depo-Provera]) injection if quick start regimen was used and patient failed 4-week follow-up visit. (Modified from Zieman M, Hatcher RA, Cwiak C, et al. *A Pocket Guide to Managing Contraception*. Tiger, GA: Bridging the Gap Foundation; 2010:142.)

BOX 5.3

HOW TO BE REASONABLY CERTAIN THAT A WOMAN IS NOT PREGNANT

If the patient has no symptoms or signs of pregnancy and meets any of the following criteria:

1. Is ≤7 days after the start of normal menses
2. Has not had sexual intercourse since the start of last normal menses
3. Has been correctly and consistently using a reliable method of contraception
4. Is ≤7 days after spontaneous or induced abortion
5. Is within 4 weeks postpartum
6. Is fully or nearly fully breastfeeding, amenorrheic, and <6 months postpartum

Adapted from Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. *MMWR Recomm Rep.* 2016;65(4):1–66.

(2) Progestin-containing (Levonorgestrel): There are four types with differing amounts of progestin. Mirena is FDA approved for 5 years; data supports an additional 2 years.[36,41] Kyleena is FDA approved for 5 years. Liletta is FDA approved for 4 years; data supports an additional year.[36,42] Skyla is FDA approved for 3 years.

(3) Changes in bleeding patterns are common in first months of use. Copper IUD may cause heavier menses. Many women using the levonorgestrel IUD will have a decrease in bleeding over time. First-line treatment for bleeding and spotting is NSAIDs.[43] Bleeding concerns that are not associated with device insertion should be evaluated for other etiologies.

b. **Subdermal implant:** Progestin-only LARC, 4-cm rod inserted into the upper arm. Newer model (Nexplanon) is radio-opaque. FDA approved for 3 years; studies show efficacy for up to 5 years.[41] Minimal or no effect on bone density or body weight; causes a change in bleeding patterns. Return to fertility is rapid after removal. May be less effective for women who are overweight or obese. Among the most effective forms of birth control.

(1) Removal requires a small incision and takes an average of 1 minute.

(2) Persistent irregular bleeding is the most common complaint resulting in implant removal, but continuation rates among adolescents remain high.[44] As opposed to levonorgestrel IUD, bleeding changes persist throughout duration of use. The bleeding pattern in the first 3 months of use is predictive of future bleeding. Important to provide preinsertion anticipatory guidance. Consider postinsertion management of bleeding with NSAIDs, combined OCPs, or doxycycline.[37,45]

c. **Depot medroxyprogesterone acetate (DMPA [Depo-Provera]) injection:** Progestin-only injection into arm every 13 to 15 weeks. Typical failure

rate: 6%. Delayed return to fertility (9 to 18 months). Menstrual irregularity is common, but often resolves after several cycles. May cause weight gain, but not a uniform finding in studies.
   (1) Patient should be encouraged to receive adequate calcium and vitamin D due to association with decrease in bone mineral density.
   (2) FDA black box warning: Should not be used for longer than 2 consecutive years unless other forms of birth control are inadequate due to bone mineral density concerns. Bone density returns after discontinuation. The risk of loss of bone mineral density should be weighed against the need for effective contraception in the context of each adolescent.[39]

d. **Combined hormonal oral contraceptive pills (OCPs):** Combination of estrogen and progestin taken daily. "Low-dose" (35 mCg or less of ethinyl estradiol) pills are the recommended dosing for adolescents. Back-up method needed for at least 7 days after initiation. Typical failure rates are approximately 9% and may be higher in teens. Known to improve dysmenorrhea and are first-line therapy for endometriosis. Newer formulations exist, known as extended-cycle regimens, which reduce the number of menstrual cycles per year.
   (1) The first pill should be taken either on the day of the visit (quick start) or between the first and seventh day after the start of the menstrual period (most commonly Sunday).
   (2) Some pill packs have 28 pills, others have 21 pills. When the 28-day pack is empty, immediately start taking pills from a new pack. When the 21-day pack is empty, wait 1 week (7 days), then begin taking pills from a new pack.
   (3) If a pill is missed, it should be taken as soon as remembered, even if it means taking two pills in 1 day. If two or more pills missed, two pills should be taken daily until back on schedule and a backup method should be used for 7 days.

e. **Progestin-only pills:** Can be used for those with contraindications to estrogen-containing formulations. Require daily use and are more sensitive to timing (should be taken at same time each day); have no pill-free interval. Considered less effective than combined hormonal methods. Irregular bleeding is a common adverse effect.

f. **Transdermal (patch) contraceptive:** Contains estrogen and progestin, measures 1.75 × 1.75 in. Place on abdomen, upper torso, upper outer arm, or buttocks. Use one patch for 3 weeks, then remove for 1 week for withdrawal bleed. Greater exposure to estrogen than with other methods; may have more estrogen-related side effects. There may be a greater risk for thromboembolism compared to OCPs, though the data is not clear.[46] May be less effective in women who weigh more than 90 kg.

g. **Vaginal ring:** Flexible latex-free ring that contains estrogen and progestin. Placed in vagina for 3 weeks, removed for 1 week for

withdrawal bleeding. May be used continuously (avoiding week of menses) by replacing with a new ring every 4 weeks (or the same day every month) to help reduce pelvic pain and dysmenorrhea. May be removed for up to 3 hours (not recommended in adolescents). Requires user comfort with insertion and removal. Screen for comfort with this method by asking if the adolescent is comfortable using tampons. Typical use failure rate similar to other combined hormonal methods (9%).

h. **Barrier methods:** Require placement prior to sexual intercourse. Include cervical sponge, cervical cap, cervical shield, diaphragm (these methods are used in conjunction with spermicide), as well as female and male condoms. Male condom is most commonly used birth control among adolescents with a failure rate of 18% with typical use.[37] Use latex condoms only with water-based lubricants; oil-based lubricants are not recommended. While barrier methods are less effective than other methods of contraception, their use should still be emphasized for prevention of STIs.

i. **Fertility awareness-based methods of pregnancy prevention:** Involves following a woman's menstrual cycle to help prevent pregnancy.

5. **Emergency contraception (EC)**[47]: Used to prevent pregnancy following unprotected sex (including sexual assault) or a recent possible failure of another method of contraception.
   a. Mechanism: Hormonal methods work by delaying ovulation. Copper IUD inhibits fertilization by affecting sperm viability and function. All methods are only effective before implantation takes place and will not disrupt an implanted pregnancy.
   b. Efficacy[48]: Copper IUD is the most effective method, but requires a clinic visit for insertion. Ulipristal is the next most effective, but requires a prescription. Levonorgestrel is the next most effective and is available over the counter. The Yuzpe regimen is the least effective and has the most side effects.
   c. Timing: Hormonal methods are most effective when given as soon as possible. Efficacy declines linearly with time but there is efficacy up to 120 hours after intercourse. Ulipristal and copper IUD maintain high efficacy when taken up to 120 hours after intercourse.
   d. Pregnancy should be excluded based on history, physical exam, or pregnancy testing before prescribing ulipristal or placing an IUD, as they may adversely affect an established pregnancy.
   e. Methods:
      (1) Progestin only: Levonorgestrel. Take 1.5 mg orally once (may be packaged as 1.5 mg tablet or two 0.75 mg tablets).
      (2) Antiprogestins: Ulipristal ("Ella"). Take 30 mg orally once. Mifepristone is an alternative agent used in some countries as EC, but is not available in the U.S. for this purpose.
      (3) Ethinyl estradiol plus levonorgestrel (Yuzpe regimen): Patients take multiple OCPs from packets designed for 28-day use. Take

equivalent of 100 mCg of ethinyl estradiol plus 500 mCg of levonorgestrel. Twelve hours later, take the same dose. For more precise instructions for a particular combination pill, refer to https://ec.princeton.edu.

(4) Copper IUD may be inserted within 120 hours of coitus.

f. Guidelines:

(1) Counseling about EC should be a routine part of anticipatory guidance for all female and male adolescents. Advance prescriptions should be considered for all adolescents.

(2) Antiemetics can be used to prevent nausea and should be used prophylactically in the Yuzpe regimen.

(3) May be combined with other ongoing methods of birth control.

(4) OCPs may be started immediately after progestin-only or combined hormonal EC dosing has been completed. DMPA may be given the same day.

(5) Patient should abstain from sexual intercourse or use barrier contraception for 7 days (14 if using ulipristal) or until next menses, whichever comes first.

(6) Scheduled follow-up is not required after use of EC. However, women whose menses are delayed by a week or more, or have any signs of pregnancy (e.g., irregular menses, abdominal cramping), should be evaluated clinically or have a pregnancy test.

6. **Follow-up recommendations for contraception:** Two or three visits per year to monitor compliance, blood pressure, side effects, and satisfaction with chosen birth control option.

E. Pregnancy[49,50]

If pregnancy is suspected in an adolescent patient, take a sexual history and explore how the patient feels about a possible pregnancy in order to guide the rest of the visit.

1. **Diagnosis:**
   a. Perform urine hCG testing to diagnose the pregnancy. False-positives and false-negatives are possible; repeat urine testing or serum hCG testing may be indicated.
   b. If pregnancy is diagnosed, estimate the gestational age using the LMP. Confirm with a brief exam of uterine size. When in doubt, arrange an ultrasound and obstetric consultation promptly, as gestational age will affect counseling options.
   c. Share the diagnosis with the patient privately. Encourage them to involve a parent or legal guardian and facilitate the discussion, if necessary. Be familiar with local confidentiality laws, which vary by state.
   d. Review the patient's medications to ensure they are safe for pregnancy. Start patient on prenatal vitamin if not taking.
2. **Prenatal testing:** All pregnant adolescents should be tested for HIV, syphilis, hepatitis B, chlamydia, and gonorrhea at the first prenatal visit. If an infection is suspected or if there may be a delay in obstetric care, the pediatrician should perform the testing.

3. **Options counseling:** Counsel the adolescent on the importance of making a timely decision. The options depend on gestational age, but may include continuing the pregnancy and raising the infant, continuing the pregnancy and making an adoption plan, or terminating the pregnancy. If a pediatrician has personal limitations in offering a discussion of all three options, he/she should make a prompt referral to a colleague or consultant. Medical and surgical abortion may be available depending on the gestational age of the pregnancy and coexisting medical conditions. Medical abortion is generally available under 9 weeks of gestation; surgical abortion is generally available under 20 to 24 weeks of gestation.
4. **Complications:** First trimester complications include ectopic pregnancy and spontaneous abortion; immediate obstetric referral may be indicated for abdominal pain and/or vaginal bleeding in the pregnant patient.

III. TRANSITIONING ADOLESCENTS INTO ADULT CARE[51]

All adolescents, particularly those with special healthcare needs or chronic conditions, benefit from careful attention to the process of transitioning to adult care. Transition planning should routinely occur during well-visits and should start at age 12. Resources for how to approach and organize the transition process including guidance on transition readiness and planning are available at http://www.gottransition.org/. See Chapter 9 for discussion of transition to adult care for youth with developmental disorders and disabilities.

IV. WEB RESOURCES

A. Websites for Clinicians

- Centers for Disease Control and Prevention (CDC) on contraception: http://www.cdc.gov/reproductivehealth/unintendedpregnancy/contraception.htm
- CDC on sexually transmitted infections (STI): https://www.cdc.gov/std/life-stages-populations/adolescents-youngadults.htm
- Society for Adolescent Health and Medicine: http://www.adolescenthealth.org

B. Websites for Patients

- Drug abuse: http://www.teens.drugabuse.gov
- Sexual health: http://www.plannedparenthood.org/, http://www.bedsider.org
- CDC resources for Lesbian, Gay, Bisexual, & Transgender (LGBT) youth: https://www.cdc.gov/lgbthealth/youth-resources.htm

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

BOX EC 5.A

OBTAINING THE SEXUAL HISTORY: THE FIVE PS

1. Partners
   - "Do you have sex with men, women, or both?"
   - "In the past 2 months, how many partners have you had sex with?"
   - "In the past 12 months, how many partners have you had sex with?"
   - "Is it possible that any of your sex partners in the past 12 months had sex with someone else while they were still in a sexual relationship with you?"
2. Prevention of Pregnancy
   - "What are you doing to prevent pregnancy?"
3. Protection from STIs
   - "What do you do to protect yourself from STIs including HIV?"
4. Practices
   - "To understand your risk for STIs, I need to understand the kind of sex you have had recently."
   - "Have you had vaginal sex, meaning 'penis in vagina sex'?" If yes, "Do you use condoms: never, sometimes, or always?"
   - "Have you had anal sex, meaning "penis in rectum/anus sex"?" If yes, "Do you use condoms: never, sometimes, or always?"
   - "Have you had oral sex, meaning 'mouth on penis/vagina sex'?"
   - "Have you had vaginal or anal sex using fingers or sex toys?"

   For condom answers:
   - If "never": "Why don't you use condoms?"
   - If "sometimes": "In what situations, or with whom, do you not use condoms?"
5. Past History of STIs
   - "Have you ever had an STI?"
   - "Have any of your partners had an STI?"

Additional questions to identify HIV and viral hepatitis risk include:

- "Have you or any of your partners ever injected drugs?"
- "Have any of your partners exchanged money or drugs for sex?"
- "Is there anything else about your sexual practices I need to know about?"

HIV, Human immunodeficiency virus; *STI*, sexually transmitted infection.

Modified from the Centers for Disease Control and Prevention (CDC). *Sexually Transmitted Diseases Treatment Guidelines 2015, Clinical Prevention Guidance.* Available at https://www.cdc.gov/std/tg2015/clinical.htm.

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Chapter 6

Analgesia and Procedural Sedation

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See additional content on Expert Consult

I. PAIN ASSESSMENT

A. Infant[1]

1. **Physiologic response**
   a. Characterized by oxygen desaturation, crying, diaphoresis, flushing or pallor, and increases in blood pressure, heart rate, and respiratory rate.
   b. Seen primarily in acute pain; subsides with continuing/chronic pain.
2. **Behavioral response**
   a. Observe characteristics and duration of cry, facial expressions, visual tracking, body movements, and response to stimuli.
   b. Neonatal Infant Pain Scale (NIPS): Behavioral assessment tool for the preterm neonate and full-term neonate up to 6 weeks after birth.
   c. FLACC scale (Table 6.1): Measures and evaluates pain interventions by quantifying pain behaviors, including **F**acial expression, **L**eg movement, **A**ctivity, **C**ry, and **C**onsolability, with scores ranging from 0 to 10.[2] The Revised FLACC scale is reliable in children with cognitive impairment.[3]

B. Preschooler

In addition to physiologic and behavioral responses, the **FACES** pain scale revised (FPS-R) can be used to assess pain intensity in children as young as 3 years of age by having the patient point to the image on the scale that best characterizes their pain (Fig. 6.1).

C. School-Age and Adolescent

Evaluate physiologic and behavioral responses; ask about description, location, and character of pain. Starting at the age of 7 years, children can use the standard subjective pain rating scale, in which 0 is no pain and 10 is the worst pain ever experienced.

II. ANALGESICS[1]

A. Safety

1. Combined Analgesics
   a. Danger of acetaminophen toxicity when using combined opioid-acetaminophen products (oxycodone or hydrocodone with acetaminophen).

TABLE 6.1

FLACC PAIN ASSESSMENT TOOL

FACE

0—No particular expression or smile
1—Occasional grimace or frown, withdrawn, disinterested
2—Frequent to constant frown, quivering chin, clenched jaw

LEGS

0—Normal position or relaxed
1—Uneasy, restless, tense
2—Kicking or legs drawn up

ACTIVITY

0—Lying quietly, normal position, moves easily
1—Squirming, shifting back and forth, tense
2—Arched, rigid, or jerking

CRY

0—No cry (awake or asleep)
1—Moans or whimpers, occasional complaint
2—Crying steadily, screams or sobs, frequent complaints

CONSOLABILITY

0—Content, relaxed
1—Reassured by occasional touching, hugging, or being talked to; distractible
2—Difficult to console or comfort

Modified from Manworren R, Hynan L. Clinical validation of FLACC: preverbal patient pain scale. *Pediatr Nurs.* 2003;29:140–146.

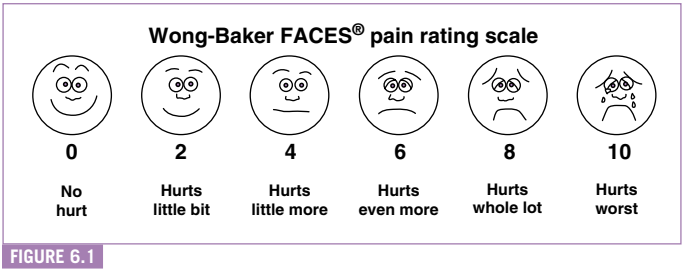

FIGURE 6.1

Wong-Baker FACES Pain Rating Scale (From wongbakerfaces.org: Wong-Baker FACES Foundation [2016]. Wong-Baker FACES® Pain Rating Scale. Retrieved with permission from http://www.WongBakerFACES.org. Originally published in *Whaley & Wong's Nursing Care of Infants and Children*. © Elsevier Inc.)

b. **Preferable to prescribe opioids and acetaminophen separately.**

2. Codeine
   a. **Not recommended for use in children.**
   b. Five percent of the population show ultra-rapid metabolism of codeine to morphine (the active metabolite), which can lead to dangerously high levels. This is especially unsafe after tonsillectomy and adenoidectomy (T&A) performed for sleep apnea.[4]

   c. Little to no analgesic effect in newborns and approximately 10% of the U.S. population.[5]
3. Meperidine
   a. Not recommended for use in children due to risk of neurotoxicity (agitation, tremors, myoclonus, and seizures), especially when renal dysfunction is present.[6]
   b. Contraindicated in patients receiving monoamine oxidase (MAO) inhibitors.
4. Tramadol
   a. Opioid pain reliever, with additional effects on nonopioid receptors.
   b. May be over-metabolized to an active opiate metabolite, resulting in potentially fatal respiratory depression.
   c. In 2017, the FDA issued its strongest warning against use in children; therefore, administration is considered off-label.[7]

B. Nonopioid Analgesics

Weak analgesics with antipyretic activity are commonly used to manage mild to moderate pain of nonvisceral origin. Can be administered alone or in combination with opioids.

1. **Acetaminophen [by mouth (PO)/per rectum (PR)/intravenous (IV)]:** Weak analgesic with no antiinflammatory activity, platelet inhibition, or gastrointestinal (GI) irritation. **Hepatotoxicity can occur with high doses.**
2. **Aspirin (PO/PR):** Associated with platelet inhibition and GI irritation. **Avoid for analgesia in pediatrics due to risk of Reye syndrome.**
3. **Nonsteroidal antiinflammatory drugs (NSAIDs):** Ibuprofen (PO/IV), ketorolac [IV/intramuscular (IM)/PO/intranasal (IN)], naproxen (PO), diclofenac (PO/IV), and celecoxib (PO).
   a. Use with extreme caution in children less than 6 months of age due to concern for adverse GI effects and risk of renal failure.
   b. Especially useful for sickle cell disease, bony, rheumatic, and inflammatory pain.
   c. Concurrent histamine-2-receptor blocker or proton pump inhibitor is recommended with prolonged use given GI side effects.
   d. Other adverse effects include interference with platelet aggregation, hepatitis, bronchoconstriction, hypersensitivity reactions, and azotemia. Avoid in patients with severe renal disease, dehydration, or heart failure.

NOTE: Ketorolac is a potent analgesic. Limit duration of therapy to less than 5 days to limit renal toxicity.

C. Opioids (Table 6.2)

1. Produce analgesia by binding to μ receptors in the brain and spinal cord.
2. **Side effects:** Pruritus, nausea, vomiting, constipation, urine retention, and (rarely) respiratory depression and hypotension. Prescribe a bowel regimen when prescribing opioids.

TABLE 6.2

COMMONLY USED OPIOIDS

Drug	Morphine Equivalence Ratio	Onset (min)	Duration (hr)	Side Effects	Comments
Fentanyl	80–100	IV: 1–2	0.5–1	Pruritus Bradycardia **Chest wall rigidity with doses >5 mCg/kg** (but can occur at all doses); **treat with naloxone or neuromuscular blockade.**	Risk of cardiovascular instability is lower than other opioids, making it relatively safer in hypovolemia, congenital heart disease, or head trauma Respiratory depressant effect much longer (4 hr) than analgesic effect Most commonly used opioid for short, painful procedures, but transdermal route is more effective in chronic pain situations[a]
Hydromorphone	4–7	IV/SQ: 5–10 PO: 30–60	3–4		Less sedation, nausea, and pruritus than morphine
Methadone	0.25–1[b]	IV: 5–10 PO: 30–60	4–24		Initial dose may produce analgesia for 3–4 hr; duration of action is increased with repeated dosing Useful for neuropathic pain and opioid weaning due to unique mechanism of NMDA blockade
Morphine	1	IV: 5–10 IM/SQ: 10–30 PO: 30–60	IV: 3–4 IM/SQ/PO: 4–5	Seizures in neonates. Can cause significant histamine release.	Available in sustained-release form for chronic pain
Oxycodone	1.5	30–60	3–4		Available in sustained-release form for chronic pain

[a]Removing a transdermal fentanyl patch does not stop opioid uptake from the skin; fentanyl will continue to be absorbed for 12–24 hours after patch removal (fentanyl 25-mCg patch administers 25 mCg/hr of fentanyl).
[b]Morphine-to-methadone conversion in the tolerant/dependent patient is variable. Consider starting at the lowest conversion ratio: 0.25.
IM, Intramuscular; *IV*, intravenous; *mCg*, microgram; *PO*, by mouth; *SQ*, subcutaneous.
Data from Yaster M, Cote C, Krane E, et al. *Pediatric Pain Management and Sedation Handbook*. St. Louis: Mosby; 1997:29–50.

3. **Patients with renal failure.**
   a. **Morphine:** Avoid use secondary to decreased excretion of the active metabolite that can result in respiratory depression.
   b. **Preferred choices:** Fentanyl, remifentanil, methadone, hydromorphone, oxycodone.
4. Long-acting opioids (methadone, extended-release tablets, and patches) are not recommended for acute pain.
5. Although opioids are essential for the treatment of moderate to severe pain, a thoughtful approach is recommended with the quantity that is dispensed, as studies have shown that over 50% of opioid doses dispensed are not consumed.[8] There is need for further research to develop evidence-based opioid prescribing guidelines for treating acute pain in children.

D. Local Anesthetics[9–12]

Administered topically or subcutaneously to surround peripheral nerves (peripheral block) or centrally (epidural/spinal block). Temporarily block nerve conduction at the sodium channel.

1. **For all local anesthetics, 1% solution = 10 mg/mL**[b]
2. **Topical local anesthetics** (Table 6.3)[12]
3. **Injectable local anesthetics** (Table 6.4):
   a. Subcutaneous infiltration of the skin at the site: Used for painful procedures such as wound closure or lumbar puncture.
   b. Use of a 27- to 30-gauge needle, alkalization, warming the solution to 37°C to 42°C, and a slow injection can reduce stinging from injection. Alkalinize by adding 1 mL (1 mEq[c]) sodium bicarbonate to 9 mL lidocaine (or 29 mL bupivacaine).
   c. To enhance efficacy and duration, add epinephrine (5 to 10 mCg[d] of epinephrine to 1 mL of local anesthetic) to decrease vascular uptake. **Never use local anesthetics with epinephrine in areas supplied by end arteries (e.g., pinna, fingers, toes, nasal tip, penis).**
   d. **Maximum volume (mL) = (maximum mg/kg dose × weight in kg)/(% solution × 10).** See Table 6.4 for maximum doses.
   e. Toxicity: Central nervous system (CNS) and cardiac toxicity are of greatest concern. CNS symptoms are seen before cardiovascular collapse. Always calculate the maximum volume of the local anesthetic and always draw up less than that. Bupivacaine is associated with more severe cardiac toxicity than lidocaine.
      (1) Progression of symptoms: Perioral numbness → dizziness → auditory disturbances → muscular twitching → unconsciousness → seizures → coma → respiratory arrest → cardiovascular collapse.

[a]mL, milliliter.
[b]mEq, milliequivalent.
[c]mCg, microgram.

TABLE 6.3

COMMONLY USED TOPICAL LOCAL ANESTHETICS

	Components	Indications	Peak Effect	Duration[a]	Cautions
EMLA	Lidocaine 2.5% Prilocaine 2.5%	**Intact skin only** Venipuncture, circumcision, LP, abscess drainage, BMA	60 min	90 min	Methemoglobinemia: Not for use in patients predisposed to methemoglobinemia (G6PD deficiency) Infants <3 months of age: Use sparingly (up to 1 g is safe)
LMX	Lidocaine 4%	Same as EMLA	30 min	60 min	Same as EMLA
LET	Lidocaine 4% Epinephrine 0.1% Tetracaine 0.5% Can be mixed with cellulose to create a gel	**Safe for nonintact skin/ lacerations** Can be used to attain hemostasis with simple lacerations	30 min	45 min	Vasoconstriction: Contraindicated in areas supplied by end arteries (e.g., pinna, nose, penis, digits) Avoid contact with mucous membranes Not for use in contaminated wounds
Viscous lidocaine	Lidocaine 2% (May be mixed with Aluminum/Magnesium Hydroxide/Simethicone (Maalox) and diphenhydramine in a 1:1:1 ratio for palatability when administered orally)	**Safe for nonintact skin** Mucous membranes (e.g., urethral catheter placement, mucositis)	10 min	30 min	Overuse can lead to life-threatening toxicity Not to be used for teething

[a]Approximate.

BMA, Bone marrow aspiration; *EMLA*, eutectic mixture of local anesthetics; *G6PD*, glucose-6-phosphate dehydrogenase; *LP*, lumbar puncture; *min*, minutes.

Data from Krauss B, Green SM. Sedation and analgesia for procedures in children. *N Engl J Med*. 2000;342:938–945; and Zempsky W, Cravero J. Relief of pain and anxiety in pediatric patients in emergency medical systems. *Pediatrics*. 2004;114:1348–1356.

TABLE 6.4

COMMONLY USED INJECTABLE LOCAL ANESTHETICS[1,10]

Agent	Concentration (%)[a]	Max Dose (mg/kg)	Onset (min)	Duration (hr)
Lidocaine	0.5–2	5	3	0.5–2
Lidocaine with epinephrine	0.5–2	7	3	1–3
Bupivacaine	0.25–0.75	2.5	15	2–4
Bupivacaine with epinephrine	0.25–0.75	3	15	4–8
Bupivacaine with Lidocaine mixture	Variable	[b]	3–15	0.5–4

[a](1% solution = 10 mg/mL).

[b][(mg/kg used of bupivacaine)/2.5 mg/kg × 100] + [(mg/kg used of lidocaine)/5 mg/kg × 100]. **Toxicity occurs when the sum is >100%.**

Data from St Germain BA. The management of pain in the emergency department. *Pediatr Clin North Am.* 2000;47:651–679; Yaster M, Cote C, Krane E, et al. *Pediatric Pain Management and Sedation Handbook.* St. Louis: Mosby; 1997:51–72.

Lipid emulsion 20% (Precise volume and flow rate are not crucial)	
Greater than 70 kg patient	Less than 70 kg patient
Bolus 100 mL lipid emulsion 20% rapidly over 2–3 minutes • Lipid emulsion infusion 200–250 mL over 15–20 minutes	**Bolus 1.5 mL/kg lipid emulsion 20%** rapidly over 2–3 minutes • Lipid emulsion infusion ~0.25 mL/kg/min (ideal body weight)
If patient remains unstable: • Re-bolus once or twice at the same dose and double infusion rate; be aware of dosing limit (12mL/kg) • Total volume of lipid emulsion can approach 1 L in a prolonged resuscitation (e.g., >30 minutes)	

FIGURE 6.2

Lipid emulsion 20%.

(2) Summary of American Society of Regional Anesthesia and Pain Medicine (ASRA) Checklist for Treatment of Local Anesthetic Systemic Toxicity (LAST) (https://www.asra.com/content/documents/asra_last_checklist_2018.pdf)
   (a) Stop injecting local anesthetic.
   (b) Call for help and obtain 20% lipid emulsion (see Fig. 6.2 for dosing).
   (c) Manage airway: ventilate with 100% FiO_2 (fraction of inspired oxygen), insert advanced airway if needed.
   (d) Control seizures with benzodiazepines; avoid large doses of propofol due to the potential to exacerbate hypotension.

(e) Treat hypotension and bradycardia—start cardiopulmonary resuscitation (CPR) if pulseless. Avoid hyperventilation.

(3) If concerned for systemic toxicity, contact an anesthesiologist and call poison control (1-800-222-1222).

E. Nonpharmacologic Measures of Pain Relief[13,14]

1. **Sucrose for neonates (Sweet-Ease):**
   a. Indications: Painful minor procedures (heel lance, venipuncture, and intramuscular injection) in neonates and infants. Has not been shown to be effective for relief of circumcision pain. Strongest evidence for infants aged 0 to 1 month,[13] but additional evidence suggests efficacy up to 12 months.[14]
   b. Procedure: Administer up to 2 mL of 24% sucrose into the infant's mouth by syringe or from a nipple/pacifier ~2 minutes before the procedure. Effective doses in very low-birth-weight infants may be as low as 0.05 to 0.1 mL.
   c. An additional dose may be administered within a relatively short period of time for multiple procedures, but it should not be administered more than twice in 1 hour.
   d. Use along with other age-appropriate nonpharmacologic measures listed below.
   e. Avoid if patient is unable to appropriately feed by mouth or cannot safely handle oral secretions.
2. **Other:** Parental presence/holding, distraction with toys, child life specialists, guided meditation/coping skills, virtual reality simulations.

III. PATIENT-CONTROLLED ANALGESIA (PCA)

A. Definition

PCA enables a patient to receive a limited number of small doses (boluses) of an analgesic with or without a continuous (basal) infusion on an as-needed basis. In children younger than 6 years old or with physical/mental disability, a family member, caregiver, or nurse may administer supplemental (bolus) doses.

B. Indications

1. Moderate to severe pain of acute or chronic nature. Commonly used in sickle cell disease, postsurgery, posttrauma, burns, and cancer.
2. Useful for preemptive pain management (e.g., dressing changes).

C. Routes of Administration

IV or epidural

D. Agents (Table 6.5)

E. Adjuvants

1. Low-dose naloxone (Narcan) infusion reduces incidence of pruritus and nausea associated with narcotic administration.

TABLE 6.5

ORDERS FOR PATIENT-CONTROLLED ANALGESIA

Drug	Basal Rate (mCg/kg/hr)	Bolus Dose (mCg/kg)	Lockout Period (min)	Boluses (hr)	Max Dose (mCg/kg/hr)
Morphine	10–30	10–30	6–10	4–6	100–150
Hydromorphone	3–5	3–5	6–10	4–6	15–20
Fentanyl	0.5–1	0.5–1.0	6–10	2–3	2–4

mCg, Microgram.

Data from Yaster M, Cote C, Krane E, et al. *Pediatric Pain Management and Sedation Handbook.* St. Louis: Mosby; 1997:100.

2. Low-dose ketamine infusion has a narcotic sparing effect. It is especially helpful in chemotherapy-induced mucositis, visceral pain, and neuropathic pain. Its mechanism of action is by N-methyl-D-aspartate (NMDA) blockade. May be used with or as an alternative to methadone.

F. Side Effects of Opioid Patient-Controlled Analgesia

Pruritus, nausea, constipation, urine retention, excessive drowsiness, and respiratory depression.

IV. OPIOID TAPERING

A. Indications

Because of the development of dependence and potential for withdrawal, a tapering schedule is required if the patient has received frequent opioid analgesics for >5 days.

B. Withdrawal

1. **See Box 18.1 for symptoms of opioid withdrawal.**
2. **Onset of signs and symptoms:** 6 to 12 hours after the last dose of morphine and 36 to 48 hours after the last dose of methadone.
3. **Duration:** 7 to 14 days, with a peak intensity reached within 2 to 4 days.

C. Recommendations for Tapering

1. **Conversion:** All drugs should be converted to a single equi-analgesic member of that group (see Table 6.2).
2. **PCA wean:** Drug dosing should be changed from continuous/intermittent IV infusion to PO basal/bolus therapy. If the patient is on PCA, once the first PO dose is administered, the PCA basal infusion should be stopped 30 to 60 minutes later. PCA bolus doses should be continued but reduced by 25% to 50%. If no further bolus doses are administered in the next 6 hours, the PCA should be discontinued. If the patient continues to experience pain, consider increasing scheduled PO dose, administering a rescue one-time PO bolus dose, or adding an adjuvant analgesic (e.g., NSAID).
3. **Slow dose decrease:** During an intermittent IV/PO wean, the total daily dose should be decreased by 10% to 20% of the original dose every 1 to 2 days (e.g., to taper a morphine dose of 40 mg/day, decrease the daily dose by 4 to 8 mg every 1 to 2 days).

4. **Oral regimen:** If not done previously, IV dosing should be converted to equivalent PO administration 1 to 2 days before discharge, and titration should be continued as outlined previously.
5. **Adjunctive therapy:**
   a. Clonidine in combination with an opioid decreases the length of time needed for opioid weaning in neonatal abstinence syndrome, with few short-term side effects. Long-term safety has yet to be thoroughly investigated, but follow-up after 1 year on motor, cognitive, and language scores showed no difference in those treated with clonidine.[15,16]
   b. PO and transdermal clonidine have a potential role for sedation, analgesia, and iatrogenic drug withdrawal in critically ill children, but current reports are retrospective or small clinical trials with significant heterogeneity in dosing, so further research is necessary. Transdermal dosing should not be used in children aged <1 year due to altered skin absorption.[17]
   c. Studies have shown efficacy of α_2-adrenergic agonists in treating opioid withdrawal and reducing doses of methadone, but the duration of treatment was longer with α_2-adrenergic agonists, and there were fewer adverse effects with methadone.[18]
   d. Dexmedetomidine is an α_2-adrenoreceptor agonist, which produces sedation and mild analgesia, with minimal to no respiratory depression. Administered as a continuous infusion, it has been shown to reduce opioid requirements and facilitate opioid weaning.

D. Examples

See Box EC 6.A for example of opioid wean.

V. PROCEDURAL SEDATION[1,9–12,19–21]

A. Definitions

1. **Mild sedation (anxiolysis):** Intent is anxiolysis with maintenance of consciousness.
2. **Moderate sedation:** Formerly known as *conscious sedation.* A controlled state of depressed consciousness during which airway reflexes and patency are maintained. Patient responds appropriately to age-appropriate commands (e.g., "Open your eyes") and light touch. Practically obtained any time a combination of a sedative-hypnotic and an analgesic are used.
3. **Deep sedation:** A controlled state of depressed consciousness during which *airway reflexes and patency may **not** be maintained*, and the child is unable to respond to physical or verbal stimuli. In practice, deep sedation is required for most painful procedures in children. Practically obtained with propofol.
4. **Dissociative sedation:** Unique state of sedation achieved with ketamine characterized by a deep level of depressed consciousness and

TABLE 6.6

FASTING RECOMMENDATIONS FOR ANESTHESIA

Food Type	Minimum Fasting Period (hr)
Clear liquids	2
Breast milk	4
Nonhuman milk, formula	6
Solids	8

Data from Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures. A report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and Use of Pharmacological Agents to Reduce the Risk of Pulmonary Aspiration (Online). http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1933410.

analgesia. Airway reflexes and patency are generally maintained; however, excessive oral secretions may become problematic, occasionally resulting in micro-aspiration or laryngospasm.

B. Preparation

1. The patient should be **NPO** for solids and liquids (Table 6.6).[19] Per American Society of Anesthesiologists (ASA) and American Academy of Pediatrics (AAP) guidelines, children receiving moderate sedation for elective procedures should follow the same fasting guidelines as those for general anesthesia.[20,22] For urgent/emergent sedation when children are not NPO, the risks of sedation and possible aspiration must be balanced against the benefits of performing the procedure promptly. Recent studies suggest that NPO status for liquids and solids may not be statistically associated with aspiration, although studies are limited as aspiration is a relatively uncommon complication.[23]
2. **Focused patient history:**
   a. Allergies, medications, and any history of a previous reaction to anesthesia or sedation.
   b. Assess for the possibility of an adverse airway event occurring with sedation (hypoxemia, hypercarbia, inability to mask ventilate, etc.). This can occur from: (1) mechanical airway obstruction (micrognathia, tonsillar and/or adenoid hypertrophy, large tongue, history of snoring, presence of noisy breathing, diagnosis of obstructive sleep apnea, obesity, presence of a craniofacial syndrome), (2) lung disease (history of prematurity, chronic lung disease or bronchopulmonary dysplasia, asthma), or (3) presence of a recent upper respiratory infection (URI). A history of a URI increases the risk of laryngospasm and/or bronchospasm; therefore, one must weigh the risks/benefits of providing sedation after a recent URI versus need for immediate interventional procedure. For elective procedures requiring sedation, it is best to wait 2 to 4 weeks after resolution of illness to reduce the risk of an adverse event.[24]
   c. Assess aspiration risk (neuromuscular disease, esophageal disease, altered mental status, obesity, pregnancy).

BOX EC 6.A

EXAMPLE OF OPIOID TAPERING

Patient on morphine patient-controlled analgesia (PCA) to be converted to oral (PO) morphine with home weaning.

For example: morphine PCA basal rate = 2 mg/hr, average bolus rate = 0.5 mg/hr

Step 1: Calculate daily dose: basal + bolus = (2 mg/hr × 24 hr) + (0.5 mg/hr × 24 hr) = 60 mg intravenous (IV) morphine

Step 2: Convert according to drug potency: morphine IV/morphine oral = approx. 3:1 potency; 3 × 60 mg = 180 mg PO morphine

Step 3: Prescribe 90 mg BID or 60 mg TID; wean 10%–20% of original dose (30 mg) every 1–2 days

BID, Twice daily; *IV*, intravenous; *mg*, milligram; *PCA*, patient controlled analgesia; *PO*, by mouth; *TID*, three times daily.

Data from Yaster M, Cote C, Krane E, et al. *Pediatric Pain Management and Sedation Handbook*. St. Louis: Mosby; 1997:29–50.

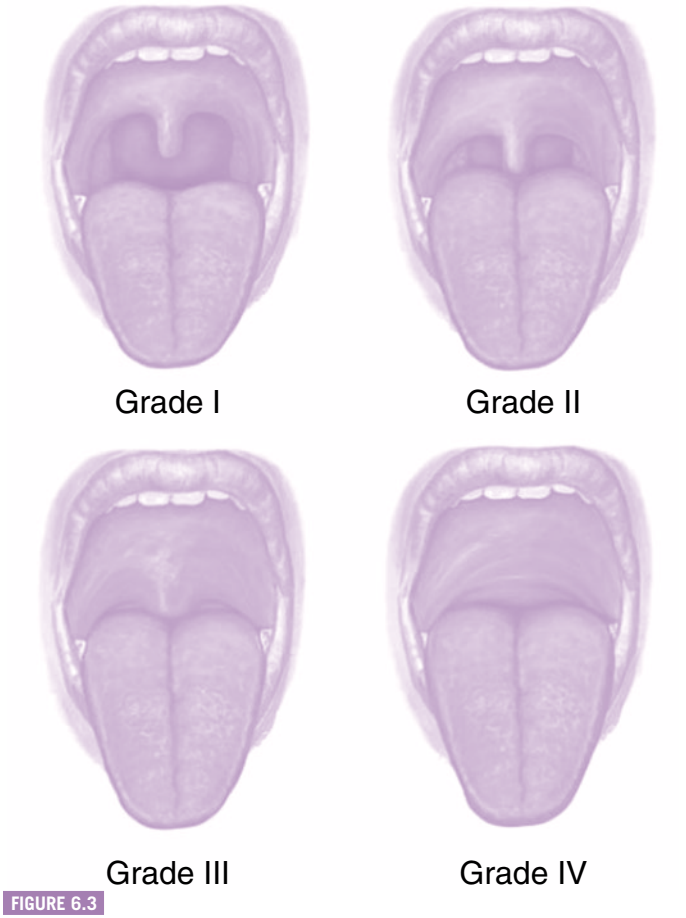

FIGURE 6.3
Mallampati classification system.

d. Presence of kidney/liver disease (may prolong sedative effect) and cardiac disease (potential for hemodynamic instability with sedative administration).

3. **Physical examination:** Specific attention to mouth opening and neck extension. Use the Mallampati classification system to assess the airway for likelihood of difficult direct laryngoscopy and intubation (Fig. 6.3).
4. **Determine ASA Physical Status Classification** (Table 6.7)**:** Class I and II patients are generally good candidates for mild, moderate, or deep sedation outside of the operating room.[20]

TABLE 6.7

ASA PHYSICAL STATUS CLASSIFICATION

Class I	A normally healthy patient
Class II	A patient with mild systemic disease (e.g., controlled reactive airway disease)
Class III	A patient with severe systemic disease (e.g., a child who is actively wheezing)
Class IV	A patient with severe systemic disease that is a constant threat to life (e.g., a child with status asthmaticus)
Class V	A moribund patient who is not expected to survive without the operation (e.g., a patient with severe cardiomyopathy requiring heart transplantation)
Class VI	A declared brain-dead patient whose organs are being removed for donor purposes

5. **Always have an emergency plan ready:**
   a. Make sure qualified backup personnel and equipment are close by.
   b. Complications most often occur 5 to 10 minutes after administration of IV medication and immediately after a procedure is completed (when the stimuli associated with the procedure are removed).[11]
6. **Personnel:** Two providers are required. One provider should perform the procedure, and a separate provider should monitor the patient during sedation and recovery.
7. **Ensure IV access** prior to induction by flushing with saline. Subcutaneous infiltration of a sedative can cause unpredictable or prolonged sedation.
8. **Have airway/intubation equipment immediately available** (see Chapter 1).
9. **Emergency medications:** Always have emergency medications for rapid sequence intubation and CPR immediately available.
10. **Reversal agents** should be readily available (naloxone, flumazenil).

C. Monitoring

1. **Vital signs:** Baseline vital signs should be obtained. Heart rate, oxygen saturation, and respiratory rate should be continuously monitored, and blood pressure monitored intermittently (every 3 to 5 minutes) until a pre-sedation level of consciousness is achieved. **NOTE: Unrecognized apnea is often followed by desaturation within 1 to 2 minutes when not receiving supplemental oxygenation. Administration of supplemental oxygen can further delay recognition of apnea because the onset of desaturation may occur more than 2 minutes after apnea.**
2. **Airway:** Airway patency and adequacy of ventilation should be frequently assessed through capnography (e.g., continuous end-tidal

carbon dioxide [CO_2]), auscultation, and direct visualization. This can help ensure immediate recognition of apnea, and appropriate measures may be taken before desaturation occurs.

D. Pharmacologic Agents

1. **Goal of procedural sedation:** The administration of medications to provide appropriate levels of analgesia, sedation, and anxiolysis so that the procedure can occur without the need to secure the airway.
2. **CNS, cardiovascular, and respiratory depression** may always occur; occurs more commonly when combining sedative drugs and/or opioids, or with rapid drug administration. It is always best to titrate medications to the desired level of sedation.
3. **Common sedative/hypnotic agents (Box 6.1).** Also see Table 6.2 and Table 6.8 for more information on opioids and barbiturates/benzodiazepines.
4. Reversal agents:
   a. Naloxone: Opioid antagonist. See Box 6.2 for naloxone administration protocol.
   b. Flumazenil: Benzodiazepine antagonist.

E. Discharge Criteria[20]

1. The patient can maintain a patent airway without requiring supplemental oxygen. There should also be no compromise in cardiovascular function.
2. The patient should be easily arousable with intact protective airway reflexes (swallow, cough, and gag).
3. The patient should have the ability to talk and sit up unaided (if age appropriate). Alternatively, for very young or intellectually disabled children, the goal is to return to their pre-sedation level of responsiveness.
4. Ensure ability to maintain adequate hydration (i.e., the patient can tolerate enteral fluids).

F. Examples of Sedation Protocols (Table 6.9 and Table EC 6.A)

BOX 6.1

PROPERTIES OF COMMON SEDATIVE-HYPNOTIC AGENTS

Sedating Antihistamines (Diphenhydramine, Hydroxyzine)

- Mild sedative-hypnotics with antiemetic and antipruritic properties; used for sedation and treatment of opioid side effects
- No anxiolytic or analgesic effects

Barbiturates

- Contraindicated in patients with porphyria
- Suitable only for nonpainful procedures
- Not reversible with flumazenil
- Narrower margin of safety than benzodiazepines
- No anxiolytic or analgesic effects

BOX 6.1—cont'd

Benzodiazepines

- Reversible with flumazenil
- Anxiolytic effects; no analgesic effects

Opioids

- Reversible with naloxone
- Analgesic effects; no anxiolytic effects

Ketamine[1,10–13]

- Causes potent dissociative amnesia and analgesia
- Nystagmus indicates likely therapeutic effect
- Vocalizations/movement may occur even with adequate sedation
- Onset: IV, 0.5–2 min; IM, 5–10 min; PO/PR, 20–45 min
- Duration: IV, 20–60 min; IM, 30–90 min; PO/PR, 60–120+ min
- ***CNS effects:*** Emergence delirium with auditory, visual, and tactile hallucinations
- ***Cardiovascular effects:*** Inhibits catecholamine reuptake, thereby causing increased HR, BP, SVR, and PVR. Rarely causes hemodynamic instability; however, in catecholamine-deplete patients (e.g., shock) it can cause direct myocardial depression and hypotension.
- ***Respiratory effects:*** Bronchodilation (useful in asthmatics), increased secretions (can result in laryngospasm), maintenance of ventilatory response to hypoxia, relative maintenance of airway reflexes
- ***Other effects:*** Increased muscle tone, myoclonic jerks, nausea, emesis
- **Contraindications:** Hypertension and preexisting psychotic disorders. Controversy exists on its safety in patients with elevated ICP or IOP. Evidence suggesting ketamine elevates intracranial pressure or causes harm in these patients is limited.

Propofol

- For deep sedation or general anesthesia
- Administered as single or multiple IV boluses +/– infusion
- Rapid onset and brief recovery (5–15 min) with bolus administration
- Can have antiemetic and euphoric effects
- Caution: Respiratory depression, apnea, hypotension
- Anxiolytic; no analgesic effects

Dexmedetomidine

- Give IV load over 10 min, followed by infusion.
- Dexmedetomidine can also be given intranasally. It will take 30–60 min to attain natural sleep, and patients will briefly awaken with stimulation.
- Rapid onset and brief recovery (5–15 min)
- Does not cause respiratory depression or apnea. Can cause hypotension and bradycardia, especially when IV load given too quickly.
- Anxiolytic and analgesic effects
- Increased cost compared with other medications

Nitrous Oxide

- Inhaled gas delivered as a mixture with oxygen
- Amnestic, anxiolytic, and analgesic effects

Continued

BOX 6.1—cont'd

- Extremely rapid onset and recovery
- Due to risk for delivery of hypoxic gas mixture, avoid concentrations higher than 70% (30% oxygen)
- Must be given in combination with other sedative drugs for more painful procedures

BP, Blood pressure; *CNS*, central nervous system; *HR*, heart rate; *ICP*, intracranial pressure; *IM*, intramuscular; *IOP*, intraocular pressure; *IV*, intravenous; *PO*, oral; *PR*, rectal; *PVR*, pulmonary vascular resistance; *SVR*, systemic vascular resistance.

Data from Yaster M, Cote C, Krane E, et al. *Pediatric Pain Management and Sedation Handbook*. St. Louis: Mosby; 1997:376–382; St Germain BA. The management of pain in the emergency department. *Pediatr Clin North Am*. 2000;47:651–679; and Cote CJ, Lerman J, Todres ID, et al. *A Practice of Anesthesia for Infants and Children*. Philadelphia: WB Saunders; 2001.

TABLE EC 6.A

SUGGESTED ANALGESIA AND SEDATION PROTOCOLS

Pain Threshold	Procedure	Suggested Choices
Nonpainful	CT/MRI/EEG/ECHO	Midazolam[a]
Mild	Phlebotomy/IV	EMLA
	LP	EMLA (± midazolam), lidocaine
	Pelvic exam	Midazolam
	Minor laceration, well vascularized	LET
	Minor laceration, not well vascularized	Lidocaine
Moderate	BM aspiration	EMLA (±midazolam)
	Arthrocentesis	Lidocaine (local) for cooperative child or ketamine for uncooperative child
	Fracture reduction	Ketamine
	Major laceration	Ketamine or fentanyl + midazolam
	Burn debridement	Ketamine or fentanyl + midazolam
	Long procedures (>30 min)	Consider general anesthesia
Severe	Fracture reduction	Ketamine
	Long procedures (>30 min)	Consider general anesthesia

[a]Consult with neurologist prior to administering a benzodiazepine for sedation during EEG.

BM, Bone marrow; *CT*, computed tomography; *ECHO*, echocardiogram; *EEG*, electroencephalogram; *EMLA*, eutectic mixture of local anesthetics; *LP*, lumbar puncture; *LET*, lidocaine, epinephrine, tetracaine; *MRI*, magnetic resonance imaging.

Modified from Yaster M, Cote C, Krane E, et al. *Pediatric Pain Management and Sedation Handbook*. St. Louis: Mosby; 1997:551–552.

TABLE 6.8

COMMONLY USED BENZODIAZEPINES[a] AND BARBITURATES[1,4]

Drug Class	Duration of Action	Drug	Route	Onset (min)	Duration (hr)	Comments
Benzodiazepines	Short	Midazolam (Versed)	IV	1–3	1–2	Has rapid and predictable onset of action, short recovery time
			IM/IN	5–10		Causes amnesia
			PO/PR	10–30		Results in mild depression of hypoxic ventilatory drive
	Intermediate	Diazepam (Valium)	IV (painful)	1–3	0.25–1	Poor choice for procedural sedation
			PR	7–15	2–3	Excellent for muscle relaxation or prolonged sedation
			PO	30–60	2–3	Painful on IV injection
	Long	Lorazepam (Ativan)	IV	1–5	3–4	Poor choice for procedural sedation
			IM	10–20	3–6	Ideal for prolonged anxiolysis, seizure treatment
			PO	30–60	3–6	
Barbiturates	Short	Methohexital	PR[b]	5–10	1–1.5	PR form used as sedative for nonpainful procedure
	Intermediate	Pentobarbital	IV	1–10	1–4	Predictable sedation and immobility for nonpainful procedures
			IM	5–15	2–4	Minimal respiratory depression when used alone
			PO/PR	15–60	2–4	Associated with slow wake up and agitation

[a]Use IV solution for PO, PR, and IN administration. Rectal diazepam gel (Diastat) is also available.

[b]IV administration produces general anesthesia; only PR should be used for sedation.

IM, Intramuscular; *IN*, intranasal; *IV*, intravenous; *min*, minute; *PO*, by mouth; *PR*, per rectum.

Data from Yaster M, Cote C, Krane E, et al. *Pediatric Pain Management and Sedation Handbook*. St. Louis: Mosby; 1997:345–374; St Germain BA. The management of pain in the emergency department. *Pediatr Clin North Am*. 2000;47:651–679; and Cote CJ, Lerman J, Todres ID, et al. *A Practice of Anesthesia for Infants and Children*. Philadelphia: WB Saunders; 2001.

BOX 6.2

NALOXONE (NARCAN) ADMINISTRATION[a]

Indications: Patients Requiring Naloxone (Narcan) Usually Meet All the Following Criteria

- Shallow respirations or respiratory rate <8 breaths/min[b]
- Pinpoint pupils
- Unresponsive to physical stimulation

Procedure

1. **Stop opioid administration** (as well as other sedative drugs), assess **ABCs** (**A**irway, **B**reathing, **C**irculation), and **call for help.**
2. **Dilute naloxone:**
   a. If child >40 kg: Mix 0.4 mg (1 ampule) of naloxone with 9 mL of normal saline (final concentration 0.04 mg/mL = 40 mCg/mL)
   b. If child <40 kg: Mix 0.4 mg (1 ampule) of naloxone with 9 mL of normal saline to make a concentration of 40 mCg/mL (as above). **Then, repeat dilution** by mixing 1 mL of the 40 mCg/mL solution with 9 mL of normal saline for final concentration of 4 mCg/mL.
3. **Administer and observe response:** Administer dilute naloxone *slowly* (1–2 mCg/kg/dose IV over 2 minutes). Observe patient response.
4. **Titrate to effect:** Within 1–2 minutes, patient should open eyes and respond. If not, continue until a total dose of 10 mCg/kg is given. If no response is obtained, evaluate for other cause of sedation/respiratory depression.
5. **Discontinue naloxone administration:** Discontinue naloxone as soon as patient responds (e.g., takes deep breaths when directed).
6. **Caution:** Another dose of naloxone may be required within 30 min of first dose (duration of action of naloxone is shorter than that of most opioids).
7. **Monitor patient:** Assign a staff member to monitor sedation/respiratory status and remind patient to take deep breaths as necessary.
8. **Alternative analgesia:** Provide nonopioids for pain relief. Resume opioid administration at half the original dose when the patient is easily aroused, and respiratory rate is >9 breaths/min.

[a]Naloxone administration for patients being treated for pain. Higher doses may be necessary for patients found in the community or those with signs of cardiopulmonary failure. Please see formulary for additional dosing.

[b]Respiratory rates that require naloxone vary according to infant's/child's usual rate.

IV, Intravenous; *kg*, kilogram; *mCg*, microgram; *mg*, milligram; *mL*, milliliter.

Modified from McCaffery M, Pasero C. *Pain: Clinical Manual*. St. Louis: Mosby; 1999:269–270.

TABLE 6.9

EXAMPLES OF SEDATION PROTOCOLS

Protocol/Doses	Comments
Ketamine × 1–3 doses	Lowest rates of adverse events when ketamine used alone[a]
Ketamine + midazolam + atropine ("ketazolam")	Atropine = antisialagogue Midazolam = counters emergence delirium
Ketamine × 1–3 doses Midazolam × 1 dose Atropine × 1 dose	Can be given IM or IV. If giving IM, combine all 3 agents in 1 syringe (using the smallest volume possible, preferably <3 mL total).
Midazolam + fentanyl	High likelihood of respiratory depression
Midazolam × 3 doses PRN	Give fentanyl no more frequently than every 3 min
Fentanyl × 3 doses PRN	Risk of rigid chest—give no faster than 1 mCg/kg/min

[a]Green, SM, Roback MG, Krauss B, et al. Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med.* 2009;54:171–180.
IM, Intramuscular; *IV*, intravenous; *mCg*, microgram; *PRN*, as needed.
Modified from Yaster M, Cote C, Krane E, et al. *Pediatric Pain Management and Sedation Handbook*. St. Louis: Mosby; 1997.

VI. WEB RESOURCES

- International Association for the Study of Pain: http://childpain.org/
- American Pain Society: http://www.ampainsoc.org/
- American Society of Anesthesiologists: http://www.asahq.org/

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 7

Cardiology

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See additional content on Expert Consult

I. PHYSICAL EXAMINATION

A. Heart Rate

Refer to the inside front cover for normal heart rate (HR) by age.

B. Blood Pressure

1. **Blood pressure (BP):**

See Tables 7.1 and 7.2 for normal BP values (systolic blood pressure [SBP], diastolic blood pressure [DBP]) by age.[1,2]

2. **Mean arterial pressure (MAP)**
   a. MAP = diastolic pressure + (pulse pressure/3) OR 1/3 systolic pressure + 2/3 diastolic pressure.
   b. Preterm infants and newborns: Normal MAP = gestational age in weeks + 5.
3. **Abnormalities in BP**
   a. Four-limb BP measurements can be used to assess for coarctation of the aorta.
   b. Pulsus paradoxus: Exaggeration of the normal drop in SBP with inspiration. Determine SBP at the end of exhalation and during inhalation; difference >10 mmHg consider pericardial effusion, tamponade, pericarditis, severe asthma, or restrictive cardiomyopathies.
4. **Hypertension (HTN)**
   a. See Chapter 1 for management of acute HTN.
   b. See Chapter 19 for screening, work-up, and management of chronic HTN.

C. Heart Sounds

1. **S_1:** Associated with closure of mitral and tricuspid valves; heard best at the apex or left lower sternal border (LLSB).
2. **S_2:** Associated with closure of pulmonary and aortic valves; heard best at the left upper sternal border (LUSB) and has normal physiologic splitting that increases with inspiration.
3. **S_3:** Heard best at the apex or LLSB.
4. **S_4:** Heard at the apex.

D. Systolic and Diastolic Sounds

See Box 7.1 for abnormal heart sounds.[3]

E. Murmurs[4]

Clinical characteristics are summarized in Table 7.3.[3]

TABLE 7.1

BLOOD PRESSURE LEVELS FOR THE 50TH, 90TH, 95TH, AND 99TH PERCENTILES OF BLOOD PRESSURE FOR GIRLS AGED 1–17 YEARS BY PERCENTILES OF HEIGHT

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	29.7	30.2	30.9	31.8	32.7	33.4	33.9	29.7	30.2	30.9	31.8	32.7	33.4	33.9
	Height (cm)	75.4	76.6	78.6	80.8	83	84.9	86.1	75.4	76.6	78.6	80.8	83	84.9	86.1
	50th	84	85	86	86	87	88	88	41	42	42	43	44	45	46
	90th	98	99	99	100	101	102	102	54	55	56	56	57	58	58
	95th	101	102	102	103	104	105	105	59	59	60	60	61	62	62
	95th + 12 mmHg	113	114	114	115	116	117	117	71	71	72	72	73	74	74
2	Height (in)	33.4	34	34.9	35.9	36.9	37.8	38.4	33.4	34	34.9	35.9	36.9	37.8	38.4
	Height (cm)	84.9	86.3	88.6	91.1	93.7	96	97.4	84.9	86.3	88.6	91.1	93.7	96	97.4
	50th	87	87	88	89	90	91	91	45	46	47	48	49	50	51
	90th	101	101	102	103	104	105	106	58	58	59	60	61	62	62
	95th	104	105	106	106	107	108	109	62	63	63	64	65	66	66
	95th + 12 mmHg	116	117	118	118	119	120	121	74	75	75	76	77	78	78
3	Height (in)	35.8	36.4	37.3	38.4	39.6	40.6	41.2	35.8	36.4	37.3	38.4	39.6	40.6	41.2
	Height (cm)	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	50th	88	89	89	90	91	92	93	48	48	49	50	51	53	53
	90th	102	103	104	104	105	106	107	60	61	61	62	63	64	65
	95th	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	95th + 12 mmHg	118	118	119	120	121	122	122	76	77	77	78	79	80	81

Continued

TABLE 7.1—CONT'D

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
4	Height (in)	38.3	38.9	39.9	41.1	42.4	43.5	44.2	38.3	38.9	39.9	41.1	42.4	43.5	44.2
	Height (cm)	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	50th	89	90	91	92	93	94	94	50	51	51	53	54	55	55
	90th	103	104	105	106	107	108	108	62	63	64	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height (in)	40.8	41.5	42.6	43.9	45.2	46.5	47.3	40.8	41.5	42.6	43.9	45.2	46.5	47.3
	Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	50th	90	91	92	93	94	95	96	52	52	53	55	56	57	57
	90th	104	105	106	107	108	109	110	64	65	66	67	68	69	70
	95th	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	95th + 12 mmHg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height (in)	43.3	44	45.2	46.6	48.1	49.4	50.3	43.4	44	45.2	46.6	48.1	49.4	50.3
	Height (cm)	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	50th	92	92	93	94	96	97	97	54	54	55	56	57	58	59
	90th	105	106	107	108	109	110	111	67	67	68	69	70	71	71
	95th	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	95th + 12 mmHg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height (in)	45.6	46.4	47.7	49.2	50.7	52.1	53	45.6	46.4	47.7	49.2	50.7	52.1	53
	Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	50th	92	93	94	95	97	98	99	55	55	56	57	58	59	60
	90th	106	106	107	109	110	111	112	68	68	69	70	71	72	72
	95th	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	95th + 12 mmHg	121	122	123	124	125	126	127	84	84	85	85	86	86	87

Continued

TABLE 7.1—CONT'D

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
8	Height (in)	47.6	48.4	49.8	51.4	53	54.5	55.5	47.6	48.4	49.8	51.4	53	54.5	55.5
	Height (cm)	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	50th	93	94	95	97	98	99	100	56	56	57	59	60	61	61
	90th	107	107	108	110	111	112	113	69	70	71	72	72	73	73
	95th	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	95th + 12 mmHg	122	123	124	125	127	128	129	84	85	86	87	87	87	87
9	Height (in)	49.3	50.2	51.7	53.4	55.1	56.7	57.7	49.3	50.2	51.7	53.4	55.1	56.7	57.7
	Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	50th	95	95	97	98	99	100	101	57	58	59	60	60	61	61
	90th	108	108	109	111	112	113	114	71	71	72	73	73	73	73
	95th	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	95th + 12 mmHg	124	124	125	126	128	129	130	86	86	87	87	87	87	87
10	Height (in)	51.1	52	53.7	55.5	57.4	59.1	60.2	51.1	52	53.7	55.5	57.4	59.1	60.2
	Height (cm)	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	50th	96	97	98	99	101	102	103	58	59	59	60	61	61	62
	90th	109	110	111	112	113	115	116	72	73	73	73	73	73	73
	95th	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	95th + 12 mmHg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height (in)	53.4	54.5	56.2	58.2	60.2	61.9	63	53.4	54.5	56.2	58.2	60.2	61.9	63
	Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	50th	98	99	101	102	104	105	106	60	60	60	61	62	63	64
	90th	111	112	113	114	116	118	120	74	74	74	74	74	75	75
	95th	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	95th + 12 mmHg	127	128	129	130	132	135	136	88	89	89	89	89	89	89

Continued

TABLE 7.1—CONT'D

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
12	Height (in)	56.2	57.3	59	60.9	62.8	64.5	65.5	56.2	57.3	59	60.9	62.8	64.5	65.5
	Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	50th	102	102	104	105	107	108	108	61	61	61	62	64	65	65
	90th	114	115	116	118	120	122	122	75	75	75	75	76	76	76
	95th	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	95th + 12 mmHg	130	131	132	134	136	137	138	90	90	90	90	91	91	91
13	Height (in)	58.3	59.3	60.9	62.7	64.5	66.1	67	58.3	59.3	60.9	62.7	64.5	66.1	67
	Height (cm)	148.1	150.6	154.7	159.2	163.7	167.8	170.2	148.1	150.6	154.7	159.2	163.7	167.8	170.2
	50th	104	105	106	107	108	108	109	62	62	63	64	65	65	66
	90th	116	117	119	121	122	123	123	75	75	75	76	76	76	76
	95th	121	122	123	124	126	126	127	79	79	79	79	80	80	81
	95th + 12 mmHg	133	134	135	136	138	138	139	91	91	91	91	92	92	93
14	Height (in)	59.3	60.2	61.8	63.5	65.2	66.8	67.7	59.3	60.2	61.8	63.5	65.2	66.8	67.7
	Height (cm)	150.6	153	156.9	161.3	165.7	169.7	172.1	150.6	153	156.9	161.3	165.7	169.7	172.1
	50th	105	106	107	108	109	109	109	63	63	64	65	66	66	66
	90th	118	118	120	122	123	123	123	76	76	76	76	77	77	77
	95th	123	123	124	125	126	127	127	80	80	80	80	81	81	82
	95th + 12 mmHg	135	135	136	137	138	139	139	92	92	92	92	93	93	94
15	Height (in)	59.7	60.6	62.2	63.9	65.6	67.2	68.1	59.7	60.6	62.2	63.9	65.6	67.2	68.1
	Height (cm)	151.7	154	157.9	162.3	166.7	170.6	173	151.7	154	157.9	162.3	166.7	170.6	173
	50th	105	106	107	108	109	109	109	64	64	64	65	66	67	67
	90th	118	119	121	122	123	123	124	76	76	76	77	77	78	78
	95th	124	124	125	126	127	127	128	80	80	80	81	82	82	82
	95th + 12 mmHg	136	136	137	138	139	139	140	92	92	92	93	94	94	94

Continued

TABLE 7.1—CONT'D

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
16	Height (in)	59.9	60.8	62.4	64.1	65.8	67.3	68.3	59.9	60.8	62.4	64.1	65.8	67.3	68.3
	Height (cm)	152.1	154.5	158.4	162.8	167.1	171.1	173.4	152.1	154.5	158.4	162.8	167.1	171.1	173.4
	50th	106	107	108	109	109	110	110	64	64	65	66	66	67	67
	90th	119	120	122	123	124	124	124	76	76	76	77	78	78	78
	95th	124	125	125	127	127	128	128	80	80	80	81	82	82	82
	95th + 12 mmHg	136	137	137	139	139	140	140	92	92	92	93	94	94	94
17	Height (in)	60.0	60.9	62.5	64.2	65.9	67.4	68.4	60.0	60.9	62.5	64.2	65.9	67.4	68.4
	Height (cm)	152.4	154.7	158.7	163.0	167.4	171.3	173.7	152.4	154.7	158.7	163.0	167.4	171.3	173.7
	50th	107	108	109	110	110	110	111	64	64	65	66	66	66	67
	90th	120	121	123	124	124	125	125	76	76	77	77	78	78	78
	95th	125	125	126	127	128	128	128	80	80	80	81	82	82	82
	95th + 12 mmHg	137	137	138	139	140	140	140	92	92	92	93	94	94	94

BP, Blood pressure; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

From Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics.* 2017;e20171904; https://doi.org/10.1542/peds.2017-1904.

TABLE 7.2

BLOOD PRESSURE LEVELS FOR THE 50TH, 90TH, 95TH, AND 99TH PERCENTILES OF BLOOD PRESSURE FOR BOYS AGED 1–17 YEARS BY PERCENTILES OF HEIGHT

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	30.4	30.8	31.6	32.4	33.3	34.1	34.6	30.4	30.8	31.6	32.4	33.3	34.1	34.6
	Height (cm)	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
	50th	85	85	86	86	87	88	88	40	40	40	41	41	42	42
	90th	98	99	99	100	100	101	101	52	52	53	53	54	54	54
	95th	102	102	103	103	104	105	105	54	54	55	55	56	57	57
	95th + 12 mmHg	114	114	115	115	116	117	117	66	66	67	67	68	69	69
2	Height (in)	33.9	34.4	35.3	36.3	37.3	38.2	38.8	33.9	34.4	35.3	36.3	37.3	38.2	38.8
	Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	50th	87	87	88	89	89	90	91	43	43	44	44	45	46	46
	90th	100	100	101	102	103	103	104	55	55	56	56	57	58	58
	95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	95th + 12 mmHg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height (in)	36.4	37	37.9	39	40.1	41.1	41.7	36.4	37	37.9	39	40.1	41.1	41.7
	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	50th	88	89	89	90	91	92	92	45	46	46	47	48	49	49
	90th	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th + 12 mmHg	118	118	119	119	120	121	121	72	73	73	74	75	76	76

Continued

TABLE 7.2—CONT'D

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
4	Height (in)	38.8	39.4	40.5	41.7	42.9	43.9	44.5	38.8	39.4	40.5	41.7	42.9	43.9	44.5
	Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	50th	90	90	91	92	93	94	94	48	49	49	50	51	52	52
	90th	102	103	104	105	105	106	107	60	61	62	62	63	64	64
	95th	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	95th + 12 mmHg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height (in)	41.1	41.8	43.0	44.3	45.5	46.7	47.4	41.1	41.8	43.0	44.3	45.5	46.7	47.4
	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	50th	91	92	93	94	95	96	96	51	51	52	53	54	55	55
	90th	103	104	105	106	107	108	108	63	64	65	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height (in)	43.4	44.2	45.4	46.8	48.2	49.4	50.2	43.4	44.2	45.4	46.8	48.2	49.4	50.2
	Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	50th	93	93	94	95	96	97	98	54	54	55	56	57	57	58
	90th	105	105	106	107	109	110	110	66	66	67	68	68	69	69
	95th	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	95th + 12 mmHg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height (in)	45.7	46.5	47.8	49.3	50.8	52.1	52.9	45.7	46.5	47.8	49.3	50.8	52.1	52.9
	Height (cm)	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	50th	94	94	95	97	98	98	99	56	56	57	58	58	59	59
	90th	106	107	108	109	110	111	111	68	68	69	70	70	71	71
	95th	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	95th + 12 mmHg	122	122	123	124	126	127	128	83	83	84	85	85	86	86

Continued

TABLE 7.2—CONT'D

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
8	Height (in)	47.8	48.6	50	51.6	53.2	54.6	55.5	47.8	48.6	50	51.6	53.2	54.6	55.5
	Height (cm)	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	50th	95	96	97	98	99	99	100	57	57	58	59	59	60	60
	90th	107	108	109	110	111	112	112	69	70	70	71	72	72	73
	95th	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	95th + 12 mmHg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height (in)	49.6	50.5	52	53.7	55.4	56.9	57.9	49.6	50.5	52	53.7	55.4	56.9	57.9
	Height (cm)	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	50th	96	97	98	99	100	101	101	57	58	59	60	61	62	62
	90th	107	108	109	110	112	113	114	70	71	72	73	74	74	74
	95th	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	95th + 12 mmHg	124	124	125	127	128	130	131	86	86	87	88	88	89	89
10	Height (in)	51.3	52.2	53.8	55.6	57.4	59.1	60.1	51.3	52.2	53.8	55.6	57.4	59.1	60.1
	Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	145.9	150.1	152.7
	50th	97	98	99	100	101	102	103	59	60	61	62	63	63	64
	90th	108	109	111	112	113	115	116	72	73	74	74	75	75	76
	95th	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	95th + 12 mmHg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height (in)	53	54	55.7	57.6	59.6	61.3	62.4	53	54	55.7	57.6	59.6	61.3	62.4
	Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
	50th	99	99	101	102	103	104	106	61	61	62	63	63	63	63
	90th	110	111	112	114	116	117	118	74	74	75	75	75	76	76
	95th	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	95th + 12 mmHg	126	126	128	130	132	135	136	89	90	90	90	90	90	90

Continued

TABLE 7.2—CONT'D

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
12	Height (in)	55.2	56.3	58.1	60.1	62.2	64	65.2	55.2	56.3	58.1	60.1	62.2	64	65.2
	Height (cm)	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	50th	101	101	102	104	106	108	109	61	62	62	62	62	63	63
	90th	113	114	115	117	119	121	122	75	75	75	75	75	76	76
	95th	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	95th + 12 mmHg	128	129	130	133	136	138	140	90	90	90	90	90	91	91
13	Height (in)	57.9	59.1	61	63.1	65.2	67.1	68.3	57.9	59.1	61	63.1	65.2	67.1	68.3
	Height (cm)	147	150	154.9	160.3	165.7	170.5	173.4	147	150	154.9	160.3	165.7	170.5	173.4
	50th	103	104	105	108	110	111	112	61	60	61	62	63	64	65
	90th	115	116	118	121	124	126	126	74	74	74	75	76	77	77
	95th	119	120	122	125	128	130	131	78	78	78	78	80	81	81
	95th + 12 mmHg	131	132	134	137	140	142	143	90	90	90	90	92	93	93
14	Height (in)	60.6	61.8	63.8	65.9	68.0	69.8	70.9	60.6	61.8	63.8	65.9	68.0	69.8	70.9
	Height (cm)	153.8	156.9	162	167.5	172.7	177.4	180.1	153.8	156.9	162	167.5	172.7	177.4	180.1
	50th	105	106	109	111	112	113	113	60	60	62	64	65	66	67
	90th	119	120	123	126	127	128	129	74	74	75	77	78	79	80
	95th	123	125	127	130	132	133	134	77	78	79	81	82	83	84
	95th + 12 mmHg	135	137	139	142	144	145	146	89	90	91	93	94	95	96

Continued

TABLE 7.2—CONT'D

Age (years)	BP Percentile	SBP (mmHg) Height Percentile or Measured Height							DBP (mmHg) Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
15	Height (in)	62.6	63.8	65.7	67.8	69.8	71.5	72.5	62.6	63.8	65.7	67.8	69.8	71.5	72.5
	Height (cm)	159	162	166.9	172.2	177.2	181.6	184.2	159	162	166.9	172.2	177.2	181.6	184.2
	50th	108	110	112	113	114	114	114	61	62	64	65	66	67	68
	90th	123	124	126	128	129	130	130	75	76	78	79	80	81	81
	95th	127	129	131	132	134	135	135	78	79	81	83	84	85	85
	95th + 12 mmHg	139	141	143	144	146	147	147	90	91	93	95	96	97	97
16	Height (in)	63.8	64.9	66.8	68.8	70.7	72.4	73.4	63.8	64.9	66.8	70.7	70.7	72.4	73.4
	Height (cm)	162.1	165	169.6	174.6	179.5	183.8	186.4	162.1	165	169.6	174.6	179.5	183.8	186.4
	50th	111	112	114	115	115	116	116	63	64	66	67	68	69	69
	90th	126	127	128	129	131	131	132	77	78	79	80	81	82	82
	95th	130	131	133	134	135	136	137	80	81	83	84	85	86	86
	95th + 12 mmHg	142	143	145	146	147	148	149	92	93	95	96	97	98	98
17	Height (in)	64.5	65.5	67.3	69.2	71.1	72.8	73.8	64.5	65.5	67.3	69.2	71.1	72.8	73.8
	Height (cm)	163.8	166.5	170.9	175.8	180.7	184.9	187.5	163.8	166.5	170.9	175.8	180.7	184.9	187.5
	50th	114	115	116	117	117	118	118	65	66	67	68	69	70	70
	90th	128	129	130	131	132	133	134	78	79	80	81	82	82	83
	95th	132	133	134	135	137	138	138	81	82	84	85	86	86	87
	95th + 12 mmHg	144	145	146	147	149	150	150	93	94	96	97	98	98	99

BP, Blood pressure; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

From Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2017;e20171904; https://doi.org/10.1542/peds.2017-1904.

BOX 7.1

SUMMARY OF ABNORMAL HEART SOUNDS

- **Widely split S_1:** Ebstein anomaly, RBBB
- **Widely split and fixed S_2:** Right ventricular volume overload (e.g., ASD, PAPVR), pressure overload (e.g., PS), electrical delay in RV contraction (e.g., RBBB), early aortic closure (e.g., MR), occasionally heard in normal child
- **Narrowly split S_2:** Pulmonary hypertension, AS, delay in LV contraction (e.g., LBBB), occasionally heard in normal child
- **Single S_2:** Pulmonary hypertension, one semilunar valve (e.g., pulmonary atresia, aortic atresia, truncus arteriosus), P2 not audible (e.g., TGA, TOF, severe PS), severe AS, occasionally heard in normal child
- **Paradoxically split S_2:** Severe AS, LBBB, Wolff-Parkinson-White syndrome (type B)
- **Abnormal intensity of P2:** Increased P2 (e.g., pulmonary hypertension), decreased P2 (e.g., severe PS, TOF, TS)
- **S_3:** Occasionally heard in healthy children or adults or may indicate dilated ventricles (e.g., large VSD, CHF)
- **S_4:** Always pathologic, indicative of decreased ventricular compliance
- **Ejection click:** Heard with stenosis of the semilunar valves, dilated great arteries in the setting of pulmonary or systemic HTN, idiopathic dilation of the PA, TOF, persistent truncus arteriosus
- **Midsystolic click:** Heard at the apex in mitral valve prolapse
- **Diastolic opening snap:** Rare in children; associated with TS/MS

AS, Aortic stenosis; *ASD*, atrial septal defect; *CHF*, congestive heart failure; *LBBB*, left bundle-branch block; *LV*, left ventricle; *MR*, mitral regurgitation; *MS*, mitral stenosis; *PA*, pulmonary artery; *PAPVR*, partial anomalous pulmonary venous return; *PS*, pulmonic stenosis; *RBBB*, right bundle-branch block; *RV*, right ventricular; *TGA*, transposition of the great arteries; *TOF*, tetralogy of fallot; *TS*, tricuspid stenosis; *VSD*, ventricular septal defect.

Modified from Park MK. *Pediatric Cardiology for Practitioners*. 5th ed. St Louis: Elsevier; 2008:25.

1. **Grading of heart murmurs:** Intensified by states of higher cardiac output (e.g., anemia, anxiety, fever, exercise).[3]
   a. Grade I: Barely audible
   b. Grade II: Murmur softer than heart sounds, but audible
   c. Grade III: Murmur moderately loud, equally loud as heart sounds, not accompanied by a thrill
   d. Grade IV: Murmur louder than heart sounds, associated with a thrill
   e. Grade V: Audible with a stethoscope barely on the chest
   f. Grade VI: Audible with a stethoscope off the chest
2. **Benign heart murmurs[4]:**
   a. Caused by a disturbance of the laminar flow of blood; frequently produced as the diameter of the blood's pathway decreases and velocity increases.
   b. Present in >80% of children sometime during childhood, most commonly beginning at age 3 to 4 years.
   c. Accentuated in high-output states, especially with fever and anemia.
   d. Normal electrocardiogram (ECG) and radiographic findings.

   NOTE: ECG and chest radiograph are not routinely used, nor are they cost-effective screening tools for distinguishing benign from pathologic murmurs.

TABLE 7.3

COMMON INNOCENT HEART MURMURS

Type (Timing)	Description of Murmur	Age Group
Classic vibratory murmur (Still's murmur; systolic)	Maximal at LMSB or between LLSB and apex Grade 2–3/6 in intensity Low-frequency vibratory, twanging string, groaning, squeaking, or musical	3–6 years; occasionally in infancy
Pulmonary ejection murmur (systolic)	Maximal at LUSB Early to midsystolic Grade 1–3/6 in intensity Blowing in quality	8–14 years
Pulmonary flow murmur of newborn (systolic)	Maximal at LUSB Transmits well to left and right chest, axilla, and back Grade 1–2/6 in intensity	Premature and full-term newborns Usually disappears by 3–6 months
Venous hum (continuous)	Maximal at right (or left) supraclavicular and infraclavicular areas Grade 1–3/6 in intensity Inaudible in supine position Intensity changes with rotation of head and disappears with compression of jugular vein	3–6 years
Carotid bruit (systolic)	Right supraclavicular area over carotids Grade 2–3/6 in intensity Occasional thrill over carotid	Any age

LLSB, Left lower sternal border; *LMSB*, left middle sternal border; *LUSB*, left upper sternal border
From Park MK. *Pediatric Cardiology for Practitioners*. 5th ed. St Louis: Elsevier; 2008:36.

3. **A murmur is more likely to be pathologic when one or more of the following are present:** Symptoms (e.g., chest pain, dyspnea with exertion, syncope with exertion); cyanosis; a systolic murmur that is loud (grade ≥3/6), harsh, pansystolic, or long in duration; diastolic murmur; abnormal heart sounds; presence of a click; abnormally strong or weak pulses.[3,4]
4. **Systolic and diastolic heart murmurs** (Box 7.2).

II. ELECTROCARDIOGRAPHY

A. Basic Electrocardiography Principles

1. **Lead placement** (Fig. 7.1)
2. **ECG complexes**
   a. P wave: Represents atrial depolarization.
   b. QRS complex: Represents ventricular depolarization.
   c. T wave: Represents ventricular repolarization.
   d. U wave: May follow the T wave and represents late phases of ventricular repolarization.
3. **Systematic approach for evaluating ECGs** (Table 7.4 shows normal ECG parameters):[3,5]
   a. **Rate**

BOX 7.2

SYSTOLIC AND DIASTOLIC HEART MURMURS

RUSB

Aortic valve stenosis (supravalvular, subvalvular)
Aortic regurgitation

LUSB

Pulmonary valve stenosis
Atrial septal defect
Pulmonary ejection murmur, innocent
Pulmonary flow murmur of newborn
Pulmonary artery stenosis
Aortic stenosis
Coarctation of the aorta
Patent ductus arteriosus
Partial anomalous pulmonary venous return (PAPVR)
Total anomalous pulmonary venous return (TAPVR)
Pulmonary regurgitation

LLSB

Ventricular septal defect, including atrioventricular septal defect
Vibratory innocent murmur (Still's murmur)
HOCM (IHSS)
Tricuspid regurgitation
Tetralogy of Fallot
Tricuspid stenosis

Apex

Mitral regurgitation
Vibratory innocent murmur (Still's murmur)
Mitral valve prolapse
Aortic stenosis
HOCM (IHSS)
Mitral stenosis

Murmurs listed by the location at which they are best heard. *Diastolic murmurs are in italics.*

HOCM, Hypertrophic obstructive cardiomyopathy; *IHSS*, idiopathic hypertrophic subaortic stenosis; *LLSB*, left lower sternal border; *LUSB*, left upper sternal border; *RUSB*, right upper sternal border.
From Park MK. *Pediatric Cardiology for Practitioners.* 5th ed. St Louis: Elsevier; 2008:30.

(1) Standardization: Paper speed is 25 mm/sec. **One small square = 1 mm = 0.04 second. One large square = 5 mm = 0.2 second. Amplitude standard: 10 mm = 1 mV.**
(2) Calculation: HR (beats/min) = 60 divided by the average R-R interval in seconds, or 1500 divided by the R-R interval in millimeters.

b. **Rhythm**
(1) Sinus rhythm: Every QRS complex is preceded by a P wave, normal PR interval (although PR interval may be prolonged, as in first-degree atrioventricular [AV] block), and normal P-wave axis (upright P in leads I and aVF).

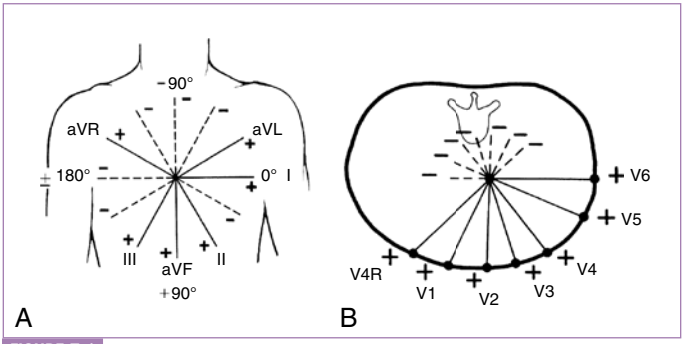

FIGURE 7.1

(A) Hexaxial reference system, (B) Horizontal reference system. (Modified from Park MK, Guntheroth WG. *How to Read Pediatric ECGs*. 4th ed. Philadelphia: Elsevier; 2006:3.)

(2) There is normal respiratory variation of the R-R interval without morphologic changes of the P wave or QRS complex.

c. **Axis**: The direction of the QRS in leads I and aVF should be observed, the quadrant determined, and comparison made with age-matched normal values (Fig. 7.2 and Table 7.4).

d. **Intervals** (PR, QRS, QTc)
   (1) See Table 7.4 for normal PR and QRS intervals.
   (2) The QTc is calculated using the Bazett formula: **QTc = QT (sec) measured/√R-R** (the average of three measurements taken from the same lead, usually lead II).
   (3) The QT interval is measured from the beginning of the QRS complex to the end of the T wave. Divide this value by the square root of the preceding R-R interval to obtain the QTc.
   (4) **Normal values for QTc are:**
      (a) 0.44 second is the 97th percentile for infants 3 to 4 days old.[6]
      (b) ≤0.45 second in all males aged >1 week and in prepubescent females.
      (c) ≤0.46 second for postpubescent females.

e. **P-wave size and shape**: A normal P wave should be <0.10 second in children and <0.08 second in infants, with an amplitude of <0.3 mV (3 mm in height, with normal standardization).

f. **R-wave progression**: In general, there is a normal increase in R-wave size and a decrease in S-wave size from leads V_1 to V_6 (with dominant S waves in the right precordial leads and dominant R waves in the left precordial leads), representing dominance of left ventricular forces. However, newborns and infants have a normal dominance of the right ventricle.

g. **Q waves**: Normal Q waves are usually <0.04 second in duration and <25% of the total QRS amplitude. Q waves are <5 mm deep in the left precordial leads and aVF, and ≤8 mm deep in lead III for children age <3 years.

TABLE 7.4

NORMAL PEDIATRIC ELECTROCARDIOGRAM PARAMETERS

					Lead V_1			Lead V_6		
Age	Heart Rate (bpm)	QRS Axis[a]	PR Interval (sec)[a]	QRS Duration (sec)[b]	R-Wave Amplitude (mm)[b]	S-Wave Amplitude (mm)[b]	R/S Ratio	R-Wave Amplitude (mm)[b]	S-Wave Amplitude (mm)[b]	R/S Ratio
0–7 days	95–160 (125)	+30 to +180 (+110)	0.08–0.12 (0.10)	0.05 (0.07)	13.3 (25.5)	7.7 (18.8)	2.5	4.8 (11.8)	3.2 (9.6)	2.2
1–3 weeks	105–180 (145)	+30 to +180 (+110)	0.08–0.12 (0.10)	0.05 (0.07)	10.6 (20.8)	4.2 (10.8)	2.9	7.6 (16.4)	3.4 (9.8)	3.3
1–6 months	110–180 (145)	+10 to +125 (+70)	0.08–0.13 (0.11)	0.05 (0.07)	9.7 (19)	5.4 (15)	2.3	12.4 (22)	2.8 (8.3)	5.6
6–12 months	110–170 (135)	+10 to +125 (+60)	0.10–0.14 (0.12)	0.05 (0.07)	9.4 (20.3)	6.4 (18.1)	1.6	12.6 (22.7)	2.1 (7.2)	7.6
1–3 years	90–150 (120)	+10 to +125 (+60)	0.10–0.14 (0.12)	0.06 (0.07)	8.5 (18)	9 (21)	1.2	14 (23.3)	1.7 (6)	10
4–5 years	65–135 (110)	0 to +110 (+60)	0.11–0.15 (0.13)	0.07 (0.08)	7.6 (16)	11 (22.5)	0.8	15.6 (25)	1.4 (4.7)	11.2
6–8 years	60–130 (100)	−15 to +110 (+60)	0.12–0.16 (0.14)	0.07 (0.08)	6 (13)	12 (24.5)	0.6	16.3 (26)	1.1 (3.9)	13
9–11 years	60–110 (85)	−15 to +110 (+60)	0.12–0.17 (0.14)	0.07 (0.09)	5.4 (12.1)	11.9 (25.4)	0.5	16.3 (25.4)	1.0 (3.9)	14.3
12–16 years	60–110 (85)	−15 to +110 (+60)	0.12–0.17 (0.15)	0.07 (0.10)	4.1 (9.9)	10.8 (21.2)	0.5	14.3 (23)	0.8 (3.7)	14.7
>16 years	60–100 (80)	−15 to +110 (+60)	0.12–0.20 (0.15)	0.08 (0.10)	3 (9)	10 (20)	0.3	10 (20)	0.8 (3.7)	12

[a]Normal range and (mean).

[b]Mean and (98th percentile).

Data from Park MK. *Pediatric Cardiology for Practitioners.* 5th ed. St Louis: Elsevier; 2008; and Davignon A, et al. Normal ECG standards for infants and children. *Pediatr Cardiol.* 1979;1:123–131.

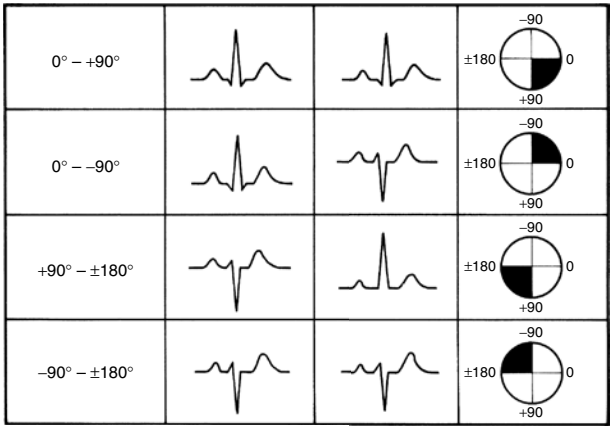

FIGURE 7.2
Location of quadrants of the mean QRS axis from leads I and aVF. (From Park MK, Guntheroth WG. *How to Read Pediatric ECGs.* 4th ed. Philadelphia: Elsevier; 2006:17.)

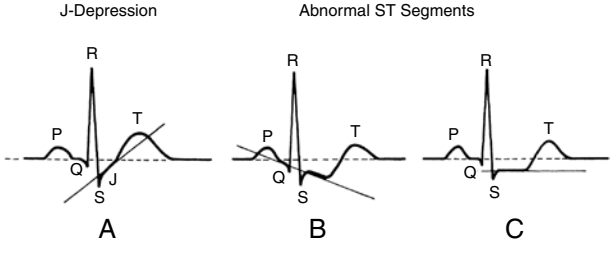

FIGURE 7.3
Non-pathologic (non-ischemic) and pathologic (ischemic) *ST* and *T* changes. (A) Characteristic non-ischemic ST-segment alteration called J-depression (note that ST slope is upward), B–C. Ischemic or pathologic ST-segment alterations, (B) Downward slope of ST segment, (C) Horizontal segment is sustained. (From Park MK, Guntheroth WG. *How to Read Pediatric ECGs.* 4th ed. Philadelphia: Elsevier; 2006:107.)

h. **ST-segment** (Fig. 7.3): ST-segment elevation or depression of >1 mm in the limb leads and >2 mm in the precordial leads is consistent with myocardial ischemia or injury. **NOTE:** J-depression is an upsloping of the ST segment and a normal variant.

TABLE 7.5

NORMAL T-WAVE AXIS

Age	V_1, V_2	AVF	I, V_5, V_6
Birth–1 day	±	+	±
1–4 days	±	+	+
4 days to adolescent	–	+	+
Adolescent to adult	+	+	+

+, T wave positive; –, T wave negative; ±, T wave normally either positive or negative.

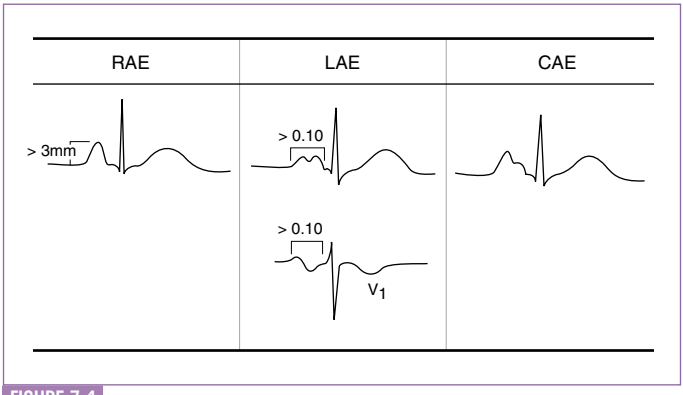

FIGURE 7.4

Criteria for Atrial Enlargement. *CAE*, Combined atrial enlargement; *LAE*, left atrial enlargement; *RAE*, right atrial enlargement. (From Park MK. *Pediatric Cardiology for Practitioners*. 5th ed. St Louis: Elsevier; 2008:53.)

i. **T wave:**
   (1) Inverted T waves in V_1 and V_2 can be normal in children up to adolescence (Table 7.5).
   (2) Tall, peaked T waves may be seen in hyperkalemia.
   (3) Flat or low T waves may be seen in hypokalemia, hypothyroidism, normal newborns, and myocardial/pericardial ischemia and inflammation.

j. **Hypertrophy/enlargement**
   (1) Atrial enlargement (Fig. 7.4).
   (2) Ventricular hypertrophy: Diagnosed by QRS axis, voltage, and R/S ratio (Box 7.3; see also Table 7.6).

B. ECG Abnormalities

1. **Nonventricular arrhythmias** (Table 7.6; Fig. 7.5)[7]
2. **Ventricular arrhythmias** (Table 7.7; Fig. 7.6)
3. **Nonventricular conduction disturbances** (Table 7.8; Fig. 7.7)[8]
4. **Ventricular conduction disturbances** (Table 7.9)

BOX 7.3

VENTRICULAR HYPERTROPHY CRITERIA

Right Ventricular Hypertrophy (RVH) Criteria

Must Have at Least One of the Following:
Upright T wave in lead V_1 after 3 days of age to adolescence
Presence of Q wave in V_1 (QR or QRS pattern)
Increased right and anterior QRS voltage (with normal QRS duration):
R in lead V_1, >98th percentile for age
S in lead V_6, >98th percentile for age
Right ventricular strain (associated with inverted T wave in V_1 with tall R wave)

Left Ventricular Hypertrophy (LVH) Criteria

Left ventricular strain (associated with inverted T wave in leads V_6, I, and/or aVF)

Supplemental Criteria

Left axis deviation (LAD) for patient's age
Volume overload (associated with Q wave >5 mm and tall T waves in V_5 or V_6)
Increased QRS voltage in left leads (with normal QRS duration):
R in lead V_6 (and I, aVL, V_5), >98th percentile for age
S in lead V_1, >98th percentile for age

C. ECG Findings Secondary to Electrolyte Disturbances, Medications, and Systemic Illnesses (Table 7.10)[7,9]

D. Long QT

1. Diagnosis:
   a. In general, QTc is similar in males and females from birth until late adolescence (0.37 to 0.44 second).
   b. In adults, prolonged QTc is generally >0.45 second.
   c. In ~10% of cases, patients may have a normal QTc. Patients may also have a family history of long QT associated with unexplained syncope, seizure, or cardiac arrest, without prolongation of QTc on ECG.
   d. Treadmill exercise testing may prolong the QTc and will sometimes induce arrhythmias.
2. **Complications:** Associated with ventricular arrhythmias (torsades de pointes), syncope, and sudden death.
3. **Management:**
   a. Congenital long QT: β-blockers and/or defibrillators; rarely requires cardiac sympathetic denervation or cardiac pacemakers.
   b. Acquired long QT: Treatment of arrhythmias, discontinuation of precipitating drugs, and correction of metabolic abnormalities.

E. Hyperkalemia:

ECG changes dependent on the serum potassium (K^+) level; however, the ECG may be normal with serum K^+ levels between 2.5 and 6 mEq/L.

1. **Serum K^+ <2.5 mEq/L:** Depressed ST segment, biphasic T wave.
2. **Serum K^+ >6 mEq/L**: Tall T wave.

TABLE 7.6

NONVENTRICULAR ARRHYTHMIAS

Name/Description	Cause	Treatment
SINUS		
TACHYCARDIA		
Normal sinus rhythm with HR >95th percentile for age (usually infants: <220 beats/min and children: <180 beats/min)	Hypovolemia, shock, anemia, sepsis, fever, anxiety, CHF, PE, myocardial disease, drugs (e.g., β-agonists, albuterol, caffeine, atropine)	Address underlying cause
BRADYCARDIA		
Normal sinus rhythm with HR <5th percentile for age	Normal (especially in athletic individuals), increased ICP, hypoxia, hyperkalemia, hypercalcemia, vagal stimulation, hypothyroidism, hypothermia, drugs (e.g., opioids, digoxin, β-blockers), long QT	Address underlying cause; if symptomatic, refer to inside back cover for bradycardia algorithm
SUPRAVENTRICULAR[a]		
PREMATURE ATRIAL CONTRACTION (PAC)		
Narrow QRS complex; ectopic focus in atria with abnormal P-wave morphology	Digitalis toxicity, medications (e.g., caffeine, theophylline, sympathomimetics), normal variant	Treat digitalis toxicity; otherwise no treatment needed
ATRIAL FLUTTER		
Atrial rate 250–350 beats/min; characteristic saw-tooth or flutter pattern with variable ventricular response rate and normal QRS complex	Dilated atria, previous intra-atrial surgery, valvular or ischemic heart disease, idiopathic in newborns	Synchronized cardioversion or overdrive pacing; treat underlying cause
ATRIAL FIBRILLATION		
Irregular; atrial rate 350–600 beats/min, yielding characteristic fibrillatory pattern (no discrete P waves) and irregular ventricular response rate of about 110–150 beats/min with normal QRS complex	Wolff-Parkinson-White syndrome and those listed previously for atrial flutter (except idiopathic), alcohol exposure, familial	Synchronized cardioversion; then may need anticoagulation based on stroke risk

Continued

TABLE 7.6—CONT'D

Name/Description	Cause	Treatment
SVT		
Sudden run of three or more consecutive premature supraventricular beats at >220 beats/min (infant) or >180 beats/min (child), with narrow QRS complex and absent/abnormal P wave; either sustained (>30 sec) or non-sustained	Most commonly idiopathic but may be seen in congenital heart disease (e.g., Ebstein anomaly, transposition)	Vagal maneuvers, adenosine; if unstable, need immediate synchronized cardioversion (0.5 J/kg up to 1 J/kg); consult cardiologist; refer to the back of the book for tachycardia with poor perfusion and tachycardia with adequate perfusion algorithms
I. *AV Reentrant:* Presence of accessory bypass pathway, in conjunction with AV node, establishes cyclic pattern of reentry independent of SA node; most common cause of non-sinus tachycardia in children (see Wolff-Parkinson-White syndrome, Table 7.9)		
II. *Junctional:* Automatic focus; simultaneous depolarization of atria and ventricles yields invisible P wave or retrograde P wave	Cardiac surgery, idiopathic	Adjust for clinical situation; consult cardiology
III. *Ectopic atrial tachycardia:* Rapid firing of ectopic focus in atrium	Idiopathic	AV nodal blockade, ablation
NODAL ESCAPE/JUNCTIONAL RHYTHM		
Abnormal rhythm driven by AV node impulse, giving normal QRS complex and invisible P wave (buried in preceding QRS or T wave) or retrograde P wave (negative in lead II, positive in aVR); seen in sinus bradycardia	Common after surgery of atria	Often requires no treatment; if rate is slow enough, may require pacemaker

[a]Abnormal rhythm resulting from ectopic focus in atria or AV node, or from accessory conduction pathways. Characterized by different P-wave shape and abnormal P-wave axis. QRS morphology usually normal. See Fig. 7.5.[6]

AV, Atrioventricular; *CHF*, congestive heart failure; *HR*, heart rate; *ICP*, intracranial pressure; *PE*, pulmonary embolism; *SA*, sinoatrial; *SVT*, supraventricular tachycardia.

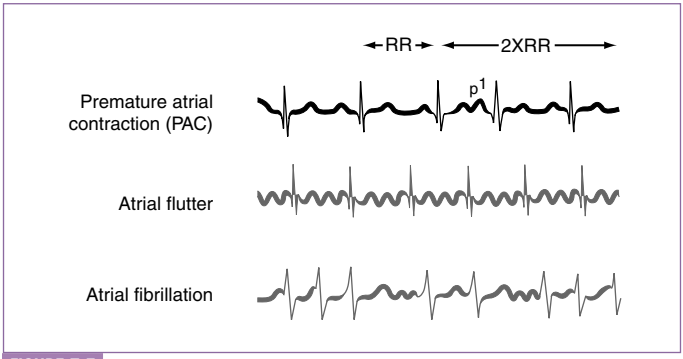

FIGURE 7.5

Supraventricular Arrhythmias. *p*[1], Premature atrial contraction. (From Park MK, Guntheroth WG. *How to Read Pediatric ECGs*. 4th ed. Philadelphia: Elsevier; 2006:129.)

TABLE 7.7

VENTRICULAR ARRHYTHMIAS

Name/Description	Cause	Treatment
PREMATURE VENTRICULAR CONTRACTION (PVC)		
Ectopic ventricular focus causing early depolarization. Abnormally wide QRS complex appears prematurely, usually with full compensatory pause. May be unifocal or multifocal **Bigeminy:** Alternating normal and abnormal QRS complexes. **Trigeminy:** Two normal QRS complexes followed by an abnormal one **Couplet:** Two consecutive PVCs	Myocarditis, myocardial injury, cardiomyopathy, long QT, congenital and acquired heart disease, drugs (catecholamines, theophylline, caffeine, anesthetics), MVP, anxiety, hypokalemia, hypoxia, hypomagnesemia; can be normal variant	None; more worrisome if associated with underlying heart disease or syncope, if worse with activity, or if they are multiform (especially couplets); address underlying cause; rule out structural heart disease
VENTRICULAR TACHYCARDIA		
Series of three or more PVCs at rapid rate (120–250 beats/min), with wide QRS complex and dissociated, retrograde, or no P wave	See causes of PVCs (70% have underlying cause)	Refer to front of book for tachycardia with poor perfusion and tachycardia with adequate perfusion algorithms
VENTRICULAR FIBRILLATION		
Depolarization of ventricles in uncoordinated asynchronous pattern, yielding abnormal QRS complexes of varying size and morphology with irregular, rapid rate; rare in children.	Myocarditis, MI, postoperative state, digitalis or quinidine toxicity, catecholamines, severe hypoxia, electrolyte disturbances, long QT	Requires immediate defibrillation; refer to front of book for asystole and pulseless arrest algorithm

MI, Myocardial infarction; *MVP*, mitral valve prolapse.

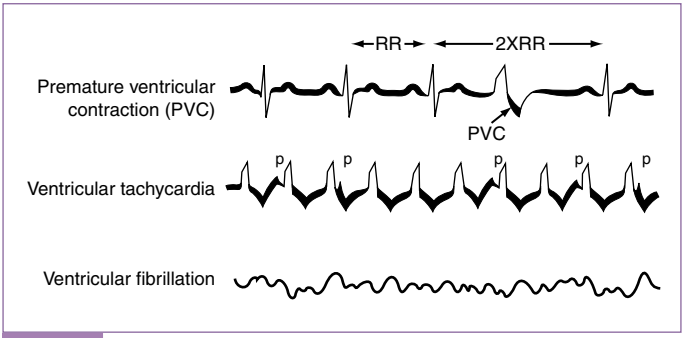

FIGURE 7.6

Ventricular Arrhythmias. *p*, P wave; *PVC*, premature ventricular contraction; *RR*, R-R interval. (From Park MK, Guntheroth WG. *How to Read Pediatric ECGs*. 4th ed. Philadelphia: Elsevier; 2006:138.)

TABLE 7.8

NONVENTRICULAR CONDUCTION DISTURBANCES

Name/Description[a]	Cause	Treatment
FIRST-DEGREE HEART BLOCK		
Abnormal but asymptomatic delay in conduction through AV node, yielding prolongation of PR interval	Acute rheumatic fever, tick-borne (e.g., Lyme) disease, connective tissue disease, congenital heart disease, cardiomyopathy, digitalis toxicity, postoperative state, normal children	No specific treatment except to address the underlying cause
SECOND-DEGREE HEART BLOCK: MOBITZ TYPE I (WENCKEBACH)		
Progressive lengthening of PR interval until a QRS complex is not conducted; common finding in asymptomatic teenagers	Myocarditis, cardiomyopathy, congenital heart disease, postoperative state, MI, toxicity (digitalis, β-blocker), normal children, Lyme disease, lupus	Address underlying cause, or none needed
SECOND-DEGREE HEART BLOCK: MOBITZ TYPE II		
Loss of conduction to ventricle without lengthening of the PR interval; may progress to complete heart block	Same as for Mobitz type I	Address underlying cause; may need pacemaker
THIRD-DEGREE (COMPLETE) HEART BLOCK		
Complete dissociation of atrial and ventricular conduction, with atrial rate faster than ventricular rate; P wave and PP interval regular; RR interval regular and much slower	Congenital due to maternal lupus or other connective tissue disease	If bradycardic and symptomatic, consider pacing; refer to back of the book for bradycardia algorithm

[a]High-degree AV block: Conduction of atrial impulse at regular intervals, yielding 2:1 block (two atrial impulses for each ventricular response), 3:1 block, etc.

AV, Atrioventricular; *MI*, myocardial infarction.

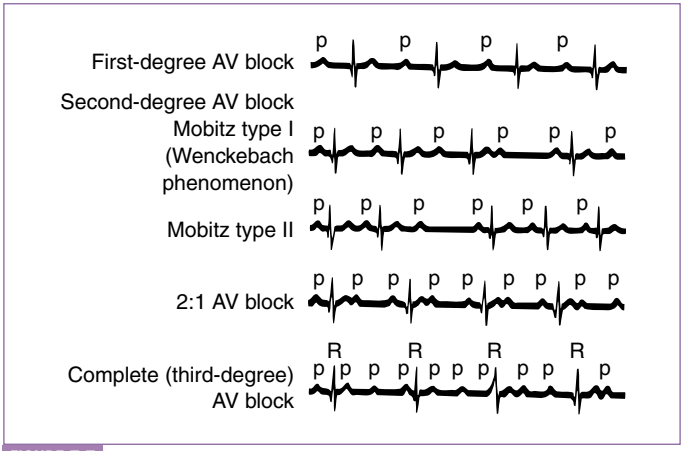

FIGURE 7.7

Conduction Blocks. *p*, P wave; *R*, QRS complex. (From Park MK, Guntheroth WG. *How to Read Pediatric ECGs*. 4th ed. Philadelphia: Elsevier; 2006:141.)

TABLE 7.9

VENTRICULAR CONDUCTION DISTURBANCES

Name/Description	Criteria	Causes/Treatment
RIGHT BUNDLE-BRANCH BLOCK (RBBB)		
Delayed right bundle conduction prolongs RV depolarization time, leading to wide QRS	1. Prolonged or wide QRS with terminal slurred R′ (m-shaped RSR′ or RR′) in V_1, V_2, aVR 2. Wide and slurred S wave in leads I and V_6	ASD, surgery with right ventriculotomy, occasionally seen in normal children
LEFT BUNDLE-BRANCH BLOCK (LBBB)		
Delayed left bundle conduction prolongs septal and LV depolarization time, leading to wide QRS with loss of usual septal signal; there is still a predominance of left ventricle forces; rare in children.	1. Wide negative QRS complex in lead V_1 with loss of septal R wave 2. Wide R or RR′ complex in lead V_6 with loss of septal Q wave	Hypertension, ischemic or valvular heart disease, cardiomyopathy
WOLFF-PARKINSON-WHITE (WPW)		
Atrial impulse transmitted via anomalous conduction pathway to ventricles, bypassing AV node and normal ventricular conduction system; leads to early and prolonged depolarization of ventricles; bypass pathway is a predisposing condition for SVT	1. Shortened PR interval 2. Delta wave 3. Wide QRS	Acute management of SVT if necessary, as previously described; consider ablation of accessory pathway if recurrent SVT; all patients need cardiology referral

ASD, Atrial septal defect; *LV*, left ventricle; *RV*, right ventricle; *SVT*, supraventricular tachycardia.

TABLE 7.10

SYSTEMIC EFFECTS ON ELECTROCARDIOGRAM

	Short QT	Long QT-U	Prolonged QRS	ST-T Changes	Sinus Tachycardia	Sinus Bradycardia	AV Block	Ventricular Tachycardia	Miscellaneous
CHEMISTRY									
Hyperkalemia			X	X			X	X	Low-voltage P waves; peaked T waves
Hypokalemia		X		X					
Hypercalcemia	X					X	X	X	
Hypocalcemia		X			X		X		
Hypermagnesemia							X		
Hypomagnesemia		X							
DRUGS									
Digitalis	X			X		T	X	T	
Phenothiazines		T						T	
Phenytoin	X								
Propranolol	X					X	X		
Tricyclic antidepressants		T	T	T	T		T	T	
Verapamil						X	X		
MISCELLANEOUS									
CNS injury		X		X	X	X	X		

TABLE 7.10—CONT'D

	Short QT	Long QT-U	Prolonged QRS	ST-T Changes	Sinus Tachycardia	Sinus Bradycardia	AV Block	Ventricular Tachycardia	Miscellaneous
Friedreich ataxia				X	X				Atrial flutter
Duchenne muscular dystrophy					X	X			Atrial flutter
Myotonic dystrophy			X	X	X		X		
Collagen vascular disease				X			X	X	
Hypothyroidism						X			Low voltage
Hyperthyroidism			X	X	X		X		
Lyme disease			X				X		
Holt-Oram, maternal lupus							X		

CNS, Central nervous system; *T*, present only with drug toxicity; *X*, present.

Data from Garson A Jr. *The Electrocardiogram in Infants and Children: A Systematic Approach.* Philadelphia: Lea & Febiger; 1983:172; and Walsh EP. Cardiac arrhythmias. In: Fyler DC, Nadas A, eds. *Pediatric Cardiology.* Philadelphia: Hanley & Belfus; 1992:141–143.

TABLE 7.11

MAJOR SYNDROMES ASSOCIATED WITH CARDIAC DEFECTS

Syndrome	Dominant Cardiac Defect
CHARGE	TOF, truncus arteriosus, aortic arch abnormalities
DiGeorge	Aortic arch anomalies, TOF, truncus arteriosus, VSD, PDA
Trisomy 21	Atrioventricular septal defect, VSD
Marfan	Aortic root dilation, mitral valve prolapse
Loeys-Dietz	Aortic root dilation with higher risk of rupture at smaller dimensions
Noonan	Supravalvular pulmonic stenosis, LVH
Turner	COA, bicuspid aortic valve, aortic root dilation as a teenager
Williams	Supravalvular aortic stenosis, pulmonary artery stenosis
FAS	Occasional: VSD, PDA, ASD, TOF
IDM	TGA, VSD, COA, cardiomyopathy
VATER/VACTERL	VSD
VCFS	Truncus arteriosus, TOF, pulmonary atresia with VSD, TGA, interrupted aortic arch

ASD, Atrial septal defect; *CHARGE*, a syndrome of associated defects including **C**oloboma of the eye, **H**eart anomaly, choanal **A**tresia, **R**etardation, and **G**enital and **E**ar anomalies; *COA*, coarctation of aorta; *FAS*, fetal alcohol syndrome; *IDM*, infant of diabetic mother; *LVH*, left ventricular hypertrophy; *PDA*, patent ductus arteriosus; *TGA*, transposition of the great arteries; *TOF*, tetralogy of Fallot; *VATER/VACTERL*, association of **V**ertebral anomalies, **A**nal atresia, **C**ardiac anomalies, **T**racheo**e**sophageal fistula, **R**enal/radial anomalies, **L**imb defects; *VCFS*, velocardiofacial syndrome; *VSD*, ventricular septal defect.

From Park MK. *Pediatric Cardiology for Practitioners*. 5th ed. St Louis: Elsevier; 2008:10–12.

3. **Serum K^+ >7.5 mEq/L:** Long PR interval, wide QRS, tall T wave.
4. **Serum K^+ >9 mEq/L**: Absent P wave, sinusoidal.

III. CONGENITAL HEART DISEASE

A. Pulse Oximetry Screening for Critical Congenital Heart Disease

1. **To be done as late as possible, but before discharge from nursery, preferably >24 hours of life, due to decreased false-positive rate.** Recommended to use the right hand and 1 foot, either in parallel or direct sequence.
2. **The screening result would be considered positive if:**
   a. Any oxygen saturation measure <90%.
   b. Oxygen saturation <95% in both extremities on three measures, each separated by 1 hour.
   c. There is a >3% absolute difference in oxygen saturation between the right hand and foot on three measures, each separated by 1 hour.

B. Common Syndromes Associated with Cardiac Lesions (Table 7.11)

C. Acyanotic Lesions (Table 7.12)

D. Cyanotic Lesions (Table 7.13)

A hyperoxia test is used to evaluate the etiology of cyanosis in neonates. A baseline arterial blood gas (ABG) with saturation at $Fio_2 = 0.21$ is obtained. Then the infant is placed in an oxygen hood at $Fio_2 = 1$ for a minimum of

TABLE 7.12

ACYANOTIC CONGENITAL HEART DISEASE

Lesion Type	Examination Findings	ECG Findings	Chest Radiograph Findings
Ventricular septal defect (VSD)	2–5/6 holosystolic murmur, loudest at the LLSB, ± systolic thrill ± apical diastolic rumble with large shunt With large VSD and pulmonary hypertension, S_2 may be narrow	Small VSD: Normal Medium VSD: LVH ± LAE Large VSD: BVH ± LAE, pure RVH	May show cardiomegaly and increased PVMs, depending on amount of left-to-right shunting
Atrial septal defect (ASD)	Wide, fixed split S_2 with grade 2–3/6 SEM at the LUSB May have mid-diastolic rumble at LLSB	Small ASD: Normal Large ASD: RAD and mild RVH or RBBB with RSR′ in V_1	May show cardiomegaly with increased PVMs if hemodynamically significant ASD
Patent ductus arteriosus (PDA)	40%–60% in VLBW infants 1–4/6 continuous "machinery" murmur loudest at LUSB Wide pulse pressure	Small–moderate PDA: Normal or LVH Large PDA: BVH	May have cardiomegaly and increased PVMs, depending on size of shunt
Atrioventricular septal defects	Most occur in Down syndrome Hyperactive precordium with systolic thrill at LLSB and loud S_2 ± grade 3–4/6 holosystolic regurgitant murmur along LLSB ± systolic murmur of MR at apex ± mid-diastolic rumble at LLSB or at apex ± gallop rhythm	Superior QRS axis RVH and LVH may be present	Cardiomegaly with increased PVMs
Pulmonary stenosis (PS)	Ejection click at LUSB with valvular PS; click intensity varies with respiration, decreasing with inspiration and increasing with expiration S_2 may split widely with P_2 diminished in intensity SEM (2–5/6) ± thrill at LUSB with radiation to back and sides	Mild PS: Normal Moderate PS: RAD and RVH Severe PS: RAE and RVH with strain	Normal heart size with normal to decreased PVMs

Continued

TABLE 7.12—CONT'D

Lesion Type	Examination Findings	ECG Findings	Chest Radiograph Findings
Aortic stenosis (AS)	Systolic thrill at RUSB, suprasternal notch, or over carotids Ejection click that does not vary with respiration if valvular AS Harsh SEM (2–4/6) at second RICS or third LICS, with radiation to neck and apex ± early diastolic decrescendo murmur due to AR Narrow pulse pressure, if severe stenosis	Mild AS: Normal Moderate–severe AS: LVH ± strain	Usually normal
Coarctation of aorta may present as: 1. Infant in CHF 2. Child with HTN 3. Child with murmur	Male/female ratio of 2:1 2–3/6 SEM at LUSB, radiating to left interscapular area Bicuspid valve is often associated, so may have systolic ejection click at apex and RUSB BP in lower extremities will be lower than in upper extremities Pulse oximetry discrepancy of >5% between upper and lower extremities is also suggestive of coarctation	*In infancy:* RVH or RBBB *In older children:* LVH	Marked cardiomegaly and pulmonary venous congestion Rib notching from collateral circulation usually not seen in children younger than 5 years because collaterals not yet established

AR, Aortic regurgitation; *ASD*, atrial septal defect; *BP*, blood pressure; *BVH*, biventricular hypertrophy; *CDG*, congenital disorders of glycosylation; *CHD*, congenital heart disease; *CHF*, congestive heart failure; *HTN*, hypertension; *LAE*, left atrial enlargement; *LICS*, left intercostal space; *LLSB*, left lower sternal border; *LUSB*, left upper sternal border; *LVH*, left ventricular hypertrophy; *MR*, mitral regurgitation; *PVM*, pulmonary vascular markings; *RAD*, right axis deviation; *RAE*, right atrial enlargement; *RBBB*, right bundle-branch block; *RICS*, right intercostal space; *RUSB*, right upper sternal border; *RVH*, right ventricular hypertrophy; *SEM*, systolic ejection murmur; *VLBW*, very low birth weight (i.e., <1500 g); *VSD*, ventricular septal defect.

TABLE 7.13

CYANOTIC CONGENITAL HEART DISEASE

Lesion	Examination Findings	ECG Findings	Chest Radiograph Findings
Tetralogy of Fallot: 1. Large VSD 2. RVOT obstruction 3. RVH 4. Overriding aorta Degree of RVOT obstruction will determine whether there is clinical cyanosis; if PS is mild, there will be a left-to-right shunt, and child will be acyanotic; increased obstruction leads to increased right-to-left shunting across VSD, and child will be cyanotic	Loud SEM at LMSB and LUSB and a loud, single S_2 ± thrill at LMSB and LLSB *Tet spells:* Occur in young infants; as RVOT obstruction increases or systemic resistance decreases, right-to-left shunting across VSD occurs; may present with tachypnea, increasing cyanosis, and decreasing murmur	RAD and RVH	Boot-shaped heart with normal heart size ± decreased PVMs
Transposition of great arteries	Nonspecific; extreme cyanosis; loud, single S_2; no murmur unless there is associated VSD or PS	RAD and RVH (due to RV acting as systemic ventricle); after 3 days of age, upright T wave in V_1 may be only abnormality	Classic finding: "egg on a string" with cardiomegaly; possible increased PVMs.
Tricuspid atresia (absent tricuspid valve and hypoplastic RV and PA; must have ASD, PDA, or VSD to survive)	Single S_2 + grade 2–3/6 systolic regurgitation murmur at LLSB if VSD is present. Occasional PDA murmur.	Superior QRS axis; RAE or CAE and LVH.	Normal or slightly enlarged heart size; may have boot-shaped heart.

Continued

TABLE 7.13—CONT'D

Lesion	Examination Findings	ECG Findings	Chest Radiograph Findings
Total anomalous pulmonary venous return: Instead of draining into LA, pulmonary veins drain into the following locations (must have ASD or PFO for survival): *Supracardiac (most common):* SVC *Cardiac:* Coronary sinus or RA *Subdiaphragmatic:* IVC, portal vein, ductus venosus, or hepatic vein *Mixed type*	Hyperactive RV impulse, quadruple rhythm, S_2 fixed and widely split, 2–3/6 SEM at LUSB, and mid-diastolic rumble at LLSB	RAD, RVH (RSR′ in V_1); may see RAE	Cardiomegaly and increased PVMs; classic finding is "snowman in a snowstorm," but this is rarely seen until after age 4 months
OTHER			
Cyanotic CHDs that each occur at a frequency of <1% include pulmonary atresia, Ebstein anomaly, truncus arteriosus, single ventricle, and double outlet right ventricle			

ASD, Atrial septal defect; *CAE*, common atrial enlargement; *ECG*, electrocardiogram; *IVC*, inferior vena cava; *LA*, left atrium; *LLSB*, left lower sternal border; *LMSB*, left midsternal border; *LUSB*, left upper sternal border; *LVH*, left ventricular hypertrophy; *PA*, pulmonary artery; *PDA*, patent ductus arteriosus; *PFO*, patent foramen ovale; *PVM*, pulmonary vascular markings; *PS*, pulmonary stenosis; *RA*, right atrium; *RAD*, right-axis deviation; *RAE*, right atrial enlargement; *RV*, right ventricle; *RVH*, right ventricular hypertrophy; *RVOT*, right ventricular outflow tract; *SEM*, systolic ejection murmur; *SVC*, superior vena cava; *VSD*, ventricular septal defect.

10 minutes, and the ABG is repeated. In cardiac disease, there will not be a significant change in Pa_{O_2} following the oxygen challenge test. A Pa_{O_2} of >200 after exposure to Fi_{O_2} of 1.0 is considered normal, and >150 indicates pulmonary rather than cardiac disease. **Note:** Pulse oximetry is not useful for following changes in oxygenation once saturation has reached 100% (approximately a Pa_{O_2} of >90 mmHg).[12–17] See Table EC 7.A for interpretation of oxygen challenge test (hyperoxia test).

IV. ACQUIRED HEART DISEASE

A. Myocardial Infarction (MI) in Children (Box 7.4; Fig. 7.8)

B. Endocarditis

1. **Common causative organisms:** Approximately 70% of endocarditis is caused by streptococcal species (*Streptococcus viridans,* enterococci), 20% by staphylococcal species *(Staphylococcus aureus, Staphylococcus epidermidis)*, and 10% by other organisms (*Haemophilus influenzae,* gram-negative bacteria, fungi).
2. **Presentation:** Heart murmur, recurrent fever, splenomegaly, petechiae, fatigue, Osler nodes (tender nodules at the fingertips), Janeway lesions (painless hemorrhagic areas on the palms or soles), splinter hemorrhages, Roth spots (retinal hemorrhages).
3. **Diagnosis**—Duke's Criteria:
   a. Pathologic criteria:
      (1) Direct evidence of endocarditis based upon histologic findings.
      (2) Gram stain positive or cultures of specimens.
   b. Clinical criteria: 1 major criterion and 1 minor OR 3 minor criteria:
      (1) Major: Persistently positive blood cultures (2 sets 1 hour apart), positive echocardiogram for vegetations, new regurgitant murmur, single positive blood culture for *Coxiella burnetii.*
      (2) Minor: Fever, predisposing valvular condition (prosthetic heart valve, valve lesion OR intravenous drug user [IVDU]), vascular phenomenon (e.g., emboli), immunologic phenomenon (e.g., Roth's spots, Osler's nodes), positive blood cultures that do not meet major criteria.
4. Management: Daily blood cultures while febrile; support heart failure symptoms with diuretics, digoxin, etc.

C. Bacterial Endocarditis Prophylaxis

See Box 7.5 for cardiac conditions that meet criteria for prophylaxis.[18]

1. **All dental procedures** that involve treatment of gingival tissue, the periapical region of the teeth, or oral mucosal perforation.
2. **Invasive procedures** that involve incision or biopsy of respiratory mucosa, such as tonsillectomy and adenoidectomy.
3. **Not recommended** for genitourinary or gastrointestinal tract procedures; solely for bacterial endocarditis prevention.
4. **Treatment**: Amoxicillin is preferred PO; ampicillin if unable to take PO; cephalexin if allergic to penicillins.[28]

TABLE EC 7.A

INTERPRETATION OF OXYGEN CHALLENGE TEST (HYPEROXIA TEST)

Condition	$FiO_2 = 0.21$ PaO_2 (% Saturation)		$FiO_2 = 1.00$ PaO_2 (% Saturation)	$PaCO_2$
Normal	70 (95)		>200 (100)	35
Pulmonary disease	50 (85)		>150 (100)	50
Neurologic disease	50 (85)		>150 (100)	50
Methemoglobinemia	70 (85)		>200 (85)	35
Cardiac disease				
•Separate circulation[a]	<40 (<75)		<50 (<85)	35
•Restricted PBF[b]	<40 (<75)		<50 (<85)	35
•Complete mixing without restricted PBF[c]	50 (85)		<150 (<100)	35
Persistent pulmonary hypertension	*Preductal*	*Postductal*		
PFO (no R to L shunt)	70 (95)	<40 (<75)	Variable	35–50
PFO (with R to L shunt)	<40 (<75)	<40 (<75)	Variable	35–50

[a]D-Transposition of the great arteries (D-TGA) with intact ventricular septum.

[b]Tricuspid atresia with pulmonary stenosis or atresia, pulmonary atresia or critical pulmonary stenosis with intact ventricular septum, or tetralogy of Fallot.

[c]Truncus arteriosus, total anomalous pulmonary venous return, single ventricle, hypoplastic left heart syndrome, D-TGA with ventricular septal defect, tricuspid atresia without pulmonary stenosis or atresia.

FiO_2, Fraction of inspired oxygen; *PBF*, pulmonary blood flow; *PFO*, patent foramen ovale.

From Lees MH. Cyanosis of the newborn infant: recognition and clinical evaluation. *J Pediatr.* 1970;77:484; Kitterman JA. Cyanosis in the newborn infant. *Pediatr Rev.* 1982;4:13; and Jones RW, Baumer JH, Joseph MC, et al. Arterial oxygen tension and response to oxygen breathing in differential diagnosis of heart disease in infancy. *Arch Dis Child.* 1976;51:667–673.

BOX 7.4

MYOCARDIAL INFARCTION IN CHILDREN[25,26]

Etiologies	Diagnosis
Anomalous origin of coronary artery Kawasaki disease Congenital heart disease Dilated cardiomyopathy Severe hypertension SLE Myocarditis Drug ingestion (cocaine, adrenergic drugs)	**ECG findings**[10,11]**:** See Fig. 7.12 **Biomarkers** Troponin I, CK-MB nonspecific for ischemic injury in children

CK-MB, Creatine kinase-MB; *ECG*, electrocardiogram; *MI*, myocardial Infarction; *SLE*, systemic lupus erythematosus.

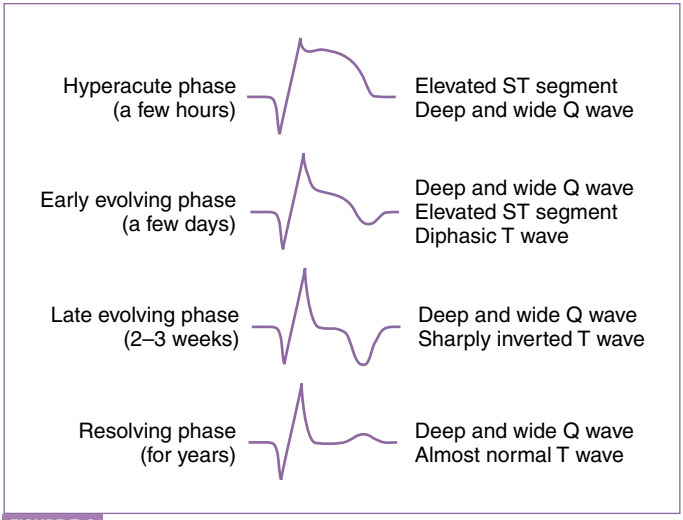

FIGURE 7.8

Sequential Changes During Myocardial Infarction. (From Park MK, Guntheroth WG. *How to Read Pediatric ECGs*. 4th ed. Philadelphia: Elsevier; 2006:115.)

D. Myocardial Disease

1. **Dilated cardiomyopathy:** End result of myocardial damage leading to atrial and ventricular dilation with decreased systolic contractile function of the ventricles.
   a. Treatment: Management of congestive heart failure (CHF) (digoxin, diuretics, vasodilation, angiotensin-converting enzyme [ACE] inhibitors).
   b. Anticoagulants should be considered to decrease the risk of thrombus formation. Cardiac transplant may eventually be required.

BOX 7.5

CARDIAC CONDITIONS FOR WHICH ANTIBIOTIC PROPHYLAXIS IS RECOMMENDED

- Prosthetic cardiac valve
- Previous bacterial endocarditis
- Congenital heart disease (CHD)—Limited to the following conditions:
  - Unrepaired cyanotic defect, including palliative shunts and conduits
  - Completely repaired CHD with prosthetic material/device (placed by surgery or catheterization), during first 6 months after procedure
  - Repaired CHD with residual defects at or adjacent to the site of prosthetic patch or device (which inhibits endothelialization)
  - Cardiac transplantation patients who develop cardiac valvulopathy

Data from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736–1754.

2. **Hypertrophic obstructive cardiomyopathy (HOCM):** Abnormality of myocardial cells leading to significant ventricular hypertrophy (usually left ventricle) with small to normal ventricular dimensions. Increased contractile function, impaired filling secondary to stiff ventricles. Most common type is asymmetrical septal hypertrophy with (HOCM) or without left ventricular outflow obstruction. There is a 4% to 6% incidence of sudden death in children and adolescents.
   a. Treatment: Moderate restriction of physical activity, negative inotropes (β-blocker, calcium channel blocker) to help improve filling, and maintenance of adequate hydration. If at increased risk for sudden death, may consider implantable defibrillator. If symptomatic with subaortic obstruction, may benefit from myectomy.
   b. Additional management: HOCM is a preload dependent lesion and, therefore, patient may benefit from higher rates of fluid administration. Avoid inotropes, tachycardia, and afterload reduction.
3. **Restrictive cardiomyopathy:** Myocardial or endocardial disease (usually infiltrative or fibrotic) resulting in stiff ventricular walls with restriction of diastolic filling but normal contractile function. Results in atrial enlargement. Associated with a high mortality rate. Very rare in children. Treatment is supportive with diuretics, anticoagulants, calcium channel blockers, a pacemaker for heart block, and cardiac transplantation, if severe.
4. **Myocarditis:** Inflammation of myocardial tissue
   a. Etiology:
      (1) Infectious: viral (coxsackie virus, echovirus, adenovirus), bacterial, rickettsial, fungal, parasitic
      (2) Other: immune-mediated disease (Kawasaki disease, acute rheumatic fever), collagen vascular disease, toxin-induced

b. Presentation: Symptoms can be nonspecific, including fatigue, shortness of breath, emesis. Exam includes signs of CHF, soft systolic murmur, arrhythmia.
c. Testing:
   (1) Imaging: ECG: Low QRS voltages throughout (<5 mm), ST-segment and T-wave changes (e.g., decreased T-wave amplitude), prolongation of QT interval, arrhythmias (especially premature contractions, first- or second-degree AV block); echo shows enlarged chambers and impaired LV function
   (2) Labs: CK, troponin
d. Treatment: Bed rest, diuretics, inotropes (dopamine, dobutamine, milrinone), digoxin, gamma globulin, ACE inhibitors, possibly steroids.
e. May require ventricular assist device and/or heart transplantation (≈20% to 25% of cases).

E. Pericardial Disease

1. **Pericarditis:** Inflammation of visceral and parietal layers of pericardium. It is often self-limited.
   a. Presentation: Chest pain (often pleuritic in nature), fever, tachycardia, distant heart sounds, friction rub.
   b. EKG: Diffuse ST-segment elevation in almost all leads (representing inflammation of adjacent myocardium); PR-segment depression.
   c. Treatment**:** Address underlying condition and provide symptomatic treatment with rest, analgesia, and anti-inflammatory drugs.
2. **Pericardial effusion:** Accumulation of excess fluid in pericardial sac.
   a. Etiology: Acute pericarditis, serous effusion from increased hydrostatic pressure (CHF), decreased plasma oncotic pressure, increased capillary permeability.
   b. Presentation: Can be asymptomatic, chest or abdominal pain, muffled heart sounds, dullness to percussion, vital sign instability from cardiac compression (e.g., hypotension).
   c. EKG: Decreased QRS voltage, electrical alternans.
   d. Treatment: Address underlying condition. Observe if asymptomatic; use pericardiocentesis if there is sudden increase in volume or hemodynamic compromise. Nonsteroidal antiinflammatory drugs (NSAIDs) or steroids may be of benefit, depending on etiology.
3. **Cardiac tamponade:** Accumulation of pericardial fluid under high pressure causing compression of cardiac chambers, limiting filling, and decreasing stroke volume and cardiac output.
   a. Etiology: Same as pericardial effusion.
   b. Presentation: Dyspnea, fatigue, signs of CHF (jugular venous distension, hepatomegaly, edema, tachypnea/rales), pulsus paradoxus.
   c. EKG: Same as pericardial effusion.
   d. Echocardiogram: RV collapse in early diastole, RA/LA collapse in end diastole and early systole.

e. Treatment is pericardiocentesis with temporary catheter left in place if necessary; pericardial window or stripping, if it is a recurrent condition.

F. Kawasaki Disease[19]

Acute febrile vasculitis of unknown etiology, which is common in children aged <8 years and is the leading cause of acquired childhood heart disease in developed countries.

1. **Etiology:** Unknown; thought to be immune regulated in response to infectious agents or environmental toxins.
2. **Diagnosis:**
   a. Typical Kawasaki disease: Based on clinical criteria. These include high fever lasting 5 days or more, plus at least four of the following five criteria:
      (1) Bilateral, painless, bulbar conjunctival injection without exudate
      (2) Erythematous mouth and pharynx, strawberry tongue, or red cracked lips
      (3) Polymorphous exanthem (may be morbilliform, maculopapular, or scarlatiniform)
      (4) Swelling of hands and feet with erythema of palms and soles
      (5) Cervical lymphadenopathy (>1.5 cm in diameter), usually single and unilateral
   b. Atypical/incomplete Kawasaki disease: A suspicion of Kawasaki disease but with fewer of the criteria required for diagnosis. Even without all criteria, there is a risk for coronary artery abnormalities.
      (1) More often seen in infants. Echocardiography should be considered in any infant <6 months with fever >7 days duration, laboratory evidence of systemic inflammation (CRP >3 and/or ESR >40), and no other explanation for the febrile illness.
      (2) See Fig. 7.9 for evaluation of incomplete Kawasaki disease.
      (3) Supplemental laboratory criteria: Albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine white blood cells/hpf ≥10 (non-catheterized specimen).
3. **Other clinical findings:** Often associated with extreme irritability, abdominal pain, diarrhea, vomiting. Also seen are arthritis and arthralgia, hepatic enlargement, jaundice, acute acalculous distention of the gallbladder, carditis.
4. **Laboratory findings:** Leukocytosis with left shift, neutrophils with vacuoles or toxic granules, elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) (seen acutely), thrombocytosis, normocytic and normochromic anemia, sterile pyuria (33%), increased transaminases (40%), hyperbilirubinemia (10%).
5. **Subacute phase (11 to 25 days after onset of illness):** Resolution of fever, rash, and lymphadenopathy. Often, desquamation of the fingertips or toes and thrombocytosis occur. Cardiovascular

complications: If untreated, 20% to 25% develop coronary artery aneurysms and dilation in subacute phase (peak prevalence occurs about 2 to 4 weeks after onset of disease; rarely appears after 6 weeks) and are at risk for coronary thrombosis acutely and coronary stenosis chronically. Carditis; aortic, mitral, and tricuspid regurgitation; pericardial effusion; CHF; MI; left ventricular dysfunction; and ECG changes may also occur.

6. **Convalescent phase:** ESR, CRP, and platelet count return to normal. Those with coronary artery abnormalities are at increased risk for MI, arrhythmias, and sudden death.
7. **Management** (see also Table EC 7.B)[19]

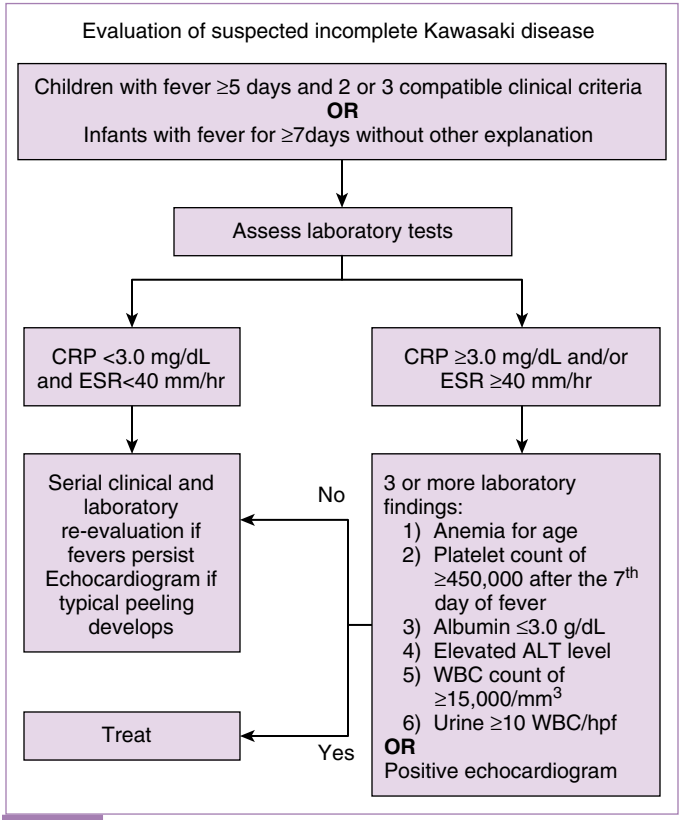

FIGURE 7.9

Evaluation of Incomplete Kawasaki Disease. (From Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals from the American Heart Association. *Circulation* 2017; Mar 29.)

a. Intravenous immunoglobulin (IVIG)
   (1) Shown to reduce incidence of coronary artery dilation to <3% and decrease duration of fever, if given in the first 10 days of illness. Current recommended regimen is a single dose of IVIG, 2 g/kg over 10 to 12 hours.[19]
   (2) Can be given to children after 10th day of fever if ESR or CRP elevated with persistent fever.
   (3) Approximately 10% of patients treated with IVIG fail to respond (persistent or recurrent fever ≥36 hours after IVIG completion). Retreat with second dose.[19]
b. Aspirin is recommended for both its anti-inflammatory and antiplatelet effects. In the United States, high-dose aspirin (80 to 100 mg/kg/day divided in four doses) is recommended 48 to 72 hours after defervescence. This is given with IVIG. Low-dose aspirin (3 to 5 mg/kg/day as a single daily dose) is continued for 6 to 8 weeks or until platelet count and ESR are normal (if there are no coronary artery abnormalities). Aspirin may be continued indefinitely, if coronary artery abnormalities persist.[19]
c. Dipyridamole is sometimes used as an alternative to aspirin, particularly if symptoms of influenza or varicella arise while on aspirin (due to concern for Reye syndrome).
d. Follow-up: Serial echocardiography is recommended to assess coronary arteries and left ventricular function (at time of diagnosis, at 2 weeks, at 6 to 8 weeks, and at 12 months [optional]). More frequent intervals and long-term follow-up are recommended if abnormalities are seen on echocardiography. Cardiac catheterization may be necessary.
e. Follow up with Cardiology depending on presence of coronary aneurysms and Z score of aneurysm (see Table EC 7.B).

G. Rheumatic Heart Disease

1. **Etiology:** Believed to be an immunologically-mediated, delayed sequela of group A streptococcal pharyngitis.
2. **Clinical findings:** History of streptococcal pharyngitis 1 to 5 weeks before onset of symptoms. Often with pallor, malaise, easy fatigability.
3. **Diagnosis:** Jones criteria (Box 7.6).
4. **Management:** Penicillin, bed rest, salicylates, supportive management of CHF (if present) with diuretics, digoxin, morphine.

V. IMAGING

A. Chest Radiograph (Fig. 7.10)
B. Echocardiography (Table EC 7.C)

VI. PROCEDURES

A. Cardiac Surgery (Fig. 7.11, Table 7.14)

B. Cardiac Catheterization[13,14]

1. Performed in pediatric patients for diagnostic and interventional purposes, including pressure measurements, angiography, embolization of

TABLE EC 7.B

GUIDELINES FOR TREATMENT AND FOLLOW-UP OF CHILDREN WITH KAWASAKI DISEASE

Risk Level	Pharmacologic Therapy	Physical Activity	Follow-Up and Diagnostic Testing	Invasive Testing
I. No coronary artery changes at any stage of illness	None beyond initial 6–8 weeks	No restrictions beyond initial 6–8 weeks	Counsel on cardiovascular risk factors every 5 years	None recommended
II. Transient coronary artery ectasia that resolves by 8 weeks after disease onset	None beyond initial 6–8 weeks	No restrictions beyond initial 6–8 weeks	Counsel on cardiovascular risk factors every 3–5 years	None recommended
III. Small-to-medium solitary coronary artery aneurysm	3–5 mg/kg/day aspirin, at least until aneurysm resolves	For patients in first decade of life, no restriction beyond initial 6–8 weeks; during the second decade of life, physical activity guided by stress testing every 2 years; avoid competitive contact and high-impact sports while on antiplatelet therapy	Annual follow-up with echocardiogram and electrocardiogram	Angiography, if stress testing or echocardiography suggests stenosis
IV. One or more large, >6 mm, aneurysms and coronary arteries with multiple small-to-medium aneurysms, without obstruction	Long-term aspirin (3–5 mg/kg/day) and warfarin or LMWH for patients with giant aneurysms	Annual stress testing guides physical activity; avoid competitive contact and high-impact sports while on anticoagulant therapy	Echocardiogram and electrocardiogram at 6-month intervals, annual stress testing, atherosclerosis risk factor counseling at each visit	Cardiac catheterization 6–12 months after acute illness with additional testing if ischemia noted or testing inconclusive
V. Coronary artery obstruction	Long-term aspirin (3–5 mg/kg/day); warfarin or LMWH if giant aneurysm persists; consider use of β-blockers to reduce myocardial work	Contact sports, isometrics, and weight training should be avoided; other physical activity recommendations guided by outcome of stress testing or myocardial perfusion scan	Echocardiogram and electrocardiogram at 6-month intervals, annual Holter and stress testing	Cardiac catheterization 6–12 months after acute illness to aid in selecting therapeutic options, additional testing if ischemia noted

LMWH, Low molecular weight heparin.

BOX 7.6

GUIDELINES FOR DIAGNOSIS OF INITIAL ATTACK OF RHEUMATIC FEVER (JONES CRITERIA)

Major Manifestations	Minor Manifestations
Carditis	Clinical findings:
Polyarthritis	Arthralgia
Chorea	Fever
Erythema marginatum	Laboratory findings:
Subcutaneous nodules	Elevated acute phase reactants (erythrocyte sedimentation rate, C-reactive protein)
	Prolonged PR interval

Plus Supporting Evidence of Antecedent Group A Streptococcal Infection

- Positive throat culture or rapid streptococcal antigen test
- Elevated or rising streptococcal antibody titer

NOTE: If supported by evidence of preceding group A streptococcal infection, the presence of two major manifestations or of one major and two minor manifestations indicates a high probability of acute rheumatic fever.

abnormal vessels, dilation of atretic valves and vessels, device closure of cardiac defects, and electrophysiology procedures.

2. Relatively common complications to be aware of: Arrhythmias (SVT, AV block, bradycardia, etc.), vascular complications (thrombosis, decreased/absent pulses), intervention-related (balloon rupture, etc.), bleeding.
3. Other less common complications: Myocardial/vessel staining, cardiac perforation, cardiac tamponade, air embolus, infection, allergic reaction, cardiac arrest, and death.

VII. COMMON CARDIAC COMPLAINTS

A. Non-Traumatic Chest Pain[20]

1. **Etiologies**
   a. Life-threatening causes
      (1) Cardiac: Congenital heart disease (CHD) with left ventricular outflow tract obstruction, coronary artery abnormality, pericarditis, myocarditis, dilated cardiomyopathy, aortic root dissection; cardiac etiologies are rare in children (prevalence <6%).[25]
      (2) Non-cardiac: Pneumothorax, pulmonary embolism, pulmonary HTN, acute chest syndrome.
   b. Common, non-cardiac causes (94% to 99% patients): Musculoskeletal (costochondritis), respiratory (asthma, pneumonia,

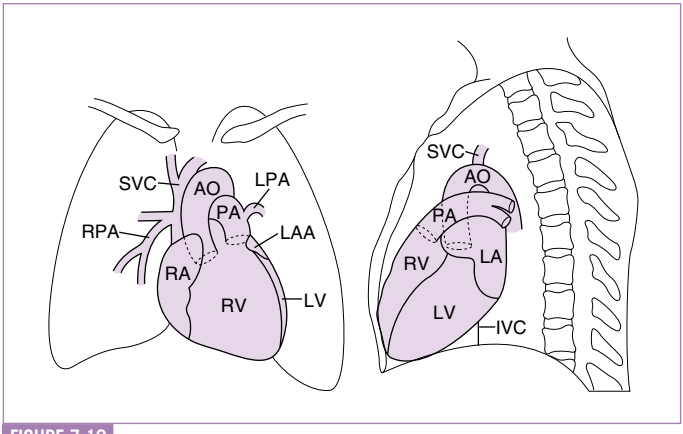

FIGURE 7.10

Radiological Contours of the Heart. *AO*, Aorta; *IVC*, inferior vena cava; *LA*, left atrium; *LAA*, left atrial appendage; *LPA*, left pulmonary artery; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RPA*, right pulmonary artery; *RV*, right ventricle; *SVC*, superior vena cava.

pleuritic), gastrointestinal (gastroesophageal reflux disease [GERD]), psychiatric (panic attack, hyperventilation syndrome).

2. **When to consider referral to cardiologist**: Symptoms that suggest cardiac etiology (palpitations, syncope with exertion, and decreased exercise tolerance), ECG changes, new murmur.

B. Syncope[21]

1. **Etiologies**
   a. Cardiac etiologies:
      (1) Electrical disturbances: Long QT syndrome, Brugada syndrome, congenital short QT syndrome, catecholaminergic polymorphic ventricular tachycardia.
      (2) Structural heart disease: Hypertrophic cardiomyopathy, coronary artery anomalies, valvular aortic stenosis, dilated cardiomyopathy, acute myocarditis, pulmonary HTN.
   b. Non-cardiac etiologies[21]:
      (1) Common: Vasovagal syncope (50% pediatric syncope), breath holding spells, orthostatic hypotension.
      (2) Life-threatening: Heat illness/stroke, anaphylaxis, toxic ingestion, hypoglycemia.
2. **When to consider referral to cardiologist:**
   a. History: Congenital/acquired heart disease, syncope with exertion, associated chest pain or palpitations.

TABLE EC 7.C

ECHOCARDIOGRAMS

	Transthoracic Echocardiogram (TTE)	Transesophageal Echocardiogram (TEE)
Approach	Transducer placed on chest externally	Transducer on end of modified endoscope to view heart from esophagus
Pros	Does not require general anesthesia Simpler to perform than TEE	Better views in obese patients Good for intraoperative use Better visualization of small lesions/vegetations
Cons	Limited views in certain patients (uncooperative, obese, suspected endocarditis)	Requires general anesthesia More difficult to perform

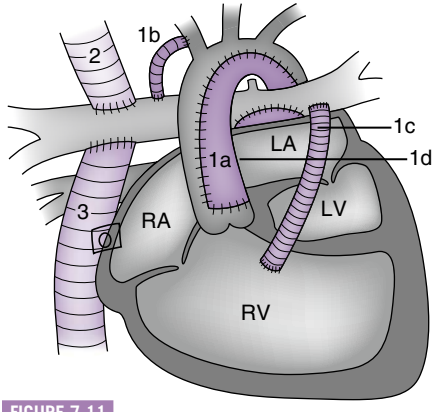

FIGURE 7.11
Schematic diagram of cardiac shunts, including the modified Blalock-Taussig *(BT)*, Sano modification, bidirectional Glenn, and Fontan shunts.

b. Family history: Early sudden cardiac death, arrhythmia, cardiomyopathy.
c. Evaluation: Abnormal cardiac exam or abnormal ECG.

VIII. EXERCISE RECOMMENDATIONS FOR PATIENTS WITH CONGENITAL HEART DISEASE

See Table EC 7.D for exercise recommendations for patients with CHD.[22]

IX. LIPID MONITORING RECOMMENDATIONS

A. Screening of Children and Adolescents[23]

1. **Universal screening:** Children 9 to 11 years old (prior to onset of puberty) and at 17 to 21 years.
2. **Targeted screening:** 2 to 8 years old and 12 to 16 years old with risk factors:
   a. Moderate or high-risk medical condition: History of prematurity, very low birth weight, CHD (repaired or unrepaired), recurrent urinary tract infections, renal or urologic malformations, family history of congenital renal disease, solid organ transplant, malignancy or bone marrow transplant, treatment with drugs known to raise BP, other systemic illness associated with HTN (e.g., neurofibromatosis, tuberous sclerosis), evidence of elevated intracranial pressure.
   b. Other cardiovascular risk factors, including diabetes, HTN, body mass index ≥95th percentile, cigarette use.

TABLE 7.14

CARDIAC SURGERIES[29]

Intervention	Indication	Procedure
Atrial septostomy	Common: TGA, HLHS with restrictive atrial septum Less common: tricuspid/mitral/aortic/pulmonary atresia, TAPVR	Percutaneous procedure with balloon-tipped catheter, intra-arterial opening created to allow mixing of blood between systemic and pulmonary systems
Palliative systemic-to-pulmonary artery shunts (e.g., Blalock-Taussig shunt)	Lesions with impaired pulmonary perfusion (TOF, HLHS, tricuspid atresia, pulmonary atresia)	Shunt created to increase pulmonary blood flow
Norwood procedure, stage 1 (neonatal period)	HLHS	MPA anastomosis to aorta with arch reconstruction Modified BTS or Sano performed to provide pulmonary blood flow ASD created for decompression of left atrium Expected oxygen saturation 75%–85%
Bidirectional Glenn shunt or hemi-Fontan (3–6 months)	HLHS Intermediate step between Norwood 1 and Fontan	Bidirectional Glenn shunt or hemi-Fontan to reduce volume overload of single right ventricle Expected oxygen saturation 80%–85%
Fontan procedure	Functionally single ventricle (tricuspid atresia, HLHS)	Anastomosis of right atria and/or IVC to pulmonary arteries, separates systemic and pulmonary circulations Expected oxygen saturation >92%
Modified Fontan	Single ventricle	Completely separates systemic and pulmonary circulations Expected oxygen saturations >92%
Arterial switch	TGA	Connects aorta to LV and PA to RV, reconnects coronary arteries to aorta Normal oxygen saturations
Ross procedure ("switch procedure")	Aortic stenosis	Pulmonary valve used to replace diseased aortic valve, pulmonary valve replaced by homograft, avoids long-term anticoagulation Normal oxygen saturations

ASD, Atrial septal defect; *BTS*, Blalock-Taussig shunt; *HLHS*, hypoplastic left heart syndrome; *LV*, left ventricle; *MPA*, main pulmonary artery; *PA*, pulmonary artery; *RV*, right ventricle; *TAPVR*, total anomalous pulmonary venous return; *TGA*, transposition of great arteries; *TOF*, tetralogy of Fallot.

c. Family history of early cardiovascular disease (CVD) or severe hypercholesterolemia:
   (1) Parent or grandparent who at <55 years old (males) or <65 years old (females) suffered an MI or sudden death, underwent a coronary artery procedure, or who had evidence of coronary atherosclerosis, peripheral vascular disease, or cerebrovascular disease.
   (2) Parent with total cholesterol ≥240 mg/dL or known dyslipidemia.

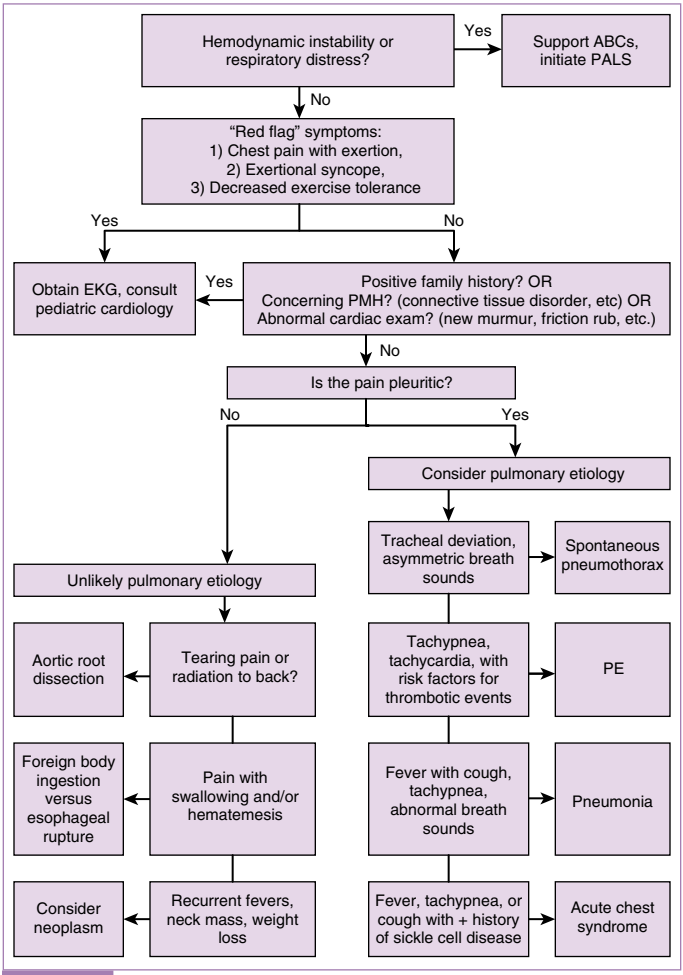

FIGURE 7.12

Algorithm for the evaluation of non-traumatic chest pain. *ABCs,* airway, breathing, and circulation; *EKG,* electrocardiogram; *PALS,* pediatric advanced life support; *PE,* pulmonary embolism; *PMH,* past medical history.

B. Goals for Lipid Levels in Childhood[23]

1. **Total cholesterol**
   a. Acceptable (<170 mg/dL): Repeat measurement in 3 to 5 years.
   b. Borderline (170 to 199 mg/dL): Repeat cholesterol and average with previous measurement. If <170 mg/dL, repeat in 3 to 5 years. If ≥ 170 mg/dL, obtain lipoprotein analysis.
   c. High (≥200 mg/dL): Obtain lipoprotein analysis.
2. **Low-density lipoprotein (LDL) cholesterol**
   a. Acceptable (<110 mg/dL)
   b. Borderline (110 to 129 mg/dL)
   c. High (≥130 mg/dL)

X. CARDIOVASCULAR SCREENING

A. Sports[24]

There is no established or mandated pre-participation sports screening. There is a recommended history and physical examination screening from the AHA.[24] Routine ECGs are not required unless there is suspicion of underlying cardiac disease Box EC 7.A).

B. Attention–Deficit/Hyperactivity Disorder (ADHD)[27]

1. **Obtain a good patient and family history as well as physical examination.**
2. **There is no increased risk of sudden cardiac death in children without cardiac disease taking ADHD medications.** There is no consensus on universal ECG screening. ECGs should be obtained in those who screen with positive answers on history, in cases of polypharmacy, in those with tachycardia while on medications, and in those with a history of significant cardiac disease. If a patient has significant heart disease or concern for cardiac disease, have patient evaluated by a pediatric cardiologist.

XI. WEB RESOURCES

- http://www.pted.org
- https://murmurquiz.org

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

TABLE EC 7.D

EXERCISE RECOMMENDATIONS FOR CONGENITAL HEART DISEASE AND SPORTS ALLOWED FOR SOME SPECIFIC CARDIAC LESIONS[18]

Diagnosis	Sports Allowed
Small ASD or VSD	No restriction
Mild aortic stenosis	No restriction
MVP (without other risk factors)	No restriction
Moderate aortic stenosis	IA, IB, IIA
Mild LV dysfunction	IA, IB, IC
Moderate LV dysfunction	IA only
Long QT syndrome	IA only
Hypertrophic cardiomyopathy	None (or IA only)
Severe aortic stenosis	None

Sports Classification	Low Dynamic (A)	Moderate Dynamic (B)	High Dynamic (C)
I. Low static	Billiards Bowling Golf Riflery	Baseball/Softball Table tennis Volleyball Fencing	Racket sports Cross-country skiing Field hockey[a] Race walking Running (long distance) Soccer[a]
II. Moderate static	Archery Auto racing[a,b] Diving[a,b] Equestrian[a,b] Motorcycling[a,b]	Fencing Field events (jumping) Figure skating[a] Football (American)[a] Surfing Rugby[a] Running (sprint) Synchronized swimming[b]	Basketball[a] Ice hockey[a] Cross-country skiing (skating technique) Swimming Lacrosse[a] Running (middle distance) Team handball
III. High static	Bobsledding Field events Gymnastics[a,b] Rock climbing Sailing Windsurfing[a,b] Waterskiing[a,b] Weight-lifting[a,b]	Bodybuilding[a,b] Downhill skiing[a,b] Skateboarding[a,b]	Boxing/Wrestling[a] Martial arts[a] Rowing Speed skating Cycling[a,b]

[a]Danger of bodily collision.

[b]Increased risk if syncope occurs.

ASD, Atrial septal defect; *LV*, left ventricular; *MVP*, mitral valve prolapse; *VSD*, ventricular septal defect.

Data from Maron BJ, Zipes DP. 36th Bethesda Conference: Eligibility recommendations for competitive athletes with cardiovascular abnormalities. *J Am Coll Cardiol*. 2005;45(8):1318–1321; and Committee on Sports Medicine and Fitness, American Academy of Pediatrics. Medical conditions affecting sports participation. *Pediatrics*. 2001;107(5):1205–1209.

BOX EC 7.A

THE 12-ELEMENT AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR PARTICIPATION: CARDIOVASCULAR SCREENING OF COMPETITIVE ATHLETES

Medical History[a]

Personal History

1. Exertional chest pain/discomfort
2. Unexplained syncope/near syncope[b]
3. Excessive exertional and unexplained dyspnea/fatigue, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure

Family History

1. Premature death (sudden and unexpected, or otherwise) before age 50 years due to heart disease, in ≥1 relative
2. Disability from heart disease in a close relative <50 years of age
3. Specific knowledge of certain cardiac conditions in family members: Hypertrophic or dilated cardiomyopathy, long-QT syndrome or other ion channelopathies, Marfan syndrome, or clinically important arrhythmias

Physical Examination

1. Heart murmur[c]
2. Femoral pulses to exclude aortic coarctation
3. Physical stigmata of Marfan syndrome
4. Brachial artery blood pressure (sitting position)[d]

[a]Parental verification is recommended for high school and middle school athletes.
[b]Judged not to be neurocardiogenic (vasovagal); of particular concern when related to exertion.
[c]Auscultation should be performed in both supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction.
[d]Preferably taken in both arms.

From Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation.* 2007;115:1643–1655.

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Chapter 8

Dermatology

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M. Cooper Lloyd, MD, MPH

See additional content on Expert Consult

I. EVALUATION AND CLINICAL DESCRIPTIONS OF SKIN FINDINGS

A. Primary Skin Lesions

1. **Macule:** Small, flat, well-circumscribed discolored lesion (<1 cm)
2. **Patch:** Large macule (>1 cm)
3. **Papule:** Small, elevated, firm, well-circumscribed superficial lesion (<1 cm)
4. **Plaque:** Large papule (>1 cm)
5. **Pustule:** Small, well-circumscribed elevation of skin containing purulent material (<1 cm)
6. **Vesicle:** Small, well-circumscribed elevation of skin containing serous fluid (<0.5 cm)
7. **Bulla:** Large vesicle (>0.5 cm)
8. **Wheal:** Transient, raised, well-circumscribed lesion with erythematous periphery and central pallor
9. **Nodule:** Soft or firm lesion in dermis or subcutaneous fat (>1 cm)
10. **Tumor/mass:** Solid, firm lesion (typically >2 cm)

B. Secondary Skin Lesions

1. **Scale:** Small, thin plates shedding from the surface of the skin
2. **Crust:** Solidified exudative material from erosions or ruptured vesicles/pustules
3. **Erosion:** Loss of the most superficial layers of the epidermis from friction, pressure, or inflammation
4. **Ulcer:** Full thickness loss of the epidermis and dermis, with clearly defined edges
5. **Fissure:** Linear or wedge-shaped epidermal tear associated with inflammation and pain
6. **Excoriation:** Superficial linear abrasions secondary to scratching
7. **Lichenification:** Thickening of the epidermis with accentuated skin lines, secondary to chronic inflammation and/or scratching
8. **Scar:** Formation of new connective tissue after full thickness injury to skin, leaving permanent change in skin

C. Shapes and Arrangements

1. **Linear:** Distributed along a line
2. **Dermatomal:** Following a dermatome
3. **Filiform:** Thread-like

4. **Serpiginous:** Wavy, coiled, serpentine pattern
5. **Annular:** Ring-like configuration
6. **Nummular/discoid:** Disk-like lesion
7. **Targetoid:** Resembling a bull's eye target with central erythema surrounded by pale edema with a peripheral border of erythema
8. **Clustered:** Lesions in a group
9. **Herpetiform:** Clustered vesicular lesions on erythematous bases
10. **Reticulated:** Net or lacey distribution
11. **Geographic:** Resembling outlines on a map such as a continent
12. **Morbilliform:** Eruption of erythematous to dusky coalescing macules with interspersed healthy skin

II. VASCULAR ANOMALIES[1]

A. Vascular Tumors

1. Infantile hemangiomas (Fig. 8.1, Color Plates).[2,3]
   a. **Pathogenesis:** Benign vascular tumor with rapid proliferation followed by spontaneous involution. Most present before 4 weeks of age. Undergo rapid growth between 1 and 2 months of age, with 80% of size reached by 3 months. Most begin to regress between 6 and 12 months of age, with the majority of tumor regression occurring by 4 years of age. 50% to 70% resolve completely.
   b. **Clinical presentation:** Newborns may demonstrate pale macules with threadlike telangiectasias that later develop into hemangiomas. May be superficial, deep, or mixed. After involution, can have residual skin changes including scarring and atrophy.
   c. **Indicators that should prompt consideration for early treatment:**
      (1) Potential for life-threatening complications: Airway hemangiomas, liver hemangiomas (associated with high-output heart failure and severe hypothyroidism), and profuse bleeding from an ulcerated hemangioma.
      (2) Risk of functional impairment: Interference with the development of vision (if near eye) and interference with feeding (if near mouth).
      (3) Ulceration: Most common complication (5% to 21%). Can be extremely painful and usually scars; risk greatest in large hemangiomas and those located in skin creases, particularly the diaper area.
      (4) Associated structural anomalies: PHACES syndrome (**P**osterior cranial fossa malformations, large segmental facial **H**emangiomas, **A**rterial lesions, **C**ardiovascular anomalies (aortic anomalies), **E**ye anomalies, **S**ternal cleft anomalies/supraumbilical raphes[4]) and LUMBAR syndrome (**L**ower body hemangioma, **U**rogenital anomalies, **U**lceration, **M**yelopathy, **B**ony deformities, **A**norectal malformations, **A**rterial anomalies, **R**enal anomalies).
      (5) Potential for disfigurement: Risk of permanent scarring or distortion of anatomic landmarks.

TABLE 8.1

INDICATIONS TO OBTAIN IMAGING OF INFANTILE HEMANGIOMAS

Indication	Imaging Modality
1. Diagnosis of infantile hemangiomas (IH) is uncertain (e.g., atypical appearance or behavior)	Ultrasound with Doppler
2. Five or more cutaneous IH	Abdominal ultrasound with Doppler (screen for hepatic IH)
3. Associated structural abnormalities (e.g., PHACE syndrome or LUMBAR syndrome) are suspected	1. If PHACE syndrome is suspected, MRI/MRA head/neck with and without contrast; echocardiography 2. If LUMBAR syndrome is suspected, spinal ultrasound and abdominal ultrasound with Doppler are initial screen, with MRI likely to follow 3. May wish to consult with hemangioma specialist on exact imaging to be ordered

From Krowchuk D, Frieden IJ, Mancini AJ, et al. Clinical practice guideline for the management of infantile hemangiomas. *Pediatrics*. 2019;143(1):1–28.

d. **Diagnosis:** Usually diagnosed clinically. Atypical clinical findings, growth pattern, and equivocal imaging should prompt tissue biopsy to exclude other neoplasms or unusual vascular malformations. See Table 8.1 for indications to order imaging.

e. **Treatment:**

(1) Most are uncomplicated and can be observed with watchful waiting. Photo documentation is used to follow the growth and regression process.

(2) If an infantile hemangioma is identified as high risk, the child should be evaluated by a hemangioma specialist promptly, as there is a narrow window of opportunity in which to intervene and prevent poor outcomes.

(3) β-adrenergic blockers such as propranolol are considered first-line therapy for complicated infantile hemangiomas and should be initiated under supervision of a pediatric dermatologist or experienced practitioner.[5] While patients should be clinically screened for cardiac disease, EKG and/or echocardiogram are not required unless there is clinical concern. Contraindications include: Reactive airways, sinus bradycardia, decompensated heart failure, greater than 1st degree heart block, hypotension, hypoglycemia, hypersensitivity to propranolol. Off label use of selective beta-blockers may be considered in certain patients. Duration should be at least 6 months and up to 12 months of age.[6]

(4) Corticosteroids are considered second line. Similar efficacy to propranolol in a prospective, randomized, investigator-blinded trial, but propranolol is better tolerated and with fewer severe side effects.[7]

(5) Topical timolol is effective in superficial, uncomplicated hemangiomas (recommend 0.5% gel forming solution).

2. Pyogenic granuloma (Lobular Capillary Hemangioma) (Fig. 8.2, Color Plates)
   a. **Clinical presentation:** Benign vascular tumor, appears as small (usually 3 to 10 mm but occasionally much larger) bright red papule that grows over several weeks to months into sessile or pedunculated papule with a "collarette," scale, or crust. Can bleed profusely with minor trauma and can ulcerate. Rarely spontaneously regresses. Seen in all ages; average age of diagnosis 6 months to 10 years. Located on head and neck, sometimes in oral mucosa but can be at any skin site and often misdiagnosed as hemangiomas.
   b. **Treatment:** Usually required, given frequent bleeding and ulceration. Options include shave excision or curettage with cautery of base, surgical excision, carbon dioxide laser excision, or pulsed dye laser therapy. For most cases, shave and cautery are quick, safe, low risk, and can be performed quickly with local anesthesia.

B. Vascular Malformations

Include capillary (port-wine stains and salmon patch/stork bite/angel kiss), lymphatic, venous, and arteriovenous malformations.

Note: For a comparison of vascular malformations to vascular tumors, please see Table EC 8.A.[8]

III. INFECTIONS

A. Viral

1. Warts
   a. **Pathogenesis:** Human papillomaviruses (HPVs) of the epithelium or mucus membrane.
   b. **Clinical presentation:**
      (1) Common warts: Skin-colored, rough, minimally scaly papules and nodules found most commonly on the hands, although can occur anywhere. Can be solitary or multiple, range from a few millimeters to several centimeters, may form large plaques or a confluent linear pattern secondary to autoinoculation. Sometimes persistent in immunocompromised patients.
      (2) Flat warts: Flesh to brown/yellow-colored, smooth, flat-topped papules commonly found over the hands, arms, and face. Usually <2 mm in diameter and often present in clusters.
      (3) Plantar warts: Occur on soles of feet as inward growing, hyperkeratotic plaques and papules. Trauma on weight-bearing surfaces results in small black dots (petechiae from thrombosed vessels on the surface of the wart). Can be painful.
   c. **Diagnosis:** Clinical diagnosis.
   d. **Treatment**[9]:
      (1) Spontaneous resolution occurs in greater than 75% of warts in otherwise healthy individuals within 3 years. No specific treatment clearly better than placebo, except possibly topical salicylic acid.

TABLE EC 8.A

DIFFERENTIATING VASCULAR TUMORS AND VASCULAR MALFORMATIONS

Vascular tumor (infantile hemangioma, pyogenic granuloma, kaposiform hemangioendothelioma, tufted angioma, other tumors)	Vascular malformation (venous, arterial, AVM, capillary, lymphatic)
• Usually not present at birth • Dynamic • Regressing • Proliferative	• Present at birth • Static • Persistent • Non-proliferative

AVM, Arteriovenous malformation.

Adapted from Cohen BA, Rozell-Shannon L. Early diagnosis and intervention of vascular anomalies (infantile hemangiomas and malformations). *Pediatric Care Online*. http://pediatriccare.solutions.aap.org. Accessed September 2018.

(2) Keratolytics (topical salicylates): Particularly effective in combination with adhesive tape occlusion. Response may take 4 to 6 months.
(3) Destructive techniques, candida antigen, cantharidin, or "beetle juice" are not clearly more effective than placebo. Additionally, destructive techniques can be painful and cause scarring. These options are not recommended in children.

2. Molluscum contagiosum (Fig. 8.3, Color Plates)
   a. **Pathogenesis:** Large DNA poxvirus. Spread by skin-to-skin contact.
   b. **Clinical presentation:** Dome-shaped, often umbilicated, translucent to white papules that range from 1 mm to 1 cm. Occur anywhere except palms and soles, most commonly on the trunk and intertriginous areas. Can occur in the genital area and lower abdomen when obtained as a sexually transmitted infection. May be pruritic and can be surrounded by erythema, resembling eczema.
   c. **Diagnosis:** Clinical diagnosis.
   d. **Treatment:** Most spontaneously resolve within 6 to 18 months and do not require intervention other than monitoring for secondary bacterial infection. Surrounding eczematous changes may indicate an immunologic reaction and serve as a harbinger of regression. Treatment may cause scarring and may not be more effective than placebo. Recurrences are common.
3. Herpes simplex virus
   a. **Pathogenesis:** Either HSV-1 or HSV-2 may be implicated, regardless of lesion location. During the initial outbreak, oral lesions last 2 to 3 weeks whereas genital lesions may last 2 to 6 weeks. Recurrent episodes are usually much shorter.
   b. **Clinical presentation (Fig. 8.6, Color Plate):** Symptoms include prodrome of tingling, itching, or burning followed by painful vesicles on erythematous base that may last 7 to 10 days, break open, and crust prior to healing, flu-like symptoms, dehydration (gingivostomatitis), dysuria (genital), ophthalmologic symptoms (keratitis). May be triggered by stress, illness, sun exposure, and menstruation. The first outbreak is typically the worst.
   c. **Diagnosis:** Diagnosed clinically and, in many centers, with viral DNA PCR (more sensitive than culture). To culture a lesion, clean with alcohol, un-roof lesion with sterile needle or wooden side of cotton swab, collect vesicular fluid on sterile swab, and send in viral transport medium.
   d. **Treatment:** Acyclovir or valacyclovir for 7 to 14 days (see Formulary for dosing). For children with herpetic gingivostomatitis, antiviral therapy should be initiated within 72 to 96 hours of onset if they are unable to drink or have significant pain. Valacyclovir is generally preferred as it is more bioavailable than acyclovir and, as a result, is dosed less frequently.

4. Erythema infectiosum ("fifth disease")
   a. **Pathogenesis:** Parvovirus B19.
   b. **Clinical presentation:** Pediatric presentation of nonspecific febrile illness with headache, coryza, and gastrointestinal complaints. Two to five days after onset of symptoms, the classic malar rash with "slapped cheek" appearance erupts, followed by a reticular rash to the trunk several days later. Associated signs and symptoms include arthralgias (more common in adults) and a transient aplastic crisis, which may be more of a problem in patients with hemoglobinopathies and pregnant women.
   c. **Diagnosis:** Clinical diagnosis, serum IgM, or serum DNA PCR.
   d. **Treatment:** Supportive care and avoiding contact with pregnant women.
5. Pityriasis rosea
   a. **Pathogenesis:** Viral etiology (possibly HHV-6, HHV-7) has been hypothesized but no definitive cause has been described.
   b. **Clinical presentation:** Typically asymptomatic or may have mild pruritus. Classic presentation with a round to oval, sharply demarcated, scaly, salmon-colored herald patch with central clearing on trunk followed by a "Christmas tree" distribution of oval crops of lesions similar to herald patch. Pediatric patients may have an atypical distribution involving the scalp, face, distal extremities, and sparing of the trunk. Lesions typically resolve in 4 to 6 weeks.
   c. **Diagnosis:** Clinical diagnosis.
   d. **Treatment:** Typically self-resolving.
6. Roseola infantum (Fig. 8.5, Color Plates)
   a. **Pathogenesis:** Human Herpesvirus 6 (HHV-6).
   b. **Clinical presentation:** Typically diagnosed in children <2 years old with peak 7 to 13 months. Febrile phase of 3 to 5 days of high fever (often >40°C), viremia, and irritability. As febrile phase resolves, patients develop a morbilliform rash on neck and trunk that spreads centripetally to face and extremities for 1 to 2 days.
   c. **Diagnosis:** Clinical diagnosis.
   d. **Treatment:** Self-resolving.
7. Hand, foot, and mouth disease
   a. **Pathogenesis:** Most commonly Coxsackievirus A serotypes.
   b. **Clinical presentation:** Oral lesions on the tongue, buccal mucosa, and palate that initially are 1 to 5 mm erythematous macules and evolve to vesicles and ulcers with a thin erythematous halo. Erythematous, non-pruritic 1 to 10 mm macules, papules, and/or vesicles on the palms and soles. Typically resolve in 3 to 4 days. Usually non-tender, unless caused by Coxsackie A6 (associated with high fevers, widespread lesions, longer duration [12 days], palmar and plantar desquamation, and nail dystrophy).
   c. **Diagnosis:** Clinical diagnosis.
   d. **Treatment:** Supportive care.

8. Reactive erythema (Fig. 8.4; Figs. 8.5–8.10, Color Plates)
   a. **Pathogenesis:** Represent cutaneous reaction patterns triggered by endogenous and environmental factors (e.g., viral infections, drug reactions).
   b. **Clinical presentation:** Group of disorders characterized by erythematous patches, plaques, and nodules that vary in size, shape, and distribution.

B. Parasitic

1. Scabies (Fig. 8.11, Color Plates)
   a. **Pathogenesis:** Caused by the mite *Sarcoptes scabiei*. Spread by skin-to-skin contact and through fomites. Can live for 2 days away from a human host. Female mites burrow and lay eggs under the skin.
   b. **Clinical presentation:** Initial lesion is a small, erythematous papule that is easy to overlook. Can have burrows (elongated, edematous papulovesicles, often with a pustule at the advancing border) which are pathognomonic. Most commonly located in interdigital webs, wrist folds, elbows, axilla, genitals, buttocks, and belt line. In temperate climates, the face and scalp are usually spared. In young infants, the palms and soles are also commonly involved. Burrows are most dramatic in patients who are unable to scratch (e.g., infants). Disseminated eczematous eruption results in generalized severe pruritus, especially at night. Can become nodular, particularly in intertriginous areas, or be susceptible to superinfection due to frequent excoriations. Immunosuppressed patients may develop diffuse scaly crusted eruption and lack pruritus.
   c. **Treatment**[10]:
      (1) Permethrin cream: 5% cream applied to skin from neck down in normal hosts including under fingernails and toenails. Rinse off after 8 to 14 hours. Can repeat in 7 to 10 days.
      (2) Ivermectin (off-label use): Single dose; can repeat in 2 weeks. Efficacy comparable to permethrin cream. May be the best choice for immunodeficient patients where total body application may be difficult.
      (3) Environment: Mites cannot live away from human skin for more than 2 to 3 days. Launder clothing and sheets. Bag and seal stuffed animals and pillows for 2 to 3 days. Consider treatment of close contacts.

C. Fungal (Figs. 8.12–8.16, Color Plates)

1. Tinea capitis (see Fig. 8.12, Color Plates)
   a. **Pathogenesis:** Mostly caused by fungi of the genus *Trichophyton* in North America (95%), less commonly *Microsporum* (5% or less), and spread through contact and fomites.
   b. **Epidemiology:** Usually occurs in young children, with higher incidence in African American children, but any age and ethnicity can be affected.

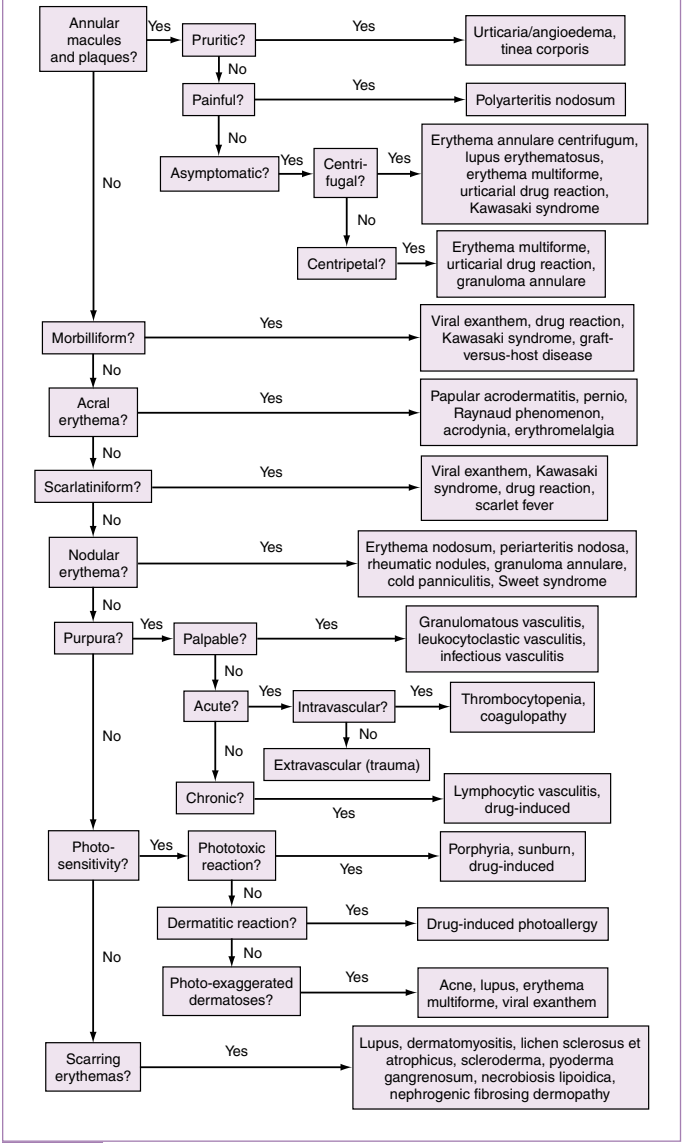

FIGURE 8.4

Reactive erythema. (Modified from Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:206.)

c. **Clinical presentation:**
   (1) Black dot: Most common. Slowly growing, erythematous, scaling patches. These areas develop alopecia and black dots are visible on scalp where hair has broken.
   (2) Gray patch ("seborrheic dermatitis type"): Erythematous, scaling, well-demarcated patches that grow centrifugally. Hair breaks off a few millimeters above the scalp and takes on a gray/frosted appearance.
   (3) Kerion (see Fig. 8.13, Color Plates): Complication of tinea capitis or tinea corporis. Type IV hypersensitivity to fungus. Raised, boggy/spongy lesions, often tender and covered with purulent exudate. Most commonly occurs months after primary infection.
   (4) All can be associated with posterior cervical lymphadenopathy.

d. **Diagnosis:** Can be made clinically, but since oral antifungal therapy is indicated, tinea capitis should be confirmed by direct microscopic exam of a potassium hydroxide (KOH) preparation of the proximal ends of hairs, gently and painlessly scraped from the affected area. Cultures may be obtained by using a sterile toothbrush or cotton swab. The scale can be scraped directly into a sterile plastic cup and/or the cotton swab tips can be broken off and placed into the sterile plastic cups.

e. **Treatment**[11]**:** Always requires systemic therapy. First-line therapy includes oral griseofulvin for 10 to 12 weeks (which should be taken with fatty foods for improved absorption) and terbinafine for 6 weeks (see Formulary for dosing). Most experts consider terbinafine superior to griseofulvin for *T. tonsurans* because of its shorter duration of therapy and superior effectiveness. The FDA recommends baseline and follow-up hepatic function testing in children taking terbinafine, though most clinicians forego laboratory testing in healthy children without history of liver disease if treatment is 6 weeks or less. Though not FDA-approved for tinea capitis, fluconazole at 6 mg/kg/day (max 400 mg/day) for 6 weeks is recommended by the AAP Red Book as an alternative treatment of tinea capitis in children younger than 2 years old.[12] All family members, particularly other children, should be examined carefully for subtle infection. Selenium sulfide 2.5% shampoo may shorten the period of shedding of fungal organisms and reduce risk of infection of unaffected family members.

2. Tinea corporis and pedis[11] (see Figs. 8.14 and 8.15, Color Plates)
   a. **Pathogenesis:** Spread through direct contact and fomites, especially in sports with close contact.
   b. **Clinical presentation:** Pruritic, erythematous, annular patch or plaque with central clearing and a scaly raised border. Typically affects glabrous skin (smooth and bare).
   c. **Diagnosis:** Usually diagnosed clinically, but a KOH preparation or fungal culture can be used to help guide diagnosis.
   d. **Treatment:** Topical antifungals (terbinafine, azole) through 1 to 2 weeks past lesion resolution. Widespread eruption may require oral antifungals.

3. Tinea versicolor (see Fig. 8.16, Color Plates)
   a. **Pathogenesis:** Caused by *Malassezia*. Exacerbated by hot/humid weather, hyperhidrosis, topical skin oil use. Most people are colonized with *Malassezia* but only a small number are prone to develop clinical lesions. Not associated with poor hygiene. Not contagious.
   b. **Clinical presentation:** Well demarcated, minimally scaly, hypopigmented macules or patches. Hypopigmented areas tend to be more prominent in the summer because affected areas do not tan. Lesions often have a fine scale that may be noted following gentle rubbing and can be mildly pruritic but are usually asymptomatic.
   c. **Diagnosis:** KOH microscopy reveals pseudohyphae and yeast cells that appear like "spaghetti and meatballs."
   d. **Treatment:** Topical antifungal shampoos and/or creams (miconazole, oxiconazole, ketoconazole) or selenium sulfide are effective. Given the risk of hepatotoxicity, oral azole antifungals are reserved for resistant or widespread disease. Oral terbinafine is not effective. Pigmentation changes may take months to resolve despite successful treatment.

D. Bacterial

1. Impetigo
   a. **Pathogenesis:** Contagious bacterial infection of the skin, most commonly caused by *Staphylococcus aureus* (99% MSSA), with a minority of cases caused by Group A *Streptococcus*.
   b. **Clinical presentation:**
      (1) Nonbullous impetigo: Papules that evolve into erythematous pustules or vesicles that break and form thick, honey-colored crusts and plaques. Commonly overlying any break to skin barrier. Primarily face and extremities.
      (2) Bullous impetigo: Painless vesicles that evolve into flaccid bullae and crusted patches with undermined border. Seen more in infants and young children. Caused by *Staphylococcus aureus* exfoliative toxin A.
   c. **Diagnosis:** Clinical diagnosis.
   d. **Treatment:** When impetigo is contained to a small area, topical mupirocin may be used for 5 days. When the infection is widespread, an oral antibiotic such as cephalexin should be used for 7 days. Consider broader coverage if MRSA is suspected, although MSSA accounts for most infections.
2. Staph scalded skin syndrome
   a. **Pathogenesis:** *Staphylococcus aureus* infections of the skin with hematogenous dissemination of exfoliative toxin A or B to the epidermis.
   b. **Clinical presentation:** Typical presentation is Ritter disease (generalized exfoliation) in a 3- to 7-day-old infant who initially is febrile and irritable with conjunctivitis and perioral erythema. In addition to newborns, this presentation is seen in young children who do not have antibodies to the toxin and often do not clear the toxin-antibody complex quickly due to decreased renal excretion. One to two days after the prodromal onset, patient develops diffuse erythema, fragile,

flaccid bullae and erosions that are Nikolsky positive in areas of mechanical stress such as intertriginous areas. Lesions are not scarring as they are intraepidermal. Older children tend to have a localized bullous impetigo with tender scarlatiniform eruption. Infants and toddlers usually have a combination of the presentations seen in neonates and older children along with white to brown thick flaking desquamation of the entire body, especially the face and neck.

c. **Diagnosis:** Typically clinically. However, cultures should be obtained from any potential source site of infection or colonization such as the medial canthi or nares.

d. **Treatment:** Nearly all cases are MSSA, with an increasing number being clindamycin resistant. First-line treatment may include oral penicillinase-resistant beta-lactams such as first or second-generation cephalosporins. Vancomycin should be considered in patients who fail to respond to treatment and/or in areas with a high prevalence of MRSA. Management should also include supportive care with topical emollients and close monitoring of fluid and electrolyte status.

3. Scarlet fever (Fig. 8.17, Color Plates)
   a. **Pathogenesis:** Exotoxin-mediated response to a *Streptococcus pyogenes* infection, typically pharyngitis.
   b. **Clinical presentation:** Sandpaper-like, coarse, erythematous, blanching rash that originates in the groin and axilla then spreads to the trunk then extremities but spares the palms and soles. May have Pastia lines. Associated with pharyngitis, circumoral pallor, and a strawberry tongue.
   c. **Diagnosis:** Clinical diagnosis. May benefit from rapid strep test and throat culture.
   d. **Treatment:** No additional treatment aside from treating the patient's *Strep* pharyngitis.
4. Cellulitis: See Chapter 17.

IV. HAIR LOSS (FIGS. 8.18–8.20, COLOR PLATES)

A. Telogen Effluvium (see Fig. 8.18, Color Plates)

1. **Pathogenesis:** Most common cause of diffuse hair loss. Mature hair follicles switch prematurely to the telogen (resting) state, with shedding within 3 months.
2. **Clinical presentation:** Diffuse hair thinning 3 months after a stressful event (major illnesses or surgery, pregnancy, severe weight loss).
3. **Treatment:** Self-limited. Regrowth usually occurs over several months.

B. Alopecia Areata (see Fig. 8.19, Color Plates)

1. **Clinical presentation:** Chronic inflammatory (probably autoimmune) disease that starts with well-circumscribed small bald patches and normal-appearing underlying skin. New lesions may demonstrate subtle erythema and be pruritic. Bald patches may enlarge to involve large areas of the scalp or other hair-bearing areas. Many experience good

hair regrowth within 1 to 2 years, although most will relapse. A minority progress to total loss of all scalp (alopecia totalis) and/or body hair (alopecia universalis).
2. **Diagnosis:** Usually clinical diagnosis.
3. **Treatment**[13]: First-line therapy is topical steroids. Referral to dermatology is warranted for consideration of other treatments. No evidence-based data that any therapy is better than placebo. Older children, adolescents, and young adults with longstanding localized areas of hair loss have the best prognosis.

C. Traction Alopecia (see Fig. 8.20, Color Plates)

1. **Pathogenesis:** Hairstyles that apply tension for long periods of time.
2. **Clinical presentation:** Noninflammatory linear areas of hair loss at margins of hairline, part line, or scattered regions, depending on hairstyling procedures used.
3. **Treatment:** Avoidance of styling products or styles that result in traction. If traction remains for long periods, condition may progress to permanent scarring hair loss.

D. Trichotillomania and Hair Pulling

1. **Pathogenesis:** Alopecia due to compulsive urge to pull out one's own hair, resulting in irregular areas of incomplete hair loss. Mainly on the scalp; can involve eyebrows and eyelashes. Onset is usually after age 10 and should be distinguished from hair twirling/pulling in younger children that resolves without treatment in most cases.
2. **Clinical presentation:** Characterized by hair of differing lengths; area of hair loss can be unusual in shape.
3. **Treatment:** Behavioral modification and consider psychiatric evaluation (can be associated with anxiety, depression, and obsessive-compulsive disorder).

V. ACNE VULGARIS

A. Pathogenetic Factors

Follicular hyperkeratinization, increased sebum production, *Cutibacterium acnes* (formerly *Propionibacterium acnes*) proliferation, and inflammation.

B. Risk Factors

Androgens, family history, and stress. No strong evidence that dietary habits affect acne.

C. Clinical Presentation

1. **Noninflammatory lesions**
   a. Closed comedone (whitehead): Accumulation of sebum and keratinous material, resulting in white/skin-colored papules without surrounding erythema.
   b. Open comedone (blackhead): Dilated follicles filled with keratinocytes, oils, and melanin.

2. **Inflammatory lesions:** Papules, pustules, nodules, and cysts with evidence of surrounding inflammation. Typically appear later in the course of acne. Nodulocystic presentations are more likely to lead to hyperpigmentation and/or permanent scarring.

D. Treatment[14–16] (Table 8.2)

1. **Skin care:** Gentle nonabrasive cleaning. Avoid picking or popping lesions. Vigorous scrubbing and abrasive cleaners can worsen acne.
2. **Topical first-line therapies:** Recommended for mild to moderate acne.
   a. Retinoids (Table EC 8.B)
      (1) Normalize follicular keratinization and decrease inflammation.
      (2) A pea-sized amount should be applied to cover the entire face.
      (3) Risks: Cause irritation and dryness of skin. Retinoids should be used at night due to inactivation by sunlight. This class should not be used during pregnancy.
      (4) Three topical retinoids (tretinoin, adapalene, and tazarotene) are available by prescription in the United States. Adapalene 0.1% gel has been approved for over-the-counter (OTC) use with significant efficacy.[17]

TABLE 8.2

PEDIATRIC TREATMENT RECOMMENDATION FOR MILD, MODERATE, AND SEVERE ACNE

Acne Classification	Initial Treatment	Inadequate Response
Mild	Benzoyl peroxide (BPO) or topical retinoid **OR** *Topical combination therapy*: BPO + Antibiotic or Retinoid + BPO or Retinoid + Antibiotic + BPO	Add BPO or retinoid if not already prescribed OR change topical retinoid concentration, type, and/or formulation OR change topical combination therapy
Moderate	*Topical combination therapy*: Retinoid + BPO or Retinoid + BPO + Antibiotic **OR** Oral Antibiotic + Topical Retinoid + BPO or Topical Retinoid + Topical Antibiotic + BPO	Change topical retinoid concentration, type, and/or formulation and/or change topical combination therapy OR add or change oral antibiotic. Consider oral isotretinoin (dermatology referral). Females: consider hormonal therapy.
Severe	*Combination therapy*: Oral Antibiotic + Topical Retinoid + BPO ± Topical Antibiotic	Consider changing oral antibiotic AND consider oral isotretinoin. Females: consider hormonal therapy. Strongly consider referral to dermatology.

Topical fixed-combination prescriptions available.

Data from Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131:S163–S186.

TABLE EC 8.B

FORMULATIONS AND CONCENTRATIONS OF TOPICAL RETINOIDS

Retinoid	Vehicle[a]	Strength (%)
TRETINOIN	Cream	0.025, 0.05, 0.1
Pregnancy Category C	Gel	0.01, 0.025
	Gel (micronized)	0.05
	Microsphere gel	0.04, 0.1
	Polymerized cream	0.025
	Polymerized gel	0.025
ADAPALENE	Cream	0.1
Pregnancy Category C	Gel	0.1, 0.3
	Solution	0.1
	Lotion	0.1
TAZAROTENE	Gel	0.05, 0.1
Pregnancy Category X	Cream	0.05, 0.1

[a]Numerous generic retinoids are available. Branded products are available under the following trade names: Atralin, Avita, and Retin-A Micro for tretinoin; Differin for adapalene; and Tazorac for tazarotene.

Data from Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics.* 2013;131:S163–S186, Table 4.

b. Benzoyl peroxide (BPO)
   (1) Oxidizing agent with antibacterial and mild anticomedolytic properties.
   (2) Washes may be most convenient formulation, as they can be used in the shower.
   (3) Risks: Can bleach hair, clothing, towels, and sheets.
c. Salicylic acid: Topical comedolytic agent that may be found in OTC face washes and serves as an alternative to a topical retinoid.

3. **Topical antimicrobials:**
   a. Azelaic acid: Antimicrobial, comedolytic, and anti-inflammatory. Recommended by the American Academy of Dermatology (AAD) for the treatment of postinflammatory dyspigmentation (see Figures EC 8.P and EC 8.S). Available in a 15% gel and a 20% cream (more efficacious).[18]
   b. Erythromycin and clindamycin: Avoid topical antibiotics as monotherapy. Topical BPO should be concurrently used to optimize efficacy and avoid bacterial resistance.
4. **Oral antibiotics** (Table EC 8.C): Recommended for moderate to severe inflammatory acne that is resistant to topical treatment. These medications should be used with BPO or topical retinoid. Do not use as monotherapy. Limit to 3 months to minimize bacterial resistance.
   a. ≥8 years old: Doxycycline or minocycline
   b. <8 years old, pregnancy, or tetracycline allergy: Azithromycin, erythromycin, or trimethoprim/sulfamethoxazole.
   c. Erythromycin should be used with care due to increased risk of resistance. The AAD recommends reserving trimethoprim/sulfamethoxazole for patients who have failed other treatments or are unable to tolerate tetracyclines and macrolides.
5. **Hormonal therapy:** Reduces sebum production and androgen levels. Good option for pubertal females who have sudden onset of moderate to severe hormonal acne (often on lower face, jawline) and have not responded to conventional first-line therapies. Should not be used as monotherapy. Combination oral contraceptives (Ortho Tri-Cyclen, Estrostep, and Yaz) or spironolactone (antiandrogen).
6. **Oral isotretinoin:** Reserved for patients with severe nodular, cystic, or scarring acne who do not respond to traditional therapy or who cannot be weaned from oral antibiotics. Should be managed by a dermatologist. Most patients have complete resolution of their acne after 16 to 20 weeks of use.
   a. Side effects:
      (1) Teratogenicity: Patients and physicians are mandated by the FDA to comply with the iPledge program to eliminate fetal exposure to isotretinoin. Female patients with child-bearing potential must use two forms of birth control with routine pregnancy testing.
      (2) Hepatotoxicity, hyperlipidemia, and bone marrow suppression, a complete blood cell count, fasting lipid profile, and liver function tests should be obtained before initiation of therapy and repeated at 4 and 8 weeks.

TABLE EC 8.C

FIRST-LINE ORAL ANTIBIOTICS USED FOR TREATMENT OF MODERATE TO SEVERE ACNE VULGARIS

Antibiotic	Potential Adverse Effects	Comments
DOXYCYCLINE	Pill esophagitis; photosensitivity; staining of forming tooth enamel (<8 years of age); vaginal candidiasis	Take with large glass of water and maintain upward position ~1 hr; optimize photoprotection; avoid in children without permanent teeth
MINOCYCLINE (IMMEDIATE RELEASE)	Cutaneous and/or mucosal hyperpigmentation; DHS (systemic, within first 1–2 months); LLS; SJS; vestibular toxicity (within first few days); staining of forming tooth enamel (<8 years of age); vaginal candidiasis	Can be taken with meals; warn patient about dizziness/vertigo; avoid in children without permanent teeth; monitor for pigmentary changes on skin
MINOCYCLINE (EXTENDED RELEASE)	Same as above although above side effects reported predominantly with immediate release formulations; lower incidence of acute vestibular side effects with weight–based dosing	Less accumulation of drug over time due to pharmacokinetic properties of extended release formulation, may correlate with decreased hyperpigmentation

DHS, Drug hypersensitivity syndrome; *LLS*, lupus-like syndrome; *SJS*, Stephens-Johnson syndrome.
Modified from Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131:S163–S186, Table 5.

VI. COMMON NEONATAL DERMATOLOGIC CONDITIONS (FIG. 8.21; FIGS. 8.22–8.30, COLOR PLATES)

A. Erythema Toxicum Neonatorum (see Fig. 8.22, Color Plates)

1. **Clinical presentation:** Most common rash of full-term infants; incidence declines with lower birth weight and prematurity. Appears as small erythematous macules and papules that evolve into pustules on erythematous bases. Rash most often occurs by 24 to 48 hours of life but can be present at birth or emerge as late as 2 to 3 weeks.
2. **Course:** Self-limited, resolves within 5 to 7 days; recurrences possible.

B. Transient Neonatal Pustular Melanosis (see Figs. 8.23–8.24, Color Plates)

1. **Clinical presentation:** More commonly affects full-term infants with darker pigmentation. At birth, appears as small pustules on nonerythematous bases that rupture and leave erythematous/hyperpigmented macules with a collarette of scale.
2. **Course:** Self-limited macules fade over weeks to months.

C. Miliaria (Heat Rash) (see Fig. 8.25, Color Plates)

1. **Clinical presentation:** Common newborn rash associated with warmer climates, incubator use, or occlusion with clothes/dressings. Appears as small erythematous papules or pustules usually on face, scalp, or intertriginous areas.
2. **Course:** Rash resolves when infant is placed in cooler environment or tight clothing/dressings are removed.

D. Milia (see Fig. 8.26, Color Plates)

1. **Clinical presentation:** Common newborn lesions. Appears as 1- to 3-mm white/yellow papules, frequently found on nose and face; due to retention of keratin and sebaceous materials in pilosebaceous follicles.
2. **Course:** Self-limited, resolves within first few weeks to few months of life.

E. Neonatal Acne (see Fig. 8.27, Color Plates)

1. **Clinical presentation:** Seen in 20% of infants. Appears as inflammatory papules or pustules without comedones, usually on face and scalp. Secondary to effect of maternal and endogenous androgens on infant's sebaceous glands.
2. **Course:** Peaks around 1 month, resolves within a few months, usually without intervention. Does not increase risk of acne as an adolescent.

F. Seborrheic Dermatitis (Cradle Cap) (see Figs. 8.28–8.29, Color Plates)

1. **Clinical presentation:** Erythematous plaques with greasy yellow scales. Located in areas rich with sebaceous glands, such as scalp, cheeks, ears, eyebrows, intertriginous areas, diaper area. Unknown etiology. Can be seen in newborns, more commonly in infants aged 1 to 4 months.
2. **Course:** Self-limited and resolves within a few weeks to months.

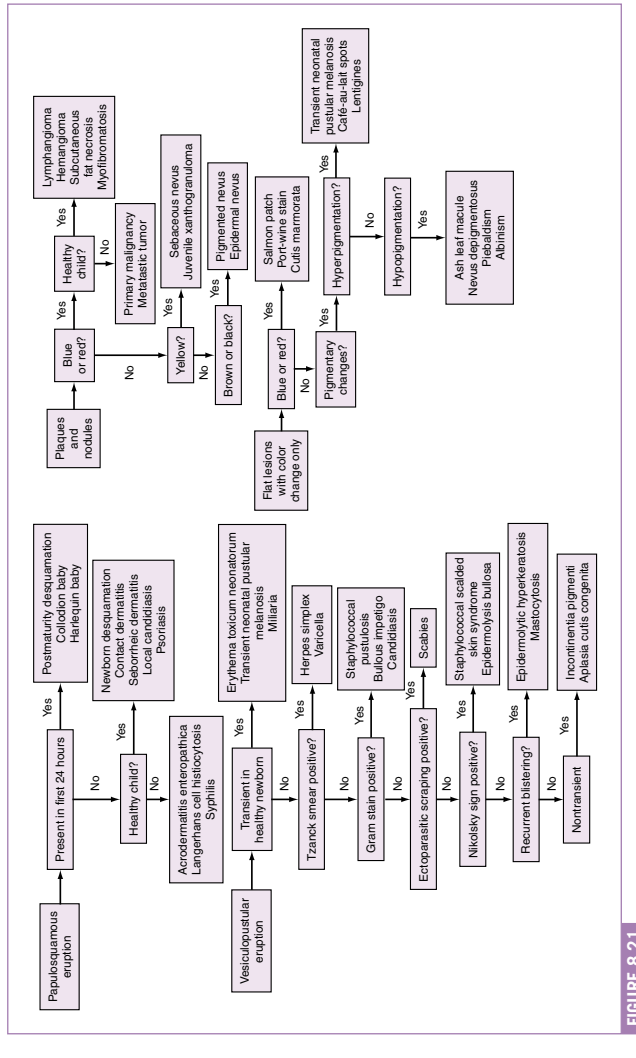

FIGURE 8.21
Evaluation of neonatal rashes. (Modified from Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:62.)

3. **Treatment:** Can remove scales on scalp with an emollient (e.g., mineral or olive oil, or petroleum jelly) and a soft brush/fine comb. In more severe cases, antifungal shampoos or low-potency topical steroid can shorten the course, although no shampoos are FDA-approved for children less than 2 years of age.

G. Congenital Dermal Melanocytosis (formerly known as Mongolian Spots)

1. **Clinical presentation:** Most common pigmented lesion of newborns, usually seen in babies with darker skin tone. Appear as blue/gray macules without definite disappearance of dermal melanocytes. Can be mistaken for child abuse thus accurate documentation at newborn and well-child visits is important.
2. **Course:** Spots typically fade within first few years of life, with majority resolved or much improved by age 10 years.

H. Diaper Dermatitis[19] (see Fig. 8.30, Color Plates)

1. **Clinical presentation:** Irritant contact dermatitis characterized by erythematous eruption on buttocks and genital areas with exclusion of other potential causes. Rarely associated with diaper candidiasis, characterized by a red, raised papular rash with small pustules at the periphery. Tends to involve the skin creases.[19]
2. **Treatment:** Frequent diaper changes, air exposure, adequate drying, gentle cleaning, and judicious use of topical barrier preparations. If persistent, can use low-potency topical steroid until cleared. For candidiasis, treatment with topical nystatin, miconazole, or clotrimazole is sufficient. Combination steroid/antifungal creams should be avoided due to steroid-related side effects and association with persistent fungal infections.[20]

VII. AUTOIMMUNE AND ALLERGIC DERMATOLOGIC CONDITIONS (FIGS. 8.31–8.38, COLOR PLATES)

A. Contact Dermatitis

1. **Irritant dermatitis:** Exposure to physical, chemical, or mechanical irritants to the skin. Common irritants include frequent hand washing, hot water, lip-licking, thumb-sucking, and exposure to chemicals, paints, or certain foods like citrus fruits.
2. **Allergic dermatitis** (see Fig. 8.31, Color Plates):
   a. **Pathogenesis:** Immune reaction to an environmental trigger that comes into contact with the skin. After initial sensitization period of 7 to 10 days in susceptible individuals, an allergic response occurs with subsequent exposures.
   b. **Common allergens:** *Toxicodendron* spp. (poison ivy, oak, sumac), nickel, cobalt, gold, dyes, fragrances, formaldehyde, and latex.
   c. **Clinical presentation:** Pruritic erythematous dermatitis that can progress to chronic scaling, lichenification, and pigment changes. Poison ivy (see Fig. 8.32, Color Plates): Exposure to urushiol causes streaks of erythematous papules, pustules, and vesicles. Highly pruritic, can become edematous, especially if rash is on face or genitals. In extreme cases, anaphylaxis can occur.

d. **Diagnosis:** Careful history taking and recognition of unusual shapes and locations suggesting an "outside job" allow for clinical diagnosis. Patch testing may also be helpful when trigger cannot be identified.
e. **Treatment**:
   (1) Remove causative agent. Moisturize with ointment like Vaseline or Aquaphor twice per day. Use antihistamine and/or oatmeal baths as needed for itching, sedation, and sleeping, though they do not directly impact the rash.
   (2) Mild/moderate: Topical steroids twice a day for 1 week, then daily for 1 to 2 weeks.
   (3) Widespread/severe: Systemic steroids for 2 to 3 weeks, with taper. There is no role for short courses of steroids because eruption will flare when drug is stopped.
   (4) For poison ivy contact, remove clothing and wash skin with mild soap and water as soon as possible.

B. Atopic Dermatitis (Eczema) (See Figs. 8.33–8.37, Color Plates)

1. **Pathogenesis:** Due to inadequate skin barrier function from combination of genetic and environmental factors, resulting in transepidermal water loss. Can be associated with elevated serum IgE.
2. **Epidemiology**[21]**:** Affects up to 20% of children in the United States, the vast majority with onset before age 5 years. Other comorbidities may follow including asthma, allergic rhinitis, and food allergies. Eczema resolves or improves in over 75% of patients by adulthood.
3. **Clinical presentation:** Dry, pruritic skin with acute changes, including erythema, vesicles, crusting, and chronic changes, including scaling, postinflammatory hypo- or hyperpigmentation (see Figures EC 8.P and EC 8.S), and lichenification.
   a. Infantile form: Erythematous, scaly lesions on the cheeks, scalp, and extensor surfaces. Covered areas (especially the diaper area) are usually spared.
   b. Childhood form: Lichenified plaques in flexural areas.
   c. Adolescence: More localized and lichenified skin changes. Predominantly on skin flexures, hands, and feet.
4. **Treatment**[21]**: See Chapter 15**
   a. Lifestyle: Avoiding triggers (products with alcohol, fragrances, astringents, sweat, allergens, and excessive bathing). Avoid scratching (eczema is the "itch that rashes").
   b. Bathing: Should be less than 5 minutes in lukewarm water with a gentle bar soap and no washcloth or scrubbing. Skin should be patted dry (not rubbed) and followed by rapid application of an emollient ("soak and smear").
   c. Consider diluted bleach baths once or twice a week (mix 1/4 cup of bleach in full tub of lukewarm water and soak for 10 minutes, then rinse off with fresh water).
   d. Skin hydration: Frequent use of bland emollients with minimal water content (Vaseline or Aquaphor). Avoid lotions, as they have high water and low oil content, which worsens dry skin.

e. Oral antihistamines: There is little evidence that antihistamines improve skin lesions in atopic dermatitis. Non-sedating antihistamines can be used for environmental allergies and hives. Sedating antihistamines may be of transient benefit for sedation at bedtime.
f. Treatment for inflammation:
(1) **Mild disease**: **Topical steroids**[22] (Table 8.3): Low and medium potency steroid ointments once or twice daily for 7 days during a flare. Severe flares may require a high-potency steroid for a longer duration of therapy, followed by a taper to a low-potency steroid. Use of topical steroids in areas where skin is thin (groin, axilla, face, under breasts) should generally be avoided. Short durations of low-potency steroids may be used as needed in these areas. Ointments can be applied over steroid.
(2) **Moderate disease**: **Crisaborole** is a topical PDE4 inhibitor approved for mild to moderate eczema with preliminary studies of the 2% ointment showing improvement in the majority of clinical signs and symptoms, particularly pruritus.[23] Topical calcineurin inhibitors (**tacrolimus ointment, pimecrolimus cream**) are second-line therapies which should only be used in consultation with a dermatologist due to FDA "black box" warnings on these medications for theoretical increased risk of cancer, although there are no data to confirm and long-term safety studies are pending.[24,25]
(3) **Severe disease**: **Phototherapy** with narrowband UVB light is a treatment option for older children and adolescents. Low-dose **methotrexate** is a consideration before cyclosporine. For many dermatologists, low-dose oral methotrexate is the first oral option for severe disease unresponsive to aggressive topical therapy. Oral **cyclosporine** is only used in severe cases of older children and adolescents who have failed other treatments due to concern for renal compromise. **Dupilumab** is an IL-4 receptor alpha antagonist prescribed for refractory cases, currently with FDA approval only for treatment in adults.

5. **Complications**[26]**:**
a. Bacterial superinfection: Usually *S. aureus*, sometimes Group A *Streptococcus*. Depending on extent of infection, treat with topical mupirocin or systemic antibiotics.
b. Eczema herpeticum superinfection with herpes simplex virus can cause severe systemic infection. Presents as vesiculopustular lesions with central punched-out erosions that do not respond to oral antibiotics. Must be treated systemically with acyclovir or valacyclovir. Should be evaluated by ophthalmologist if there is concern for eye involvement.

C. Papular Urticaria (See Fig. 8.38, Color Plates)

1. **Pathogenesis:** Type IV hypersensitivity reaction to fleas, mosquitos, or bedbugs; also known as insect bite–induced hypersensitivity (IBIH).

TABLE 8.3

RELATIVE POTENCIES OF TOPICAL CORTICOSTEROIDS

Class	Drug	Vehicle(s)	Strength (%)
I. VERY HIGH POTENCY	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. HIGH POTENCY	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone propionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment, gel	0.25 (C,O), 0.05 (G)
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III–IV. MEDIUM POTENCY	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide, Fluradrenolide	Cream, ointment	0.025 (C), 0.05 (O)
	Fluticasone propionate	Cream, Ointment	0.05 (C), 0.005 (O)
	Triamcinolone acetonide, Mometasone furoate	Cream	0.1
V. LOWER-MEDIUM POTENCY	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate, Prednicarbate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
VI. LOW POTENCY	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinonide acetonide	Cream, solution	0.01
VII.LOWEST POTENCY	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion	0.25
		Cream, ointment	0.5
		Cream, solution	1
	Hydrocortisone acetate	Cream, ointment	0.5–1

C, Cream; *G*, gel; O, ointment.

Modified from Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dernatol.* 2014;71(1):116–132, Table 5.

2. **Clinical presentation/epidemiology:** Summarized by the SCRATCH principles[27]:
   a. **S**ymmetric eruption: Exposed areas and scalp commonly affected. Spares diaper region, palms, and soles.
   b. **C**luster: Appear as "meal clusters" or "breakfast, lunch, and dinner" which are linear or triangular groupings of lesions. Associated with bedbugs and fleas.
   c. **R**over not required: A remote animal exposure or lack of pet at home does not rule out IBIH.
   d. **A**ge: Tends to peak by age 2. Not seen in newborn period. Most tend to develop tolerance by age 10.
   e. **T**arget lesions: Especially in darkly pigmented patients. **T**ime: Emphasize chronic nature of eruption and need for patience and watchful waiting.
   f. **C**onfused pediatrician/parent: Diagnosis often met with disbelief by parent and/or referring pediatrician.
   g. **H**ousehold: Because of the nature of the hypersensitivity, usually only affects one family member in the household.
3. Management (3 Ps):
   a. **P**revention: Wear protective clothing, use insect repellent when outside (AAP guidelines recommend up to 30% DEET or 12% picaridin containing repellents), launder bedding and mattress pads for bedbugs, and maximize flea control for pets.
   b. **P**ruritis control: Topical steroids or antihistamines may be of some benefit.
   c. **P**atience: Can be frustrating because of its persistent, recurrent nature. Ensure patients that their symptoms will resolve and they will eventually develop tolerance.

D. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

1. **Pathogenesis:** Severe mucocutaneous reaction with partial to full epidermal necrosis due to keratinocyte necrosis. Stevens-Johnson syndrome (SJS) has less than 10% involvement of body surface area (BSA), whereas toxic epidermal necrolysis (TEN) has greater than 30% BSA involvement. SJS/TEN defines the gap of 10% to 30% involvement. Overall mortality for pediatric patients is less than 8%. Commonly caused by medications initiated in previous 8 weeks including sulfonamide antibiotics, lamotrigine, carbamazepine, phenobarbital, and several oncologic drugs. May also be caused by *Mycoplasma pneumonia* infections. Nearly one third of cases have no identified trigger.
2. **Clinical presentation:** Fever and flu-like prodrome for 1 to 3 days prior to mucocutaneous lesions. Ophthalmologic and oropharyngeal symptoms are often first sites of mucosal involvement. Urogenital mucosal involvement seen in two-thirds of patients may lead to urinary retention and have significant long-term anatomic changes in female patients. Epidermal lesions are described as exquisitely tender (with pain out of

proportion), ill-defined, coalescing macules and patches of erythema with central purple-to-black areas. Lesions typically start on face and trunk then spread in a symmetric distribution sparing the scalp, palms, and soles. Bullae form with disease progression. Then, the epidermis sloughs with positive Nikolsky and Asboe-Hansen (lateral expansion of bullae with pressure) signs. Acute phase may last 8 to 12 days with reepithelization requiring up to four weeks.

3. **Diagnosis:** Although usually not necessary, clinical diagnosis may be confirmed with a skin biopsy. Additional work up includes CBC, CMP, ESR, CRP, bacterial and fungal cultures, *M. pneumoniae* PCR, and CXR.
4. **Treatment:** Remove offending agent, supportive care, and close monitoring of all organ systems in the inpatient/ICU setting. There is controversy regarding IVIG and single dose of TNF-alpha inhibitor early in course. Systemic steroids probably should not be used.
5. **Complications:** At risk for serious complications including secondary bacterial infections (*Staphylococcus aureus* and *Pseudomonas aeruginosa*), septic shock, pneumonia, acute respiratory distress syndrome (ARDS), and epithelial necrosis of the GI tract. Most common complication in children is corneal scarring and dry eye.

E. Autoimmune Bullous Diseases: See Section X, Online Content.

VIII. NAIL DISORDERS[28]: SEE SECTION X, ONLINE CONTENT

IX. DISORDERS OF PIGMENTATION: SEE SECTION X, ONLINE CONTENT

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

X. ONLINE CONTENT

A. Autoimmune and Allergic Lesions

1. **Autoimmune** bullous diseases
   a. Very rare in children but should be considered if bullous lesions do not respond to standard therapy. Suspicion for any of the following should warrant referral to a dermatologist for diagnosis and management.
   b. **Pemphigus vulgaris** (Figure EC 8.A):
      (1) Pathogenesis: IgG autoantibodies to epidermal adhesion molecules, which interrupt integrity of epidermis and/or mucosa and result in extensive blister formation.
      (2) Clinical presentation: Flaccid bullae that start in the mouth and spread to face, scalp, trunk, extremities, and other mucosal membranes. Positive Nikolsky sign. Ruptured blisters are painful and prone to secondary infection. Can lead to impaired oral intake if there is significant oral mucosal involvement.
      (3) Treatment: Systemic glucocorticoids, rituximab, and/or intravenous immunoglobulin.
   c. **Pemphigus foliaceus:**
      (1) Pathogenesis: IgG autoantibodies bind to the same antigen as in bullous impetigo and staphylococcal scalded skin syndrome; thus lesions are superficial and rupture easily. Can be triggered by certain drugs, including thiol compounds and penicillins.
      (2) Clinical presentation: Scaling, crusting erosions on erythematous base that appear on face, scalp, trunk, and back. No mucosal involvement. Lesions are more superficial than in pemphigus vulgaris.
      (3) Treatment: Systemic glucocorticoids or rituximab. There is currently a move away from systemic steroids due to good efficacy and safety data on rituximab.
   d. **Bullous pemphigoid:**
      (1) Pathogenesis: Autoantibodies to the epithelial basement membrane that results in an inflammatory cascade and causes separation of epidermis from dermis and epithelium from subepithelium.

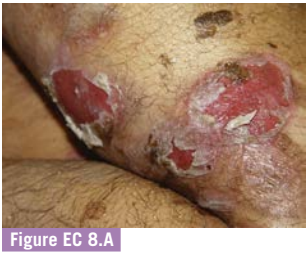

Figure EC 8.A

Pemphigus vulgaris. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

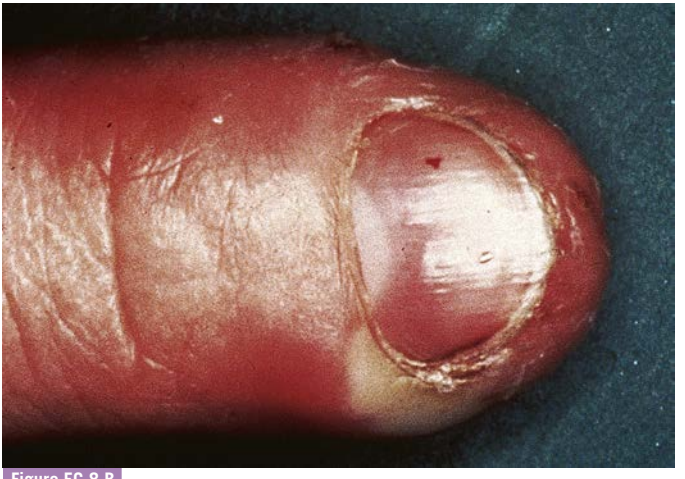

Figure EC 8.B
Acute paronychia. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

(2) Clinical presentation: Prodrome of inflammatory lesions that progresses into large (1 to 3 cm), tense, extremely pruritic bullae on trunk, flexural regions, and intertriginous areas. Few patients have oral mucosal lesions. Negative Nikolsky sign.
(3) Treatment: Immunosuppression (topical glucocorticoids, systemic glucocorticoids, glucocorticoid-sparing agents like methotrexate, mycophenolate, or azathioprine).

e. **Dermatitis herpetiformis:**
(1) Pathogenesis: Strong genetic predisposition and link to gluten intolerance/celiac disease. IgA deposits found in dermal papillae.
(2) Clinical presentation: Symmetric, intensely pruritic papulovesicles clustered on extensor surfaces.
(3) Treatment: Dapsone, strict gluten-free diet.

B. Nail Disorders[28]

1. Acquired nail disorders
a. Paronychia: Red, tender swelling of proximal or lateral nail folds (Figures EC 8.B and EC 8.C)
(1) Acute form: Caused by bacterial invasion after trauma to cuticle
(a) Clinical features: Exquisite pain, sudden swelling, and abscess formation around one nail.
(b) Treatment: Responds quickly to drainage of abscess and warm tap-water soaks; occasionally anti-staphylococcal antibiotics required.

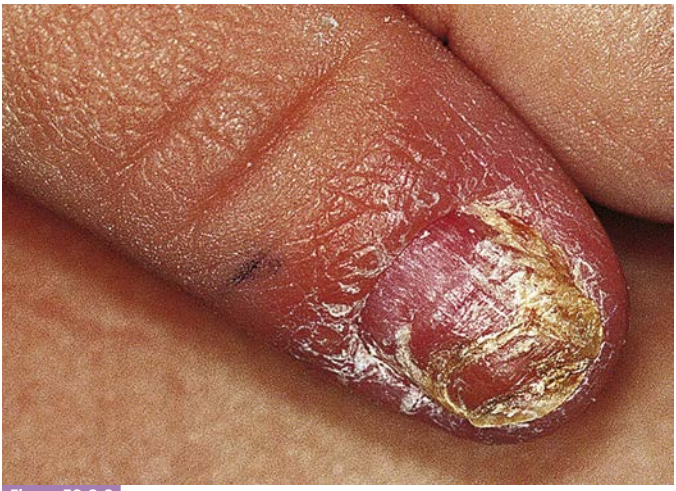

Figure EC 8.C

Chronic paronychia. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

(2) Chronic form: May involve one or several nails, history of frequent exposure to water or thumb-sucking; causative organisms *Candida* species, usually *C. albicans.*
   (a) Clinical features: Mild tenderness, minimal purulence, nail may be discolored or dystrophic.
   (b) Treatment: Resolves with topical antifungal agents and water avoidance; heals without scarring when thumb-sucking ends.

b. Nail dystrophy: Distortion and discoloration of normal nail-plate structure; often traumatic or inflammatory causes (Figures EC 8.D-EC 8.I).
   (1) Onychomycosis: A result of dermatophyte fungal infection, unusual before puberty. Oral and topical antifungals (terbinafine, itraconazole, ciclopirox) are used off-label with high cure rates and few adverse effects.[29]
   (2) Subungual hematoma: Brown-black nail discoloration following crush injury. Usually resolves without treatment; large, painful blood collections may be drained. Must differentiate from melanoma and melanonychia.

c. Nail changes and systemic disease (Figures EC 8.J and EC 8.K)
   (1) Clubbing: Complication of chronic lung or heart disease.
   (2) Beau lines: Transverse, white lines/grooves that move distally with nail growth; due to growth arrest from systemic illness, medications, or toxins.
   (3) Onychomadesis: Accentuated Beau lines often with separation of the nail from base of nail. Usually self-limited and very common following Coxsackie A6 hand, foot, and mouth disease.

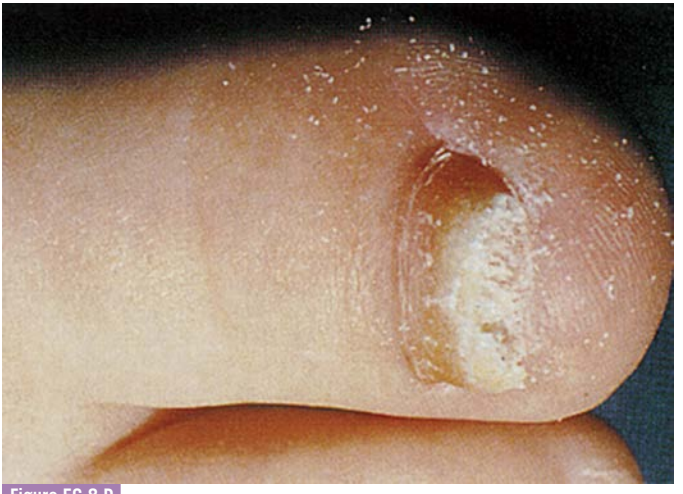

Figure EC 8.D
Onychomycosis. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

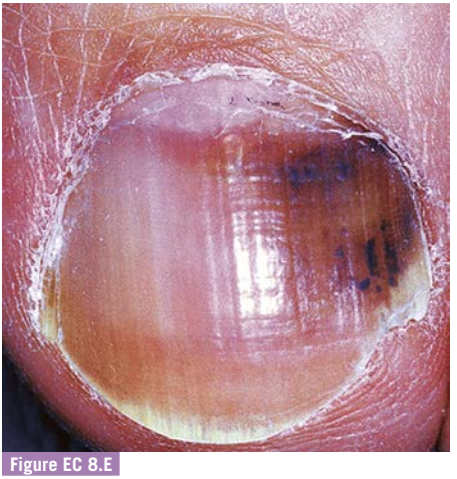

Figure EC 8.E
Traumatic subungual hemorrhage. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

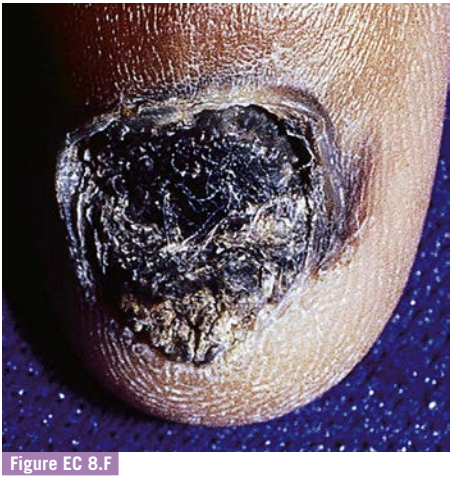

Figure EC 8.F

Acral melanoma. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

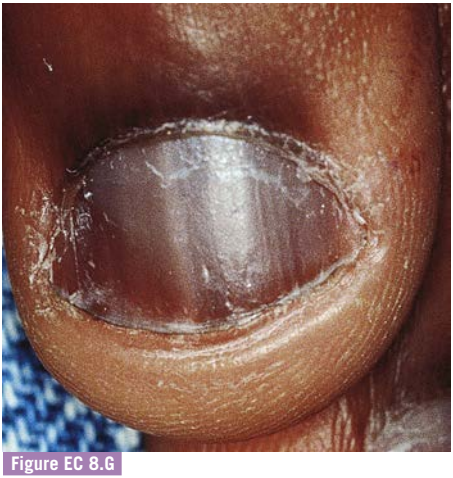

Figure EC 8.G

Melanonychia. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

Figure EC 8.H
Nail psoriasis. (From Cohen BA. Disorders of the Hair and Nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

Figure EC 8.I
Atopic nails. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

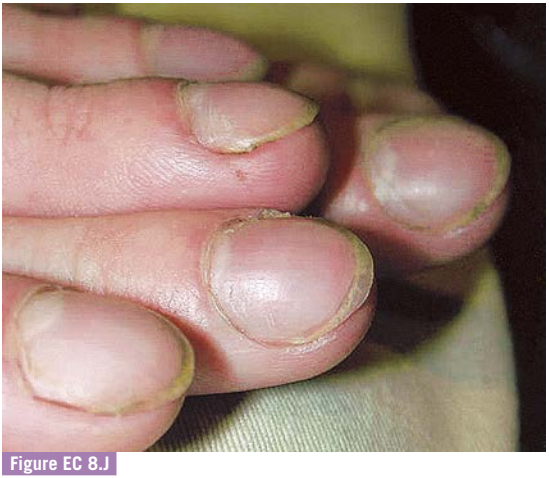

Figure EC 8.J
Nail clubbing. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

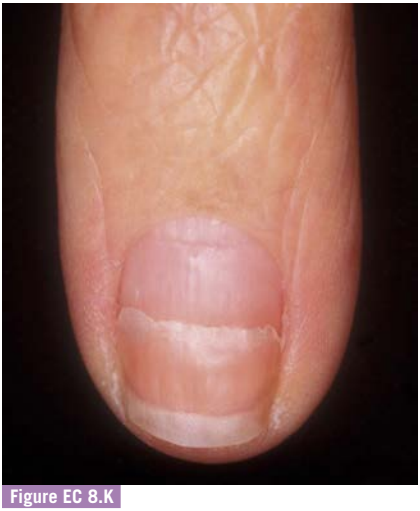

Figure EC 8.K
Beau lines. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

2. **Congenital/hereditary nail disorders**
   a. Isolated nail disorders (Figures EC 8.L and EC 8.M)
      (1) Congenital nail dystrophy: Clubbing and spooning (koilonychia), may be autosomal dominant with no other anomalies.
      (2) Congenital ingrown toenails: Most self-limiting.
   b. Genodermatosis and systemic disease (Figures EC 8.N and EC 8.O)
      (1) Periungual fibromas: Arise in proximal nail groove, common finding in tuberous sclerosis.
      (2) Congenital nail hypoplasia: Can occur with intrauterine exposure to anticonvulsants, alcohol, and warfarin.

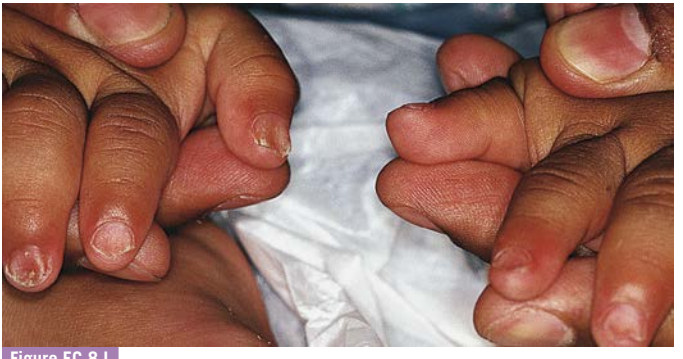

Figure EC 8.L
Koilonychia. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

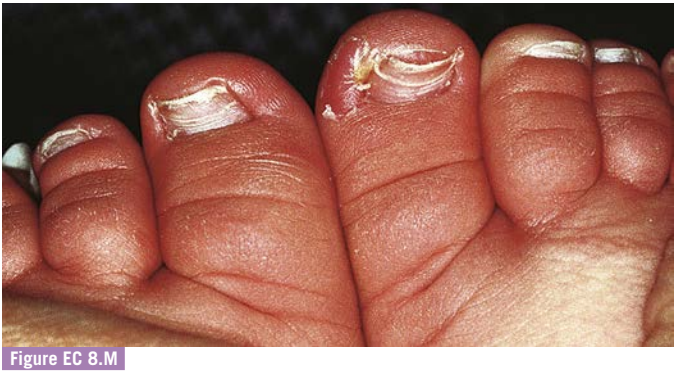

Figure EC 8.M
Congenital ingrown nails. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

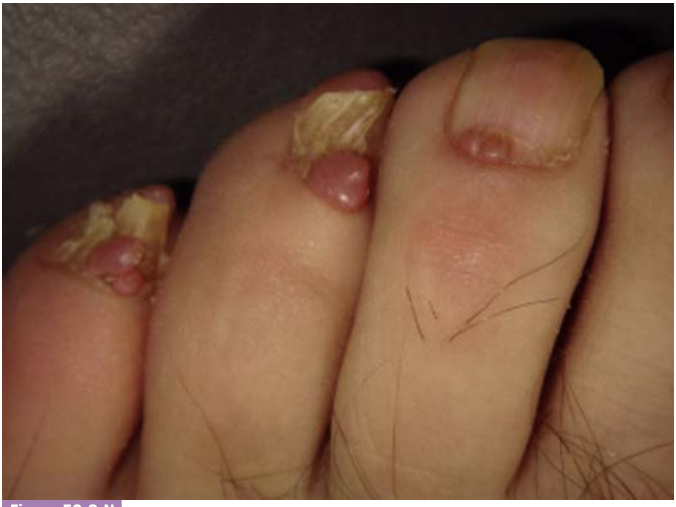

Figure EC 8.N
Periungual fibromas. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

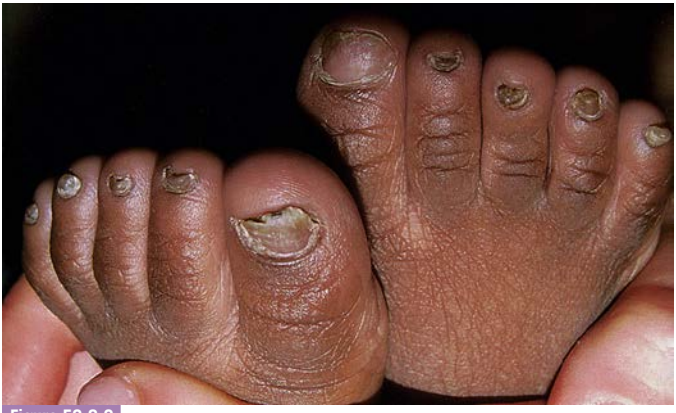

Figure EC 8.O
Fetal alcohol syndrome with congenital hypoplastic and dysplastic nails. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

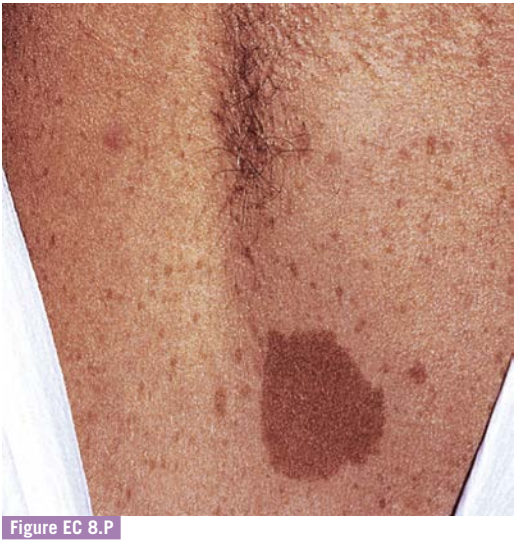

Figure EC 8.P

Café-au-lait spot. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

C. Disorders of Pigmentation[30]

1. **Hyperpigmentation**
   a. Congenital melanocytic nevi (CMN): Melanocytic nevi that are either present at birth or appear within the first few months of life in 1% to 3% of neonates.[31]
      (1) Appearance: Black or tan in color with irregular borders and often dark terminal hairs.
      (2) Risks:
         (a) Melanoma—At least 5% of large CMN greater than 20 cm with 70% of this cohort having cancerous transformation by 10 years of age.[32] The presence of approximately 20 satellite nevi (smaller congenital nevi) also increases risk of melanoma.
         (b) Neurocutaneous melanosis—Children with large, multiple, satellite nevi, or lesions over the spine are at risk for leptomeningeal involvement with symptoms that may include hydrocephalus and seizures that may require evaluation by gadolinium contrast MRI.[33,34]
   b. Epidermal melanosis: Most lesions appear tan or light brown
      (1) Café au lait spots (Figure EC 8.P): Discrete tan macules that appear at birth or during childhood in 10% to 20% of normal individuals, sizes vary from freckles to patches, may involve any

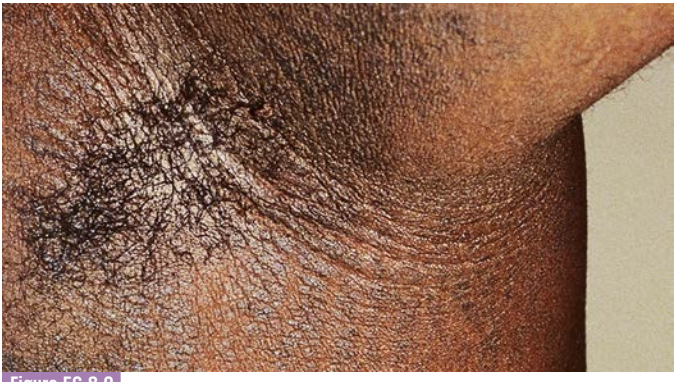

Figure EC 8.Q
Acanthosis nigricans, axilla. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

Figure EC 8.R
Acanthosis nigricans, neck. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

site on skin. May be diagnostic marker for Neurofibromatosis type 1 (≥6 lesions, each greater than 5 mm in diameter in prepubertal, or greater than 15 mm in postpubertal child) or other syndromes.

(2) Freckles (ephelides): Reddish-tan and brown macules on sun-exposed surfaces, usually 2 to 3 mm in diameter. Serve as an independent risk factor for skin cancers in adulthood and can be an added sign of the importance of photoprotection which may decrease additional lesions.

(3) Acanthosis nigricans (Figures EC 8.Q and EC 8.R): Brown-to-black hyperpigmentation with velvety or warty skin in intertriginous areas, typically found in the skin folds of the neck and

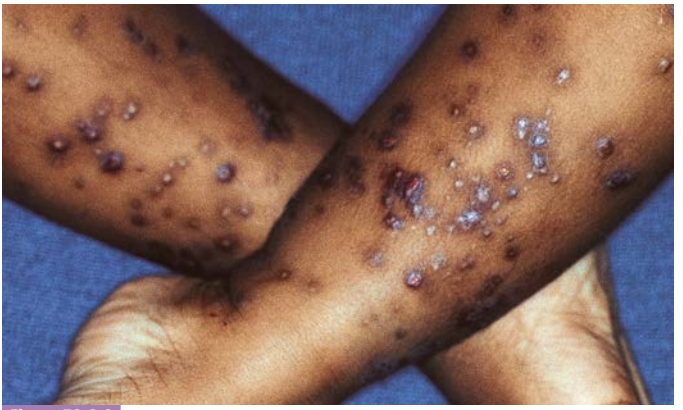

Figure EC 8.S

Postinflammatory hyperpigmentation. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

axilla. Most commonly occur in obese individuals with insulin resistance at risk for type II diabetes. Finding may decrease after puberty with weight reduction.

c. Dermal melanosis: Slate-gray, dark brown, or bluish-green lesions.
   (1) Post-inflammatory hyperpigmentation (Figure EC 8.S): Most common cause of increased pigmentation.
      (a) Pathogenesis: Follows inflammatory processes in the skin (e.g., diaper dermatitis, insect bites, drug reactions, traumatic injuries).
      (b) Clinical features: Localized lesions, follow distribution of resolving disorder. More prominent in darkly pigmented children.
      (c) Treatment: Lesions typically fade over several months. Photoprotection is critical with protective clothing and sunscreen of at least SPF 30. Individuals should also avoid physical trauma to areas as well as medications that may worsen hyperpigmentation. Intervention with medication is not always required; however, when it is, hydroquinone is first-line therapy.[35]
   (2) Acquired nevomelanocytic nevi (aka pigmented nevi or moles) (Figure EC 8.T)
      (a) Pathogenesis: Develop in early childhood as flat lesions called junctional nevi, then develop into compound nevi when nevus cells migrate into the dermis and lesions enlarge and become papular.
      (b) Clinical features: Increase in darkness, size, and number during puberty; generally do not exceed 5 mm and retain regularity in color, texture, and symmetry; on sun-exposed areas.
      (c) Treatment: Excision unnecessary, unless cosmetic concern.

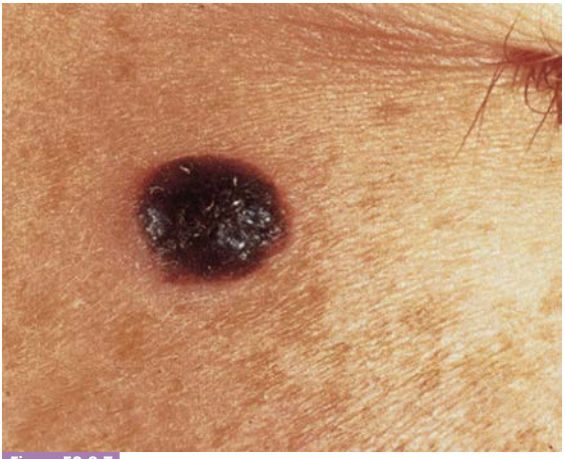

Figure EC 8.T
Compound nevomelanocytic nevus. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

(d) Changes associated with development of melanoma: See ABCDEs of Melanoma as well as burning, itching, or redness.

(3) Melanomas (Figure EC 8.U)
   (a) Pathogenesis: May occur de novo or within acquired or congenital nevi.
   (b) Epidemiology: High lifetime risk in those with presence of multiple, large, and irregularly pigmented, bordered, textured nevi and family history of malignant melanomas.
   (c) Management: Children in high-risk families must be carefully observed for atypical nevi development especially in adolescence. Changing nevi with unusual appearance or an "ugly duckling" (mole that is different from all other moles) must be considered for biopsy.
   (d) ABCDEs of Melanoma: Criteria for older children and adults is as follows: **A**symmetric shape, **B**orders that are irregular, **C**olor that is variable throughout lesion, **D**iameter greater than the size of a pencil eraser (>6 mm), **E**volution (change is the most important factor in melanoma diagnosis).[36] Pediatric patients up to age 20 have their own ABCD criteria: **A**melanotic, **B**leeding, **B**ump, **C**olor uniformity, **D**e novo, any **D**iameter.[37]

(4) Melanonychia (see Figure EC 8.G): Darkened nail pigment that most commonly is caused by melanin or hemosiderin deposits in the nail plate. Regular, organized longitudinal lines tend to be benign whereas irregularities are associated with nail melanoma in adults. However, nail matrix nevi in children often have features that would be considered red flags in the adult population; thus,

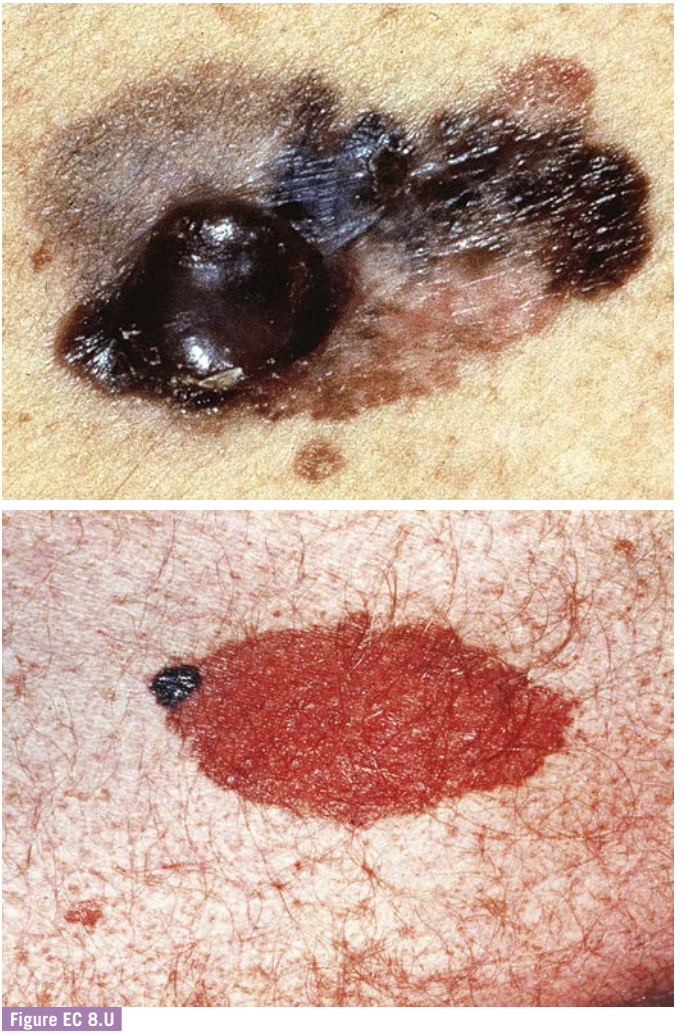

Figure EC 8.U

Melanoma. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

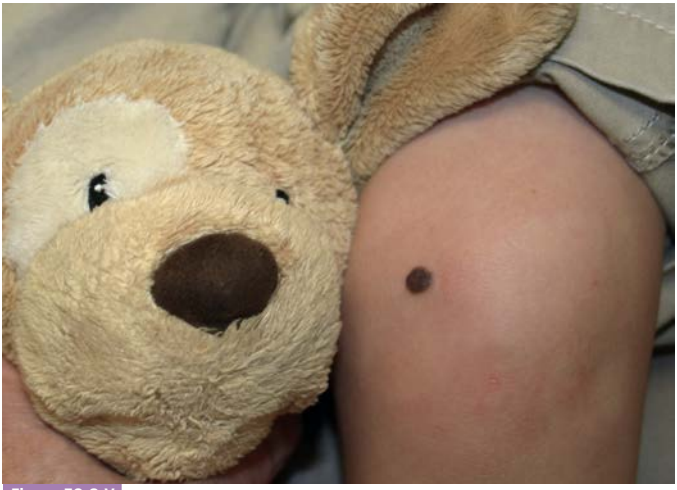

Figure EC 8.V
Pigmented spitz nevus. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

these criteria may not be applied to children. There are no pediatric specific guidelines for management. Typically, this clinical finding is due to nail matric nevi. Nail melanomas are very rare though children with this clinical finding warrant close follow up.[38,39]

(5) Spitz nevus (aka spindle and epithelial cell nevus) (Figure EC 8.V): Innocent nevomelanocytic nevus often confused with malignant melanoma.
   (a) Clinical features: Rapidly growing, dome-shaped, red or reddish-brown papules or nodules on face or lower extremities that reach full size quickly.
   (b) Management: Observe if features of innocent acquired nevus are present. Consider referral to pediatric dermatology if unusual atypical features present.

2. **Hypopigmentation and depigmentation**
   a. Localized hypopigmentation
      (1) Hypopigmented macules (Figure EC 8.W)
         (a) Epidemiology: 0.1% to 0.5% of normal newborns have a single hypopigmented macule but it may be a marker for tuberous sclerosis as 70% to 90% of those affected have such macules on the trunk at birth.
         (b) Clinical features: Trunk involvement is most common. Majority are lancet or ash-leaf shaped, but may be round, oval, dermatomal, segmental, or irregularly shaped. Vary from pinpoint confetti spots to large patches (>10 cm).

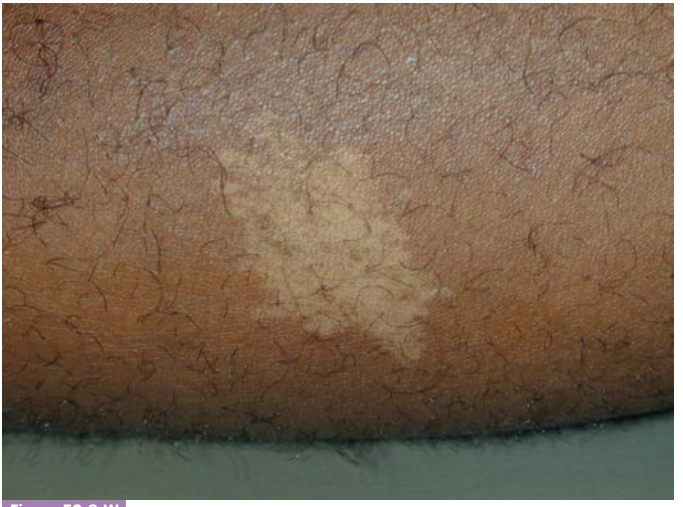

Figure EC 8.W

Congenital hypopigmented macule. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

(c) Diagnosis: Wood lamp helpful in lightly pigmented children.
(d) Management: In those where systemic disease is suspected, close observation for other cutaneous findings and systemic symptoms is indicated.

(2) Post-inflammatory hypopigmentation (Figure EC 8.X)
(a) Pathogenesis: May appear after an inflammatory skin condition.
(b) Clinical features: Seen in association with primary lesions of underlying disorder (such as atopic dermatitis). Patches usually variable in size and irregularly shaped. Concomitant hyperpigmentation is common.

b. Diffuse hypopigmentation
(1) Albinism: Heterogeneous group of inherited disorders manifested by generalized hypopigmentation or depigmentation of skin, eyes, and hair. These individuals should undergo ophthalmologic examination to evaluate for various associated conditions. Sun protection is important as well as regular skin exams.

3. **Dyspigmentation**
a. Blaschkoid dyspigmentation[40]: Congenital hypopigmentation and hyperpigmentation along the lines of Blaschko (Figure EC 8.Y).
(1) Patterns of hyper- or hypopigmentation: Whorl shape on trunk, V-shape on the back, waves on the vertex scalp.
(2) Pathogenesis: Blaschko lines occur due to genetic mosaicism.
(3) Children unlikely to have or develop serious extracutaneous involvement.

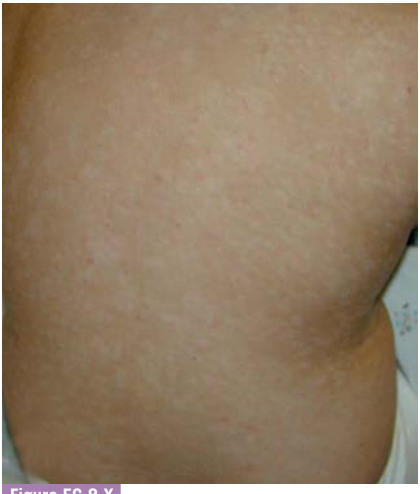

Figure EC 8.X

Postinflammatory hypopigmentation. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

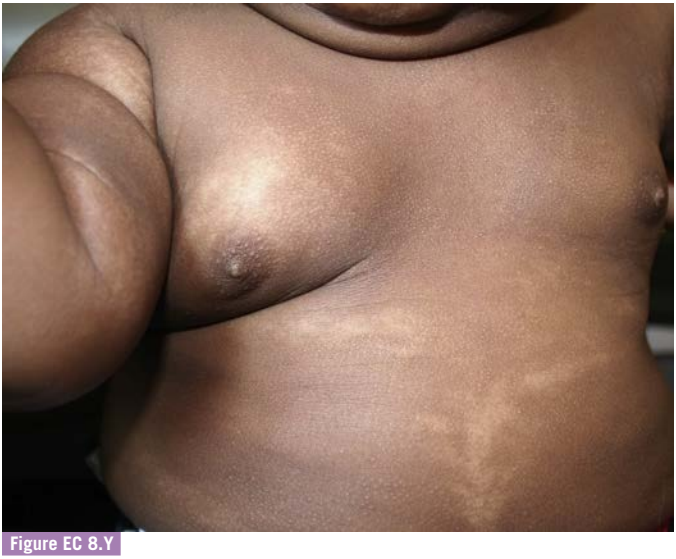

Figure EC 8.Y

Blaschkoid dyspigmentation. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

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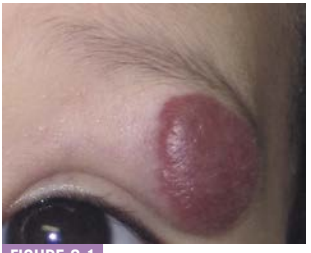

FIGURE 8.1
Infantile hemangioma. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005:126.)

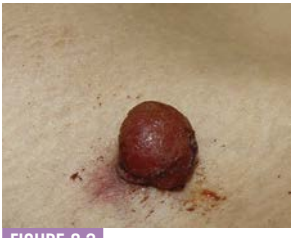

FIGURE 8.2
Pyogenic granuloma. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

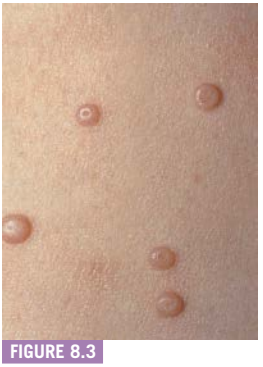

FIGURE 8.3
Molluscum contagiosum. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:131.)

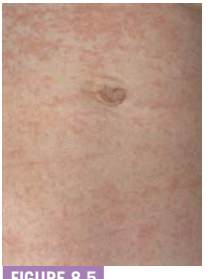

FIGURE 8.5
Roseola. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:177.)

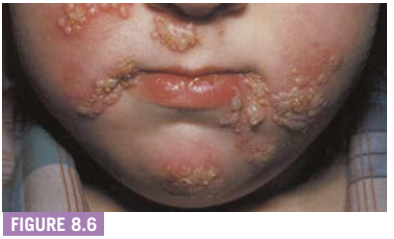

FIGURE 8.6
Herpetic gingivostomatitis. (Modified from Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:106.)

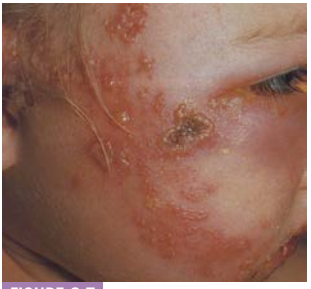

FIGURE 8.7
Herpes zoster. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:110.)

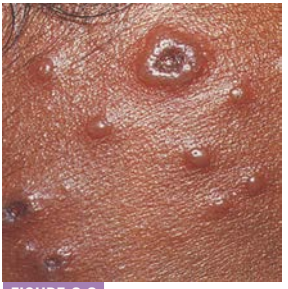

FIGURE 8.8
Varicella. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:108.)

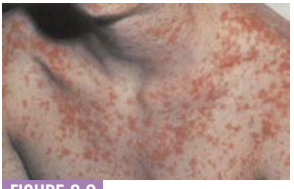

FIGURE 8.9
Measles. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:175.)

FIGURE 8.10
Fifth disease. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:176.)

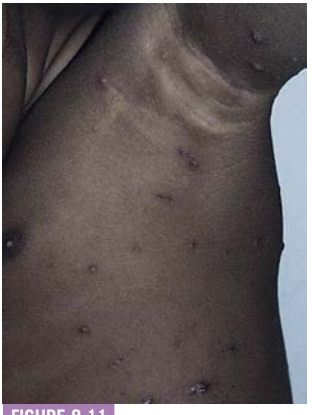

FIGURE 8.11
Scabies. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005:126.)

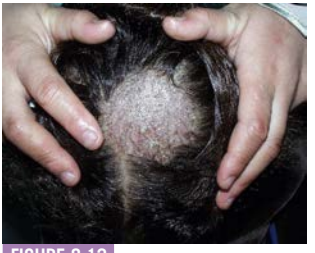

FIGURE 8.12
Tinea capitis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 1993.)

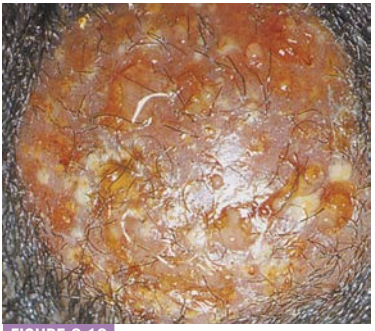

FIGURE 8.13
Kerion. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:218c.)

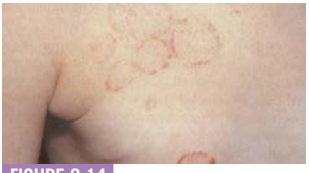

FIGURE 8.14
Tinea corporis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:96.)

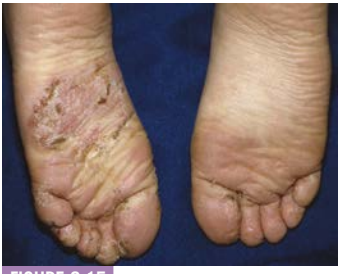

FIGURE 8.15
Tinea pedis. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

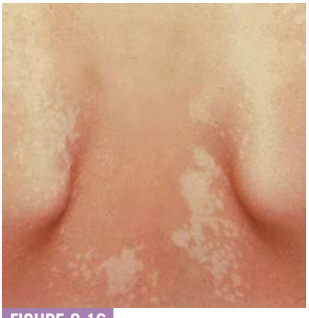

FIGURE 8.16
Tinea versicolor. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:99.)

FIGURE 8.17
Scarlet fever. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

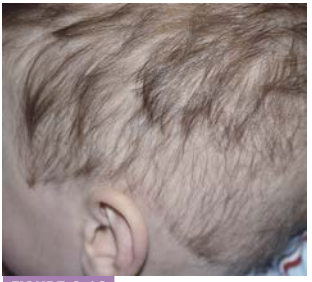

FIGURE 8.18
Telogen effluvium. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

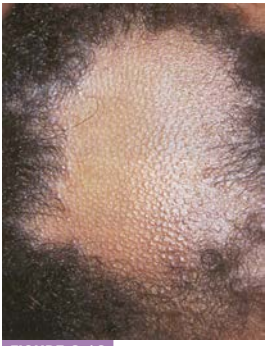

FIGURE 8.19
Alopecia areata. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:219.)

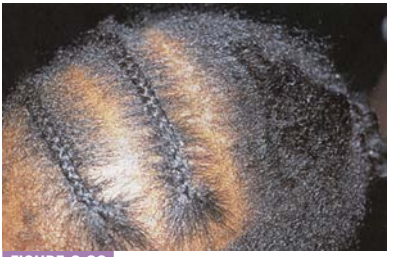

FIGURE 8.20
Traction alopecia. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:220.)

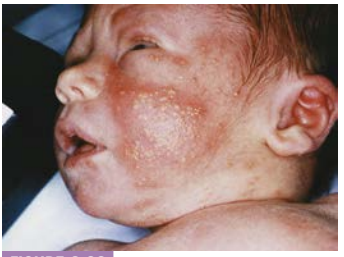

FIGURE 8.22
Erythema toxicum neonatorum. (From Cohen BA. *Pediatric Dermatology*. 2nd ed. St Louis: Mosby; 1999:18.)

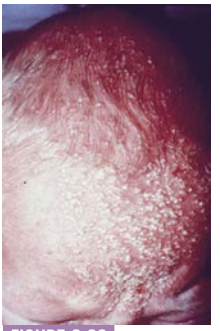

FIGURE 8.23
Transient neonatal pustular melanosis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:20.)

FIGURE 8.24
Hyperpigmentation from resolving transient neonatal pustular melanosis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:20.)

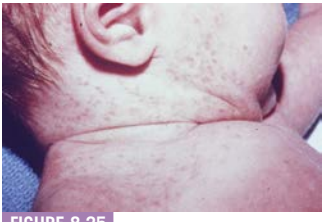

FIGURE 8.25
Miliaria rubra. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:21.)

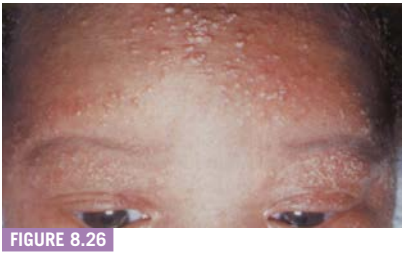

FIGURE 8.26
Milia. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:22.)

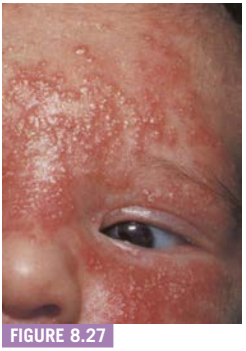

FIGURE 8.27
Neonatal acne. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:22.)

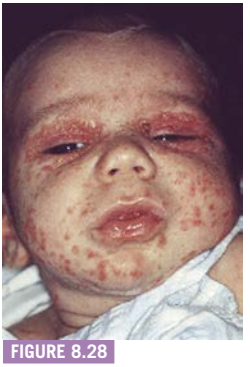

FIGURE 8.28
Seborrheic dermatitis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:32.)

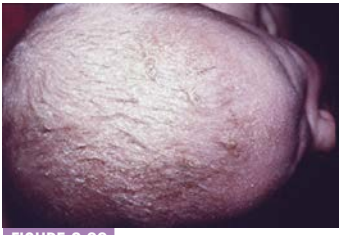

FIGURE 8.29
Seborrheic dermatitis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:32.)

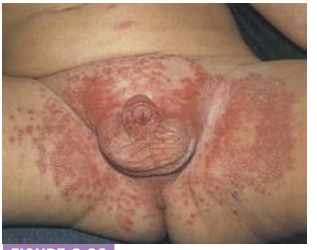

FIGURE 8.30
Diaper candidiasis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:33.)

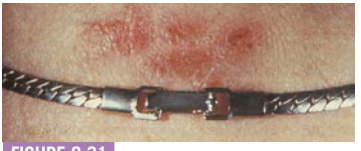

FIGURE 8.31
Allergic contact dermatitis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:77.)

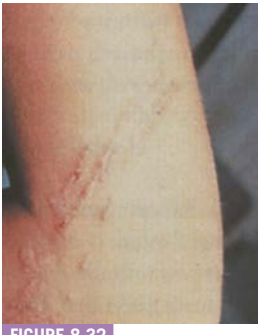

FIGURE 8.32
Poison ivy. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

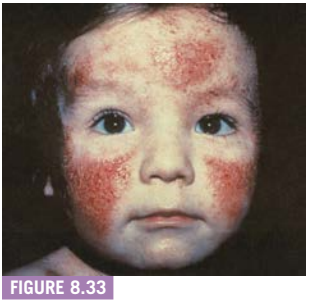

FIGURE 8.33
Infantile eczema. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005:79.)

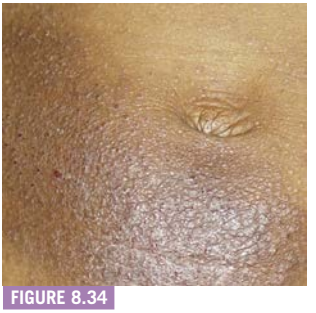

FIGURE 8.34
Childhood eczema. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

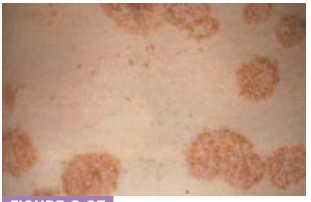

FIGURE 8.35
Nummular eczema. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005:80.)

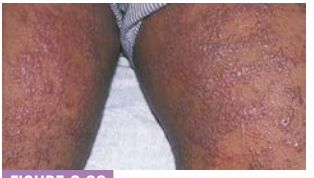

FIGURE 8.36
Follicular eczema. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:83.)

FIGURE 8.37
Childhood eczema with lesion in suprapubic area. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005.)

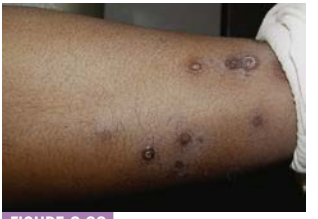

FIGURE 8.38

Papular urticaria. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

Chapter 9

Development, Behavior, and Developmental Disability

Brittany Badesch, MD

See additional content on Expert Consult

I. DEVELOPMENTAL DEFINITIONS[1,2]

A. Developmental Streams

1. **Gross Motor Skills:** Descriptions of posture and locomotion—in general, how a child moves from one location to another.
2. **Fine-Motor and Visual-Motor Problem-Solving Skills:** Upper extremity and hand manipulative abilities and hand-eye coordination. These require an intact motor substrate and a given level of nonverbal cognitive ability.
3. **Language:** The ability to understand and communicate with another person. This is the best predictor of intellectual performance in the absence of a communication disorder or significant hearing impairment.
4. **Personal-Social Skills:** Communicative in origin; represent the cumulative impact of language comprehension and problem-solving skills.
5. **Adaptive Skills:** Skills concerned with self-help or activities of daily living.

B. Developmental Quotient (DQ)

1. **A calculation that reflects the rate of development** in any given stream; represents the percentage of normal development present at the time of testing.

$$DQ = \frac{\text{Developmental age}}{\text{Chronological age}} \times 100$$

2. **Two separate developmental assessments** over time are more predictive of later abilities than a single assessment.
3. In contrast to developmental quotient (DQ), intelligence quotient (IQ) has statistical reliability and validity.[2]

C. Abnormal Development

1. **Delay**: Performance significantly below average (DQ <70) in a given area of development. May occur in a single stream or several streams ("global developmental delay").
2. **Deviancy**: Atypical development within a single stream, such as developmental milestones occurring out of sequence. Deviancy does not necessarily imply abnormality, but should alert one to the possibility that problems may exist.
   Example: An infant who rolls at an early age may have abnormally increased tone.

3. **Dissociation**: A substantial difference in the rate of development between two or more streams.
   Example: Increased motor delay relative to cognition seen in some children with cerebral palsy (CP).

II. GUIDELINES FOR NORMAL DEVELOPMENT AND BEHAVIOR

A. Developmental Milestones (Table 9.1)

Developmental assessment is based on the premise that milestone acquisition occurs at a specific rate in an orderly and sequential manner.

B. Age-Appropriate Behavioral Issues in Infancy and Early Childhood: See Table 9.2.

III. DEVELOPMENTAL SCREENING AND EVALUATION OF DEVELOPMENTAL DISORDERS

A. Developmental Surveillance and Screening Guidelines

1. **Developmental *surveillance* should be included in every well-child visit, and any concerns should be addressed immediately with formal screening.** This includes direct observation of the child and eliciting and attending to the parent's concerns.
2. **Standardized developmental *screening* should be administered at 9-month, 18-month, and 30-month well-child visits**, in the absence of developmental concerns. If a 30-month visit is not possible, this screening can be done at the 24-month visit.
3. See full American Academy of Pediatrics (AAP) guideline for developmental screening algorithm.[3]

B. Commonly Used Developmental Screening and Assessment Tools: See Table 9.3

C. Identification of Developmental "Red Flags": See Table 9.4

D. Evaluation of Abnormal Development

1. Referral to developmental and appropriate subspecialists.
2. Referral to early intervention services for children aged 0 to 3 years (see Section V).
3. Medical evaluation as outlined in Tables 9.5–9.7.
4. Genetic evaluation (Table 9.8) is warranted for all children with developmental delay or intellectual disability (ID) if the cause is not known (e.g., previous traumatic brain injury or neurologic insult).

IV. SPECIFIC DISORDERS OF DEVELOPMENT

A. Overview

1. Mental and/or physical impairment(s) that cause significant limitations in functioning.
2. **Developmental diagnosis** is a functional description; identification of an etiology is important to further inform treatment, prognosis, comorbidities, and future risk.

TABLE 9.1

DEVELOPMENTAL MILESTONES

Age	Gross Motor	Visual–Motor/Problem-Solving	Language	Social/Adaptive
1 month	Raises head from prone position	Visually fixes, follows to midline, has tight grasp	Alerts to sound	Regards face
2 months	Holds head in midline, lifts chest off table	No longer clenches fists tightly, follows object past midline	Smiles socially (after being stroked or talked to)	Recognizes parent
3 months	Supports on forearms in prone position, holds head up steadily	Holds hands open at rest, follows in circular fashion, responds to visual threat	Coos (produces long vowel sounds in musical fashion)	Reaches for familiar people or objects, anticipates feeding
4 months	Rolls over, supports on wrists, shifts weight	Reaches with arms in unison, brings hands to midline	Laughs, orients to voice	Enjoys looking around
6 months	Sits unsupported, puts feet in mouth in supine position	Unilateral reach, uses raking grasp, transfers objects	Babbles, ah-goo, razz, lateral orientation to bell	Recognizes that someone is a stranger
9 months	Pivots when sitting, crawls well, pulls to stand, cruises	Uses immature pincer grasp, probes with forefinger, holds bottle, throws objects	Says "mama, dada" indiscriminately, gestures, waves bye-bye, understands "no"	Starts exploring environment, plays gesture games (e.g., pat-a-cake)
12 months	Walks alone	Uses mature pincer grasp, can make a crayon mark, releases voluntarily	Uses two words other than "mama, dada" or proper nouns, jargoning (runs several unintelligible words together with tone or inflection), one-step command with gesture	Imitates actions, comes when called, cooperates with dressing
15 months	Creeps up stairs, walks backward independently	Scribbles in imitation, builds tower of two blocks in imitation	Uses 4–6 words, follows one-step command without gesture	15–18 months: uses spoon and cup
18 months	Runs, throws objects from standing without falling	Scribbles spontaneously, builds tower of three blocks, turns two or three pages at a time	Mature jargoning (includes intelligible words), 7–10-word vocabulary, knows five body parts	Copies parent in tasks (sweeping, dusting), plays in company of other children

Continued

TABLE 9.1—CONT'D

DEVELOPMENTAL MILESTONES

Age	Gross Motor	Visual–Motor/Problem-Solving	Language	Social/Adaptive
24 months	Walks up and down steps without help	Imitates stroke with pencil, builds tower of seven blocks, turns pages one at a time, removes shoes, pants, etc.	Uses pronouns (I, you, me) inappropriately, follows two-step commands, 50-word vocabulary, uses two-word sentences	Parallel play
3 years	Can alternate feet going up steps, pedals tricycle	Copies a circle, undresses completely, dresses partially, dries hands if reminded, unbuttons	Uses minimum of 250 words, three-word sentences, uses plurals, knows all pronouns, repeats two digits	Group play, shares toys, takes turns, plays well with others, knows full name, age, gender
4 years	Hops, skips, alternates feet going down steps	Copies a square, buttons clothing, dresses self completely, catches ball	Knows colors, says song or poem from memory, asks questions	Tells "tall tales," plays cooperatively with a group of children
5 years	Skips alternating feet, jumps over low obstacles	Copies triangle, ties shoes, spreads with knife	Prints first name, asks what a word means	Plays competitive games, abides by rules, likes to help in household tasks

From Capute AJ, Biehl RF. Functional developmental evaluation: prerequisite to habilitation. *Pediatr Clin North Am.* 1973;20:3; Capute AJ, Accardo PJ. Linguistic and auditory milestones during the first two years of life: a language inventory for the practitioner. *Clin Pediatr.* 1978;17:847; and Capute AJ, Shapiro BK, Wachtel RC, et al. The Clinical Linguistic and Auditory Milestone Scale (CLAMS): identification of cognitive defects in motor delayed children. *Am J Dis Child.* 1986;140:694. Rounded norms from Capute AJ, Palmer FB, Shapiro BK, et al. Clinical Linguistic and Auditory Milestone Scale: prediction of cognition in infancy. *Dev Med Child Neurol.* 1986;28:762.

TABLE 9.2

AGE-APPROPRIATE BEHAVIORAL ISSUES IN INFANCY AND EARLY CHILDHOOD

Age	Behavioral Issue	Symptoms	Guidance
1–3 months	Colic	Paroxysms of fussiness/crying, ≥3 per day, ≥3 days/week, may pull knees up to chest, pass flatus	Crying usually peaks at 6 weeks and resolves by 3–4 months. Prevent overstimulation; swaddle infant; use white noise, swing, or car rides to soothe. Avoid medication and formula changes. Encourage breaks for the primary caregiver.
3–4 months	Trained night feeding	Night awakening	Comfort quietly, avoid reinforcing behavior (i.e., avoid night feeds). Do not play at night. Introducing cereal or solid food does not reduce awakening. Develop a consistent bedtime routine. Place baby in bed while drowsy and not fully asleep.
9 months	Stranger anxiety/separation anxiety	Distress when separated from parent or approached by a stranger	Use a transitional object (e.g., special toy, blanket). Use routine or ritual to separate from parent. May continue until 24 months but can reduce in intensity.
	Developmental night waking	Separation anxiety at night	Keep lights off. Avoid picking child up or feeding. May reassure verbally at regular intervals or place a transitional object in crib.
12 months	Aggression	Biting, hitting, kicking in frustration	Say "no" with negative facial cues. Begin time out (1 minute/year of age). No eye contact or interaction, place in a nonstimulating location. May restrain child gently until cooperation is achieved.
	Need for limit setting	Exploration of environment, danger of injury	Avoid punishing exploration or poor judgment. Emphasize child-proofing and distraction.
18 months	Temper tantrums	Occur with frustration, attention-seeking rage, negativity/refusal	Try to determine cause, react appropriately (i.e., help child who is frustrated, ignore attention-seeking behavior). Make sure child is in a safe location.
24 months	Toilet training	Child needs to demonstrate readiness: shows interest, neurologic maturity (i.e., recognizes urge to urinate or defecate), ability to walk to bathroom and undress self, desire to please/imitate parents, increasing periods of daytime dryness	Age range for toilet training is usually 2–4 years. Give guidance early; may introduce potty seat but avoid pressure or punishment for accidents. Wait until the child is ready. Expect some periods of regression, especially with stressors.

Continued

TABLE 9.2—CONT'D

AGE-APPROPRIATE BEHAVIORAL ISSUES IN INFANCY AND EARLY CHILDHOOD

Age	Behavioral Issue	Symptoms	Guidance
24–36 months	New sibling	Regression, aggressive behavior	Allow for special time with parent, 10–20 min daily of one-on-one time exclusively devoted to the older sibling(s). Child chooses activity with parent. No interruptions. May not be taken away as punishment.
36 months	Nightmares	Awakens crying, may or may not complain of bad dream	Reassure child, explain that he or she had a bad dream. Leave bedroom door open, use a nightlight, demonstrate there are no monsters under the bed. Discuss dream the following day. Avoid scary movies or television shows.
	Night terrors	Agitation, screaming 1–2 hours after going to bed. Child may have eyes open but not respond to parent. May occur at same time each night	May be familial, not volitional. *Prevention:* For several nights, awaken child 15 min before terrors typically occur. Avoid overtiredness. *Acute:* Be calm; speak in soft, soothing, repetitive tones; help child return to sleep. Protect child against injury.

From Dixon SD, Stein MT. *Encounters With Children: Pediatric Behavior and Development.* St Louis: Mosby; 2000.

TABLE 9.3

DEVELOPMENTAL SCREENING TESTS BY DIAGNOSIS

Diagnosis Evaluated	Screening Test	Age	Completed by	Comments	Weblink
Cognitive and motor development	Ages and Stages Questionnaire (ASQ)	4–60 months	Parent	Increased time efficiency (can fill out while waiting) Documents milestones that are difficult to assess in the office	www.agesandstages.com
Developmental and behavioral problems	Parents' Evaluation of Developmental Status (PEDS)	0–8 years	Parent	May also be useful as a surveillance tool	www.pedstest.com
Language, problem-solving development	Capute Scales: Clinical Linguistic and Auditory Milestone Scale (CLAMS), Clinical Adaptive Test (CAT)	3–36 months	Clinician	Give quantitative DQs for language (CLAMS) and visual-motor/problem-solving (CAT) abilities	http://www.brookespublishing.com/resource-center/screening-and-assessment/the-capute-scales/
Autism spectrum disorders	Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F)	16–30 months	Parent	Positive screens require clinician follow-up	www.m-chat.org
	Communication and Symbolic Behavior Scales and Developmental Profile (CSBS DP; Infant Toddler Checklist)	6–24 months	Parent	The Infant Toddler Checklist is a one-page questionnaire that is part of a larger standardized screening tool (CSBS DP) Can be used in patients as young as 6 months	www.brookespublishing.com/checklist.pdf
	Childhood Autism Screening Test (CAST)	4–11 years	Parent	Only screening tool evaluated in preschool population	http://www.autismresearchcentre.com/project_9_cast

Modified from American Academy of Pediatrics. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics.* 2006;118:405–420; American Academy of Pediatrics. Identification and evaluation of children with autism spectrum disorders. *Pediatrics.* 2007;120: 1183–1215; Robins DL, Casagrande K, Barton M, et al. Validation of the Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F). *Pediatrics.* 2014;133:37–45.

TABLE 9.4

DEVELOPMENTAL RED FLAGS

Age of Patient	Red Flag Symptom
Any age	Loss of previously obtained developmental skills Parental or professional concerns about vision, fixing, or following an object or a confirmed visual impairment Hearing loss Persistently low muscle tone or floppiness Asymmetry of movements or other features suggestive of cerebral palsy, such as increased muscle tone Head circumference above the 99.6th percentile, below 0.4th percentile, or has crossed two major percentile lines (up or down)
5 months (corrected for gestation)	Not able to hold object placed in hand
6 months (corrected for gestation)	Not reaching for objects
12 months	Unable to sit unsupported
18 months	Not walking in male patients Not pointing at objects to share interest with others
24 months	Not walking in female patients
30 months and older	Unable to run Persistent toe walking

From Bellman M, Byrne O, Sege R. Developmental assessment of children. *BMJ.* 2013;346:31–36.

TABLE 9.5

DEVELOPMENTAL EVALUATION: PERTINENT HISTORY AND PHYSICAL

Prenatal and Birth History	Prenatal genetic screening Perception of fetal movement Pregnancy complications Toxins/teratogens Gestational age Birthweight Days in hospital/NICU admission Newborn screen results
Past Medical Problems	Trauma Infection Medication
Developmental History	Timing of milestone achievement Delayed skills Loss of skills (regression)
Behavioral History	Social skills Eye contact Affection Hyperactivity, impulsivity, inattention, distractibility Self-regulation Perseveration Worries/avoidance Stereotypies, peculiar habits

TABLE 9.5—CONT'D

DEVELOPMENTAL EVALUATION: PERTINENT HISTORY AND PHYSICAL

Educational History	Need for special services Grade retention Established educational plans
Family History	History of developmental disabilities, ADHD, seizures, tics, stillbirths, neonatal death, congenital malformations, mental illness, or recurrent miscarriages Family members who were late talkers or walkers Family member school performance Family pedigree (see Chapter 13)
General Exam	Height, weight, and head circumference Dysmorphic features Cardiac murmurs Midline defects Hepatosplenomegaly Skin exam
Age-directed Neuro Exam	Cranial nerves Tone and strength Postural reactions (Table EC 9.A) Functional abilities Reflexes [including primitive reflexes for infants (Table 9.6)]
In-Clinic Activities/Tests	Goodenough–Harris Draw-a-Person Test Gesell figures (Figure EC 9.A): Ask the child to copy various shapes Gesell block skills (Figure EC 9.B): Ask the child to reproduce block structures as built by the examiner

TABLE 9.6

PRIMITIVE REFLEXES

Primitive Reflexes	Elicitation	Response	Timing
Moro reflex ("embrace" response) of fingers, wrists, and elbows	*Supine:* Sudden neck extension; allow head to fall back about 3 cm	Extension, adduction, and then abduction of UEs, with semiflexion	Present at birth; disappears by 3–6 months
Galant reflex (GR)	*Prone suspension:* Stroking paravertebral area from thoracic to sacral region	Produces truncal incurvature with concavity toward stimulated side	Present at birth; disappears by 2–6 months
Asymmetrical tonic neck reflex (ATNR, "fencer" response)	*Supine:* Rotate head laterally about 45–90 degrees	Relative extension of limbs on chin side and flexion on occiput side	Present at birth; disappears by 4–9 months
Symmetrical tonic neck reflex (STNR, "cat" reflex)	*Sitting:* Head extension/flexion	Extension of UEs and flexion of LEs/flexion of UEs and LE extension	Appears at 5 months; not present in most normal children; disappears by 8–9 months
Tonic labyrinthine supine (TLS)	*Supine:* Extension of the neck (alters relation of the labyrinths)	Tonic extension of trunk and LEs, shoulder retraction and adduction, usually with elbow flexion	Present at birth; disappears by 6–9 months

Continued

TABLE EC 9.A

POSTURAL REACTIONS

Postural Reaction	Age of Appearance	Description	Importance
Head righting	6 weeks–3 months	Lifts chin from table top in prone position	Necessary for adequate head control and sitting
Landau response	2–3 months	Extension of head, then trunk and legs when held prone	Early measure of developing trunk control
Derotational righting	4–5 months	Following passive or active head turning, body rotates to follow direction of head	Prerequisite to independent rolling
Anterior propping	4–5 months	Arm extension anteriorly in supported sitting	Necessary for tripod sitting
Parachute	5–6 months	Arm extension when falling	Facial protection when falling
Lateral propping	6–7 months	Arm extension laterally in protective response	Allows independent sitting
Posterior propping	8–10 months	Arm extension posteriorly	Allows pivoting in sitting

Modified from Milani-Comparetti A, Gidoni EA. Routine developmental examination in normal and retarded children. *Dev Med Child Neurol*. 1967;9:631–638; Capute AJ. Early neuromotor reflexes in infancy. *Pediatr Ann*. 1986;15:217–218, 221–223, 226; Capute AJ, Palmer FB, Shapiro BK, et al. Primitive reflex profile: a quantitation of primitive reflexes in infancy. *Dev Med Child Neurol*. 1984;26:375–383; and Palmer FB, Capute AJ. Developmental disabilities. In: Oski FA, ed. *Principles and Practice of Pediatrics*. Philadelphia: JB Lippincott; 1994.

15 months	Imitates scribble
18 months	Scribbles spontaneously
2 years	Imitates stroke
$2^1/_2$ years	Differentiates horizontal and vertical stroke

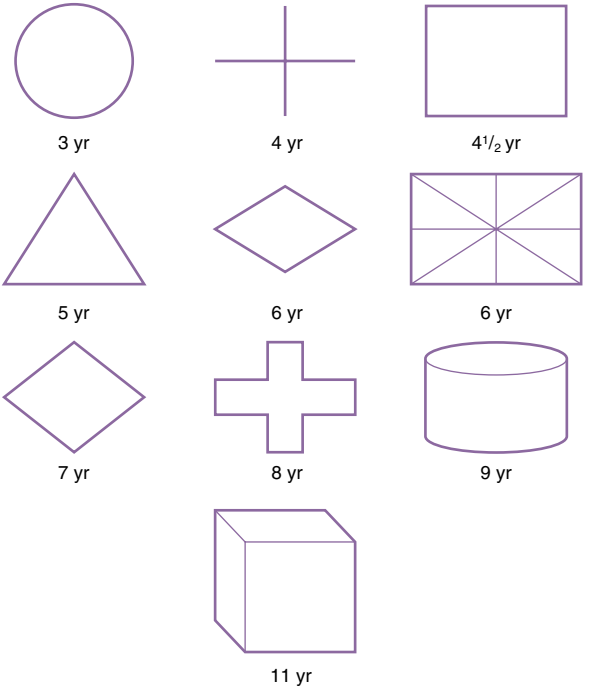

FIGURE EC 9.A

Gesell Figures. (From Illingsworth RS. *The Development of the Infant and Young Child, Normal and Abnormal*. 5th ed. Baltimore: Williams & Wilkins; 1972:229–232; and Cattel P. *The Measurement of Intelligence of Infants and Young Children*. New York: Psychological Corporation; 1960:97–261.)

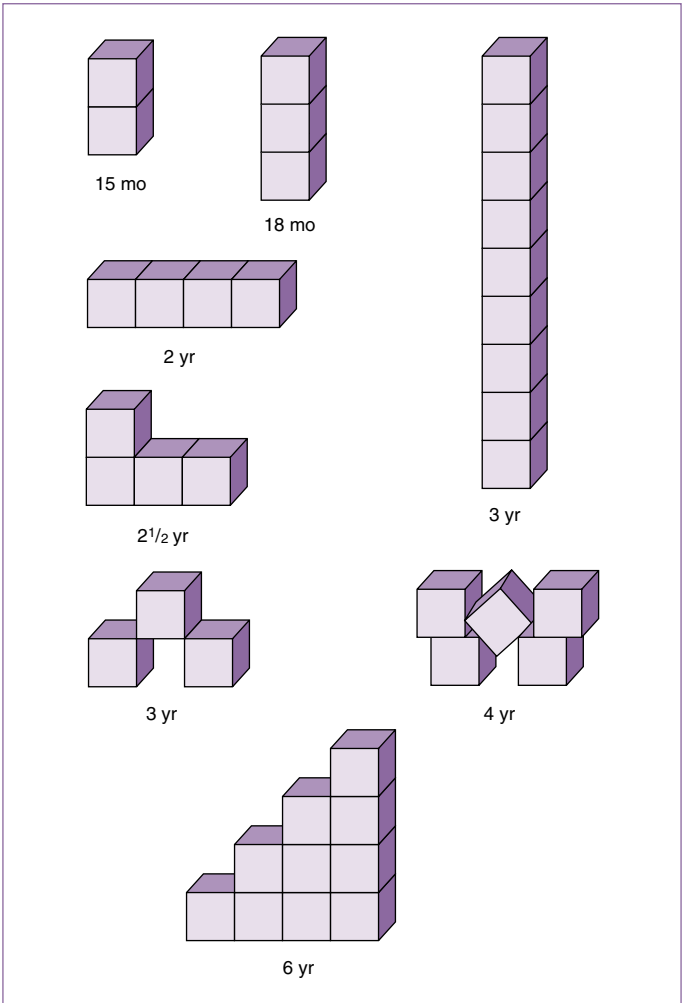

FIGURE EC 9.B

Gesell Block Skills. (From Capute AJ, Accardo PJ. *The Pediatrician and the Developmentally Disabled Child: A Clinical Textbook on Mental Retardation*. Baltimore: University Park Press; 1979:122.)

TABLE 9.6—CONT'D

PRIMITIVE REFLEXES

Primitive Reflexes	Elicitation	Response	Timing
Tonic labyrinthine prone (TLP)	*Prone:* Flexion of the neck	Active flexion of trunk with protraction of shoulders	Present at birth; disappears by 6–9 months
Positive support reflex (PSR)	*Vertical suspension:* Bouncing hallucal areas on firm surface	*Neonatal:* momentary LE extension followed by flexion	Present at birth; disappears by 2–4 months
		Mature: extension of LEs and support of body weight	Appears by 6 months
Stepping reflex (SR, walking reflex)	*Vertical suspension:* Hallucal stimulation	Stepping gait	Disappears by 2–3 months
Crossed extension reflex (CER)	*Prone:* Hallucal stimulation of LE in full extension	Initial flexion, adduction, then extension of contralateral limb	Present at birth; disappears by 9 months
Plantar grasp	Stimulation of hallucal areas	Plantar flexion grasp	Present at birth; disappears by 9 months
Palmar grasp	Stimulation of palm	Palmar grasp	Present at birth; disappears by 9 months
Lower extremity placing (LEP)	*Vertical suspension:* Rubbing tibia or dorsum of foot against edge of table top	Initial flexion, then extension, then placing of LE on table top	Appears at 1 day
Upper extremity placing (UEP)	Rubbing lateral surface of forearm along edge of table top from elbow to wrist to dorsal hand	Flexion, extension, then placing of hand on table top	Appears at 3 months
Downward thrust (DT)	*Vertical suspension:* Thrust LEs downward	Full extension of LEs	Appears at 3 months

LE, Lower extremity; *UE*, upper extremity.

TABLE 9.7

DEVELOPMENTAL EVALUATION: INITIAL LABS AND OTHER STUDIES

Hearing screening	Formal audiologic testing is indicated for all children with global developmental delay or any delay in communication or language
Neuroimaging	Consider if abnormal neurologic exam, concern about head circumference growth velocity, or global developmental delay present
Electroencephalogram	Consider if history of or concern for seizure disorder
Laboratory studies	Consider CBC, CMP, lead level, CK, TSH based on history and exam Confirm newborn screen results

CBC, Complete blood count; *CK*, creatine kinase; *CMP*, complete metabolic panel; *TSH*, thyroid stimulating hormone.

TABLE 9.8

DEVELOPMENTAL EVALUATION: GENETIC WORK-UP

Chromosomal microarray (CMA)	Considered first-tier diagnostic test in ***all*** children with GDD/ID.[24]
Fragile X testing	Should be performed in all boys ***and*** girls with GDD/ID of unknown cause. Of boys with GDD/ID of unknown cause, 2%–3% will have fragile X syndrome, as will 1%–2% of girls.

TABLE 9.8—CONT'D

DEVELOPMENTAL EVALUATION: GENETIC WORK-UP

Testing for X-linked conditions	Consider genetic testing for X-linked genes in boys with GDD/ID after negative CMA and negative fragile X testing. Should be specifically in those patients whose pedigree is suggestive of an X-linked condition.

The tests discussed above do not require referral to a genetic specialist and can be ordered by the patient's pediatrician as a part of the evaluation of global developmental delay/intellectual disability (GDD/ID). If unrevealing and severe DD/ID present, refer to genetic specialist for consideration of additional testing such as metabolic testing or whole exome sequencing.

From Moeschler JB, Shevell M. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics*. 2014;134(3):e903–e918.

3. School- and home-based programs are helpful interventions for all developmental disorders (see Section V).

B. Intellectual Disability

1. **Definition and Epidemiology**
   a. Deficits in general mental abilities
   b. Affects approximately 1% of the population[4]
2. **Clinical Presentation**
   a. Delay in milestones (motor, language, social)
   b. Academic difficulty
   c. Identifiable features of known associated genetic syndrome (e.g., Trisomy 21, fragile X, Rett syndrome)
3. **Diagnosis**
   a. Diagnostic criteria: (1) deficits in intellectual functioning, (2) deficits in adaptive functioning, (3) onset of these deficits during the developmental period
   b. Deficits in adaptive functioning must be in one or more domains of activities of daily living.
   c. ID is further categorized as mild, moderate, severe, or profound in the DSM-5 based on the degree of functional deficit (Table EC 9.B).
4. **Interventions/Treatment**
   Support, employment, and recreational programs through resources such as The Arc (www.thearc.org).

C. Communication Disorders

1. **Definition**
   a. Deficits in communication, language, or speech
   b. Can be subdivided into[5]:
      (1) Receptive/expressive language disorder
      (2) Speech sound disorders
      (3) Childhood-onset fluency disorder (stuttering)
      (4) Social pragmatic communication disorder

TABLE EC 9.B

SEVERITY LEVELS FOR INTELLECTUAL DISABILITY

Severity Level	Conceptual Domain	Social Domain
Mild	For preschool children, there may be no obvious conceptual differences. For school-aged children and adults, there are difficulties in learning academic skills involving reading, writing, arithmetic, time, or money, with support needed in one or more areas to meet age-related expectations. In adults, abstract thinking, executive function (i.e., planning, strategizing, priority setting, and cognitive flexibility), and short-term memory, as well as functional use of academic skills (e.g., reading, money management) are impaired. There is a somewhat concrete approach to problems and solutions compared with age mates.	Compared with typically developing age mates, the individual is immature in social interactions (e.g., difficulty in accurately perceiving peers' social cues). Communication, conversation, and language are more concrete or immature than expected for age. There may be difficulties regulating emotion and behavior in age-appropriate fashion; these difficulties are noticed by peers in social situations. There is limited understanding of risk in social situations; social judgment is immature for age, and the person is at risk of being manipulated by others (gullibility).
Moderate	All through development, the individual's conceptual skills lag markedly behind those of peers. For preschoolers, language and preacademic skills may develop slowly. For school-aged children, progress in reading, writing, mathematics, and understanding of time and money occurs slowly across the school years, and is markedly limited compared with that of peers. For adults, academic skill development is typically at an elementary level, and support is required for all use of academic skills in work and personal life. Ongoing assistance on a daily basis is needed to complete conceptual tasks of day-to-day life, and others may take over these responsibilities fully for the individual.	The individual shows marked differences from peers in social and communicative behavior across development. Spoken language is typically a primary tool for social communication, but is much less complex than that of peers. Capacity for relationships is evident in ties to family and friends, and the individual may have successful friendships across life and sometimes romantic relations in adulthood. However, individuals may not perceive or interpret social cues accurately. Social judgment and decision-making abilities are limited, and caretakers must assist the person with life decisions. Friendships with typically developing peers are often affected by communication or social limitations. Significant social and communicative support is needed in work settings for success.

Continued

Table EC 9.B—CONT'D

SEVERITY LEVELS FOR INTELLECTUAL DISABILITY

Severity Level	Conceptual Domain	Social Domain
Severe	Attainment of conceptual skills is limited. The individual generally has little understanding of written language or of concepts involving numbers, quantity, time, and money. Caretakers provide extensive support for problem solving throughout life.	Spoken language is quite limited in terms of vocabulary and grammar. Speech may be single words or phrases, and may be supplemented through augmentative means. Speech and communication are focused on the here and now within everyday events. Language is used for social communication more than for explication. Individuals understand simple speech and gestural communication. Relationships with family members and familiar others are a source of pleasure and help.
Profound	Conceptual skills generally involve the physical world rather than symbolic processes. The individual may use objects in goal-directed fashion for self-care, work, and recreation. Certain visuospatial skills (e.g., matching and sorting based on physical characteristics) may be acquired. However, co-occurring motor and sensory impairments may prevent functional use of objects.	The individual has very limited understanding of symbolic communication in speech or gesture. He or she may understand some simple instructions or gestures. The individual expresses his or her own desires and emotions largely through nonverbal, nonsymbolic communication. The individual enjoys relationships with well-known family members, caretakers, and familiar others, and initiates and responds to social interactions through gestural and emotional cues. Co-occurring sensory and physical impairments may prevent many social activities.

Reprinted with permission from the American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington: APA; 2013.

c. Differential diagnosis includes ID, hearing loss, significant motor impairment, or severe mental health difficulties.

2. **Interventions/Treatment**
   Referrals to speech-language pathology (SLP), audiology

D. Learning Disabilities[4]

1. **Definition**
   A heterogeneous group of deficits in an individual's ability to perceive or process information efficiently and accurately.
2. **Diagnosis**
   a. Achievement on standardized tests that is substantially below expected for age, schooling, and level of intelligence in one or more of the following areas: basic reading skills, reading comprehension, reading fluency skills, oral expression, listening comprehension, written expression, mathematic calculation, and mathematic problem solving.
   b. There is no alternative diagnosis such as sensory impairment or ID.[6,7]
3. **Interventions/Treatment**
   School-based services through IEPs and 504 plans tailored to specific learning needs.

E. Cerebral Palsy (CP)

1. **Definition and Epidemiology**
   a. A group of disorders of the development of movement and posture attributed to *non-progressive* disturbances that occurred in the developing fetal or infant brain.[8]
   b. Prevalence: 2 to 3/1000 live births[2]
2. **Clinical Presentation**
   a. Delayed motor development, abnormal tone, atypical postures, persistent primitive reflexes past 6 months.
   b. History of known or suspected brain injury.
   c. Manifestations may change with brain maturation and development.
3. **Diagnosis**
   a. Classification is based on physiologic and topographic characteristics as well as severity (Table 9.9).[9]
   b. Brain imaging should be obtained with magnetic resonance imaging (MRI); abnormal in 70% to 90% of individuals with CP.[10]
4. **Interventions/Treatment**
   a. Baseline and ongoing medical subspecialty care, including developmental pediatrics, neurology, orthopedics, and neurosurgery.
   b. Interdisciplinary team involvement (see Section V).
   c. Equipment to promote mobility and communication, including Augmentative and Alternative Communication - any form of communication other than oral speech (Table EC 9.C).[11]
      (1) Augmentative Communication: Communication supports/methods used by individuals who have some speech but limited use of their speech.

TABLE EC 9.C

TYPES OF ALTERNATIVE AND AUGMENTATIVE COMMUNICATION

Type of AAC	Description	Formats	Access Method
Low-tech AAC	Generally paper-based supports Messages represented by gestures, symbols/photos, objects, words, phrases, or spelling with letters	Basic signs, pencil/paper (writing), eye pointing board, communication board or book, Velcro/ magnet/pull-off messages	Direct selection with upper extremities/ stylus/laser pointer/head-stick/ mouth-stick/eye pointing Indirect selection with partner assisted scanning
Mid-tech AAC	Generally non-computer-based devices with recordable/digitized speech Messages represented by symbols/photos, words, phrases No spelling options; device can't blend letters together to make a spoken word May require physical dexterity to change pages Generally, more limited vocabulary possibilities as compared to high-tech AAC	Single button with single message or multiple messages to scan through Multi-level devices with changeable paper overlay Single level device with non-changing vocabulary overlay	Direct selection with fingers/hand// stylus/laser pointer/head-stick/ mouth-stick Indirect selection with switch scanning
High-tech AAC	Computer-based devices with synthesized or digitized speech Messages could be represented by symbols, photos, words, phrases, or spelling Over 40 different picture-based vocabulary setups are available on the market, to match to patients' language and access needs	Tablet/smartphone/smart watch with AAC application Dedicated speech generating devices, talking word processor Non-dedicated/integrated devices with computer access options	Direct selection with fingers/hand/stylus/laser pointer/head-stick/mouth-stick/eye pointing/mouse Indirect selection with switch scanning

From personal communication with Tooley, Lauren M.S., CCC-SLP, Kennedy Krieger Institute and from Augmentative and Alternative Communication. *American Speech-Language-Hearing Association,* https://www.asha.org/PRPSpecificTopic.aspx?folderid=8589942773&section=Key_Issues.

TABLE 9.9

CLINICAL CLASSIFICATION OF CEREBRAL PALSY[9]

Type	Pattern of Involvement
I. SPASTIC (INCREASED TONE, CLASPED KNIFE, CLONUS, FURTHER CLASSIFIED BY DISTRIBUTION)	
Bilateral spasticity	Diplegia (legs primarily affected) Quadriplegia (all four extremities impaired; legs worse than arms)
Unilateral spasticity	Hemiplegia (ipsilateral arm and leg; arm worse than leg) Monoplegia (one extremity, usually upper; probably reflects a mild hemiplegia)
II. DYSKINETIC (LEAD-PIPE OR CANDLE-WAX RIGIDITY, VARIABLE TONE, ± CLONUS)	
Dystonic Choreoathetoid	Complex disorders often reflecting basal ganglia pathology, resulting in involuntary and uncontrolled movements. May be focal or generalized.
III. OTHER	
Ataxic	Movement and tone disorders often reflecting cerebellar origin
Hypotonic	Usually related to diffuse, often severe cerebral and/or cerebellar cortical dysfunction. May be axial, appendicular, or generalized.
Rigid	Muscle contraction, seen in rare neurogenetic diseases

From Graham HK, Rosenbaum P, et al. Cerebral palsy. *Nat Rev Disease Primers*. 2016;2(15082).

(2) Alternative Communication: Communication supports/methods used by individuals who have no speech.

d. Pharmacotherapy for spasticity (e.g., botulinum toxin injections, baclofen), dyskinesia, hypersalivation (e.g., glycopyrrolate, scopolamine patch).[12]

e. In carefully selected patients: Intrathecal baclofen, selective dorsal rhizotomy, deep brain stimulation.

F. Autism Spectrum Disorders

1. **Definition and Epidemiology**
   a. Encompasses previously named disorders of autistic disorder (autism), Asperger disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS).
   b. Increasing prevalence: 1 in 59 children in the United States has an autism spectrum disorder (ASD) in 2018.[13,14]
   c. Almost five times more common in males than females.[13]
2. **Screening**
   a. **Formal screening for ASD recommended at the 18- and 24-month visits** (see the AAP practice guidelines for more detailed recommendations).[15]
   b. Recommendation upheld by the AAP despite a U.S. Preventive Services Task Force (USPSTF) draft recommendation statement citing insufficient evidence for screening.[16,17]
   c. Evaluate using screening tools such as the **Modified Checklist for Autism in Toddlers (M-CHAT-R/F)** and **Childhood Autism Screening Test (CAST)** (see Table 9.4)

3. **Diagnosis**
   a. Symptoms vary by age, developmental level, language ability, and supports in place.
   b. Diagnostic criteria include[4]:
      (1) **Impaired social communication and interaction.**
      Examples: Lack of joint attention behaviors (e.g., showing toys, pointing for showing), diminished eye contact, no sharing of emotions, lack of imitation
      (2) **Restricted repetitive patterns of behavior, interests, or activities.**
      Examples: Simple motor stereotypies (hand flapping, finger flicking), repetitive use of objects (spinning coins, lining up toys), repetitive speech (echolalia), resistance to change, unusual sensory responses
      (3) Presentation in early childhood and significant limitation of functioning.
4. **Interventions/Treatment**
   a. Educational interventions, visual supports, naturalistic developmental behavioral interventions (integrating behavioral and child-responsive strategies to teach developmentally appropriate skills in a more natural and interactive setting).[16,17]
   b. Referral to SLP, OT/sensory-based interventions.

G. Attention Deficit/Hyperactivity Disorder: See Chapter 24

V. LONGITUDINAL CARE OF CHILDREN WITH DEVELOPMENTAL DISORDERS AND DISABILITIES

A. Interdisciplinary Involvement

1. Neurodevelopmental pediatrician, child neurologist, developmental/behavioral pediatrician, other medical subspecialties as indicated (e.g., orthopedics for CP can be very important).
2. Genetic counseling for families of children with a genetic condition.
3. Psychologists for formal testing, counseling.
4. Rehabilitation and therapists, including physical therapy (PT), occupational therapy (OT), and SLP.
5. Educators

B. Relevant Laws and Regulation

1. The **Individuals with Disabilities Education Act (IDEA)** sets forth regulations in the following areas for states that receive federal funding[6,18]:
   a. Entitles all children with qualifying disabilities to a free and appropriate public education in the least restrictive environment.
   b. **Early intervention services**: Infants and toddlers younger than 3 years may be referred for evaluation to receive developmental services. Eligibility criteria vary by state; see The National Early Childhood Technical Assistance Center (www.ectacenter.org) for details.

   c. **Qualifying disabilities**: Children aged 3 to 21 years with autism spectrum disorder, ID, specific learning disability (LD), hearing or visual impairment, speech or language impairment, orthopedic impairment, traumatic brain injury, emotional disturbance, or other health impairment are eligible.
   d. **Individualized Education Program (IEP)**: Written statement that includes a child's current capabilities, goals and how they will be measured, and services required. A comprehensive team is needed to develop and implement the IEP.
   e. **Transition Services**: School systems must provide transitions services that prepare students for post-secondary activities and IEPs must include a statement of transition service needs starting no later than age 14. The student must be included in the IEP process starting at age 14.
2. **Head Start** and **Early Head Start**: Programs instituted by the federal government to promote school readiness of low-income children aged 3 to 5 years and younger than 3 years, respectively, within their communities.[19]
3. **Section 504** of the Rehabilitation Act of 1973 and the Americans with Disabilities Act (ADA) prohibit discrimination against individuals with any disability, more broadly defined as an impairment that limits function.[20]

VI. TRANSITIONS FROM PEDIATRIC TO ADULT CARE FOR YOUTH WITH DEVELOPMENTAL DISABILITIES

A. The Need

Research reveals health disparities between adults with developmental disabilities and those without. Disparities include:

1. Increased ED utilization
2. Lack of identified adult provider
3. Worse self-perception of health[21]

B. The Role of the Pediatric Provider

AAP Consensus Statement on Transitions[22,23]:

1. Identify a health professional as point person to work with the youth and family on transition process.
2. **Create health care transition plan by age 14** with the youth and family.
3. Apply same guidelines for primary and preventive care for all adolescents and young adults.
4. Ensure affordable, continuous insurance coverage.

C. Transition Domains

Transitions for young adults with disabilities occur across many domains of life and warrant support from an interdisciplinary team (Table 9.10).

TABLE 9.10

TRANSITION DOMAINS FOR YOUTH WITH DEVELOPMENTAL DISORDERS AND DISABILITIES

Transition Domain	Common Issues	Necessary Support Personnel/ Services
Physical/Emotional Health	Difficulty identifying adult providers, retained in pediatric care, lost to follow-up, increased ED usage, insurance difficulties	Pediatrician, adult PCP, sub-specialists
Education/ Employment	Education services through IDEA end at 21 years old. Subsequent difficulty finding and engaging in post-secondary education and/or employment opportunities.	Educational team members (teachers, therapists), vocational rehab specialists, college counselors, post-secondary education programs
Legal/Financial	Difficulties with issues of SSI, guardianship, conservatorship	Attorney, legal counsel, family advocate
Housing/ Transportation	Access to accessible housing and transportation, development and ongoing support of skills needs for independent living	Life skills courses, group homes, independent living supports/ aides, resources through state departments of disability and the US Department of Housing and Urban Development, state mobility services
Leisure Pursuits/ Respite Care	Decreased structure of leisure pursuits with termination of school services at 21, increased burden on caregivers	Day programs, social engagement programs (e.g., Best Buddies, Special Olympics), respite care services for caregivers
Sexuality	Romantic and sexual relationships, vulnerability, reproductive rights, contraception, parenthood, access to appropriate screening and health care	Education team members (sexual education while in school), family members; OB/Gyn providers, adult healthcare providers

ED, Emergency department; *IDEA*, Individuals with Disabilities Education Act; *OB/Gyn*, obstetrician/gynecologist; *PCP*, primary care physician; *SSI*, supplemental security income.

VII. WEB RESOURCES

- Autism Speaks: www.autismspeaks.org
- Bright Futures: www.brightfutures.org
- Cerebral Palsy Foundation: yourcpf.org
- Disability Programs and Services: https://www.dol.gov/odep/topics/disability.htm
- Got Transition: www.gottransition.org
- Individuals with Disabilities Education Act (IDEA): idea.ed.gov
- Intellectual Disability: aaidd.org
- National Center for Learning Disabilities: www.ncld.org
- National Early Childhood Technical Assistance Center: www.ectacenter.org
- Reach Out and Read: www.reachoutandread.org

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 10

Endocrinology

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See additional content on Expert Consult

I. DIABETES

A. Diagnosis of Diabetes Mellitus[1-3]

Diagnostic criteria (must meet one of four):

1. Symptoms of diabetes (polyuria, polydipsia, weight loss, frequent yeast infections) and random blood glucose (BG) ≥200 mg/dL
2. Fasting plasma glucose (FPG = no caloric intake for at least 8 hours) ≥126 mg/dL
3. Oral glucose tolerance test (OGTT) with a 2-hour post-load plasma glucose of ≥200 mg/dL
4. Hemoglobin A_{1c} (HbA_{1c}) ≥6.5%

NOTE: In the absence of symptoms of hyperglycemia, FPG or OGTT should be repeated on another day.

B. Definition of Increased Risk (Prediabetes)

1. FPG 100 to 125 mg/dL
2. 2-hour post-OGTT 140 to 199 mg/dL
3. HbA_{1c} 5.7% to 6.4%

C. Interpreting Hemoglobin A_{1c}[1,2]

1. Estimates average BG for the past 3 months.
2. HbA_{1c} of 6% approximately equals an average BG of 130 mg/dL; each additional 1% ≈ 30 mg/dL more.
3. Unreliable in patients with abnormal red cell lifespan or morphology (e.g., sickle cell disease, spherocytosis).
4. Although the HbA_{1c} criterion has been accepted by the American Diabetes Association for the diagnosis of diabetes in adults, this criterion remains controversial in children, especially as it relates to type 2 diabetes mellitus (T2DM).

D. Etiology: Distinguishing Between Types of Diabetes Mellitus[1,2]

1. Type 1 (T1DM) versus T2DM (most common types, polygenic; Table 10.1)
2. Other forms of diabetes[4,5]
   a. Monogenic diabetes: 1% to 2% of diabetes mellitus (DM). Due to single-gene mutations, typically relating to insulin production or release. Identifying gene can have clinical significance.
      (1) Suspect if autosomal dominant inheritance pattern of early-onset (<25 years) DM, insulin independence, absent T2DM phenotype (non-obese), or preservation of C-peptide.

TABLE 10.1

CHARACTERISTICS SUGGESTIVE OF TYPE 1 VERSUS TYPE 2 DIABETES

Characteristic	Type 1	Type 2
Onset	As early as 1-year-old through adulthood	Usually post-pubertal
Polydipsia and polyuria	Present for days to weeks	Absent or present for weeks to months
Ethnicity	Caucasian	African American, Hispanic, Asian, Native American
Weight	Weight loss	Obese (although weight loss is common in presentation with severe hyperglycemia)
Other physical findings		Acanthosis nigricans
Family history	Autoimmune diseases	Type 2 diabetes
Ketoacidosis	More common (1/3 at onset)	Less common (6% at onset)
Lab characteristics	Autoantibodies common; C-peptide generally should be unmeasurable >2 years after diagnosis	Autoantibodies less common, but sometimes present

(2) Well-described subtypes: MODY1 and MODY3, due to mutations in transcription factors for insulin production; responsive to sulfonylureas.

b. Neonatal diabetes (NDM): Defined as DM onset <6 months of age.
   (1) Rare: 1:160,000 to 260,000 live births, typically a de novo mutation
   (2) May be transient (50% recur) or permanent
   (3) Subset respond to sulfonylureas

c. Cystic fibrosis-related diabetes (CFRD): OGTT rather than HbA_{1c} is the recommended screening test.

d. Other causes of DM: Diseases of exocrine pancreas due to pancreatitis, trauma, infection, invasive disease (e.g., hemochromatosis).

E. Screening for Type 2 Diabetes Mellitus[1,6]

1. **Who to screen**: Children who are overweight [body mass index (BMI) >85th percentile] *and* have one or more of the following risk factors:
   a. Maternal history of diabetes or gestational diabetes mellitus during child's gestation
   b. Family history of T2DM in a first- or second-degree relative
   c. Race/ethnicity: African American, Native American, Hispanic, Asian, or Pacific Islander
   d. Signs associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, or small-for-gestational-age birth weight)
2. **How to screen:** Fasting plasma glucose, OGTT, or HbA_{1c}
3. **When to screen:** Begin at the age of 10 years or at the onset of puberty (whichever occurs first), and repeat at a minimum of every 3 years or more often if BMI is increasing.

TABLE 10.2

SUBCUTANEOUS INSULIN DOSING

	Insulin	Dose Calculation	Sample Calculation for 24-kg Child	Dose
Total daily dose		0.5–1 unit/kg/day	0.75 × 24 = 18 units/day	18 units
Basal	Glargine *OR* Detemir	1/2 daily total 1/2 daily total ÷ BID	½ × 18 units = 9 ½ × 18 units = 9	9 units daily 4.5 units BID
Carbohydrate coverage ratio	Lispro, aspart *OR* Regular	500 ÷ daily total 450 ÷ daily total	500 ÷ 18 = 28 450/18 = 25	1 unit: 28 g carbohydrate 1 unit: 25 g carbohydrate
Correction factor	Lispro, aspart *OR* Regular	1800 ÷ daily total 1500 ÷ daily total	1800 ÷ 18 = 100 1500/18 = 83	1 unit expected to drop BG by 100 mg/dL 1 unit expected to drop BG by 83 mg/dL

F. Additional Testing in New-Onset Diabetes

1. **Diabetes autoantibodies**[1,2]: Recommended for all children with suspected T2DM. No universal agreement regarding whether to test all patients.
   a. Includes islet cell autoantibodies (ICAs) and antibodies to GAD (GAD65), insulin, and tyrosine phosphotases IA-2, IA-2β, ZnT8.
   b. Suggestive of T1DM if present, though about 5% of T1DM will not have measurable ICAs, and some children with T2DM will have measureable ICAs.
2. **Screening for autoimmune diseases in T1DM**[6]**:**
   a. Thyroid disease (present in 17% to 30% of patients with T1DM): Screen with TSH when clinically well and consider screening for thyroid antibodies. If TSH normal, recheck every 1 to 2 years or sooner if symptoms develop.
   b. Celiac disease (present in 1.6% to 16.4% of patients with T1DM): Screen with tissue transglutaminase (TTG) IgA antibody and total IgA. Repeat within 2 years of diabetes diagnosis and again after 5 years. Repeat more frequently if there are symptoms or a first degree relative with celiac disease.

G. Management of Diabetes[6-8]

1. **Diabetes medications FDA-approved for children:**
   a. Insulin: See Tables 10.2 and 10.3 for calculations. Insulin doses are subsequently adjusted based on actual blood sugars.
   b. Metformin: FDA-approved in children ≥10 years old, though sometimes used off-label in younger children. Main side effects are

TABLE 10.3

TYPES OF INSULIN PREPARATIONS AND SUGGESTED ACTION PROFILES FOR SUBCUTANEOUS ADMINISTRATION[54]

Insulin[a]	Onset	Peak	Effective Duration
Ultra rapid acting analog (faster aspart)	5–10 min	1–3 hr	3–5 hr
Rapid acting (lispro, aspart, glulisine)	10–20 min	1–3 hr	3–5 hr
Short acting (regular)	30–60 min	2–4 hr	5–8 hr
Intermediate acting (NPH)	2–4 hr	4–12 hr	12–24 hr
Long acting			
Glargine	2–4 hr	8–12 hr	22–24 hr
Detemir	1–2 hr	4–7 hr	20–24 hr
Degludec	30–90 min	No peak	>42 hr

[a]Assuming 0.1–0.2 U/kg per injection. Onset and duration vary significantly by injection site.

NOTE: Be aware that there are stronger concentrations of various types of insulin available (e.g., U-500 regular insulin, which is 5 times more concentrated than U-100 regular insulin; U-300 insulin glargine). There are also pre-mixed combinations of rapid or short AND intermediate acting insulin (e.g., 70% NPH/30% regular [Humulin 70/30]).

NPH, Neutral protamine Hagedorn.

Modified from The American Diabetes Association. *Practical Insulin: A Handbook for Prescribing Providers*. 2nd ed. Alexandria, VA: American Diabetes Association; 2007.

gastrointestinal and are often transient. Extended release option available for patients with GI side effects.

2. **T1DM management:** The majority of children with T1DM should be treated with intensive insulin regimens, either via multiple daily injections or continuous subcutaneous infusion.
3. **T2DM management:**
   a. Lifestyle modification therapy (nutrition and physical activity) and metformin should be initiated at time of diagnosis.
   b. Insulin therapy should be initiated if distinction between T1DM and T2DM is unclear, when HbA_{1c} ≥8.5%, when random BG ≥250, or when patient with known T2DM is not meeting glycemic target with metformin and lifestyle modification alone. **NOTE:** If significant hyperglycemia (BG > 600) or ketosis is present, patient should be evaluated for DKA/HHS.
4. **Goals of therapy:** A1c <7.5% for T1DM and <7% for T2DM in patients on metformin alone (individualized to avoid excessive hypoglycemia).
5. Interdisciplinary care team should include mental health provider and medical nutrition therapy with initial education and annual update. Regularly assess for eating disorders, disease-related coping, depression, and psychosocial stressors impacting diabetes management.

H. Diabetes-Related Devices[9,10]

1. Technology is rapidly changing, but general principles are described below.
2. **Insulin pumps**: Contain rapid acting insulin only and provide basal and bolus insulin. Doses can be programmed to vary throughout the day. Settings consist of:

a. Basal rate—continuous insulin infusion
b. Carbohydrate coverage—insulin to carbohydrate ratio
c. Hyperglycemia correction—based on correction factor and target blood glucose

NOTE: There is risk for DKA with interruptions in insulin delivery (e.g., pump malfunction) given lack of long-acting insulin.

3. **Continuous glucose monitors (CGMs):** Measure glucose concentration in interstitial fluid continuously and provide alerts for high and low glucose levels.
4. **Sensor augmented insulin pump therapy**: Integration of continuous glucose monitor and insulin pump to adjust insulin delivery based on blood glucose.

I. Monitoring[6,8,9,11]

1. **Glycemic control:**
   a. Assessment of blood glucose using glucometer or CGM—multiple times daily (before meals/snacks, at bedtime, prior to exercise, with symptoms of hypoglycemia, after treating for hypoglycemia, before driving, etc.)
   b. HbA_{1c} every 3 months
2. Urine ketones should be checked with persistent hyperglycemia, any illness (regardless of blood glucose level), or with nausea/vomiting.
3. **Associated conditions or complications:** See Table 10.4.

J. Diabetic Emergencies[12,13]

1. **Diabetic ketoacidosis (DKA)**
   a. Definition**:** Hyperglycemia (or euglycemia in a patient with known diabetes), ketonemia, ketonuria, and metabolic acidosis (pH <7.30, bicarbonate <15 mEq/L)
   b. BG reflects hydration status, pH reflects DKA severity
   c. Symptoms: Nausea, emesis, abdominal pain, fruity breath, altered mental status, Kussmaul respirations
   d. Precipitating factors: New-onset DM, known diabetes with missed insulin doses, insulin pump/infusion site malfunction, or physiologic stress due to acute illness
   e. Management**:** See Fig. 10.1. Because the fluid and electrolyte requirements vary greatly from patient to patient, guidelines are only a starting point and therapy must be individualized based on patient characteristics. **NOTE:** Initial insulin administration may cause transient worsening of the acidosis as potassium is driven into cells in exchange for hydrogen ions.
   f. Cerebral edema: Most severe complication of DKA. Overly aggressive hydration and rapid correction of hyperglycemia may play a role in its development. Risk factors include severe acidosis, evidence of renal insufficiency, young age and new onset, use of bicarbonate.

TABLE 10.4

SCREENING FOR DIABETES-ASSOCIATED CONDITIONS AND COMPLICATIONS[6,11]

Type of Condition or Complication	Screening Test	Frequency
Hypertension	Blood pressure measurement	At every visit
Hyperlipidemia	Lipid profile	At diagnosis, then yearly if T2DM or T1DM and overweight; every 5 years if low-density lipoprotein [LDL] <100 mg/dL
Retinopathy	Dilated eye examination	T1DM: yearly after 3–5 years of diabetes, provided ≥ age 10; T2DM: at diagnosis, yearly
Diabetic nephropathy	Random spot urine microalbumin-to-creatinine ratio	T1DM: yearly after 5 years of diabetes, provided ≥ age 10; T2DM: at diagnosis, yearly
Neuropathy	Foot exam	T1DM: yearly after 5 years of diabetes, provided ≥ age 10; T2DM: at diagnosis, yearly
Nonalcoholic steatohepatitis (NASH)	ALT, AST	T2DM: at diagnosis, yearly
Obstructive sleep apnea (OSA)	Review of symptoms	T2DM: at every visit
Polycystic ovary syndrome (PCOS)	Menstrual history ± lab evaluation	T2DM: at every visit

ALT, Alanine amino transferase; *AST*, aspartate amino transferase; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

g. Once DKA is resolved, transition to subcutaneous (SQ) insulin. See Tables 10.2 and 10.3 for calculations or resume home insulin doses.

2. **Hyperglycemic hyperosmolar state (HHS)**
   a. Definition: Extreme hyperglycemia (BG >600 mg/dL) and hyperosmolarity (>320 mOsm/kg), **without significant ketosis or acidosis.**
   b. Characteristics of HHS: Gradually increasing polyuria and polydipsia leading to profound dehydration, altered consciousness.
   c. Management:
      (1) Fluids: Fluids alone will decrease BG due to dilution, promotion of glucosuria, and increased glucose uptake with improved circulation. Fluid replacement should be more rapid than in DKA with goal of gradual decline in serum sodium (about 0.5 mEq/dL/h) and osmolality. Bolus ≥20 cc/kg 0.9% saline and repeat until perfusion improved. Then start maintenance fluids plus deficit replacement over 24 to 48 hours using 0.45% to 0.75% saline (if perfusion inadequate, consider isotonic fluids). Urine output should also be replaced.
      (2) Insulin therapy: Start insulin (0.025 to 0.05 unit/kg/h) when BG no longer declining at least 50 mg/dL/h with fluids alone. Titrate insulin to decrease BG by 75 to 100 mg/dL/h.

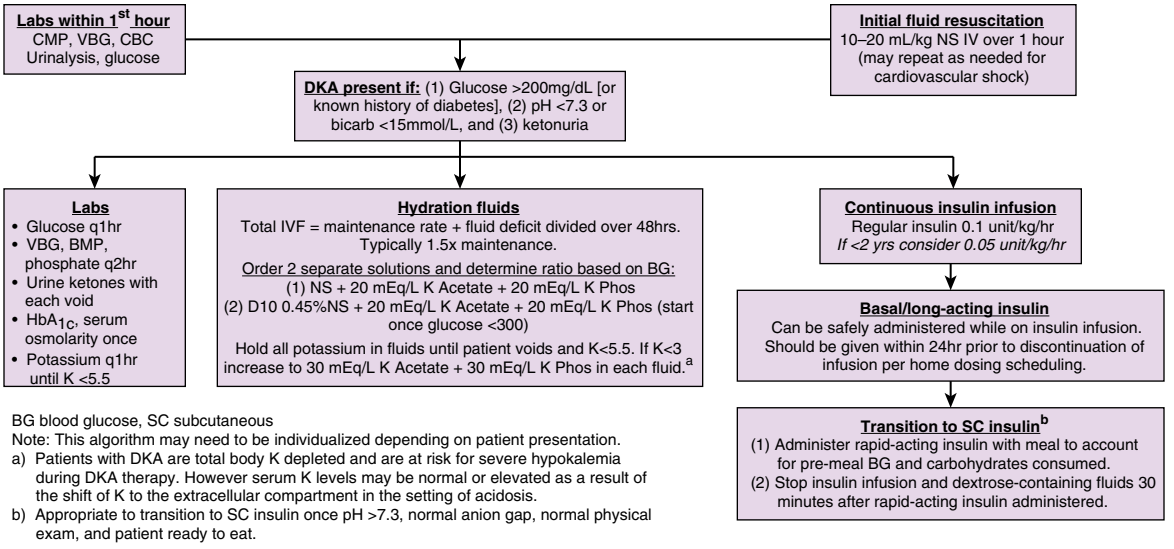

FIGURE 10.1

Management of Diabetic Ketoacidosis. (Modified from Cooke DW, Plotnick L. Management of diabetic ketoacidosis in children and adolescents. *Pediatr Rev.* 2008;29:431–436.)

TABLE 10.5

AGE-BASED NORMAL VALUES FOR ROUTINE THYROID FUNCTION TESTS

Test	Age	Normal Range	
TSH (mIU/L)	Birth–6 days	0.70–15.2	
	1 week–3 months	0.72–11.0	
	3 months–12 months	0.73–8.35	
	1–5 years	0.70–5.97	
	6–10 years	0.60–4.84	
	>10 years	0.45–4.50	
Free T_4 (ng/dL)	Birth–3 days	0.66–2.71	
	4–30 days	0.83–3.09	
	31 days–12 months	0.48–2.34	
	13 months–5 years	0.85–1.75	
	6–10 years	0.90–1.67	
	11–19 years	0.93–1.60	
	>19 years	0.82–1.77	
Total T_4 (mCg/dL)		Male	Female
	< 1 months	4.5–17.2	4.5–17.2
	1–23 months	5.9–13.9	5.9–13.9
	2–12 years	5.7–11.6	5.7–11.6
	13–20 years	5.1–10.3	5.3–11.7
	>20 years	4.9–10.5	5.1–11.9

T_4, Thyroxine; *TSH*, thyroid-stimulating hormone.

NOTE: If age-specific reference ranges are provided by the laboratory that is running the assay, please refer to those ranges.

TSH and Free T_4 reference ranges from Labcorp; Total T_4 reference range from Quest Diagnostics.

(3) Electrolytes: Potassium, phosphate, and magnesium deficits greater than in DKA; monitor every 2 to 4 hours. Start potassium replacement with 40 mEq/L once K <5 mEq/L.

II. THYROID GLAND[14-16]

A. Thyroid Tests[15,17,18]

1. **Normal thyroid function values:** See reference values for age (Table 10.5). Preterm infants have different ranges (Table 10.6).
2. **Interpretation of abnormal thyroid function values:** See Table 10.7.
3. **Imaging studies:**
   a. Thyroid ultrasound: Most useful in assessing thyroid nodules for features suspicious for malignancy.
   b. Thyroid uptake scan: Measures uptake of Technetium (^{99m}Tc) pertechnetate or radioactive iodine by metabolically active thyroid tissue, helping to identify etiology of hyperthyroidism.

B. Hypothyroidism

1. **Types of hypothyroidism:** Can be either congenital or acquired and either primary or central**.** See Table 10.8 for details on identification and management.

TABLE 10.6

MEAN TSH AND T_4 OF PRETERM AND TERM INFANTS 0–28 DAYS[18]

Age ± SD	Cord (Day 0)	Day 7	Day 14	Day 28
T_4 (mCg/DL)				
23–27[a]	5.44 ± 2.02	4.04 ± 1.79	4.74 ± 2.56	6.14 ± 2.33
28–30	6.29 ± 2.02	6.29 ± 2.10	6.60 ± 2.25	7.46 ± 2.33
31–34	7.61 ± 2.25	9.40 ± 3.42	9.09 ± 3.57	8.94 ± 2.95
>37	9.17 ± 1.94	12.67 ± 2.87	10.72 ± 1.40	9.71 ± 2.18
FT_4 (NG/DL)				
23–27	1.28 ± 0.41	1.47 ± 0.56	1.45 ± 0.51	1.50 ± 0.43
28–30	1.45 ± 0.43	1.82 ± 0.66	1.65 ± 0.44	1.71 ± 0.43
31–34	1.49 ± 0.33	2.14 ± 0.57	1.96 ± 0.43	1.88 ± 0.46
>37	1.41 ± 0.39	2.70 ± 0.57	2.03 ± 0.28	1.65 ± 0.34
TSH (MIU/L)				
23–27	6.80 ± 2.90	3.50 ± 2.60	3.90 ± 2.70	3.80 ± 4.70
28–30	7.00 ± 3.70	3.60 ± 2.50	4.90 ± 11.2	3.60 ± 2.50
31–34	7.90 ± 5.20	3.60 ± 4.80	3.80 ± 9.30	3.50 ± 3.40
>37	6.70 ± 4.80	2.60 ± 1.80	2.50 ± 2.00	1.80 ± 0.90

[a]Weeks gestational age

FT_4, Free thyroxine; *T_4*, thyroxine; *TSH*, thyroid-stimulating hormone.

Data modified from Williams FL, Simpson J, Delahunty C, et al. Collaboration from The Scottish Preterm Thyroid Group: Developmental trends in cord and postpartum serum thyroid hormones in preterm infants. *J Clin Endocrinol Metab.* 2004;89:5314–5320.

TABLE 10.7

THYROID FUNCTION TESTS: INTERPRETATION

Disorder	TSH	T_4	Free T_4
Primary hyperthyroidism	L	H	High N to H
Primary hypothyroidism	H	L	L
Hypothalamic/pituitary hypothyroidism	L, N, H[a]	L	L
TBG deficiency	N	L	N
Euthyroid sick syndrome	L, N, H[a]	L	L to low N
TSH adenoma or pituitary resistance	N to H	H	H
Subclinical hypothyroidism[b]	H	N	N

[a]Can be normal, low, or slightly high.

[b]Treatment may not be necessary.

H, High; *L*, low; *N*, normal; *T_4*, thyroxine; *TBG*, thyroxine-binding globulin; *TSH*, thyroid-stimulating hormone.

2. **Subclinical hypothyroidism and obesity**[19]**:** Moderate elevations in thyroid-stimulating hormone (TSH [4 to 10 mIU/L]), with normal or slightly elevated triiodothyronine (T_3) and thyroxine (T_4) are seen in 10% to 23% of obese children. There does not appear to be a benefit to treating these individuals. Values tend to normalize with weight loss. Could consider testing for thyroid antibodies to further clarify whether there is true thyroid dysfunction.

TABLE 10.8

HYPOTHYROIDISM[55,56]

Clinical Symptoms	Onset	Etiology	Management	Follow-up
PRIMARY/CONGENITAL				
Large fontanelles, lethargy, constipation, hoarse cry, hypotonia, hypothermia, jaundice. Most often picked up on newborn screen.	Symptoms usually develop by 2 weeks; almost always by 6 weeks. Some infants may be relatively asymptomatic if not caused by absence of thyroid gland.	**Primary:** Defect of fetal thyroid development most common. Other causes include TSH receptor mutation or thyroid dyshormonogenesis. *OR* **Central:** Deficiency of TSH or thyrotropin-releasing hormone (TRH).	Replacement with L-thyroxine once newborn screen is positive, pending results of confirmatory testing.[a] Goal T_4 in upper half of normal range. In primary hypothyroidism, TSH should be kept in normal range for age.	Monitor T_4 and TSH 1–2 weeks after initiation and then every 2 weeks until TSH normalizes. Once levels are adequate follow per schedule listed below. Treated patients are still at risk for developmental delay.
ACQUIRED				
Growth deceleration, coarse brittle hair, dry skin, delayed tooth eruption, cold intolerance.	Can occur as early as 2 years old.	**Primary:** Can be caused by Hashimoto thyroiditis (diagnosis supported by + antithyroglobulin or antimicrosomal antibodies), head/neck radiation. *OR* **Central:** Caused by pituitary/hypothalamic insults including brain tumor.	Replacement with L-thyroxine.[a] Targets for TSH and T_4 same as for congenital hypothyroidism above.	Follow every 1–3 months during the first 12 months, every 2–4 months until 3 years, and then every 3–12 months until growth complete. Follow 4–6 weeks after any dose change.

[a]Because of the risk of inducing adrenal crisis if adrenocorticotropic hormone (ACTH) deficiency is present, the treatment of central hypothyroidism *should not be* started until normal ACTH/cortisol function is documented.

NOTE: Thyroid hormone levels in premature infants are lower than those seen in full-term infants. Furthermore, the TSH surge seen at approximately 24 hours of age in full-term babies does not appear in preterm infants. In this population, lower levels are associated with increased illness; however, the effect of replacement therapy remains controversial.

L-thyroxine, Levothyroxine; *TSH*, thyroid-stimulating hormone.

TABLE 10.9
HYPERTHYROIDISM

Presentation	Distinguishing Imaging/Lab Findings	Management
GRAVES DISEASE		
Typical symptoms of hyperthyroidism plus diffuse goiter, eye symptoms, localized dermopathy, and lymphoid hyperplasia	TSH is often undetectable. ↑ ^{99m}Tc-pertechnate uptake. Positive TSI.	First-line treatment in children is methimazole. Radioactive iodine (^{131}I) or surgical thyroidectomy are options for initial treatment or refractory cases. Follow symptoms, T_4, and TSH levels.
HASHIMOTO THYROIDITIS		
± Initial hyperthyroidism, followed by eventual thyroid burnout and hypothyroidism.	Often low but detectable TSH and less significant increase in T_4. ↓ ^{99m}Tc-pertechnate uptake. Significant elevation of thyroglobulin and/or microsomal antibody.	Hyperthyroid phase is usually self-limited; patient may eventually need thyroid replacement therapy. Propranolol if symptomatic during hyperthyroid phase.

^{99m}*Tc*, Technetium; *T_4*, thyroxine; *TSH*, thyroid stimulating hormone; *TSI*, thyroid stimulating immunoglobulin.

3. **Newborn screening for hypothyroidism**[16,20]**:** Mandated in all 50 states. Measures a combination of TSH and T_4, based on the particular state's algorithm; 1:25 abnormal tests are confirmed. Congenital hypothyroidism has prevalence of 1:3000 to 1:4000 U.S. infants. If abnormal results are found, clinicians should follow recommendations of the American College of Medical Genetics ACT Sheets and Algorithm for confirmation testing.

C. Hyperthyroidism

1. **General features:**
   a. Epidemiology: Prevalence increases with age, rare before adolescence; female-to-male predominance.
   b. Etiology: Most common cause is Graves disease, followed by subacute thyroiditis. Less common causes are Hashitoxicosis, autonomously functioning thyroid nodule, factitious hyperthyroidism (intake of exogenous hormone), TSH-secreting pituitary tumor (rare), and pituitary resistance to thyroid hormone. See Table 10.9 for comparison of Graves and Hashimoto disease.
   c. Laboratory findings: See Table 10.7. Further tests include TSH receptor–stimulating antibody, thyroid-stimulating immunoglobulin (TSI), antithyroglobulin and antimicrosomal (thyroid peroxidase) antibodies.

2. **Thyroid storm[21]:**
   a. Presentation: Acute onset of hyperthermia, tachycardia, and restlessness. May progress to delirium, coma, and death.
   b. Treatment: Admission to ICU. Emergent pediatric endocrinology consultation recommended. Therapy aimed at relieving symptoms (propranolol) and reducing peripheral conversion of T4 to T3 (hydrocortisone), thyroid hormone production (antithyroid drugs), release of hormone from thyroid gland (potassium iodide), and reabsorption from enterohepatic circulation (cholestyramine).
3. **Neonatal thyrotoxicosis:**
   a. Presentation: Microcephaly, frontal bossing, intrauterine growth restriction (IUGR), tachycardia, systolic hypertension leading to widened pulse pressure, irritability, failure to thrive, exophthalmos, goiter, flushing, vomiting, diarrhea, jaundice, thrombocytopenia, and cardiac failure or arrhythmias. Onset from immediately after birth to weeks.
   b. Etiology: Occurs exclusively in infants born to mothers with Graves disease. Caused by transplacental passage of maternal TSI. Occasionally, mothers are unaware they have Graves. Even if a mother has received definitive treatment (thyroidectomy or radiation therapy), passage of TSI remains possible.
   c. Treatment and monitoring: Propranolol for symptom control. Methimazole to lower thyroxine levels. Digoxin may be indicated for heart failure. Disease usually resolves by 6 months of age.

III. PARATHYROID GLAND AND VITAMIN D[22-24]

A. Parathyroid Hormone Function

1. Increases serum calcium by increasing bone resorption
2. Increases calcium and magnesium reuptake and phosphorus excretion in the kidney
3. Increases 25-hydroxy vitamin D conversion to 1,25-dihydroxy vitamin D, in order to increase calcium absorption in the intestine

B. Distinguishing Between Abnormalities Related to Parathyroid Hormone and Vitamin D

See Table 10.10.

C. Vitamin D Supplementation

Please see Chapter 21 for additional information.

IV. ADRENAL GLAND[25-29]

A. Adrenal Insufficiency

1. **Causes of adrenal insufficiency:**
   a. Impaired steroidogenesis, as in congenital adrenal hyperplasia.
   b. Adrenal destruction or dysfunction as in primary adrenal insufficiency (AI) (Addison disease), autoimmune polyendocrine syndrome, or adrenoleukodystrophy.

TABLE 10.10

DISTINGUISHING BETWEEN DISORDERS OF PARATHYROID GLANDS AND VITAMIN D REGULATION

	Hypoparathyroidism	Hyperparathyroidism	PTH Resistance/ Pseudo-Hypoparathyroidism	Vitamin D Deficiency
PTH	↓ or inappropriately normal in the setting of hypocalcemia	↑	↑	-/↑
1,25-D	↓	↑	↓	-
25-OHD	-	-/↓	-	↓
Calcium	↓	↑	↓	-/↓
Phosphorus	↑	↓	↑	-/↓
Alkaline Phosphate	-/↓	-/↑	↑	↑
Common Causes	DiGeorge, autoimmune (APS), iatrogenic	Primary: Adenoma, hyperplasia Secondary: Renal failure, rickets	Genetic mutations	Nutritional deficiency
First line Rx	Calcium, calcitriol	Hydration with normal saline, surgical resection	Calcitriol	Vitamin D +/- calcium

1,25-D, 1,25 dihydroxy vitamin D; *25-OHD*, 25-hydroxy vitamin D; *APS*, autoimmune polyendocrine syndrome; *MEN*, multiple endocrine neoplasia; *PTH*, parathyroid hormone; *Rx*, treatment.

TABLE 10.11

17-HYDROXYPROGESTERONE, SERUM

Age	Baseline (ng/dL)
Premature (31–35 weeks)	≤360
Term infants (3 days)	≤420
1–12 months	11–170
1–4 years	4–115
5–9 years	≤90
10–13 years	≤169
14–17 years	16–283
Males, Tanner II–III	12–130
Females, Tanner II–III	18–220
Males, Tanner IV–V	51–190
Females, Tanner IV–V	36–200
Male (18–30 years)	32–307
Adult female	
Follicular phase	≤185
Midcycle phase	≤225
Luteal phase	≤285

Reference ranges from Quest Diagnostics LC/MS assay (liquid chromatography/tandem mass spectroscopy).
For preterm infants or infants born small for gestational age, see Olgemöller B, Roscher AA, Liebl B, et al. Screening for congenital adrenal hyperplasia: adjustment of 17-hydroxyprogesterone cut-off values to both age and birth weight markedly improves the predictive value. *J Clin Endocrinol Metab.* 2003;88:5790–5794.

c. Secondary AI caused by impaired circulating adrenocorticotropic hormone (ACTH) due to hypothalamic or pituitary pathology.
d. Acquired insufficiency secondary to long-term corticosteroid use leading to HPA suppression. **NOTE**: This is the most common cause seen in clinical practice and may also occur in setting of chronic high-dose inhaled corticosteroids.

2. **Laboratory findings in adrenal insufficiency:**
   a. In primary AI, there is deficient mineralocorticoid and glucocorticoid production. In central AI, there is only deficient glucocorticoid production, and mineralocorticoid production is normal.
   b. Primary AI: Elevated ACTH, elevated plasma renin activity, low cortisol, low aldosterone, hypoglycemia, hyponatremia, hyperkalemia.
   c. Central AI: Normal/low ACTH, normal plasma renin activity (no impairment of mineralocorticoid function), low cortisol, normal aldosterone, hyponatremia, hypoglycemia.
   d. In infants with congenital adrenal hyperplasia (CAH), 17-hydroxyprogesterone (17-OHP) is increased (see Table 10.11 for normal values by age).
3. **Diagnosis of adrenal insufficiency:**
   a. Initial screening with AM cortisol level, which may be drawn concomitantly with an ACTH level.
   b. See Table 10.12 for interpretation of AM cortisol results.

TABLE 10.12

CORTISOL, 8 AM

Interpretation	Cortisol (mCg/dL)
Suggestive of adrenal insufficiency	<5 mCg/dL
Indeterminate	5–14 mCg/dL
Adrenal insufficiency unlikely	>14 mCg/dL

BOX 10.1

PERFORMANCE AND INTERPRETATION OF ACTH STIMULATION TEST

Standard Dose ACTH Stimulation Test

Obtain initial baseline cortisol level
Give 250 mg IV ACTH
Measure cortisol at 30 min
Measure cortisol at 60 min

Interpretation of Results

For evaluation of primary adrenal insufficiency:
<18 mCg/dL: Highly suggestive of adrenal insufficiency
≥18 mCg/dL: Normal (rules out adrenal insufficiency)

For evaluation of central adrenal insufficiency:
<16 mCg/dL: Highly suggestive of adrenal insufficiency
16–30 mCg/dL: Adrenal insufficiency less likely but not excluded
>30 mCg/dL: Normal (rules out adrenal insufficiency)

NOTE: No test for adrenal insufficiency has perfect sensitivity or specificity, so results must be interpreted in the individual clinical context. Measurement of serum ACTH is also beneficial (elevated in Addison's, low/normal in secondary insufficiency).

c. Plasma ACTH elevation >100 pg/mL with concomitant hypocortisolemia <10 ug/dL is consistent with glucocorticoid deficiency due to primary AI.
d. Standard dose ACTH stimulation test is used to confirm diagnosis.

4. **ACTH stimulation test:**
   a. In brief, with ACTH deficiency or prolonged adrenal suppression, there is an inadequate rise in cortisol after a single ACTH dose.
   b. See Box 10.1 for interpretation of ACTH stimulation test.
5. **Congenital adrenal hyperplasia (CAH):**
   a. See Fig. 10.2.
   b. Group of autosomal recessive disorders characterized by a defect in one of the enzymes required in the synthesis of adrenal hormones.
   c. The enzymatic defect results in impaired synthesis of adrenal steroids beyond the enzymatic block and overproduction of the precursors before the block.
   d. 21-hydroxylase deficiency accounts for 90% of cases.
   e. Most common cause of ambiguous genitalia in females.

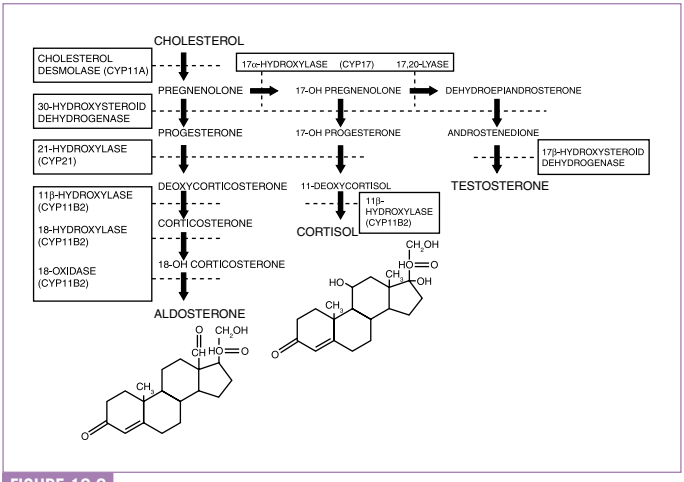

FIGURE 10.2
Biosynthetic Pathway for Steroid Hormones.

6. **Diagnosis of CAH on newborn screen:**
   a. The test measures 17-OHP and is 2% specific, resulting in a 98% false-positive rate due to artificial elevations from prematurity, sickness, stress.[27]
   b. If 17-OHP is 40 to 100 ng/mL, repeat test.
   c. If 17-OHP is higher than 100 ng/mL, obtain electrolytes and serum 17-OHP. If evidence of hyperkalemia or hyponatremia, initiate treatment with hydrocortisone.
   d. In complete enzyme deficiency, adrenal crisis in untreated patients occurs at 1 to 2 weeks of age due to salt wasting.
7. **Diagnosis of CAH outside of newborn period:**
   a. Suspect partial enzyme deficiency if evidence of androgen excess (premature adrenarche, hirsutism, irregular menses, acne, advanced bone age).
   b. Morning 17-OHP levels may be elevated.
   c. Diagnosis may require an ACTH stimulation test. A significant rise in the 17-OHP level 60 minutes after ACTH injection is diagnostic. Cortisol response may be decreased.
8. **Addison disease[30]:**
   a. Primary AI due to autoimmune destruction of the adrenal glands.
   b. In children, it may be part of autoimmune polyendocrine syndrome type 1 (APS-1), which also includes hypoparathyroidism and chronic mucocutaneous candidiasis.
   c. Individuals with autoimmune Addison disease should also be screened for other endocrinopathies (T1DM, celiac disease, hypothyroidism, hypoparathyroidism).

TABLE 10.13

POTENCY OF VARIOUS THERAPEUTIC STEROIDS[c]

Steroid	Glucocorticoid Effect[a] (in mg of Cortisol per mg of Steroid)	Mineralocorticoid Effect[b] (in mg of Cortisol per mg of Steroid)
Cortisol (hydrocortisone)	1	1
Cortisone acetate (oral)	0.8	0.8
Cortisone acetate (intramuscular)	0.8	0.8
Prednisone	4	0.25
Prednisolone	4	0.25
Methylprednisolone	5	0.4
β-Methasone	25	0
Triamcinolone	5	0
Dexamethasone	30	0
9α-Fluorocortisone (fludrocortisone)	15	200
Deoxycorticosterone acetate	0	20
Aldosterone	0.3	200–1,000

[a]To determine cortisol equivalent of a given steroid dose, multiply dose of steroid by corresponding number in column for glucocorticoid or mineralocorticoid effect. To determine dose of a given steroid based on desired cortisol dose, divide desired hydrocortisone dose by corresponding number in the column.

[b]Total physiologic replacement for salt retention is usually 0.1 mg fludrocortisone, regardless of patient size.

[c]Set relative to potency of cortisol.

Modified from Sperling MA. *Pediatric Endocrinology.* 3rd ed. Philadelphia: Elsevier; 2008:476.

TABLE 10.14

MAINTENANCE DOSING STEROIDS

Adrenal Hormone	Dose
Glucocorticoid dosing	1. PO hydrocortisone 6–18 mg/m^2/day ÷ TID OR 2. PO prednisone 1.5–3.5 mg/m^2/day ÷ BID
Mineralocorticoid dosing[a]	1. PO fludrocortisone acetate 0.1 mg/m^2/day OR 2. If unable to take PO: IV hydrocortisone 50 mg/m^2/day[b] PLUS 3. Infants require an additional 1–2 g (17–34 mEq) of sodium supplementation daily

[a]Required in salt losing forms of adrenal insufficiency.

[b]Synthetic steroids (e.g., prednisone, dexamethasone) do not have sufficient mineralocorticoid effect.

9. **Treatment of adrenal insufficiency:**
   a. See Table 10.13 for relative steroid potencies.
   b. See Table 10.14 for maintenance glucocorticoid and mineralocorticoid dosing.
   c. Typically, lower doses are required for central AI, intermediate doses for primary AI, and higher doses for CAH.

TABLE 10.15

STRESS DOSING STEROIDS

Degree of Stress	Dose
Moderate Stress (minor illness, fever)	1. PO hydrocortisone 30–50 mg/m²/day ÷ TID OR 2. PO prednisone 6–10 mg/m²/day ÷ BID
Severe Stress (surgery, severe illness, compensated shock)	1. IV bolus of hydrocortisone 50 mg/m² then 50–100 mg/m²/day IV as continuous infusion or divided Q6 hr OR 2. IM injection of 25 mg/m²/dose Q6 hr

BOX 10.2

RAPID APPROXIMATION OF STRESS DOSE STEROID REQUIREMENT

Infant: 25 mg hydrocortisone
Small child: 50 mg hydrocortisone
Large child/adolescent: 100 mg hydrocortisone

10. **Stress dosing of steroids:**
    a. **Hydrocortisone and cortisone are the only glucocorticoids that provide the necessary mineralocorticoid effects**; prednisone and dexamethasone do not.
    b. See Table 10.15 for calculation of moderate and major stress dose steroid calculations.
    c. See Box 10.2 for rapid approximation of steroid dosing in the setting of acute adrenal crisis.
11. **Indications for stress dosing of steroids:**
    a. "Stress" is defined as systemic infection, febrile illness, diarrheal illness, trauma/fracture, burns, or surgery.
    b. Stress glucocorticoids should be given to patients:
       (1) With known primary or secondary AI
       (2) Following discontinuation of exogenous steroid (given for greater than 2 weeks at doses greater than physiologic replacement) until there is recovery of endogenous cortisol production (consider the need for 8am cortisol or ACTH stimulation test)
    c. Consider for hypotension refractory to fluid resuscitation in patients with suspicion for AI (even if not clinically diagnosed).

B. Adrenal Cortex Hormone Excess[29]

1. **Causes:**
    a. Hypercortisolism (Cushing syndrome):
       (1) Exogenous steroid use
       (2) Excess cortisol secretion from the adrenals
       (3) Excess ACTH production from ectopic ACTH producing tumor
       (4) Excess ACTH production from a pituitary tumor (known as Cushing *disease*)

b. Hyperaldosteronism:
   (1) Benign tumor of adrenal cortex (Conn syndrome)
   (2) Overproduction by both adrenal glands (idiopathic hyperaldosteronism)
   (3) Rarely glucocorticoid remediable aldosteronism
   (4) Less common in children than hypercortisolism
   (5) Lab findings include hypokalemia and hypernatremia

2. **Diagnosis of Cushing Syndrome[31]:**
   a. Step 1: Demonstrate hypercortisolism with two separate measurements. Multiple screening tests are available; specificity increases when they are used in combination:
      (1) 24-hour urine cortisol (>90 μg/24 hour consistent with hypercortisolism).
      (2) Midnight salivary cortisol level (>0.13 mCg/dL consistent with hypercortisolism).
      (3) Overnight low dose dexamethasone suppression test: Give 1 mg dexamethasone at 11pm followed by an 8am serum cortisol the next morning (normal suppression <1.8 mCg/dL).
   b. Step 2: Determine etiology of hypercortisolism (ACTH-dependent vs. independent)
      (1) Obtain plasma ACTH between 11pm–1am: >23 pg/mL in a patient with hypercortisolism (as diagnosed above) indicates ACTH dependency (Cushing Disease vs. ectopic tumor).
      (2) If cause is Cushing disease (ACTH-dependent), ACTH level will be >100x elevated.
      (3) In ACTH-independent Cushing syndrome, level will be <5 pg/mL.

C. Adrenal Medulla Hormone Excess: Pheochromocytoma[32-34]

1. **Clinical findings:**
   a. Extreme, sustained elevations in blood pressure (accounts for <1% of pediatric hypertension).
   b. Associated with syndromes: multiple endocrine neoplasia (MEN) IIa and IIb, von Hippel-Lindau, neurofibromatosis (NF) 1, familial paraganglioma syndrome.
2. **Diagnosis:**
   a. Urine metanephrines (see Table EC 10.A for age-specific normal values).
   b. Plasma metanephrines (see Table EC 10.B for age-specific normal values).

V. DISORDERS OF SO DIUM AND WATER REGULATION[35]

A. Distinguishing Between Disorders of Sodium and Water Regulation: See **Table 10.16**

B. Correction of Hypo- and Hypernatremia: See **Chapter 11.**

C. Conducting a Water Deprivation Test

1. Begin test after a 24-hour period of adequate hydration and stable weight.

TABLE EC 10.A

CATECHOLAMINES,[a] URINE

Compound	3–8 Years	9–12 Years	13–17 Years	Adults	
Dopamine (mCg/24 hr)	80–378	51–474	51–645	52–480	
Epinephrine (mCg/24 hr)	1–7	≤8	≤11	2–14	
Norepinephrine (mCg/24 hr)	5–41	5–50	12–88	15–100	
Homovanillic acid (mg/24 hr)	0.5–6.7	1.1–6.8	1.4–7.2	1.6–7.5	
Vanillylmandelic acid (g/24 hr)	≤2.3	≤3.4	≤3.9	≤6.0	
	3 months–4 years	**5–9 years**	**10–13 years**	**14–17 years**	**18–29 years**
Metanephrines (mCg/24 hr)	25–117	11–139	51–275	40–189	25–222
Normetanephrines (mCg/24 hr)	54–249	31–398	67–503	69–531	40–412

[a]Catecholamines are elevated in a variety of tumors, including neuroblastoma, ganglioneuroma, ganglioblastoma, and pheochromocytoma.

Data from JHH laboratories.

TABLE EC 10.B

CATECHOLAMINES, PLASMA

	Supine (pg/mL)	Sitting (pg/mL)
EPINEPHRINE		
3–15 years	≤464	Not determined
Adult	≤50	≤95
NOREPINEPHRINE		
3–15 years	≤1251	Not determined
Adult	112–658	217–1109
DOPAMINE		
3–15 years	≤60	Not determined
Adult	≤30	≤30

Data from Blondell R, Foster MB, Dave KC. Disorders of puberty. *Am Family Phys.* 1999;60:209–218; and JHH Laboratories.

TABLE 10.16

DIFFERENTIATING BETWEEN DISORDERS OF SODIUM AND WATER REGULATION

	SIADH	Cerebral Salt Wasting	DI
Serum Na+	<135 mEq/L	<135 mEq/L	>145 mEq/L[a]
Serum Osm	<280 mOsm/kg	<280 mOsm/kg	>300 mOsm/kg[a]
Urine Na+	>40 mEq/L	>40 mEq/L	< 40 mEq/L[b]
Urine Osm	>100 mOsm/kg (inappropriately concentrated)	>100 mOsm/kg (inappropriately concentrated)	<300 mOsm/kg (inappropriately dilute)
Volume Status	Euvolemia	Hypovolemia	Hypovolemia
Urine Output	Decreased	Increased	Increased
Other lab findings	High vasopressin	Low vasopressin	1. Central: low vasopressin (<0.5 pg/mL) 2. Nephrogenic: high vasopressin
Causes	Nausea, CNS and pulmonary pathology, surgery, certain medications	CNS disorders, hypersecretion of atrial natriuretic peptide	1. Central:↓ADH secretion from posterior pituitary 2. Nephrogenic: ADH resistance at the nephron collecting duct
Treatment	Fluid restriction and correction of underlying cause Treatment with sodium will cause diuresis	Replacement of urine volume with IV solutions ± salt replacement	1. Central: Intranasal Desmopressin acetate (DDAVP) 2. Nephrogenic: Access to free water, salt restriction, consider thiazide diuretics, indomethacin

[a]Normal serum sodium and osmolality can be seen in compensated diabetes insipidus, and water deprivation test should be performed if clinical suspicion is high.

[b]Urine sodium generally low in diabetes insipidus, however this depends on solute intake.

ADH, Antidiuretic hormone; *CNS*, central nervous system; *DI*, diabetes insipidus; *Na+*, sodium; *Osm*, osmolarity; *SIADH*, syndrome of inappropriate ADH secretion; *IV*, intravenous.

2. Obtain a baseline weight after bladder emptying, as well as baseline urine and blood osmolality and electrolytes.
3. Restrict fluids (max 7 hours, 4 hours for infants).
4. Measure body weight and urine–specific gravity and volume hourly.
5. If urine specific gravity ≥1.014, or weight loss approaching 5%, terminate test and obtain urine and blood for osmolality and electrolytes.

D. Interpretation of Water Deprivation Test Results: See Table 10.17

E. Differentiating Between Central Versus Nephrogenic Causes of Diabetes Insipidus

1. Administer vasopressin subcutaneously at end of water deprivation test. Assess urine output, urine specific gravity, and water intake.
2. See Table 10.18 for interpretation of vasopressin test.

TABLE 10.17

RESULTS OF WATER DEPRIVATION TEST IN NORMAL VERSUS CENTRAL/NEPHROGENIC DIABETES INSIPIDUS

	Normal (Psychogenic Polydipsia)	Central/Nephrogenic DI
Urine volume	Decreased	No change
Weight loss	No change	≤5%
Urine osmolality (mOsm/L)	500–1400 (>1000 generally excludes diagnosis of DI)	<150
Plasma osmolality (mOsm/L)	288–291	>290
Urine specific gravity	≥1.010	<1.005
Urine: plasma osmolality ratio	>2	<2

DI, Diabetes insipidus.

TABLE 10.18

RESULTS OF VASOPRESSIN ADMINISTRATION IN EVALUATION OF DIABETES INSIPIDUS

	Psychogenic Polydipsia	Central[a]	Nephrogenic
Urine volume	↓	↓	No change
Urine specific gravity	≥1.010	≥1.010	No change
Oral fluid intake	No change	↓	No change

[a]In central diabetes insipidus, urine osmolality increases by 200% or more in response to vasopressin administration.

TABLE 10.19

ESTIMATED GROWTH VELOCITY IN CHILDREN BASED ON AGE

Age	Growth
Birth to 1 year old	25 cm/year
1 year old to 4 years old	10 cm/year
4 years old to 8 years old	5 cm/year
8 years old to 12 years old	5 cm/year[a]

[a]Rates may be considerably higher at later end of this age range when individuals have entered their pubertal growth spurt.

VI. GROWTH[35-37]

A. Assessing Height

1. **Mid-parental height and target height range:**
   a. Mid-parental height for boys: (Paternal height + maternal height + 5 in or 13 cm)/2
   b. Mid-parental height for girls: (Paternal height + maternal height – 5 in or 13 cm)/2
   c. Target height range: Mid-parental height ± 2 SD (1 SD = 2 in or 5 cm)
2. **Determining average growth velocity:** See Table 10.19.
3. See Figs. EC 10.A and EC 10.B for normal growth velocity curves for American females and males, respectively.

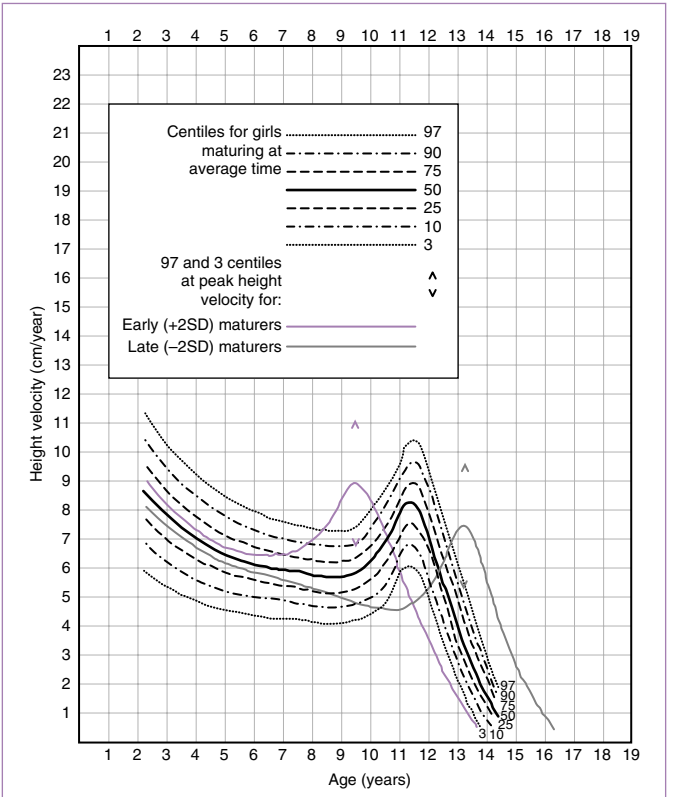

FIGURE EC 10.A

Height Velocity by Age for American Girls. (From Kelly A, Winer KK, Kalkwarf H, et al. Age-based references ranges for annual height velocity in US children. *J Clin Endocrinol Metab.* 2014;99:2104.)

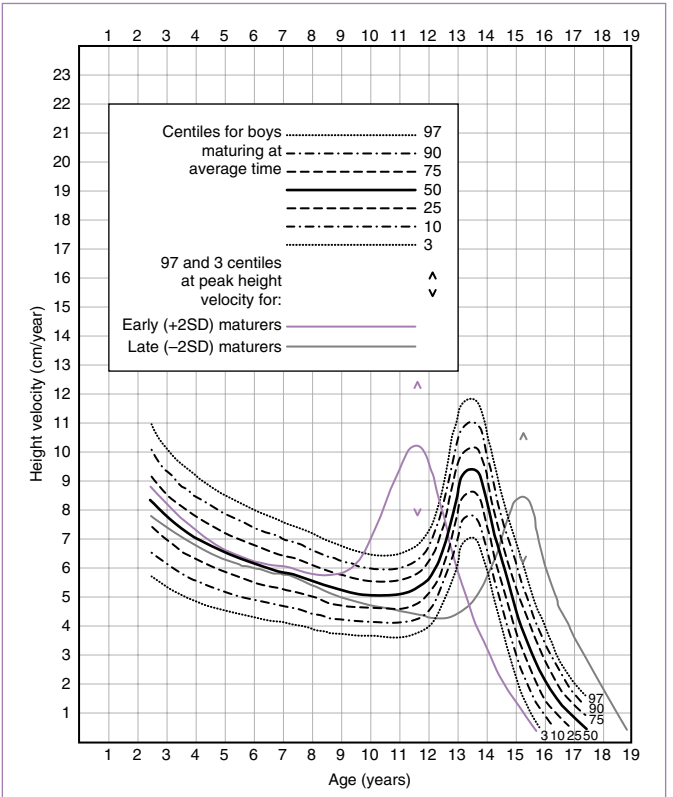

FIGURE EC 10.B

Height Velocity by Age for American Boys. (From Kelly A, Winer KK, Kalkwarf H, et al. Age-based references ranges for annual height velocity in US children. *J Clin Endocrinol Metab.* 2014;99:2104.)

TABLE 10.20

PATHOLOGIC VERSUS NONPATHOLGIC CAUSES OF SHORT STATURE

	Familial Short Stature	Constitutional Growth Delay	Pathologic Causes (endocrine, genetic, etc.)
Growth velocity	Normal	Normal	Decreased
Onset of puberty	Normal	Delayed	Depends on cause
Family history	Short stature	Delayed puberty	+/–
Bone age	Normal	Delayed	Usually delayed (may be normal in genetic causes)
Eventual adult height	Short, near mid-parental height	Normal	Depends on cause

B. Short Stature

1. **Definition:**
   a. Short stature is height <2 SD below mean or <3rd percentile for age and sex.
   b. Growth failure is defined as height <2 SD below mid-parental height or height velocity <10th percentile for age resulting in a downward trend crossing height percentiles.
   c. Majority of children with short stature are healthy; true growth failure is typically pathologic and requires evaluation.
2. **Determining etiology:**
   a. See Table 10.20 for approach to differentiating between pathologic and non-pathologic causes of short stature.
   b. Bone age is determined by radiographs of left wrist and hand.
   c. See Fig. 10.3 for initial work up.
   d. A more extensive work-up can be guided by history and physical exam and could include:
      (1) TTG and IgA (celiac disease)
      (2) CBC with differential (anemia, malignancy, inflammation)
      (3) CRP/ESR (inflammation, infection)
      (4) CMP (renal/liver disorders, malnutrition, calcium disorders)
      (5) TSH, free T4 (hypothyroidism)
      (6) Karyotype or targeted gene testing (Turner syndrome, SHOX mutation)
      (7) IGF1, IGFBP-3 [proxy measurements for growth hormone (GH)]; IGFBP-3 has a higher specificity in children <10); see Table 10.21 and Table EC 10.C for normal values of IGF-1 and IGFBP-3, respectively
3. **Indications for growth hormone use[38]:**
   The FDA has approved growth hormone for:
   a. Growth hormone deficiency
   b. Children born small-for-gestational-age (SGA) who between 2 and 4 years of age have shown inadequate catch-up growth or evidence of normal growth velocity with height < 2.5 SD below mean

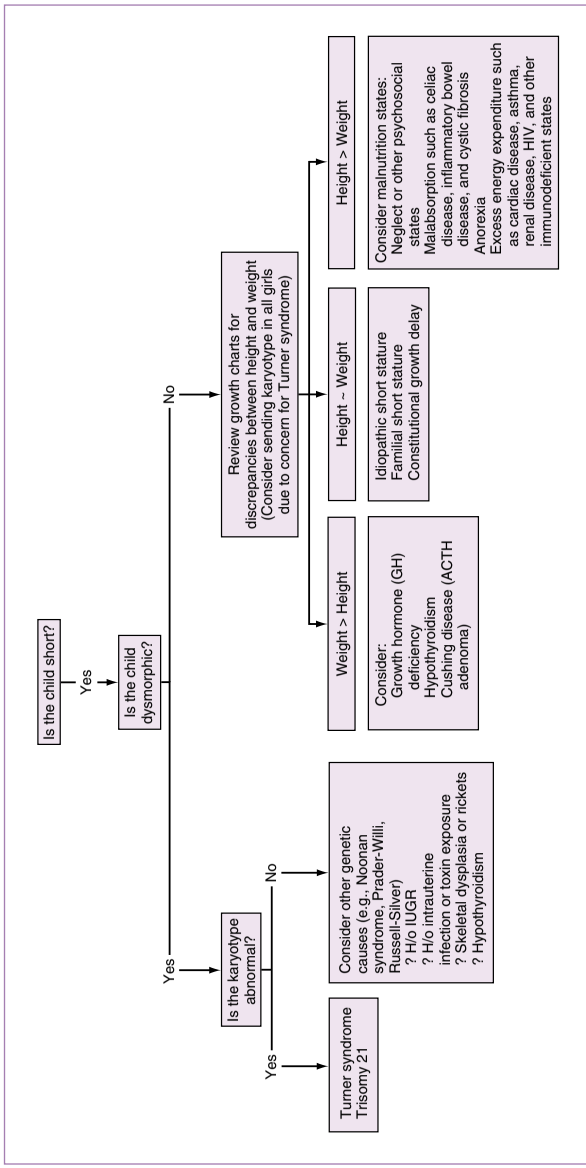

FIGURE 10.3
Differential Diagnosis of Short Stature.

TABLE 10.21

INSULIN-LIKE GROWTH FACTOR 1[a]

Age (Years)	Male (ng/mL)	Females (ng/mL)
<1	≤142	≤185
1–1.9	≤134	≤175
2–2.9	≤135	≤178
3–3.9	30–155	38–214
4–4.9	28–181	34–238
5–5.9	31–214	37–272
6–6.9	38–253	45–316
7–7.9	48–298	58–367
8–8.9	62–347	76–424
9–9.9	80–398	99–483
10–10.9	100–449	125–541
11–11.9	123–497	152–593
12–12.9	146–541	178–636
13–13.9	168–576	200–664
14–14.9	187–599	214–673
15–15.9	201–609	218–659
16–16.9	209–602	208–619
17–17.9	207–576	185–551

[a]A clearly normal IGF-1 level argues against growth hormone (GH) deficiency, except in young children in whom there is considerable overlap between normal levels and those with GH deficiency.
Reference ranges from Quest Diagnostics LC/MS (liquid chromatography/tandem mass spectrometry) assay.

c. Chronic kidney disease
d. Turner syndrome, Noonan syndrome, Prader-Willi syndrome
e. Short stature homeobox containing gene (SHOX) deficiency
f. Children with idiopathic short stature (height <2.25 SD below mean and unlikely to attain normal adult height)

VII. SEXUAL DEVELOPMENT[39-45]

A. Puberty

1. For normal pubertal stages, please see Chapter 5.
2. For definitions of precocious and delayed puberty, see Table 10.22.

B. Lab Evaluation

1. LH, FSH, estradiol, and testosterone (free and total), see Tables 10.23–10.27 for normal values. **NOTE**: Early in puberty, LH production peaks overnight and is lower during the day, so consider obtaining levels in the early morning.
2. GnRH stimulation test[46]:
   a. Purpose: To evaluate for biochemical evidence of puberty when LH, FSH, and sex hormone testing is inconclusive.
   b. Method: Give GnRH analog (Leuprolide) SQ, and measure LH and FSH levels at 0 and 60 minutes.

TABLE EC 10.C

INSULIN-LIKE GROWTH FACTOR–BINDING PROTEIN (IGF-BP3)[a]

Age	mg/L	Tanner Stage	Female (mg/L)	Male (mg/L)
0–7 days	≤0.7	Tanner I	1.2–6.4	1.4–5.2
8–15 days	0.5–1.4	Tanner II	2.8–6.9	2.3–6.3
16 days–1 years	0.7–3.6	Tanner III	3.9–9.4	3.2–8.9
2 years	0.8–3.9	Tanner IV	3.3–8.1	3.7–8.7
3 years	0.9–4.3	Tanner V	2.7–9.1	2.6–8.6
4 years	1.0–4.7			
5 years	1.1–5.2			
6 years	1.3–5.6			
7 years	1.4–6.1			
8 years	1.6–6.5			
9 years	1.8–7.1			
10 years	2.1–7.7			
11 years	2.4–8.4			
12 years	2.7–8.9			
13 years	3.1–9.5			
14 years	3.3–10.0			
15 years	3.5–10.0			
16 years	3.4–9.5			
17 years	3.2–8.7			
18 years	3.1–7.9			
19 years	2.9–7.3			
Adults continue to vary by age				

[a]Levels below the 5th percentile suggest growth hormone deficiency. This test may have greater discrimination than the IGF-1 test in younger patients.

Data from Quest Diagnostics immunochemiluminometric assay (ICMA).

TABLE 10.22

DEFINITIONS OF PRECOCIOUS AND DELAYED SEXUAL MATURATION

	Females	Males
Precocious	Before age 8 years: Thelarche (may be benign or progressive as seen in precocious puberty) Adrenarche (may be isolated or a feature of precocious puberty)	Before age 9 years: Testicular enlargement Adrenarche (may be isolated or a feature of precocious puberty)
Delayed	No thelarche by 13 years or >5 years between thelarche and menarche. Primary amenorrhea: no menarche by age 16 years in the presence of secondary sexual characteristics, or no menarche and no secondary sexual characteristics by age 14 years.	No testicular enlargement by 14 years.

TABLE 10.23

LUTEINIZING HORMONE

Age	Males (mIU/mL)	Females (mIU/mL)
0–2 years	Not established	Not established
3–7 years	≤0.26	≤0.26
8–9 years	≤0.46	≤0.69
10–11 years	≤3.13	≤4.38
12–14 years	0.23–4.41	0.04–10.80
15–17 years	0.29–4.77	0.97–14.70
Tanner Stages	**Males (mIU/mL)**	**Females (mIU/mL)**
I	≤0.52	≤0.15
II	≤1.76	≤2.91
III	≤4.06	≤7.01
IV–V	0.06–4.77	0.10–14.70

Data from Quest Diagnostics immunoassay. For more information, see www.questdiagnostics.com.

TABLE 10.24

FOLLICLE-STIMULATING HORMONE

Age	Male (mIU/mL)	Female (mIU/mL)
0–4 years	Not established	Not established
5–9 years	0.21–4.33	0.72–5.33
10–13 years	0.53–4.92	0.87–9.16
14–17 years	0.85–8.74	0.64–10.98

Data from Quest Diagnostics immunoassay. For more information, see www.questdiagnostics.com.

TABLE 10.25

ESTRADIOL[a]

Age	Level (pg/mL)
Prepubertal children	<25
Men	6–44
Women	
Luteal phase	26–165
Follicular phase	None detected–266
Midcycle	118–355
Adult women on OCP	None detected–102

[a]Normal infants have elevated estradiol at birth, which decreases to prepubertal values during the first week of life. Estradiol levels increase again between age 1 and 2 months and return to pre-pubertal values by age 6–12 months.
Data from JHH Laboratories.
OCP, Oral contraceptive pill.

TABLE 10.26

TESTOSTERONE, TOTAL SERUM[a]

Age	Male (ng/dL)	Female (ng/dL)
Cord blood	17–61	16–44
1–10 days	≤187	≤24
1–3 months	72–344	≤17
3–5 months	≤201	≤12
5–7 months	≤59	≤13
7–12 months	≤16	≤11
1–5.9 years	≤5	≤8
6–7.9 years	≤25	≤20
8–10.9 years	≤42	≤35
11–11.9 years	≤260	≤40
12–13.9 years	≤420	≤40
14–17.9 years	≤1000	≤40
≥18 (adult)	250–1100	2–45
TANNER STAGE		
Stage I	≤5	≤8
Stage II	≤167	≤24
Stage III	21–719	≤28
Stage IV	25–912	≤31
Stage V	110–975	≤33

[a]Normal testosterone/dihydrotestosterone (T/DHT) ratio is <18 in adults and older children and <10 in neonates. A T/DHT ratio >20 suggests 5-α-reductase deficiency or androgen insensitivity syndrome.
Data from Quest Diagnostics LC/MS (liquid chromatography/tandem mass spectrometry) assay.

TABLE 10.27

TESTOSTERONE, FREE

Age	Male (pg/mL)	Female (pg/mL)
1–11 years	≤1.3	≤1.5
12–13 years	≤64.0	≤1.5
14–17 years	4.0–100.0	≤3.6
18–69 years	46.0–224.0	0.2–5.0

Data from Quest Diagnostics LC/MS (liquid chromatography/tandem mass spectrometry) assay.

c. Interpretation: Prepubertal children should show no or minimal increase in LH and FSH in response to GnRH. A rise of LH to >3.3 to 5.0 IU/L is evidence of central puberty.

3. **Delayed puberty[41,45,47]:** See Fig. 10.4 for information on evaluation and management of delayed puberty.
4. **Precocious puberty[42,47]:** See Fig. 10.5 for information on evaluation and management of precocious puberty.

C. Polycystic Ovarian Syndrome[48]

1. **Clinical features in adolescents:**
   a. Diagnostic criteria (must have features of both):
      (1) Hyperandrogenism: Either clinical or biochemical
         (a) Clinical: Hirsutism, acne, male pattern alopecia
         (b) Biochemical characteristics: Elevated androgens including DHEA-S (see Table 10.28 for normal values), free or total testosterone
      (2) Menstrual abnormalities: Amenorrhea or oligomenorrhea (chronic anovulation).

   NOTE: Appearance of multiple ovarian cysts is a diagnostic criterion for adults, but not for adolescents, as this can be a normal finding in adolescent females.
   b. Common cause of female infertility.
   c. Often LH>FSH, but this is not required for diagnosis.
   d. Chronic anovulation and unopposed estrogen exposure increase risk for endometrial cancer.
   e. Associated with insulin resistance and increased risk of type 2 diabetes.
2. **Management:**
   a. Combined oral contraceptives: First-line for management of menstrual abnormalities and hirsutism/acne. Increases SHBG (thus decreasing free testosterone), which may result in increased insulin sensitivity and restoration of ovulation.
   b. Anti-androgen therapy, such as spironolactone, to treat hirsutism.
   c. Weight reduction and other lifestyle changes.
   d. Metformin: Can be considered as possible treatment if goal is to treat insulin resistance.

D. Ambiguous Genitalia[49]

1. **Clinical findings in a neonate suspicious for ambiguous genitalia:**
   a. Apparent female with clitoromegaly (length >1 cm or width >6 mm in term infant), inguinal or labial mass, or posterior labial fusion.
   b. Micropenis (stretched penile length that is –2.5 SD below mean for age, see Table 10.29 for normal values).
   c. Non-palpable gonads in an apparent male.
   d. Hypospadias associated with separation of scrotal sacs or undescended testis.
   e. Discordance between prenatal karyotype and genital appearance.

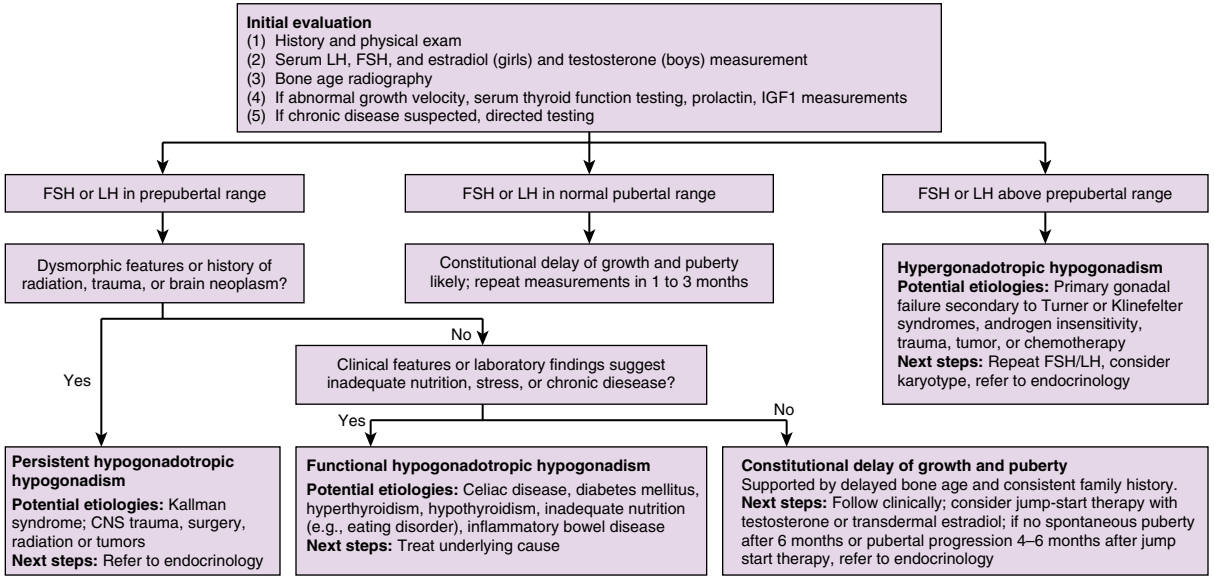

FIGURE 10.4

An Approach to the Child Presenting With Delayed Puberty. *CNS*, Central nervous system; *FSH*, follicle-stimulating hormone; *IGF1*, insulin-like growth factor 1; *LH*, luteinizing hormone; *MRI*, magnetic resonance imaging. (From Klein DA, Emerick JE, Sylvester JE, Vogt KS. Disorders of puberty. An approach to diagnosis and management. *Am Fam Physician*. 2017;96(9):590–599.)

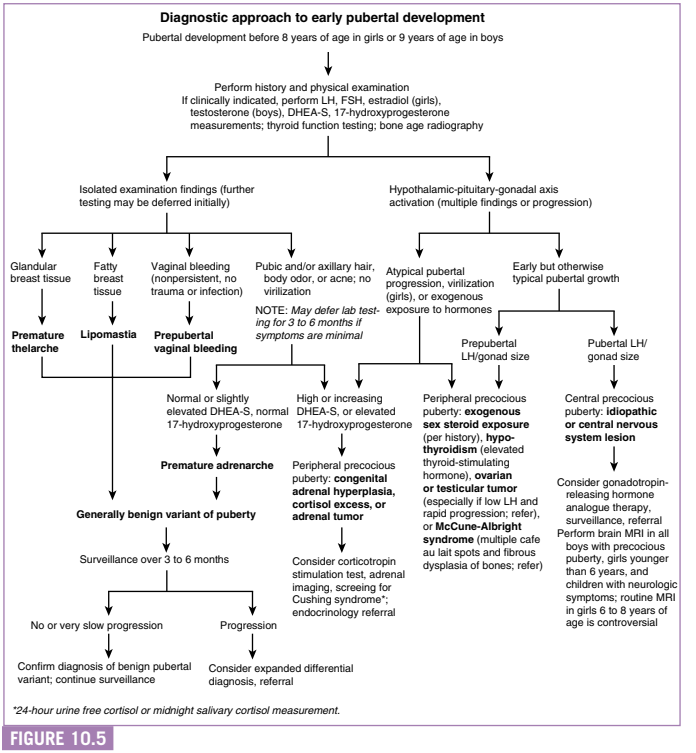

FIGURE 10.5

An Approach to the Child Presenting With Early Puberty. *DHEA-S*, Dehydroepiandrosterone sulfate; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *MRI*, magnetic resonance imaging. (Reprinted with permission from Disorders of Puberty: An Approach to Diagnosis and Management, November 1, 2017, Vol 96, No 9, American Family Physician Copyright © 2017 American Academy of Family Physicians. All Rights Reserved.)

TABLE 10.28

DEHYDROEPIANDROSTERONE SULFATE (DHEA-S)

Age	Male (mCg/dL)	Female (mCg/dL)
<1 months	≤316	15–261
1–6 months	≤58	≤74
7–11 months	≤26	≤26
1–3 years	≤15	≤22
4–6 years	≤27	≤34
7–9 years	≤91	≤92
10–13 years	≤138	≤148
14–17 years	38–340	37–307

continued

TABLE 10.28

DEHYDROEPIANDROSTERONE SULFATE (DHEA-S)—CONT'D

Age	Male (mCg/dL)	Female (mCg/dL)
TANNER STAGES (AGES 7–17)		
I	≤49	≤46
II	≤81	15–133
III	22–126	42–126
IV	33–177	42–241
V	110–370	45–320

Data from Quest Diagnostics assay. For more information see www.questdiagnostics.com.

TABLE 10.29

MEAN STRETCHED PENILE LENGTH (CM)[a]

Age	Mean ± SD	−2.5 SD
BIRTH		
30 week gestation	2.5 ± 0.4	1.5
34 week gestation	3.0 ± 0.4	2.0
Full term	3.5 ± 0.4	2.5
0–5 months	3.9 ± 0.8	1.9
6–12 months	4.3 ± 0.8	2.3
1–2 years	4.7 ± 0.8	2.6
2–3 years	5.1 ± 0.9	2.9
3–4 years	5.5 ± 0.9	3.3
4–5 years	5.7 ± 0.9	3.5
5–6 years	6.0 ± 0.9	3.8
6–7 years	6.1 ± 0.9	3.9
7–8 years	6.2 ± 1.0	3.7
8–9 years	6.3 ± 1.0	3.8
9–10 years	6.3 ± 1.0	3.8
10–11 years	6.4 ± 1.1	3.7
Adult	13.3 ± 1.6	9.3

[a]Measured from the pubic ramus to the tip of the glans while traction is applied along the length of the phallus to the point of increased resistance.

SD, standard deviation.

Data from Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. *J Pediatr.* 1975;86:395.

2. **Etiology:**
   a. Due to undervirilization of male genitalia or virilization of female genitalia
   b. Most common cause is CAH
   c. Other causes by male versus female karyotype:
      (1) 46,XY karyotype: Testicular regression, androgen insensitivity, testosterone biosynthesis disorders, rare forms of CAH, absence of SRY
      (2) 46,XX karyotype: SRY+, classical (21-hydroxylase deficiency) or more rare forms of CAH
      (3) Other: Sex chromosome mosaicism (46,XY/46,XX, 46,XY/45, XO, etc.)

3. **Evaluation:**
   a. Labs: Timing of collection is important.
      (1) Initial testing: LH, FSH, testosterone, dihydrotestosterone (DHT, see Table EC 10.D), anti-Müllerian hormone (AMH) and expedited determination of sex chromosomes (ask that resulting lab rush results of sex chromosomes)
      (2) After 36 hours of life: 17-hydroxyprogesterone
      (3) Daily electrolytes until salt-wasting CAH is ruled out
      (4) Further testing as needed to evaluate for more rare forms of CAH: DHEA, 17-hydroxypregnenolone, 11-deoxycortisol, cortisol, ACTH
   b. Imaging: Options include genitogram (contrast study of the urogenital sinus and internal duct structures) or voiding cysto-urethrogram (VCUG), pelvic and abdominal US, and pelvic magnetic resonance imaging (MRI) to evaluate internal anatomy.
   c. Care should be taken to avoid premature gender/sex designation, completion of birth certificate, and naming of infant.

E. Cryptorchidism[50]

1. **Epidemiology and clinical course:**
   a. Can be present at birth (congenital) or after birth (acquired). Congenital rate is 1% to 4.6% of males born >2.5 kg.
   b. Increased risk with preterm birth or low birthweight.
   c. About 1/3 to 1/2 of cryptorchid testicles descend spontaneously, usually by age 3 months.
   d. Neoplasm more common in males with cryptorchidism and may occur in contralateral testis; early orchidopexy decreases risk of malignancy.
   e. Males with bilateral cryptorchidism have higher risk for reduced fertility.
   f. There is a higher risk of testicular torsion prior to repair.
2. **Evaluation:**
   a. Providers should palpate testes for quality and position in all males at each well child visit.
   b. Any phenotypic male newborn with bilateral, *nonpalpable* testes should undergo evaluation for CAH with karyotype and hormonal profile.
   c. In those without CAH, distinguish between cryptorchidism and anorchia (absent testes) with serum Müllerian inhibiting substance and consider additional hormone testing (inhibin B, FSH, LH, and testosterone).
3. **Treatment:** Observe for 6 months, at which time if testis remains undescended, referral to specialist recommended. Orchidopexy between 6 and 18 months of age recommended.

TABLE EC 10.D

DIHYDROTESTOSTERONE

Age	Males (ng/dL)	Females (ng/dL)
Cord blood	<2–8	<2–5
1–6 months	12–85	<5
Prepubertal	<5	<5
Tanner stage II–III	3–33	5–19
Tanner stage IV–V	22–75	3–30

Data from Quest Diagnostics RIA (radioimmunoassay).

TABLE EC 10.E

ANDROSTENEDIONE, SERUM

Age	Males (ng/dL)	Females (ng/dL)
Premature (31–35 weeks)	≤480	≤480
Full-term infants	≤290	≤290
1–12 months	6–78	6–78
1–4 years	5–51	5–51
5–9 years	6–115	6–115
10–13 years	12–221	12–221
14–17 years	22–225	22–225
Tanner stage II–III	17–82	43–180
Tanner stage IV–V	57–150	73–220
Adult male (18–30 years)	50–220	
Female follicular phase		35–250
Female luteal phase		30–235

Data from Quest Diagnostics LC/MS (liquid chromatography/tandem mass spectrometry) analysis.

VIII. NEONATAL HYPOGLYCEMIA EVALUATION[51,52]

A. Definition

1. Serum glucose level insufficient to meet metabolic requirements. For practical purposes, value is defined as a point-of-care glucose (POCG) <45 to 50 mg/dL within first 48 hours of life and <70 mg/dL beyond this period.

NOTE: Bedside glucometer is a convenient tool to screen for hypoglycemia but can be inaccurate by 10 to 15 mg/dL when in the range of hypoglycemia. STAT plasma glucose must be sent to establish diagnosis of hypoglycemia.

B. Treatment Goals

1. For neonates with suspected congenital hypoglycemia disorder and infants/children with confirmed hypoglycemia disorder, maintain plasma glucose >70 mg/dL.
2. For high risk neonates without a suspected congenital hypoglycemia disorder, maintain plasma glucose >45 to 50 mg/dL for those <48 hours of age and >60 mg/dL for those aged >48 hours.

C. Management

See Chapter 18.

D. Further Work-up

1. If serum glucose is consistently <70 mg/dL after 48 hours of life, at the time of hypoglycemia (serum glucose <45 to 50 mg/dL via glucometer), obtain STAT serum glucose, insulin, growth hormone, cortisol, free fatty acids, and β-hydroxybutyrate.
2. Consider **glucagon stimulation test**: Administer glucagon and obtain serum glucose levels Q10 min ×4. Repeat growth hormone and cortisol levels 30 minutes after documented hypoglycemia.

E. Interpretation of Results

1. A rise in glucose ≥30 mg/dL on glucagon stimulation test, along with elevated plasma insulin levels >2 μU/mL (absence of detectable insulin does not rule out hyperinsulinism, as insulin may be present below the lower limit of detection of the assay), low serum levels of free fatty acids (<1.5 mmol/L) and β-hydroxybutyrate (<2 mmol/L), and a persistent glucose requirement >8 mg/kg/min suggests a diagnosis of hyperinsulinemia.
2. Hypoglycemia with midline defects and micropenis in a male suggest hypopituitarism, supported by low serum levels of growth hormone and cortisol at the time of hypoglycemia.

F. Hyperinsulinemia

1. Hyperinsulinemia is the most common cause of neonatal hypoglycemia beyond the first 7 days of life and may be congenital or transient.
2. Congenital hyperinsulinism can be caused by dominant or recessive mutations in genes responsible for regulating insulin secretion from pancreatic β cells.

3. Transient hyperinsulinemia is commonly seen in infants of diabetic mothers and less commonly in the setting of perinatal asphyxia and intrauterine growth restriction.
4. Long-term management of persistent hyperinsulinism includes diazoxide, which inhibits pancreatic secretion of insulin by keeping β-cell ATP-sensitive potassium channels open; however, it has been rarely associated with pulmonary hypertension (black box warning[53]).

IX. ADDITIONAL NORMAL VALUES

Normal values may differ among laboratories because of variation in technique and type of assay used.

See the following tables for normal values:
Table EC 10.A, Catecholamines, urine
Table EC 10.B, Catecholamines, plasma
Table EC 10.C, Insulin-like growth factor binding protein
Table EC 10.D, DHT
Table EC 10.E, Androstenedione, serum

X. WEB RESOURCES

A. Children with Diabetes (www.childrenwithdiabetes.com)

B. American Diabetes Association (www.diabetes.org)

C. International Society for Pediatric and Adolescent Diabetes (www.ispad.org)

D. Pediatric Endocrine Society (www.lwpes.org)

E. The Endocrine Society (www.endocrine.org)

F. American Thyroid Association (www.thyroid.org)

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 11

Fluids and Electrolytes

Lauren Burgunder, MD

See additional content on Expert Consult

I. INTRODUCTION

Intravenous fluids (IVFs) should be thought of as a medication by those who prescribe them. Since the late 1950s, IVF choice has been largely guided by Holliday and Segar's estimations of sodium requirements. Using the electrolyte composition of human milk, they calculated that the average child requires 3 mEq sodium (Na) and 2 mEq potassium (K) per 100 to 120 mL water (H_2O).[1] According to their calculation, basic solute needs can be met by administering ¼ normal saline (NS), a hypotonic fluid. While this estimation led to a long-standing tradition in pediatric maintenance IVF (MIVF) therapy, evidence published over the past few decades culminated in new American Academy of Pediatrics (AAP) guidelines recommending isotonic fluids as the maintenance fluid of choice for the majority of hospitalized children.[2]

II. FLUID RESUSCITATION

A. Calculating Maintenance Fluid Volume

1. The Holliday-Segar method (Table 11.1 and Box 11.1) is the most widely used method to approximate maintenance fluid volume. This method estimates caloric expenditure in fixed-weight categories and assumes the average patient will require 100 mL of water for each 100 calories metabolized, with approximately 100 kcal burned per kg.[1]
2. NOTE: The Holliday-Segar method is not suitable for neonates <14 days old, because it generally overestimates fluid needs in neonates. (See Chapter 18 for neonatal fluid management.)

B. Calculating Fluid Loss

1. Total body water (TBW) is equal to **60% of a child's weight in kg (75% in infants).**[3]

EQUATION 11.1: TBW^a = weight (kg) × 0.6
[a]TBW uses preillness weight; 1 L water = 1 kg water

2. In a euvolemic child, 60% of TBW resides in the intracellular compartment [where potassium (K) concentration is 140 mEq/L and sodium (Na) is negligible], and 40% of TBW is in the extracellular compartment (where Na concentration is ~140 mEq/L and K is negligible).[4-6]
3. The most precise method of assessing fluid deficit uses weight loss:

EQUATION 11.2: Fluid deficit (L) = preillness weight (kg) – illness weight (kg)

TABLE 11.1

HOLLIDAY-SEGAR METHOD

Body Weight	Fluid Volume	
	mL/kg/day	mL/kg/hr
First 10 kg	100	≈4
Second 10 kg	50	≈2
Each additional kg	20	≈1

BOX 11.1

HOLLIDAY-SEGAR METHOD

Example: Determine the correct fluid rate for an 8-year-old child weighing 25 kg:

First 10 kg:	4 mL/kg/hr × 10 kg = 40 mL/hr	100 mL/kg/day × 10 kg = 1000 mL/day
Second 10 kg:	2 mL/kg/hr × 10 kg = 20 mL/hr	50 mL/kg/day × 10 kg = 500 mL/day
Each additional 1 kg:	1 mL/kg/hr × 5 kg = 5 mL/hr	20 mL/kg/day × 5 kg = 100 mL/day
	Answer: 65 mL/hr	Answer: 1600 mL/day

TABLE 11.2

CLINICAL OBSERVATIONS IN DEHYDRATION[7]

	Older Child		
	3% (30 mL/kg)	6% (60 mL/kg)	9% (90 mL/kg)
	Infant		
	5% (50 mL/kg)	10% (100 mL/kg)	15% (150 mL/kg)
Dehydration Classification	Mild	Moderate	Severe
Mental status	Alert		Lethargic/obtunded
Fontanelle	Flat	Soft	Sunken
Eyes	Normal	Deep set	Sunken
Tears	Present	Reduced	None
Buccal mucosa/lips	Dry	Dry	Parched/cracked
Pulse rate	Normal	Slightly increased	Increased
Skin (touch)	Normal	Dry	Clammy
Skin turgor	Normal	Tenting	None
Capillary refill	Normal	≈2–3 seconds	>3 seconds
Pulse quality	Normal	Weak	Feeble/impalpable
Urine output	Normal/mild oliguria	Mild oliguria	Severe oliguria

4. Clinical assessment: If weight loss is not known, clinical observation may be used to approximate the percentage of dehydration (Table 11.2).[7,8]

EQUATION 11.3: $\%\ \text{Dehydration} = \dfrac{\text{fluid deficit}^{a}}{\text{preillness weight}} \times 100\%$

[a]1 % dehydration = 10 mL/kg of fluid deficit;
[a]1 L of water = 1 kg of water

5. In a healthy child, insensible fluid volume loss is approximated as ⅓ of the Holliday-Segar MIVF per day. **NOTE**: This calculation is based on fluid requirements of healthy children. Many hospitalized children have increased insensible losses (e.g., secondary to fever or increased respiratory rate) that must be factored into fluid determinations.

C. Maintenance Fluid Choice in Hospitalized Children

1. Based on a growing body of evidence, the AAP recommends isotonic fluid as the most appropriate MIVF therapy for the vast majority of hospitalized children between the ages of 28 days and 18 years.[2] See Table 11.3 for isotonic fluid options.
2. Various disease states can lead to an increased secretion of antidiuretic hormone (ADH), which promotes the retention of free water, leading to hyponatremia.[9,10] See Box 11.2 for examples.
3. Exceptions exist in certain patient populations, such as children with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, acute kidney injury, chronic kidney disease, nephrotic syndrome, diabetes insipidus, and voluminous watery diarrhea or severe burns.[2]
4. See Table 11.3 and Table 11.4 for electrolyte composition of various parenteral and enteral fluid replacement options.
5. Unless hyperkalemia is present or the child is in renal failure, maintenance potassium requirements (20 mEq/L of fluid) should be given.[11] Do not add potassium (K^+) to fluids until urine output has been established.[12,13]

D. Volume Replacement Strategy[7,12,13]

1. Volume resuscitation and deficit replacement should generally be completed over 24 hours.
2. See Table 11.5 for a three-phase approach to fluid replacement.
3. Children with isonatremic hypovolemia can be repleted with isotonic fluid per AAP recommendations.[2] See Box 11.3 for sample calculations in isonatremic hypovolemia.
4. If ongoing losses can be measured directly, they should be replaced 1:1 concurrently with maintenance fluid administration. If the losses cannot be measured, an estimate of 10 mL/kg body weight for each watery stool and 2 mL/kg body weight for each episode of emesis should be administered.[3] See Table 11.6 for electrolyte composition of certain bodily fluids.
5. Oral intake is the preferred method for repletion and maintenance, if possible.

III. ELECTROLYTE MANAGEMENT

See Chapter 28 for age specific normal values of electrolytes.

A. Serum Osmolality and Tonicity[2,7,14]

1. Fluids can be expressed in terms of their tonicity and their osmolality.

TABLE 11.3

COMPOSITION OF FREQUENTLY USED PARENTERAL REHYDRATION FLUIDS

	D% CHO (g/100 mL)	Protein[a] (g/100 mL)	Cal/L	Na (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^-[b] (mEq/L)	Mg^{2+}	Ca^{2+} (mEq/L)	mOsm/L
HYPOTONIC										
D_5W	5	—	170	—	—	—	—	—	—	252
$D_{10}W$	10	—	340	—	—	—	—	—	—	505
D_5 1/4 NS (0.225% NaCl)	5	—	170	38.5	—	34	—	—	—	329
1/2 NS (0.45% NaCl)	—	—	—	77	—	77	—	—	—	154
ISOTONIC										
Lactated Ringer	0–10	—	0–340	130	4	109	28	—	3	273
Plamalyte	—	—	—	140	5	98	27	3		294
Ringer solution	0–10	—	0–340	147	4	155.5	—	—	≈4	—
NS (0.9% NaCl)	—	—	—	154	—	154	—	—	—	308
HYPERTONIC										
2% NaCl	—	—	—	342	—	342	—	—	—	684
3% NaCl	—	—	—	513	—	513	—	—	—	1027
8.4% sodium bicarbonate (1 mEq/mL)	—	—	—	1000	—	—	1000	—	—	2000
COLLOID										
Plasmanate	—	5	200	110	2	50	29	—	—	—
Amino acid 8.5% (Travasol)	—	8.5	340	3	—	34	52	—	—	880
Albumin 25% (salt poor)	—	25	1000	100–160	—	<120	—	—	—	300
Intralipid[c]	2.25	—	1100	2.5	0.5	4.0	—	—	—	258–284

[a]Protein or amino acid equivalent.

[b]Bicarbonate or equivalent (citrate, acetate, lactate).

[c]Values are approximate; may vary from lot to lot. Also contains < 1.2% egg phosphatides.

CHO, Carbohydrate; *HCO_3^-*, bicarbonate; *NS*, normal saline.

BOX 11.2

CLINICAL SETTING OF INCREASED ADH RELEASE IN CHILDREN[7,26]

Hemodynamic Stimuli for ADH Release (Decreased Effective Volume)	Nonosmotic and Nonhemodynamic Stimuli for ADH Release
Hypovolemia	CNS disturbances (infection, brain tumors, head injury, thrombosis)
Nephrosis	Pulmonary disease (pneumonia, asthma, bronchiolitis, PPV)
Cirrhosis	Cancer
Congestive heart failure	Medications (MDMA, AEDs, cytoxan, vincristine, opiates, TCAs, SSRIs)
Hypoaldosteronism	GI disturbances (nausea and emesis)
Hypotension	Pain or stress
Hypoalbuminemia	Postoperative state

ADH, Antidiuretic hormone; *AED*, antiepileptic drugs; *CNS*, central nervous system; *GI*, gastrointestinal; *MDMA*, 3,4-methylenedioxymethamphetamine (ecstasy); *PPV*, positive pressure ventilation; *SSRI*, selective serotonin reuptake inhibitor; *TCA*, tricyclic antidepressant.

2. Serum osmolality (285 to 295 mOsm/kg) is a measure of both permeable and nonpermeable solutes and is calculated using the following equation:

EQUATION 11.4: $$\text{Osmolality} = 2\,\text{Na} + \frac{\text{glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$$

3. Osmolality is measured as osmoles per weight (kg) versus osmolarity, which is measured as osmoles per volume (L).
4. Tonicity is effective osmolality. It is the net force on water across a semipermeable membrane (e.g., the cell membrane) based on the osmotic pressures. It is relative and determined largely by sodium content. Substances that flow freely across membranes, such as urea, are ineffective osmoles and influence osmolality but not tonicity.

B. Sodium

The equations within this section are **theoretical** and are not validated. They offer a starting point for calculation of electrolyte abnormalities, but clinical context is **ALWAYS** of the utmost importance and frequent monitoring is necessary. **Children with neurosurgical disorders, cardiac disease, hepatic disease, cancer, kidney disease, diabetes insipidus, and severe burns may require consultation with subspecialists before fluid choice and volume is administered.** When correcting dysnatremias, frequent lab monitoring (~2 to 4 hours) is indicated with adjustment of fluid type and rate as needed.

1. **Hyponatremia**: Excess Na loss (Na <135 mEq/L)
   a. Clinical manifestations and differential diagnosis (Table 11.7)
   b. Pseudohyponatremia etiologies:
      (1) Increased serum osmolality: Hyperglycemia: Na artificially decreased 1.6 mEq/L for each 100-mg/dL rise in glucose
      (2) Normal serum osmolality:
         (a) Hyperlipidemia: Na artificially decreased by 0.002 × lipid (mg/dL)

TABLE 11.4

COMPOSITION OF ORAL REHYDRATION FLUIDS

	D% CHO (g/100 mL)	Na (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^-[b] (mEq/L)	Ca^{2+} (mEq/L)	mOsm/L
ORAL FLUIDS							
Pedialyte	2.5	45	20	35	30	—	250
WHO solution	2	90	20	80	30	—	310
Rehydralyte	2.5	75	20	65	30	—	310
COMMONLY CONSUMED FLUIDS (NOT RECOMMENDED FOR ORAL REHYDRATION)[a]							
Apple juice	11.9	0.4	26	—	—	—	700
Coca-Cola	10.9	4.3	0.1	—	13.4	—	656
Gatorade	5.9	21	2.5	17	—	—	377
G2	4.7	20	3.2	—	—	—	
Ginger ale	9	3.5	0.1	—	3.6	—	565
Milk	4.9	22	36	28	30	—	260
Orange juice	10.4	0.2	49	—	50	—	654
Powerade	5.8	18	2.7	—	—	—	264

[a]Electrolyte values are approximate

[b]Bicarbonate or equivalent (citrate, acetate, lactate).

CHO, Carbohydrate; *HCO_3^-*, bicarbonate; *NS*, normal saline; *WHO*, World Health Organization

TABLE 11.5

VOLUME REPLACEMENT STRATEGY

Phase I	Phase II	Phase III
Initial stabilization	**Deficit repletion, maintenance volume, and ongoing losses**	**Recovery and ongoing losses**
Rapid fluid resuscitation with isotonic fluid.[a] 20 mL/kg represents only a 2% volume replacement	Replace half of the remaining deficit over the first 8 hr (this includes any fluid given in the initial stabilization phase). Replace the second half of deficit over the following 16 hr, making sure to also include maintenance fluid volume replacement during this time.	Continue maintenance fluid replacement, taking ongoing losses into consideration.

[a]Should be used in patients in need of rapid volume expansion.
See Box 11.3 for sample calculation

BOX 11.3

SAMPLE CALCULATIONS: ISONATREMIC DEHYDRATION

Example: A 15-kg (preillness weight) child with 10% dehydration and normal serum sodium

Requirement	Formula	Sample Calculation
Maintenance fluid requirements	Holliday–Segar formula	(100 mL/kg/day × 10 kg) + (50 mL/kg/day × 5 kg) = 1250 mL/24 hr = 52 mL/hr
Fluid deficit	Equation 11.2 or Equation 11.3	10 mL × 15 kg × 10% = 1500 mL
	Fluid Replacement Rate Over 24 hrs	
½ fluid deficit replaced in first 8 hrs	750 mL/8 hr = 94 mL/hr + 52 mL/hr maintenance = 146 mL/hr	
½ fluid deficit replaced over 16 hrs	750 mL/16 hr = 47 mL/hr + 52 mL/hr maintenance = 99 mL/hr	

Note: If patient received an initial 20 mL/kg bolus (300 mL): 1500 mL – 300 mL = 1200 mL
½ fluid deficit in first 8 hrs: 600 cc/8 hr = 75 mL + 52 mL/hr maintenance = 127 mL/hr
½ fluid deficit over next 16 hrs: 600 cc/16 hr = 38 mL/hr + 52 mL/hr maintenance = 90 mL/hr

(b) Hyperproteinemia: Na artificially decreased by 0.25 × [protein (g/dL) – 8]

c. Management

(1) The traditional equation used to calculate the excess sodium deficit in hyponatremia is:

EQUATION 11.5[3]:

$$\text{Na deficit(mEq)}^{a} = [\text{Desired Na (mEq/L)} - \text{Serum Na (mEq/L)}] \times \text{TBW (L)}$$

[a]This represents the *excess* sodium deficit in hyponatremic dehydration. It must be added to the daily sodium requirement for hospitalized patients of **~14 mEq/100 mL fluid given**.

(2) Hyponatremia should be corrected **by no more than 10 to 12 mEq per 24 hr** to avoid rapid change of serum sodium, which can cause osmotic demyelination syndrome.[6,13,15]

TABLE 11.6

ELECTROLYTE COMPOSITION OF VARIOUS FLUIDS

Source of Fluid	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)
Gastric	20–80	5–20	100–150
Pancreatic	120–140	5–15	90–120
Small bowel	100–140	5–15	90–130
Bile	120–140	5–15	80–120
Ileostomy	45–135	3–15	20–115
Diarrhea	10–90	10–80	10–110
Skin with burns[a]	140	5	110
Sweat			
Normal	10–30	3–10	10–35
Cystic fibrosis[b]	50–130	5–25	50–110

[a]3–5 g/dL of protein may be lost in fluid from burn wounds.

[b]Replacement fluid dependent on sodium content.

Modified from Kliegman RM, Stanton B, St. Gene J, et al. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia: Saunders; 2011.

TABLE 11.7

HYPONATREMIA[7,14]

CLINICAL MANIFESTATIONS			
Related to rate of change: Nausea, headache, muscle cramps, weakness, confusion, apnea, lethargy, seizure, coma, hypothermia, depressed DTRs			
ETIOLOGIES			
Hypovolemic		**Euvolemic**	**Hypervolemic**
Renal Losses	**Extrarenal Losses**		
Na-losing nephropathy Diuretics Juvenile nephronopthisis Hypoaldosteronism (CAH, pseudohypoaldosteronism, UTI/obstruction) Cerebral salt-wasting syndrome Postobstructive diuresis ATN (polyuric phase)	GI losses Skin losses Third spacing Cystic fibrosis	SIADH (see Chapter 10) Excess salt-free infusions Desmopressin acetate Water intoxication Hypothyroidism Sepsis Primary polydipsia[c] Malnutrition[c]	Nephrotic syndrome Hypoalbuminemia Heart failure Cirrhosis Renal failure Glucocorticoid deficiency
LABORATORY DATA			
↑ Urine Na (> 20 mEq/L) ↑ Urine volume ↓ Specific gravity ↓ Urine osmolality[a] (< 100 mOsm/L)	↓ Urine Na (< 20 mEq/L) ↓ Urine volume ↑ Specific gravity ↑ Urine osmolality (> 100 mOsm/L)	↓ Urine volume ↑ Specific gravity ↑ Urine osmolality (> 100 mOsm/L)	↓ Urine Na[b] (< 20 mEq/L) ↓ Urine volume
MANAGEMENT			
Replace losses (see hypovolemic hyponatremia)		Restrict fluids Address the underlying cause	

[a]Minimum possible urine osmolality = 50 mOsm/kg

[b]Urine Na may be appropriate for the level of Na intake in patients with SIADH and water intoxication.

[c]Urine osmolality is <100 mOsm/L

ATN, Acute tubular necrosis; *CAH*, congenital adrenal hyperplasia; *DTR*, deep tendon reflex; *GI*, gastrointestinal; *Na*, sodium; *SIADH*, syndrome of inappropriate antidiuretic hormone secretion; *UTI*, urinary tract infection.

(3) Witnessed onset of hyponatremia over the course of hours does not pose as great of a risk and can be corrected in a similar amount of time that it developed.[7]

(4) If central nervous system (CNS) symptoms are present, hypertonic saline (HTS) should be administered over 3 to 4 hours to correct the hyponatremia by ~5 mEq/L.[5,6,11] Use Equation 11.7 to determine rate of HTS.

(5) To determine the sodium content of the fluid necessary for repletion:

EQUATION 11.6:

$$\text{Na content (mEq/L)} = \frac{[\text{Na deficit} + (14\ \text{mEq}/100\ \text{mL} \times \text{maintenance fluid volume [mL]})}{\text{volume deficit}^a}$$

[a]Use daily maintenance volume requirements if euvolemic

(6) Once the fluid type is determined, the starting rate can be calculated using the following:

EQUATION 11.7:

$$\text{Fluid rate (mL/hour)} = \frac{\text{Na deficit (mEq)} \times 1000\ \text{mL}}{\text{infusate Na (mEq)} \times \text{hours IVF will run in a day}}$$

(7) See Box 11.4 and 11.5 for sample calculations in hyponatremic dehydration.

2. **Hypernatremia**: Excess free water loss (Na >145 mEq/L)
   a. Clinical manifestations and differential diagnosis (Table 11.8)
   b. Management
      (1) Hypernatremic hypovolemia occurs in scenarios in which free water is either unavailable/restricted or there is excessive loss of solute-free water (see Table 11.8).
      (2) Hypernatremia is dangerous because of complications from potential treatment sequelae, the most serious of which is cerebral edema.[4,7]
      (3) Plan to correct the serum Na by no more than 10 mEq/24 hours and correct the free water deficit over 48 hours to minimize the risk of cerebral edema.[4,10,11,16]
      (4) As with hyponatremia, witnessed onset of hypernatremia over the course of hours can be corrected rapidly; this is because the brain has not had time to produce idiogenic osmoles to adapt to the change in osmolality.[7,11]
      (5) Expert opinion recommends starting with D5 ½ NS.[16] However, the sodium and fluid needs can also be calculated.
      (6) The free water deficit is as follows:

EQUATION 11.8[4,6]:

$$\text{FWD (mL)} = \text{TBW (mL)} \times \left[1 - \frac{\text{Desired Na (mEq/L)}}{\text{Serum Na (mEq/L)}}\right]^a$$

[a]The difference in desired and serum Na should be no more than 10 mEq/L/day

BOX 11.4

SAMPLE CALCULATIONS: HYPONATREMIC DEHYDRATION

Example: A 15-kg (preillness weight) child with 10% dehydration and serum sodium 125 mEq/L without central nervous system symptoms

Requirement	Formula	Sample Calculation
Maintenance fluid requirements	Holliday-Segar formula	(100 mL/kg/d × 10 kg) + (50 mL/kg/d × 5 kg) = 1250 mL/24 hr = 52 mL/hr
Fluid deficit	Equation 11.2 or Equation 11.3	10 mL × 15 kg × 10% = 1500 mL
Fluid Replacement Rate Over 24 hrs		
1500 mL/24 hr = 63 mL/hr + 52 mL/hr maintenance = 115 mL/hr		
Calculations for Fluid Selection		
Maintenance sodium requirements	3 mEq per 100 mL of maintenance fluid	3 mEq × (1250 mL/100 mL) = 38 mEq Na^+
Isotonic sodium deficit	8–10 mEq Na^+ per each 100 mL of fluid deficit	10 mEq × (1500 mL/100 mL) = 150 mEq Na^+
Sodium deficit	Equation 11.5	(135 mEq − 125 mEq) × 9 = 90 mEq Na^+
Total sodium content	Equation 11.6	90 mEq + (14 mEq/100ml × 1250) = 265 mEq
Sodium required per L	Divide total sodium by fluid deficit in L	278 mEq/1.5 L = 185 mEq

BOX 11.5

SAMPLE CALCULATIONS: SEVERE SYMPTOMATIC HYPONATREMIC DEHYDRATION

Initial Fluid Replacement for Neurologic Stabilization

Example: A 15-kg (preillness weight) child with altered mental status and serum sodium 110 mEq/L

Fluid to be used: 3% hypertonic saline (HTS)

Requirement	Formula	Sample Calculation
Sodium deficit	Equation 11.5	5 mEq/L × 9 = 45 mEq Na^+
Rate of administration	Equation 11.7	[(45 mEq × 1000 mL) /513 mEq × 4 hrs] = 22 mL/hr of 3% HTS

(7) The FWD is used to calculate the solute fluid deficit (SFD) (i.e., the amount of fluid that contains electrolytes).

EQUATION 11.9: SFD = Fluid Deficit [a] − FWD

[a]See equation 11.2 for fluid deficit calculations

(8) Despite the hypernatremia, there is also a Na deficit that should be accounted for:

TABLE 11.8

HYPERNATREMIA[7,25]

CLINICAL MANIFESTATIONS		
With hypernatremic hypovolemia, there is better preservation of intravascular volume compared to hypovolemic hyponatremia. Lethargy, weakness, altered mental status, irritability, coma, and seizures. High-pitched cry, thrombosis, brain hemorrhage, muscle cramps, hyperpnea, and respiratory failure.		
ETIOLOGIES		
Low urine osmolality	**Elevated urine osmolality**[b]	
	↓ Urine Na (< 20 mEq/L)	**↑ Urine Na (> 20 mEq/L)**
Diabetes insipidus (central and nephrogenic) (see Chapters 10 and 19)	GI losses	Exogenous Na^+ (meds, infant formula)
Postobstructive diuresis	Skin losses	Mineralocorticoid excess (e.g., hyperaldosteronism)
CKD	Respiratory[a]	
Diuretic use	Increased insensible losses	
Polyuric phase of ATN	Adipsia	
MANAGEMENT		
Timeline of onset can mirror timeline for correction.		

[a]This cause of hypernatremia is usually secondary to free water loss; therefore the fractional excretion of sodium may be decreased or normal.
[b]>1000 mosm/kg
ATN, Acute tubular necrosis; *CKD*, chronic kidney disease; *GI*, gastrointestinal; *Na*, sodium.

11

EQUATION 11.10:

$$\text{Na required (mEq)} = [\text{SFD (mL)} + \text{maintenance fluid volume (mL)}] \times \frac{14\ \text{mEq}}{100\text{mL}}$$

(9) The amount of sodium is then divided by the total fluid deficit in addition to the maintenance fluid volume. This will help approximate the fluid tonicity required.

EQUATION 11.11:

$$\text{Na content of fluid (mEq/L)} = \frac{\text{Na required (mEq)}}{\text{Fluid Deficit (L)} + \text{maintenance fluid volume (L)}}$$

(10) See Box 11.6 for sample calculations in hypernatremic dehydration.

(11) If the fluid necessary contains >154 mEq of Na, then the following equation can be used to make a 1-L bag at the desired tonicity:[16]

EQUATION 11.12:

$$\text{mL of 3\% saline} = 1000\ \text{mL} \times \frac{\text{desired Na (mEq/L)} - 154\ \text{(mEq/L)}}{513\ \text{(mEq/L)} - \text{desired Na (mEq/L)}}$$

(12) This equation can also be used to calculate rate to run HTS with NS bolus in a severely hypernatremic child. See Box 11.7.

BOX 11.6

SAMPLE CALCULATIONS: HYPERNATREMIC DEHYDRATION

Example: A 15-kg (preillness weight) child with 10% dehydration and serum sodium 155 mEq/L

Requirement	Formula	Sample Calculation
Maintenance fluid requirements	Holliday-Segar formula	(100 mL/kg/d × 10 kg) + (50 mL/kg/d × 5 kg) = 1250 mL/24 hr = 52 mL/hr
Total fluid deficit	Equation 11.2 or Equation 11.3	10 mL × 15 kg × 10% = 1500 mL
Fluid Replacement Rate Over 24 hrs		
1500 mL/24 hr = 63 mL/hr + 52 mL/hr maintenance = 115 mL/hr		
Calculations for Fluid Selection		
Free water deficit	Equation 11.8	4 mL/kg × 15 kg × (155 mEq/L − 145 mEq/L) = 600 mL
Solute fluid deficit	Equation 11.9	1500 mL − 600 mL = 900 mL
Total sodium required	Equation 11.10	(900 mL + 1250 mL) × 14 mEq/100 mL = 300 mEq Na^+
Na content of fluid	Equation 11.11	300 mEq / (1.25 + 1.5 L) = 110 mEq Na

BOX 11.7

SAMPLE CALCULATIONS: SEVERE HYPERNATREMIC DEHYDRATION

Initial Fluid Resuscitation Strategy to Avoid Rapid Sodium Correction when Serum Na^+ >175 mEq/L[16]

Example: A 3-kg (preillness-weight) breastfed neonate appearing severely dehydrated with serum sodium 185 mEq/L and hemodynamic instability

Resuscitation with normal saline (NS) may drop the serum Na^+ too quickly. Plan to simultaneously run NS and 3% hypertonic saline (HTS), given rapidly together (i.e., over 5 minutes), to effectively give resuscitation fluid with a concentration no more than 15 mEq/L below the child's serum Na^+. Repeat the boluses as needed to achieve hemodynamic stability.

Requirement	Formula	Sample Calculation
Ideal bolus fluid concentration	Serum sodium (in mEq/L) − 15 mEq/L	185 mEq/L − 15 mEq/L = 170 mEq/L
mL of HTS required per L of NS	Equation 11.12	1000 mL × (170 mEq/L − 154 mEq/L) / (513 mEq/L − 170 mEq/L) = 47 mL
Bolus NS amount in mL	20 mL/kg × wt (in kg)	20 mL/kg × 3 kg = 60 mL
Bolus amount HTS in mL	mL HTS required per L of NS × NS bolus amount (in mL) / 1000 mL	47 mL × 60 mL / 1000 mL = 2.8 mL

Note: In clinical practice, one will often not have laboratory data available quickly enough to employ this strategy. However, severe hypernatremia should be suspected in the clinical scenario of a solely breastfed neonate who appears severely dehydrated.[16] STAT labs should be sent, and this strategy may be employed as soon as laboratory values are available.

3. Calculations pertaining to dysnatremias can be double-checked using the following equation:

EQUATION 11.13:[4-6]

$$\frac{\text{Change in Serum Na}}{\text{1L of parenteral fluid administration}} = \frac{(\text{Infusate Na} + \text{Infusate K}) - \text{Serum Na}}{\text{TBW} + 1}$$

C. Potassium

1. **Hypokalemia**
   a. Clinical manifestations and differential diagnosis (Table 11.9)
   b. The transtubular potassium gradient (TTKG) can help differentiate between etiologies of hypokalemia, as noted in Table 11.9:

EQUATION 11.14:[7]

$$^{7}\text{TTKG}^{a} = \frac{[K]_{urine}}{[K]_{plasma}} \times \left(\frac{\text{plasma osmolality}}{\text{urine osmolality}}\right)$$

[a]The urine osmolality must be greater than the serum osmolality for the calculation to be valid

   c. Management: Potassium infusion rates generally should not exceed 1 mEq/kg/hr.[3]
2. **Hyperkalemia**
   a. Clinical manifestations and differential diagnosis (Table 11.10)
   b. Management (Fig. 11.1)

D. Calcium

1. **Hypocalcemia**
   a. Clinical manifestations and differential diagnosis (Table 11.11)
   b. Special considerations:
      i. Albumin readily binds serum calcium. Correction for albumin: Δ of 1 g/dL changes the total serum calcium in the same direction by 0.8 mg/dL.
      ii. pH: Acidosis increases ionized calcium.
      iii. Symptoms of hypocalcemia refractory to calcium supplementation may be caused by hypomagnesemia.
      iv. Significant hyperphosphatemia should be corrected before the correction of hypocalcemia because renal calculi or soft-tissue calcification may occur if total $\mathbf{[Ca^{2+}] \times [PO_4^{3-}] \geq 70}$.[7]
2. **Hypercalcemia:** Table 11.11

E. Magnesium

1. Hypomagnesemia: Table 11.12
2. Hypermagnesemia: Table 11.12

F. Phosphate

1. Hypophosphatemia: Table 11.13
2. Hyperphosphatemia: Table 11.13

TABLE 11.9

HYPOKALEMIA[7,25]

CLINICAL MANIFESTATIONS

Manifest at levels <2.5 mEq/L. Skeletal muscle weakness or ascending paralysis, muscle cramps, ileus, urinary retention, and cardiac arrhythmias.
Electrocardiogram (ECG) changes:
Delayed depolarization, flat T waves, depressed ST segment, and U waves.

ETIOLOGIES

Decreased Stores					
Metabolic Alkalosis					
Hypertensive	**Normotensive**	**Metabolic Acidosis**	**No Change in Serum pH**	**Extrarenal**	**Normal Stores[a]**
Renovascular disease Excess renin Cushing syndrome CAH Adrenal adenoma Licorice ingestion Liddle syndrome	Gitleman syndrome Bartter syndrome Hypoparathyrodism Cystic fibrosis EAST syndrome Loop and thiazide diuretics Emesis	RTA (type I and II) DKA Uretosigmoidoscopy Fanconi Syndrome	Meds (amphotericin, cis-platin, aminoglycosides, penicillin or penicillin derivatives, diuretics) Interstitial nephritis	Skin losses GI losses/laxative abuse/enema abuse Clay ingestion Kayexalate Malnutrition/Anorexia nervosa	Acute metabolic alkalosis Hyperinsulinemia Leukocytosis (if sample sits at room temperature) Meds (adrenergic agonists, theophylline, toluene, cesium chloride, hydroxy-chloroquine, barium) Familial hypokalemic periodic paralysis Familial

LABORATORY DATA

TTKG > 4				TTKG ≤ 4	~ Urine K^+

MANAGEMENT

Acute	Calculate deficit and replace with potassium acetate or potassium chloride. Enteral replacement is safer when feasible. Follow K^+ closely. IV replacement generally should not exceed 1 mEq/kg given over 1 hr.
Chronic	Determine daily requirement and replace with potassium chloride or potassium gluconate.

[a]Blood pressure may vary.

CAH, Congenial adrenal hyperplasia; *DKA*, diabetic ketoacidosis; *GI*, gastrointestinal; K^+, potassium; *RTA*, renal tubular acidosis; *EAST*, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; *TTKG*, transtubular potassium gradient.

TABLE 11.10

HYPERKALEMIA[7]

CLINICAL MANIFESTATIONS

Skeletal muscle weakness, fasciculations, paresthesias, and ascending paralysis.

The typical ECG progression with increasing serum K^+ values:

1. Peaked T waves
2. Prolonged PR and widening of QRS
3. Loss of P waves
4. ST segment depression with further widening of QRS
5. Bradycardia, atrioventricular (AV) block, ventricular arrhythmias, torsades de pointes, and cardiac arrest

ETIOLOGIES

Increased total body K^+		Intracellular shifts (no change in total body K^+)
Increased urine K^+	**Decreased urine K^+**	
Transfusion with aged blood	Renal failure	Tumor lysis syndrome
Exogenous K^+	Hypoaldosteronism	Leukocytosis (>200 x 10^3/μL)
Spitzer syndrome	Aldosterone insensitivity	Thrombocytosis (>750 x 10^3/μL)[b]
	↓ Insulin causing hyperglycemia and/or DKA	Metabolic acidosis[a]
	K^+-sparing diuretics	Blood drawing (hemolyzed sample)
	Congenital adrenal hyperplasia	Rhabdomyolysis/crush injury
	Type IV RTA	Malignant hyperthermia
	Meds: ACE inhibitors, angiotensin II blockers, K sparing diuretics, calcineurin inhibitors, NSAIDs, heparin, TMX, drospirenone	Theophylline intoxication

MANAGEMENT

See Fig. 11.1.

[a]For every 0.1-unit reduction in arterial pH, there is approximately a 0.2–0.4 mEq/L increase in plasma K^+.

[b]For every platelet increase of 100,000/μL, there is a 0.15 mEq/L increase in serum K^+.

ACE, Angiotensin converting enzyme; *DKA*, diabetic ketoacidosis; *ECG*, electrocardiogram; *K^+*, potassium; *NSAIDS*, nonsteroidal antiinflammatory drugs; *RTA*, renal tubular acidosis; *TMX*, trimethoprim.

IV. ALGORITHM FOR EVALUATING ACID-BASE DISTURBANCES[7,17,18]

A. Determine the pH

The body does not fully compensate for primary acid-base disorders; therefore the primary disturbance will shift the pH away from 7.40.

1. **Acidemia (pH < 7.35):**
   a. Respiratory acidosis: PCO_2 > 45 mm Hg
   b. Metabolic acidosis: Arterial bicarbonate < 20 mmol/L
2. **Alkalemia (pH > 7.45):**
   a. Respiratory alkalosis: PCO_2 < 35 mm Hg
   b. Metabolic alkalosis: Arterial bicarbonate > 28 mmol/L

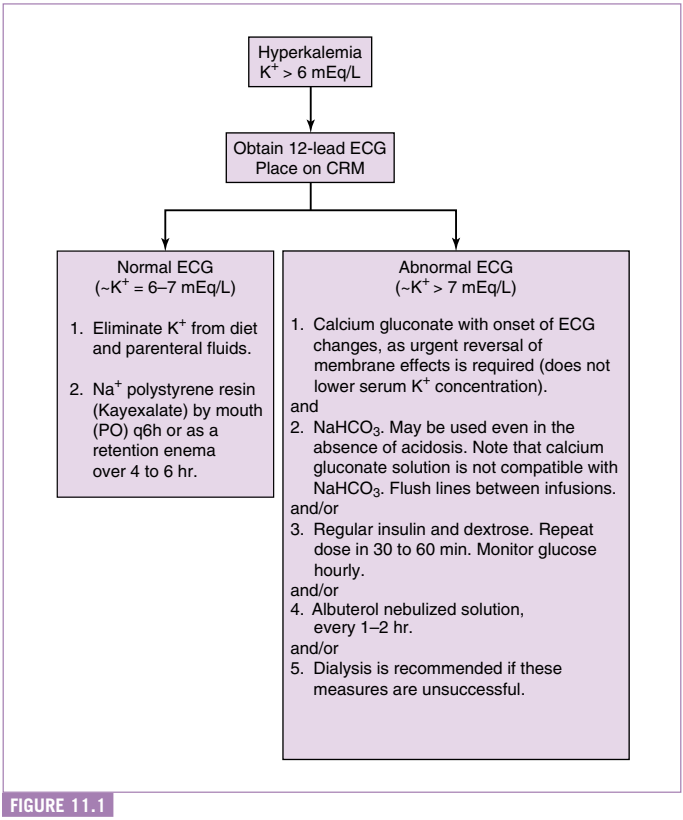

FIGURE 11.1

Algorithm for hyperkalemia. *CRM*, Cardiorespiratory monitor; *D25W*, 25% dextrose in water; *ECG*, electrocardiogram; *INH*, inhaled; *IV*, intravenous.

TABLE 11.11

HYPOCALCEMIA AND HYPERCALCEMIA

Hypocalcemia	Hypercalcemia
CLINICAL MANIFESTATIONS	
Tetany, neuromuscular irritability with weakness, paresthesias, fatigue, cramping, altered mental status, seizures, laryngospasm, and cardiac arrhythmias[18,19]: • ECG changes (prolonged QT interval) • Trousseau's sign (carpopedal spasm after arterial occlusion of an extremity for 3 minutes) • Chvostek sign (muscle twitching on percussion of the facial nerve)	Weakness, irritability, lethargy, seizures, coma, abdominal cramping, anorexia, nausea, vomiting, polyuria, polydipsia, renal calculi, pancreatitis, and ECG changes (shortened QT interval)
ETIOLOGIES	
Hypoparathyroidism Vitamin D deficiency Hyperphosphatemia Pancreatitis Malabsorption (malnutrition) Drugs (anticonvulsants, cimetidine, aminoglycosides, calcium channel blockers) Hypomagnesemia/hypermagnesemia Maternal hyperparathyroidism (in neonates) Ethylene glycol ingestion Calcitriol (activated vitamin D) insufficiency Tumor lysis syndrome	Hyperparathyroidism Vitamin D intoxication Excessive exogenous calcium administration Malignancy Prolonged immobilization Thiazide diuretics Subcutaneous fat necrosis Williams syndrome Granulomatous disease (e.g., sarcoidosis) Hyperthyroidism Milk-alkali syndrome
MANAGEMENT	
Acute: Consider IV replacement (calcium gluconate, calcium gluceptate, or calcium chloride [cardiac arrest dose]) Chronic: Consider use of oral supplements of calcium carbonate, calcium gluconate, calcium glubionate, or calcium lactate	Increase UOP and Ca^{2+} excretion: 1. If the glomerular filtration rate and blood pressure are stable, give NS with maintenance K^+ at 2-3 times the maintenance rate 2. Diuresis with furosemide Consider hemodialysis for severe or refractory cases Consider steroids in malignancy, granulomatous disease, and vitamin D toxicity to decrease vitamin D and Ca^{2+} absorption Severe or persistently elevated Ca^{2+}: Consider calcitonin or bisphosphonate

Ca^{2+}, Calcium; *ECG*, electrocardiogram; *UOP*, urine output.

B. Calculate the anion gap (AG)

1. **AG:** Represents anions other than bicarbonate and chloride required to balance the positive charge of Na. Normal: 12 mEq/L ± 2 mEq/L.

EQUATION 11.15: $AG = Na^+ - (Cl^- + HCO_3^-)$

TABLE 11.12

HYPOMAGNESEMIA AND HYPERMAGNESEMIA[7]

Hypomagnesemia				Hypermagnesemia
CLINICAL MANIFESTATIONS				
Typically, dominant manifestations are caused by concurrent hypocalcemia (Table 11.11) Typically occur at levels <0.7 mg/dL: Anorexia, nausea, weakness, malaise, depression, nonspecific psychiatric symptoms, hyperreflexia, ECG changes: flattening of T wave and lengthening of ST segment				Typically occur at levels >4.5 mg/dL: Hypotonia, hyporeflexia, paralysis, lethargy, confusion, hypotension, and prolonged QT, QRS, and PR intervals. Respiratory failure and cardiac arrest at >15 mg/dL
ETIOLOGIES				
GI Disorders	**Genetic**	**Medications**	**Miscellaneous**	**Renal Failure and Excessive Administration**
Diarrhea	Gitelman syndrome	Amphotericin	Decreased intake	Status asthmaticus eclampsia/preeclampsia, cathartics, enemas, phosphate binders, laxatives, lithium ingestions, milk-alkali syndrome
Malabsorption diseases	Bartter syndrome	Cisplatin	Hungry bone syndrome	
Short bowel	EAST syndrome	Cyclosporine	Exchange transfusion	
Malnutrition	AD hypoparathyroidism	Loop and thiazide diuretics	Diabetes mellitus	
Pancreatitis	Mitochondrial disorders	Mannitol	Steatorrhea	
	Miscellaneous disorders	Pentamidine	Hyperaldosteronism	
MANAGEMENT				
Acute			IV Magnesium sulfate	Stop supplemental Mg^{2+} Diuresis
Chronic			PO Magnesium oxide or magnesium sulfate	Ca^{2+} supplements, such as calcium chloride (cardiac arrest doses) or calcium gluconate

AD, Autosomal dominant; *Ca^{2+}*, calcium; *EAST*, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; *ECG*, electrocardiogram; *GI*, gastrointestinal; *IV*, intravenous; *Mg^{2+}*, magnesium ; *PO*, by mouth.

2. The majority of unmeasured anions contributing to the AG in normal individuals are albumin and phosphate. Correcting the AG for albumin concentration increases the utility of the traditional method.[19]

EQUATION 11.16: Corrected AG =
Observed AG + 2.5 × (Normal albumin − measured albumin)

AG > 15 : Anion gap metabolic acidosis (AGMA)

AG < 12 : Nonelevated anion gap metabolic acidosis (NAGMA)

AG > 20 mEq / L : Primary AGMA regardless of the pH or serum HCO_3^- concentration

TABLE 11.13

HYPOPHOSPHATEMIA AND HYPERPHOSPHATEMIA[7]

Hypophosphatemia	Hyperphosphatemia
CLINICAL MANIFESTATIONS	
Symptomatic only at very low levels (<1 mg/dL). Acute: rhabdomyolysis, tremor, paresthesias, irritability, confusion, hemolysis, delirium, seizure, myocardial depression, and coma. Chronic: Rickets, proximal muscle weakness	Symptoms of resulting hypocalcemia and systemic calcification (i.e., deposition of phosphorus calcium salts in tissues).
ETIOLOGIES	
Refeeding syndrome Insulin BMT Hungry bone Decreased intake Antacids Glucocorticoids Rickets Hyperparathyroidism Increased renal losses (e.g., renal tubular defects, diuretic use) McCune-Albright syndrome Epidermal nevus syndrome Fanconi syndrome Metabolic acidosis/respiratory alkalosis Glycosuria Volume expansion Sepsis	Tumor lysis syndrome Rhabdomyolysis DKA/lactic acidosis Hemolysis Renal failure Hypoparathyroidism Hyperthyroidism Excessive intake (enemas/laxatives and cow's milk) Vitamin D intoxication Familial tumoral calcinosis Acromegaly
MANAGEMENT	
Acute IV potassium phosphate or sodium phosphate Chronic PO potassium phosphate or sodium phosphate	Restrict dietary phosphate. Phosphate binders (calcium carbonate, aluminum hydroxide)

BMT, Bone marrow transplant; *DKA*, diabetic ketoacidosis. *IV*, intravenous; *PO*, by mouth.

C. Calculate the delta gap (DG)[20]:

If there is an AGMA, calculating the DG will help to determine if there is another, concurrent metabolic abnormality:

EQUATION 11.17: $DG = (AG - 12) - (24 - HCO_3^-)$

$DG > 6$: combined AGMA and metabolic alkalosis.

$DG < -6$: combined AGMA and NAGMA.

D. Calculate the osmolal gap

EQUATION 11.18: Serum osmolal gap = calculated serum osmolality – laboratory measured osmolality

TABLE 11.14

CALCULATION OF EXPECTED COMPENSATORY RESPONSE[7,20]

Disturbance	Primary Change	Expected Compensatory Response
Acute respiratory acidosis	↑$PaCO_2$	↑HCO_3^- by 1 mEq/L for each 10 mmHg rise in $Paco_2$
Acute respiratory alkalosis	↓$PaCO_2$	↓HCO_3^- by 2 mEq/L for each 10 mmHg fall in $PaCO_2$
Chronic respiratory acidosis	↑$PaCO_2$	↑HCO_3^- by 4 mEq/L for each 10 mmHg rise in $PaCO_2$
Chronic respiratory alkalosis	↓$PaCO_2$	↓HCO_3^- by 4 mEq/L for each 10 mmHg fall in $PaCO_2$
Metabolic acidosis	↓HCO_3^-	$PaCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	↑HCO_3^-	↑$PaCO_2$ by 7 mmHg for each 10 mEq/L rise in HCO_3^-

1. There is always a difference (<6) between calculated osmolality and measured osmolality.[21]
2. A markedly elevated osmolar gap (>10) in the setting of an AG acidosis is highly suggestive of acute methanol or ethylene glycol intoxication.[22–24]

E. Calculate expected compensatory response: (Table 11.14)

1. Pure **respiratory** acidosis (or alkalosis): 10 mmHg rise (fall) in $PaCO_2$ results in an average 0.08 fall (rise) in pH.
2. Pure **metabolic** acidosis (or alkalosis): 10 mEq/L fall (rise) in HCO_3^- results in an average 0.15 fall (rise) in pH.

F. Determine the likely etiology

Check for appropriate compensation

G. If there is not appropriate compensation, consider an additional acid-base derangement (Fig. 11.2)

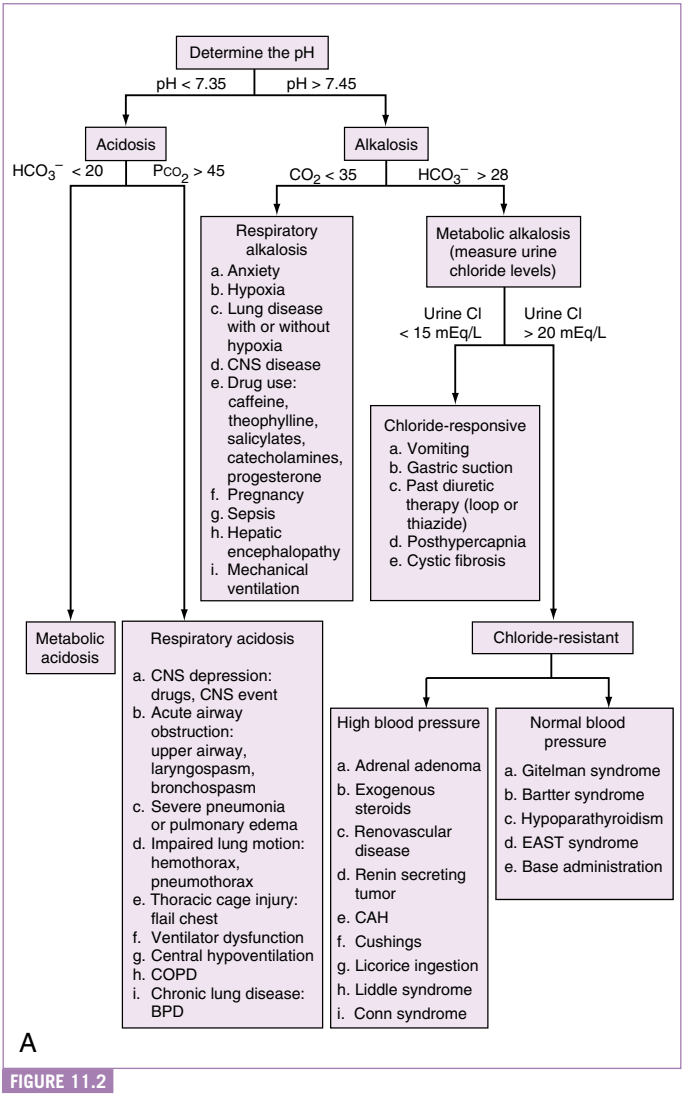

FIGURE 11.2

(A and B) Etiology of acid-base disturbances. *BPD*, bronchopulmonary dysplasia; *CAH,* congenital adrenal hyperplasia; *CNS*, central nervous system; *COPD*, chronic obstructive pulmonary disease; *EAST,* epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; *NSAID*, nonsteroidal antiinflammatory drug.

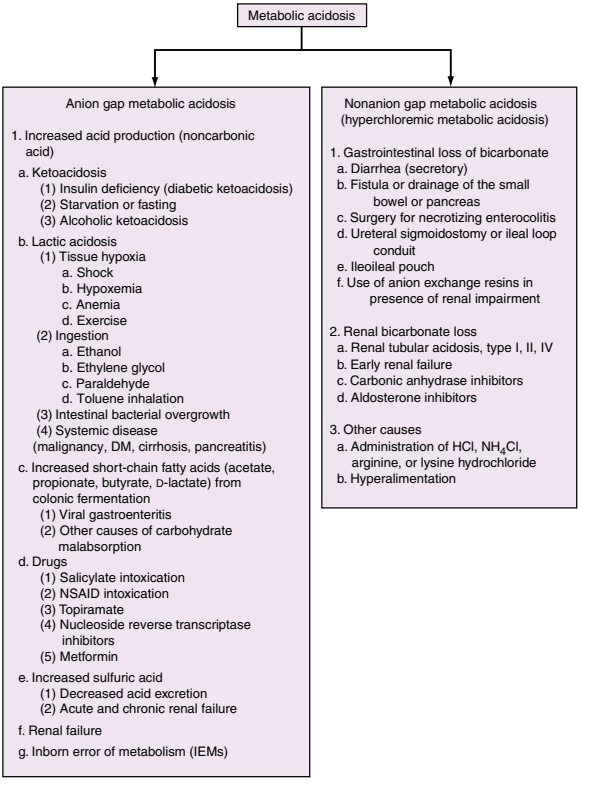

FIGURE 11.2, cont'd

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Chapter 12

Gastroenterology

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See additional content on Expert Consult

I. GASTROINTESTINAL EMERGENCIES

A. Gastrointestinal Bleeding

1. **Presentation**: Blood loss from the gastrointestinal (GI) tract occurs in four ways: hematemesis, hematochezia, melena, and occult bleeding.
2. **Differential diagnosis of GI bleeding:** Table 12.1
3. **Diagnosis/Management**
   a. Assess airway, breathing, circulation, and hemodynamic stability.
   b. Perform full physical exam, verify bleeding with rectal examination, and testing of stool or emesis for occult blood. Notable exam findings include abdominal tenderness, guarding, rebound, hepatosplenomegaly, perianal skin tags, or fissures.
   c. Obtain baseline laboratory tests. Complete blood cell count (CBC), coagulation studies, type and screen, reticulocyte count, complete metabolic panel (CMP), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), and assess for disseminated intravascular coagulation (D dimer, fibrinogen).
   d. If concerned for hemodynamic instability, begin initial fluid resuscitation. Consider transfusion if there is continued bleeding, symptomatic anemia, and/or a hematocrit level <21%. Initiate intravenous (IV) proton pump inhibitor (PPI).
   e. Further evaluation and therapy based on the assessment and site of bleeding:
      (1) Upper GI Bleeding: Consider esophagogastroduodenoscopy (EGD) and testing for *Helicobacter pylori*.[1]
      (2) Lower GI Bleeding: Consider abdominal radiograph, upper GI study (± small bowel follow-through), air-contrast barium enema, colonoscopy, Meckel scan, tagged red cell scan, computed tomography (CT), and magnetic resonance enterography (MRE). Consider stool cultures, stool ova and parasites, *Clostridium difficile* toxin, and stool calprotectin.

B. Acute Abdomen[2]

1. **Definition:** Severe abdominal pain that may require emergency surgical intervention.
2. **Differential diagnosis:** Table 12.2
3. **Diagnosis:**
   a. **History:** Course and characterization of the pain, emesis, melena, hematochezia, diet, stool history, fever, travel history, menstrual

TABLE 12.1

DIFFERENTIAL DIAGNOSIS OF GASTROINTESTINAL BLEEDING

Age	Upper Gastrointestinal Tract	Lower Gastrointestinal Tract
Newborns (0–30 days)	Swallowed maternal blood Gastritis	Necrotizing enterocolitis Malrotation with midgut volvulus Anal fissure Hirschsprung disease
Infant (30 days–1 year)	Gastritis Esophagitis Peptic ulcer disease Pyloric stenosis	Anal fissure Allergic proctocolitis Intussusception Meckel diverticulum Lymphonodular hyperplasia Intestinal duplication Infectious colitis Hirschsprung disease
Preschool (1–5 years)	Gastritis Esophagitis Peptic ulcer disease Esophageal varices Epistaxis Mallory-Weiss tear	Juvenile polyps Lymphonodular hyperplasia Meckel diverticulum Hemolytic-uremic syndrome Henoch-Schönlein purpura Infectious colitis Anal fissure
School age and adolescence	Esophageal varices Peptic ulcer disease Epistaxis Gastritis Mallory-Weiss tear	Inflammatory bowel disease Infectious colitis Juvenile polyps Anal fissure Hemorrhoids

Modified from Pearl R. The approach to common abdominal diagnoses in infants and children. Part II. *Pediatr Clin North Am.* 1998;45:1287–1326.

TABLE 12.2

ACUTE ABDOMINAL PAIN

Gastrointestinal source	Appendicitis, pancreatitis, intussusception, malrotation with volvulus, inflammatory bowel disease, gastritis, bowel obstruction, mesenteric lymphadenitis, irritable bowel syndrome, abscess, hepatitis, perforated ulcer, Meckel diverticulitis, cholecystitis, choledocholithiasis, constipation, gastroenteritis, abdominal trauma, mesenteric ischemia, and abdominal migraine
Renal source	Urinary tract infection, pyelonephritis, and nephrolithiasis
Genitourinary source	Ectopic pregnancy, ovarian cyst/torsion, pelvic inflammatory disease, and testicular torsion
Oncologic source	Wilms tumor, neuroblastoma, rhabdomyosarcoma, and lymphoma
Other sources	Henoch-Schönlein purpura, pneumonia, sickle cell anemia, diabetic ketoacidosis, juvenile rheumatoid arthritis, and incarcerated hernia

TABLE 12.3

DIFFERENTIAL DIAGNOSIS OF VOMITING

Age	Typically Nonbilious	Typically Bilious
Newborn and infant (0 days–1 year)	Overfeeding, physiologic reflux, milk protein sensitivity, pyloric stenosis, necrotizing enterocolitis, metabolic disorder, infection (GU, respiratory, GI), esophageal/intestinal atresia/stenosis, and Hirschsprung disease	Malrotation ± volvulus, intestinal atresia/stenosis, intussusception, pancreatitis
Preschool (1–5 years)	Cyclic vomiting, infectious (GI, GU), toxin ingestion, diabetic ketoacidosis (DKA), CNS mass effect, eosinophilic esophagitis, post-tussive, peptic disease, and appendicitis	Malrotation, intussusception, incarcerated hernia, pancreatitis, intestinal dysmotility
School age and adolescence	Eating disorders, pregnancy, CNS mass effect, eosinophilic esophagitis, DKA, peptic disease, cyclic vomiting, toxins/drugs of abuse, infectious (GU, GI), and appendicitis	Peritoneal adhesions, malrotation, incarcerated hernia, pancreatitis, and intestinal dysmotility

CNS, Central nervous system; *DKA*, diabetic ketoacidosis; *GI*, gastrointestinal; *GU*, genitourinary.

history, vaginal/testicular symptoms, urinary symptoms, respiratory symptoms, and recent surgeries.

b. **Physical Exam:** Rashes, arthritis, and jaundice. Abdominal tenderness on palpation, rebound/guarding, rigidity, masses, distention, or abnormal bowel sounds, rectal examination with stool hemoccult testing, pelvic examination (discharge, masses, adnexal/cervical motion tenderness), and genital examinations.

c. **Labs:** CBC, CMP, coagulation studies, lactate, type and screen, urinalysis, amylase, lipase, gonorrhea/chlamydia testing, β-human chorionic gonadotropin (β-hCG), ESR, and CRP.

d. **Imaging**: Two-view abdominal radiographs to assess for obstruction, constipation, free air, gallstones, and kidney stones. Consider chest radiograph to evaluate for pneumonia, abdominal/pelvic ultrasonography, and abdominal CT with contrast or magnetic resonance imaging (MRI).

4. **Management:** Ensure patient is NPO and begin IV hydration. Consider nasogastric decompression, serial abdominal examinations, surgical/gynecologic/GI evaluation, pain control, and antibiotics as indicated.

II. CONDITIONS OF THE GASTROINTESTINAL TRACT

A. Vomiting

1. **Definition:** Forceful oral expulsion of gastric contents can be bilious or nonbilious.
2. **Differential Diagnosis:** Table 12.3

3. **Diagnosis:**
   a. **History:** Diet, medications, timing (acute vs. chronic), exposures, character (bilious, bloody, projectile) and associated symptoms. Pay special attention to vomiting **without** concomitant diarrhea.
   b. **Physical Exam:** HEENT and neurologic exam with specific attention to mucus membranes, skin and dentition, as well as a thorough abdominal exam.
   c. **Labs:** Although not always necessary, consider CMP, CBC, UA, β-hCG, and lipase.
   d. **Imaging:** Plain abdominal radiograph with upright view (to rule out obstruction or free air), abdominal ultrasound (US), upper GI series. Consider neurologic imaging if indicated.
4. **Management:** Hydration. Gastric decompression if GI obstruction suspected. Antiemetic therapy can be used in the acute setting, avoid chronic use (see Chapter 22 for discussion of antiemetic therapy). Consider surgical consultation if the vomiting is bilious.

B. Gastrointestinal Reflux Disease[3]

1. **Definition:** Gastroesophageal reflux (GER) is physiologic passage of gastric contents into the esophagus, and gastroesophageal reflux disease (GERD) is defined as troublesome symptoms or complications of GER.
2. **Differential Diagnosis**: Dysmotility including achalasia, gastroparesis, ileus, and obstruction. Inflammatory conditions such as esophagitis, gastritis/dyspepsia, peptic ulcer disease. Anatomic abnormalities such as Zenker diverticulum, tracheoesophageal fistula, vascular ring, pyloric stenosis. Functional disorders including abdominal migraines and cyclical vomiting syndrome. Food allergies/intolerance in infants.
3. **Diagnosis:**
   a. **History:** Recurrent regurgitation, choking, vomiting, heartburn, chest pain, dysphagia, stridor or wheezing, cough, recurrent aspiration pneumonia, dental erosions, and sleep disturbances. In infants, GERD may present as irritability, weight loss, feeding refusal, or Sandifer syndrome. History is typically sufficient for diagnosis and to initiate management.
   b. **Testing:** Esophageal pH monitoring and esophageal impedance monitoring if diagnosis unclear.[4]
4. **Management:**
   a. **Lifestyle:** A prone or left-sided sleeping position and elevation of head of bed may improve GER symptoms in older children, but current studies for infants have been inconclusive. Infants up to 12 months should continue to sleep supine—risk of sleep-related infant death far outweighs benefit of prone or lateral sleeping in GERD. After feeds, infants should be kept upright and a trial of smaller more frequent feeds may be beneficial. Avoidance of second-hand smoke exposure.
   b. **Diet:** Milk-thickening agents can be beneficial for symptom relief. If severe and unresponsive to conservative management, consider 2- to 4-week trial of extensively hydrolyzed protein formula in infants

or elimination of cow's milk in maternal diet to eliminate milk protein sensitivity as a cause of unexplained vomiting.

c. **Pharmacotherapy:** Medication is not recommended for "happy spitters" or infants with uncomplicated GER. Both PPIs and H2 receptor antagonists (H2RAs) are effective in relieving symptoms and promoting mucosal healing.[5] There is insufficient evidence to support routine use of prokinetic therapies (metoclopramide and erythromycin).

C. Eosinophilic Esophagitis[6,7]

1. **Definition:** A chronic, immune/antigen-mediated disease characterized by symptoms of esophageal dysfunction with ≥15 eosinophils/high-power field (hpf) on esophageal biopsy.
2. **Diagnosis:**
   a. **History:** Dysphagia, food impaction, chest pain, food refusal or intolerance, GER symptoms, emesis, abdominal pain, and failure to thrive. Majority of patients with EoE have concurrent atopic disorder.
   b. **Diagnosis:** EGD with esophageal biopsies demonstrating at least 15 eos/hpf histoligically with chronic symptoms of esophageal dysfunction; Must evaluate for other causes or contributions to esophageal eosinophilia. Importantly histologic evidence without clinical correlation is not diagnostic. Per the AGREE conference, a PPI trial is no longer needed for diagnosis. Consider obtaining allergy testing (see Chapter 15).
3. **Management[8]:**
   a. **Dietary therapy:** 6-food elimination diet (milk, wheat, eggs, soy, peanuts/tree nuts, seafood), elemental diet, or targeted elimination diet determined by allergy testing.
   b. **Pharmacotherapy:** Topical swallowed steroids delivered via inhaler are preferred as first line therapy to induce remission with limited side effects (6- to 8-week course of fluticasone or budesonide metered-dose inhaler administered orally **without** a spacer). PPI therapy can also be trialed for initial treatment. Systemic steroids for short-term use (e.g., dysphagia leading to dehydration or weight loss). No current evidence to support routine use of biologics.
   c. **Complications:** Symptomatic strictures requiring esophageal dilation.

D. Celiac Disease[9]

1. **Definition:** An immune-mediated inflammatory enteropathy caused by sensitivity to dietary gluten and related proteins (wheat, barley, and rye) in genetically susceptible individuals.
2. **Diagnosis:**
   a. **History:** Presentation can be variable, and some patients are asymptomatic. Most common symptoms include diarrhea, vomiting, abdominal pain, constipation, distention, and failure to thrive. Non-GI symptoms include rash (dermatitis herpetiformis), osteoporosis, short stature, delayed puberty, and iron deficiency anemia that is resistant to oral iron. Increased occurrence in children with autoimmune disorders, Down syndrome, Turner syndrome, William syndrome, immunoglobulin A (IgA) deficiency, and in first-degree relatives of those with celiac disease.

   b. **Labs**: First line screening is IgA antibody to human recombinant tissue transglutaminase (TTG) and serum IgA. If known selective IgA deficiency with symptoms suggestive of celiac disease, testing with TTG IgG is recommended. CBC, iron studies, hepatic function panel, thyroid tests, calcium, and vitamin D are recommended. Additional antibody testing may be necessary for inconclusive clinical scenarios.
   c. **Procedures**: Biopsy is "gold standard" for diagnosis. Intestinal biopsies showing villous atrophy supports diagnosis. Results dependent on adequate consumption of gluten prior to testing; ensure 6 to 8 weeks of gluten ingestion prior to endoscopy.
3. **Management:** Lifetime, gluten-free diet. Annual screening with TTG is recommended to monitor adherence to diet.
4. **Complications:** More often seen in adulthood but at risk for vitamin deficiencies and other autoimmune disorders. Higher risk of non-Hodgkin lymphoma, specifically enteropathy associated T-cell lymphoma.

E. Inflammatory Bowel Disease (EoE)[10,11]

1. **Classification:**
   a. **Crohn disease:** Transmural inflammatory process affecting any segment of the GI tract, most commonly terminal ileum. Commonly presents with abdominal pain, weight loss, diarrhea, and poor growth.
   b. **Ulcerative colitis (UC):** Chronic, relapsing, inflammatory disease of the colon and rectum. Commonly presents with rectal bleeding and diarrhea.
2. **Diagnosis:**
   a. **History:** Abdominal pain, weight loss, diarrhea, lethargy, nausea, vomiting, malnutrition, psychiatric symptoms, arthropathy, and rashes. Family history, exposure to infectious agents, or antibiotic treatment.
   b. **Physical Exam:** Stomatitis, perianal skin tags, fissures, and fistulas. Assessment of hydration and nutritional status. Fever, orthostasis, tachycardia, abdominal tenderness, distention, or masses suggests moderate to severe disease and need for hospitalization.
   c. **Labs**: CBC, CMP, ESR, CRP. Fecal calprotectin has been shown to be elevated in inflammatory bowel disease (IBD) and may serve as a sensitive, noninvasive test.[12] IBD often associated with anemia, hypoalbuminemia, thrombocytosis, and elevated inflammatory markers. Stool studies to exclude infectious process are necessary.
   d. **Imaging**: MRE is the preferred imaging modality for diagnosis of pediatric IBD due to high diagnostic accuracy and no radiation exposure. CT and fluoroscopy are other alternative strategies if MRE unavailable.
   e. **Procedures:** Diagnostic endoscopy with biopsies used to confirm diagnosis.

3. **Management**[13-16]**:**
   a. **Induction of remission:**
      (1) Crohn: Exclusive enteral formula-based nutrition (80%–100% caloric need by liquid formula), 5-aminosalicylates, antitumor necrosis factor (TNF) agents, and, if indicated, antibiotics or surgery. Corticosteroids can be used if necessary.
      (2) UC: Corticosteroids, 5-aminosalicylates, TNF agents, and if indicated, antibiotics or surgery. Therapy guided by severity of illness.
   b. **Maintenance of remission:** Immunosuppression includes thiopurines, methotrexate, cyclosporine, tacrolimus, and anti-TNF monoclonal antibodies. Avoid prolonged steroid use.
   c. **Other:** Surgical intervention indicated only after medical management has failed in both Crohn's disease and UC. In Crohn disease, surgery is indicated for localized disease (strictures), abscess, or disease refractory to medical management.

F. Constipation[17]

Normal stooling patterns by age: Infants 0 to 3 months, 2 to 3 bowel movements/day (breastfed infants may stool after every feed or go 5 to 7 days with no stool); 6 to 12 months, 1.8/day; 1 to 3 years, 1.4/day; >3 years, 1/day. If an exclusively breastfed <1 month old is not stooling regularly, it may be a sign of insufficient milk intake; monitor weight gain.

1. **Definitions:**
   a. **Constipation:** Delay or difficulty in defecation for 2 or more weeks. Functional causes of constipation are the most common. History and physical exam are often sufficient for diagnosis.
      (1) Functional: Consider Rome IV Criteria (Table EC 12.A)
      (2) Nonfunctional: See Table 12.4 for differential diagnosis.
2. **Diagnosis:**
   a. **History:** Age of onset, toilet training experience, frequency/consistency/size of stools, pain or bleeding with defecation, presence of abdominal pain, soiling of underwear, stool-withholding behavior, change in appetite, abdominal distention, allergies, dietary history, medications, developmental history, psychosocial history. Refer to Bristol Stool Form Scale for classification of stool history (Fig. 12.1. Delayed meconium, poor weight gain or weight loss, anorexia, nausea, vomiting, and family history (e.g., thyroid disorders, cystic fibrosis) would warrant further evaluation for nonfunctional causes.
   b. **Physical Exam:** External perineum, perianal examination. Fecal impaction may be palpated on abdominal or digital rectal examination. Plain abdominal single view radiography can be considered when physical examination is unreliable.
3. **Management of functional constipation:** Box 12.1 and Table EC 12.B.
   a. **Disimpaction:**
      (1) Oral/Nasogastric Approach: Polyethylene glycol (PEG) solutions are effective for initial disimpaction. May also use other osmotic laxatives.

TABLE EC 12.A

ROME CRITERIA FOR FUNCTIONAL CONSTIPATION

In the absence of organic pathology, must include two or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:

1. ≤2 defecations in the toilet per week in child of developmental age of at least 4 years
2. At least 1 episodes of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large diameter stools that can obstruct the toilet

Modified from Constipation Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Evaluation and treatment of constipation in infants and children: Evidence-Based Recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr.* 2014;58(2):261 and Rome IV Criteria.

TABLE 12.4

DIFFERENTIAL DIAGNOSIS OF CONSTIPATION[a]

Anatomic malformations	Anal stenosis, anterior displaced anus, imperforate anus, and pelvic mass (e.g., sacral teratoma)
Metabolic and gastrointestinal	Cystic fibrosis, diabetes mellitus, gluten enteropathy, hypercalcemia, hypokalemia, hypothyroidism, and multiple endocrine neoplasia type 2B
Neuropathic conditions	Neurofibromatosis, spinal cord abnormalities, spinal cord trauma, static encephalopathy, and tethered cord
Intestinal nerve or muscle disorders	Hirschsprung disease, intestinal neuronal dysplasia, visceral myopathies, and visceral neuropathies
Abnormal abdominal musculature	Down syndrome, gastroschisis, and prune belly
Connective tissue disorders	Ehlers-Danlos syndrome, scleroderma, and systemic lupus erythematosus
Drugs	Antacids, anticholinergics, antidepressants, antihypertensives, opiates, phenobarbital, sucralfate, and sympathomimetics
Other	Botulism, cow's milk protein intolerance, heavy metal ingestion (lead), and vitamin D intoxication

[a]Remember that functional constipation remains the most common cause.

Constipation Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Evaluation and treatment of constipation in infants and children: Evidence-Based Recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr.* 2014;58(2):258–274.

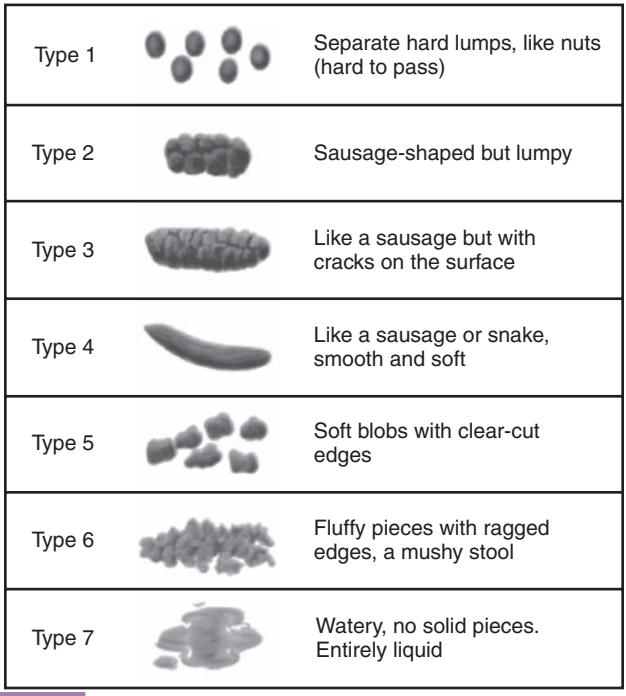

FIGURE 12.1

Bristol Stool Form Scale. (From *Campbell-Walsh-Wein Urology.* 12th ed. Philadelphia: Elsevier; 2020, Fig. 36.1.)

BOX 12.1

MANAGEMENT OF CONSTIPATION

HOME CLEANOUT INSTRUCTIONS

Step 1: Take a stimulant laxative (bisacodyl, senna) with 8 oz of liquid, as per dosing instructions below. This should be done 6 hr prior to intended effect.

Step 2: Drink polyethylene glycol (PEG). Mix with water or another clear noncarbonated liquid. Drink full amount in 2 hr. See below for dosing instructions.

Step 3: 1–2 hr after finishing PEG, should begin passing formed/thick brown stool. The stool should become thinner and clearer stooling continues.

Step 4: If not stooling or passing very thick stools 4 hr after the PEG is finished, drink 1 capful of PEG in 8 oz of liquid every hour until stools are clear.

Step 5: Cleanout is finished when stool is mostly clear with very little sand-like material mixed in. Proceed to maintenance instructions below.

DOSING INSTRUCTIONS

Weight	Polyethylene Glycol (PEG) Dose	Stimulant Laxative Recommendation
8–10 kg	Mix 2.5 capfuls of PEG in 8 oz of clear drink	<2 years old: No stimulant laxative use 2 years to <3 years old: Chewable senna (chocolate squares)[a] ≥3 years old: Oral chewable senna (chocolate squares) until child can swallow pills, then oral bisacodyl laxative[a]
10.1–15 kg	Mix 3.5 capfuls of PEG in 16 oz of clear drink	
15.1–20 kg	Mix 5 capfuls of PEG in 20 oz of clear drink	
20.1–25 kg	Mix 6 capfuls of PEG in 24 oz of clear drink	
25.1–30 kg	Mix 7 capfuls of PEG in 28 oz of clear drink	
30.1–40 kg	Mix 9.5 capfuls of PEG in 40 oz of clear drink	
40.1–50 kg	Mix 12 capfuls of PEG in 48 oz of clear drink	
50.1 kg or more	Mix 14 capfuls of PEG in 56 oz of clear drink	

DAILY MAINTENANCE THERAPY

The day after colon cleanse, the patient should begin taking maintenance daily PEG for continued management of constipation.

Advise patient/family to mix PEG in clear noncarbonated drink or water at least once daily. See formulary for dosing. Advise to drink the entire solution in 30 min or less for it to work well. It is best to give the PEG after school and before dinner. Do not give PEG right before bedtime.

The goal of daily maintenance PEG is for the child to have 1 or 2 soft and easily passable bowel movements every day.

Advise to have child to sit on the toilet after every meal or whenever they feel the need to stool.

[a]See Formulary for dosing recommendations.

Modified from handout given to patients who visit the Johns Hopkins Children's Center Pediatric Chronic Constipation Center, as an example of constipation management; variations are found at other institutions.

TABLE EC 12.B

PHARMACOLOGIC MANAGEMENT OF CONSTIPATION

OSMOTIC LAXATIVES	
Polyethylene Glycol (PEG)—oral	First line for disimpaction and maintenance
Lactulose—oral	If PEG not available, best and safest alternative (if >1 year of age)
Magnesium Hydroxide (Milk of Magnesia)—oral	
Sodium Phosphate—oral/enema	Risk of acute phosphate nephropathy Should not be used in children <2 years
Glycerin—suppository/enema	Suppository may be used in infants <1 year old
STIMULANT LAXATIVES	
Bisacodyl—oral/enema/suppository	
Senna—oral	
STOOL SOFTENERS	
Mineral Oil—oral/enema	
Sodium Docusate—oral/enema	

Modified from Management of Functional Constipation in Children: Therapy in Practice. *Paediatr Drugs*. 2015;17(5):349–360.

(2) Rectal approach: Saline or mineral oil enemas effective. Avoid enemas in infants, glycerin suppositories may be used in infants less than 1 year.

b. **Maintenance therapy** (usually 3 to 12 months): Goal is to prevent recurrence.
   (1) **Dietary changes:** Evidence supporting dietary intervention is weak; however, increased intake of fruits, vegetables, whole grains, and fluids other than milk is recommended.
   (2) **Behavioral modifications:** Regular toilet habits with positive reinforcement. Referral to a mental health specialist for motivational or behavioral concerns if soiling an issue.
   (3) **Medications:** Daily PEG. Lactulose as second line treatment. The use of stimulant laxatives and stool softeners may also be considered. Avoid prolonged use of stimulant laxatives. Discontinue therapy gradually only after return of regular bowel movements with good evacuation. Evidence does not support use of probiotics.

c. **Special considerations in infants aged <1 year:** 2 to 4 oz of 100% fruit juice (e.g., prune or pear) recommended in younger infants. Glycerin suppositories may be useful. While use is off label, PEG is routinely used in children <1 year of age. Avoid mineral oil, stimulant laxatives, and phosphate enemas.

G. Diarrhea[18]

1. **Definition:** Acute diarrhea is more than three loose or watery stools per day. Chronic diarrhea is diarrhea lasting more than 2 to 4 weeks.
2. **Pathogenesis:** It can be infectious or malabsorptive with an osmotic or secretory mechanism.
   a. **Osmotic diarrhea:** Water is drawn into intestinal lumen by maldigested osmotic compounds, as seen in celiac disease, pancreatic disease, or lactose intolerance. Stool volume depends on diet and decreases with fasting (stool osmolar gap ≥100 mOsm/kg).
   b. **Secretory diarrhea:** Water accompanies secreted or unabsorbed electrolytes into the intestinal lumen (e.g., excessive secretion of chloride ions caused by cholera toxin). Stool volume is increased and does not vary with diet (stool osmolar gap <50 mOsm/kg).
   c. Stool osmolar gap: The standard value is 290 mOsm/kg.[19]

$$\text{Stool osmolar gap} = \text{Stool Osm} - \{2\times [\text{stool (Na) mEq/L} + \text{stool (K) mEq/L}]\}$$

3. **Differential Diagnosis:** Table 12.5
4. **Diagnosis:**
   a. **History**: acute vs. chronic, travel history, recent antibiotic use, and immune status.
   b. **Labs:** CMP, CBC, stool hemoccult testing, stool culture, *C. difficile* toxin, ova and parasites, and viral antigens (see Chapter 17 for common bacterial and viral pathogens).

TABLE 12.5

DIFFERENTIAL DIAGNOSIS OF COMMON CAUSES OF DIARRHEA

Diagnosis	Major Clinical Features
Infectious colitis (viral, bacterial, protozoal)	Blood or mucous in stool, possible exposure history (e.g., travel)
Lactose malabsorption	Bloating, flatulence, abdominal pain, and elevated breath hydrogen concentration postlactose ingestion
Small bowel bacterial overgrowth	Abdominal discomfort and increased risk if ileocecal valve removed
Irritable bowel syndrome	Constipation and/or diarrhea and absence of laboratory or imaging findings
Allergic enteropathy	Growth failure, hypoalbuminemia, anemia, and may have elevated serum IgE
Hirschsprung disease	Distended abdomen, abnormal barium enema, absent ganglion cells on rectal biopsy
Cystic fibrosis	Decreased fecal elastase, steatorrhea, and poor growth
IBD and celiac disease	See sections III.D and III.E
Other: Hyperthyroidism, UTI, and encopresis	Dependent on etiology

IBD, Inflammatory bowel disease; *IgE*, immunoglobulin E; *UTI*, urinary tract infection.
Modified from Zella GC, Israel EJ. Chronic Diarrhea in Children. *Pediatrics in Review*. 2012;33(5):207–218.

5. **Management**
   a. **Oral rehydration therapy (ORT)**[20]**:** Enteral hydration has proven superior in reducing the length of hospital stay and adverse events.[21] Parenteral hydration is indicated in severe dehydration, hemodynamic instability, or failure of ORT.
   b. **Diet:** Restart regular diet as soon as tolerated.
   c. **Pharmacotherapy:** No supporting evidence for use of nonspecific antidiarrheal agents, antimotility agents (e.g., loperamide), antisecretory drugs, and toxin binders (e.g., cholestyramine). Consider evidence-based antimicrobial therapy for infectious diarrhea (see Chapter 17). If malabsorptive (e.g., celiac disease or IBD), therapy should be tailored to disease process.
   d. **Probiotics**[22]**:** Evidence supporting use of probiotics is limited; however, their efficacy has been demonstrated in the following circumstances: antibiotic-associated diarrhea, mild to moderate acute diarrhea, *C. difficile* diarrhea (severe recurrent disease only), hepatic encephalopathy, the prevention of atopic dermatitis, and possibly preventing necrotizing enterocolitis in premature infants.[23]

III. CONDITIONS OF THE LIVER

A. Liver Laboratory Studies: Table 12.6

1. **Synthetic/Metabolic function:** Albumin, prealbumin, international normalized ratio (INR), activated partial thromboplastin time (aPTT), cholesterol levels, bilirubin, and ammonia.

TABLE 12.6

LIVER LABORATORY TESTS

Enzyme	Source	Increased	Decreased	Comments
AST/ALT	Liver, heart, skeletal muscle, pancreas, RBCs, and kidney	Hepatocellular injury, rhabdomyolysis, muscular dystrophy, hemolysis, and liver cancer	Vitamin B_6 deficiency and uremia	ALT more specific than AST for liver, AST > ALT in hemolysis
Alkaline phosphatase	Osteoblasts, liver, small intestine, kidney, and placenta	Hepatocellular injury, bone growth, disease, trauma, pregnancy, and familial	Low phosphate, Wilson disease, zinc deficiency, hypothyroidism, and pernicious anemia	Highest in cholestatic conditions; must be differentiated from bone source
GGT	Renal tubules, bile ducts, pancreas, small intestine, and brain	Cholestasis, newborn period, and induced by drugs	Estrogen therapy, artificially low in hyperbilirubinemia	Not found in bone, increased in 90% of primary liver disease, specific for hepatobiliary disease in nonpregnant patient
Ammonia	Bowel flora and protein metabolism	Hepatic disease secondary to urea cycle dysfunction, hemodialysis, valproic acid therapy, urea cycle enzyme deficiency, organic academia, and carnitine deficiency		Converted to urea in liver

AST/ALT, Aspartate aminotransferase/alanine aminotransferase; *GGT*, γ-glutamyl transpeptidase; *RBCs*, red blood cells.

TABLE 12.7

DIFFERENTIAL DIAGNOSIS OF ACUTE LIVER FAILURE

Infection	Herpes simplex virus, hepatitis A, hepatitis B, adenovirus, cytomegalovirus, Epstein-Barr virus, enterovirus, human herpes virus 6, parvovirus B19, and Dengue fever
Vascular	Budd-Chiari syndrome, portal vein thrombosis, venoocclusive disease, and ischemic hepatitis
Inherited/Metabolic	Wilson disease, mitochondrial, tyrosinemia, galactosemia, hemochromatosis, fatty acid oxidation defect, and iron storage disease
Immune Dysregulation	Natural killer cell dysfunction (hemophagocytic lymphohistiocytosis), autoimmune, and macrophage activation syndrome
Drugs/Toxins	Acetaminophen, anticonvulsants, and chemotherapy
Other	Idiopathic and cancer/leukemia

2. **Liver cell injury:** aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase.
3. **Biliary system:** bilirubin (total and direct), urobilinogen, γ-glutamyltransferase, and alkaline phosphatase.

B. Acute Liver Failure[24,25]

1. **Definition:** Laboratory evidence of liver injury with no known history of chronic liver disease, the presence of coagulopathy not corrected by vitamin K administration, and an INR >1.5 if patient has encephalopathy or >2.0 if patient does not have encephalopathy.
2. **Differential Diagnosis:** Table 12.7
3. **Diagnosis:**
   a. **History:** Fatigue, nausea, vomiting, irritability, confusion, drowsiness, skin changes, medications, ingestion, illicit drug use, family history, developmental delay, transfusion history.
   b. **Physical Exam:** Neurologic status, skin exam, hepatosplenomegaly, nutritional status, growth, bruising, petechiae. Slit lamp exam if concern for Wilson disease. Findings of chronic liver disease include clubbing, palmar erythema, cutaneous xanthoma, ascites, and prominent abdominal vessels.
   c. **Labs:** Liver synthetic/metabolic function, liver cell injury, and biliary system tests (see earlier). BMP, magnesium, phosphorus, CBC with peripheral smear, reticulocyte count, ammonia, lipase. Factors V, VII (depleted first in ALF), VIII, and fibrinogen. A urine toxicology screen and a serum acetaminophen level should be obtained (see Chapter 3). Viral hepatitis studies, autoantibodies, and evaluation for metabolic syndromes must be considered.
   NOTE: See Chapter 17 for interpretation of serologic markers of hepatitis B.

d. **Imaging:** Abdominal US with Doppler flow. Consider head CT scan to exclude hemorrhage/edema, and chest radiography.
e. **Procedures:** Liver biopsy
f. **Management:** Evaluate for underlying cause. Consider intensive care unit (ICU) level care with close monitoring of mental status, fluid balance, metabolic disturbances, hepatorenal syndrome, sepsis, and coagulopathies. Cerebral edema is life-threatening and may require intracranial pressure monitoring. Consider liver transplant when indicated.

C. Nonalcoholic Fatty Liver Disease[26]

1. **Definition:** Chronic liver disease from excessive fat accumulation in the liver, often secondary to insulin resistance and obesity. Most common liver disease in children in the United States.
2. **Diagnosis:** Screen between 9 and 11 years for obese children and overweight children with risk factors. ALT is the recommended test. If ALT persistently elevated >2 times upper limit of normal for >3 months, further evaluation is warranted. Must exclude alternative etiologies.
3. **Management**: Extensive lifestyle modifications, well-balanced healthy diet. No medications have proven benefit. Bariatric surgery can be considered if severe comorbidities. Screen for diabetes and other comorbid conditions.

D. Hyperbilirubinemia[27-29]

1. **Definition**: Bilirubin is the product of hemoglobin metabolism. There are two forms: direct (conjugated) and indirect (unconjugated). Hyperbilirubinemia is usually the result of increased hemoglobin load, reduced hepatic uptake, reduced hepatic conjugation, or decreased excretion. Direct hyperbilirubinemia is defined as a direct bilirubin >20% of the total bilirubin or a direct bilirubin of >2 mg/dL.
2. **Differential Diagnosis:** Table 12.8
3. **Management**: Dependent upon etiology. Evaluation and diagnosis should be guided by history; however, liver laboratory studies (see earlier) and USs are warranted in many patients. Refer to Chapter 18 for evaluation and treatment of neonatal hyperbilirubinemia.

IV. PANCREATITIS[30-32]

Definition: Inflammatory disease of the pancreas.

A. Acute Pancreatitis[33]

1. **Diagnosis:**
   a. **History:** Abdominal pain, irritability, epigastric tenderness, nausea and vomiting. Multiple etiologies (Table 12.9). Per INSPPIRE criteria, diagnosis of acute pancreatitis requires at least two of the following:
      (1) Abdominal pain compatible with acute pancreatitis
      (2) Serum amylase and/or lipase values >3 times upper limit of normal
      (3) Imaging findings consistent with acute pancreatitis

TABLE 12.8

DIFFERENTIAL DIAGNOSIS OF HYPERBILIRUBINEMIA

INDIRECT HYPERBILIRUBINEMIA	
Transient neonatal jaundice	Breast milk jaundice and physiologic jaundice Polycythemia and reabsorption of extravascular blood
Hemolytic disorders	Autoimmune disease, blood group incompatibility, hemoglobinopathies, microangiopathies, red cell enzyme deficiencies, and red cell membrane disorders
Enterohepatic recirculation	Cystic fibrosis, Hirschsprung disease, ileal atresia, and pyloric stenosis
Disorders of bilirubin metabolism	Acidosis, Crigler-Najjar syndrome, Gilbert syndrome, hypothyroidism, and hypoxia
Miscellaneous	Dehydration, drugs, hypoalbuminemia, sepsis, and panhypopituitarism
DIRECT HYPERBILIRUBINEMIA	
Biliary obstruction	Biliary atresia, choledochal cyst, fibrosing pancreatitis, gallstones or biliary sludge, inspissated bile syndrome, neoplasm, and primary sclerosing cholangitis
Infection	Cholangitis, cytomegalovirus, adenovirus, enterovirus, Epstein-Barr virus, herpes simplex virus, histoplasmosis, human immunodeficiency virus, leptospirosis, liver abscess, sepsis, syphilis, rubella, toxocariasis, toxoplasmosis, tuberculosis, urinary tract infection, varicella-zoster virus, and viral hepatitis
Genetic/metabolic disorders	α_1-Antitrypsin deficiency, Alagille syndrome, Caroli disease, cystic fibrosis, Dubin-Johnson syndrome, galactokinase deficiency, galactosemia, glycogen storage disease, hereditary fructose intolerance, hypothyroidism, Niemann-Pick disease, progressive familial intrahepatic cholestasis (PFIC), Rotor syndrome, tyrosinemia, and Wilson disease
Chromosomal abnormalities	Trisomy 18, trisomy 21, and Turner syndrome
Drugs	Acetaminophen, aspirin, erythromycin, ethanol, iron, isoniazid, methotrexate, parenteral nutrition, oxacillin, rifampin, steroids, sulfonamides, tetracycline, and vitamin A
Miscellaneous	Neonatal hepatitis syndrome, parenteral alimentation, and Reye syndrome

b. **Labs:** CMP, GGT, CBC, amylase, lipase, calcium, and triglycerides.
c. **Imaging:** Transabdominal US recommended. CT or MRI reserved for more complicated cases depending on etiology.

2. **Management:**
   a. **Analgesia:** Acetaminophen or NSAIDs as first line therapy; opiates for refractory pain.
   b. **Nutrition:** Aggressive IV fluid hydration within initial 48 hours. Early enteral feeding recommended (within 72 hours of presentation and hemodynamically stable) and associated with shorter hospitalization and decreases comorbidity.

TABLE 12.9

CONDITIONS ASSOCIATED WITH ACUTE PANCREATITIS

SYSTEMIC DISEASES	
Infections	Coxsackie, CMV, cryptosporidium, EBV, hepatitis, influenza A or B, leptospirosis, mycoplasma, mumps, rubella, typhoid fever, and varicella
Inflammatory and vasculitic disorders	Collagen vascular diseases, hemolytic uremic syndrome, Henoch-Schönlein purpura, IBD, and Kawasaki disease
Sepsis/peritonitis/shock	
IDIOPATHIC (UP TO 25% OF CASES)	
MECHANICAL/STRUCTURAL	
Trauma	Blunt trauma, child abuse, and ERCP
Anatomic anomalies	Annular pancreas, choledochal cyst, pancreatic divisum, stenosis, and other
Obstruction	Parasites, stones, and tumors
METABOLIC AND TOXIC FACTORS	
Drugs/toxins	Salicylates, cytotoxic drugs (L-asparaginase), corticosteroids, chlorothiazides, furosemide, oral contraceptives (estrogen), tetracyclines, sulfonamides, valproic acid, azathioprine, and 6-mercaptopurine
Cystic fibrosis	
Diabetes mellitus	
Hypercalcemia	
Hyperlipidemia	
Hypothermia	
Malnutrition	
Organic academia	
Renal disease	

CMV, Cytomegalovirus; *EBV*, Epstein-Barr virus; *ERCP*, endoscopic retrograde cholangiopancreatography; *IBD*, inflammatory bowel disease.

c. **Complications**: Multiorgan dysfunction, shock, pseudocysts, fluid collections, and necrosis. Antibiotics reserved for infected necrosis. Surgical consult as indicated.

B. Chronic Pancreatitis[34,35]

1. **Diagnosis:**
   a. **History:** Abdominal pain consistent with pancreatic origin, pancreatic insufficiency; plus consistent imaging findings or biopsy with histopathologic features. Must be distinguished from acute recurrent pancreatitis (ARP), which is defined as at least two distinct episodes of pancreatitis with complete resolution of pain or normalization of laboratory levels.
   b. **Labs**: Same as acute pancreatitis. Normal amylase/lipase does not exclude diagnosis of chronic pancreatitis or ARP. Fecal elastase to screen for exocrine function and fat-soluble vitamins assessment. Consider genetic testing.

TABLE 12.10

PROPOSED ETIOLOGIES OF CHRONIC PANCREATITIS IN CHILDHOOD

Calcific	Cystic fibrosis, hereditary pancreatitis (e.g., PRSS1 and SPINK1 mutations), hypercalcemia, hyperlipidemia, idiopathic, and juvenile tropical pancreatitis
Obstructive (noncalcific)	Congenital anomalies, idiopathic fibrosing pancreatitis, renal disease, sclerosing cholangitis, sphincter of Oddi dysfunction, and trauma

Modified from Robertson MA. Pancreatitis. In: Walker WA et al, eds. *Pediatric Gastrointestinal Disease*. 3rd ed. New York: BC Decker; 2000:1321–1344; Werlin SL. Pancreatitis. In: McMillan JA et al, eds. *Oski's Pediatrics*. Philadelphia: Lippincott Williams & Wilkins; 2006:2010–2012.

c. **Imaging**: Repeat imaging recommended with US and/or MRCP. **Note:** See Table 12.10 for proposed etiologies of chronic pancreatitis in childhood.

2. **Management:** (For acute exacerbations) same as management of acute pancreatitis. Maintenance to focus on nonmedication strategies, adequate nutrition for growth, nonopioids and planned opioids.

V. WEB RESOURCES

- North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition: www.naspghan.org
- Children's Digestive Health Information for Kids and Parents: www.gikids.org
- Celiac Disease Foundation: clinical.celiac.org
- Rome Foundation for Diagnosis and Treatment of Functional Gastrointestinal Disorders: www.theromefoundation.org

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 13

Genetics: Metabolism and Dysmorphology

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See additional content on Expert Consult

I. METABOLISM[1-7]

A. Clinical Presentation of Metabolic Disease (Box 13.1)

1. Metabolic disease can be conceptualized into broad categories (Table 13.1).
2. When considering a particular diagnosis, a complete patient history, including details of conception, pregnancy, prenatal screening and diagnostic studies, delivery, postnatal growth, development, and a three-generation family history in the form of a pedigree (Fig. EC 13.A) should accompany a comprehensive physical examination. The family history may be remarkable for close relatives who died of similar presentations (may be mistaken for "sepsis" or "SIDS").
3. A high index of suspicion is required, as routine investigations may be unrevealing.
4. Routine newborn screening (see Section II) is meant to detect many metabolic disorders before onset of clinical symptoms, but the conditions tested for vary by state and not all countries test, so clinical suspicion should remain high if clinical picture is concerning.

B. Evaluation

1. **Initial laboratory tests:** Comprehensive metabolic panel, blood glucose, venous blood gas (VBG), ammonia (beware false-positives from tourniquets, struggling children, or sample delay), lactate, creatine kinase (CK), complete blood cell count with differential, urine ketones.
2. **Subsequent evaluation for metabolic disease:**
   a. Consult a geneticist.
   b. A basic metabolic work-up includes plasma amino acids (PAA), urine organic acids (UOA), acylcarnitine profile, quantitative (free and total) plasma carnitine, lactate/pyruvate ratio. Further specialized biochemical testing is available.
3. **Additional labs given specific circumstances:**
   a. **Metabolic acidosis**: Ammonia, lactate, b-hydroxybutyrate, acetoacetate, UOA, urinalysis with urine pH, acylcarnitine profile, quantitative (free and total) plasma carnitine (Fig. 13.1).
   b. **Hyperammonemia**: VBG, UOA, PAA, acylcarnitine profile, urine orotic acid (Fig. 13.2).

BOX 13.1

WHEN TO SUSPECT METABOLIC DISEASE[1-3]

Overwhelming illness in the neonatal period
Vomiting
Acute acidosis, anion gap
Massive ketosis
Hypoglycemia
Coagulopathy
Coma
Seizures, especially myoclonic
Hypotonia
Unusual odor of urine
Extensive dermatosis
Neutropenia, thrombocytopenia, or pancytopenia
Family history of siblings dying early

TABLE 13.1

BROAD CLASSIFICATION OF METABOLIC DISEASE[1-6]

Intoxication disorders Toxic accumulation of small molecules upstream of a defective enzyme. Tend to present early in life with nonspecific symptoms that may include recurrent vomiting, irritability, lethargy progressing to coma, organ dysfunction. Symptoms may wax and wane with intercurrent illness.	Table 13.2 Acidosis algorithm Fig. 13.1 Hyperammonemia algorithm Fig. 13.2
Disorders of reduced fasting tolerance Disorders in the body's ability to tolerate fasting, with early onset of hypoglycemia. Can present in infancy or later when trying to sleep through the night, including morning symptoms or seizures. Look for laboratory abnormalities and symptoms not usually found in typical fasting.	Table 13.3 Hypoglycemia algorithm Fig. 13.4
Disorders of complex molecules These disorders have a broad phenotypic spectrum and typical biochemical screening can be unrevealing. Features can be present at birth and/or slowly progressive affecting multiple organ systems. Often enzymatic and/or broad molecular genetic testing is needed.	Table 13.4
Mitochondrial disorders Defect in energy production through the electron transport chain. There is a broad spectrum of clinical manifestations, often involving high-energy organs including brain, muscle, and/or heart.	Table 13.5
Neurotransmitter disorders Defect in neurotransmission which can present around birth with severe infantile epileptic encephalopathy, or later with parkinsonism-dystonia, neruodevelopmental or psychiatric disorders.	Table 13.6

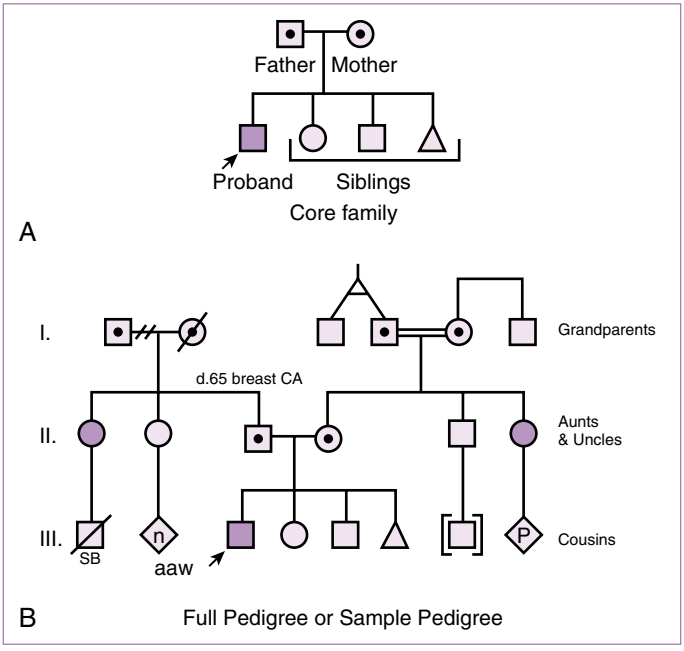

FIG. EC 13.A
Pedigree construction.

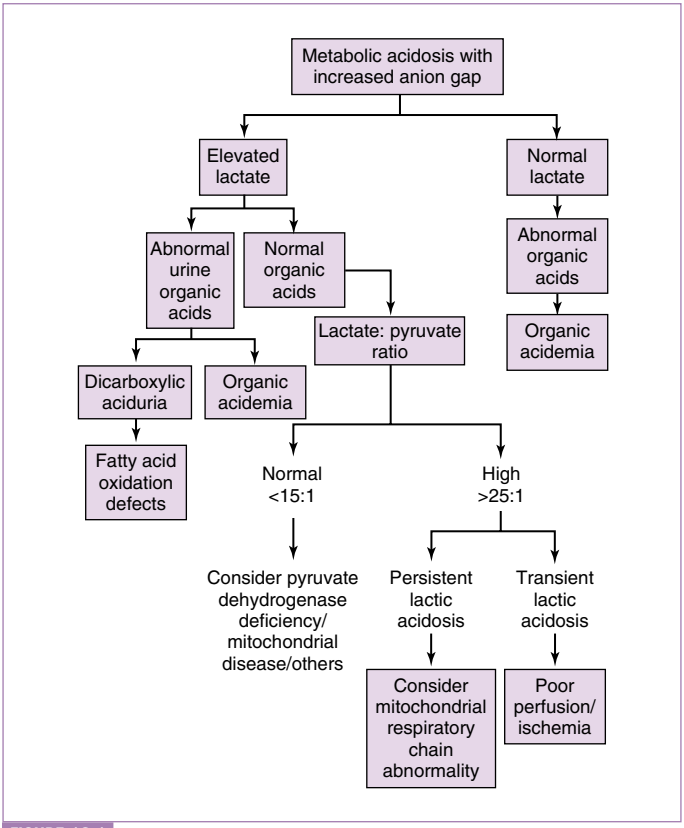

FIGURE 13.1

Evaluation of metabolic acidosis with increased anion gap. (From Burton B. Inborn errors of metabolism in infancy: a guide to diagnosis. *Pediatrics*. 1998;102:E69.)

c. **Hypoglycemia**: Samples at time of hypoglycemia—glucose, insulin, growth hormone, free fatty acids, b-hydroxybutyrate (see Chapter 10). Cortisol, fasting and postprandial lactate, urine ketones, creatine kinase, acylcarnitine profile, PAA, UOA (Fig. 13.3).

d. **Neonatal seizures:** Cerebrospinal fluid (CSF) amino acids and PAA, CSF/serum glucose ratio, serum and CSF neurotransmitters, CSF and plasma lactate, plasma very-long-chain fatty acids, UOA, serum uric acid, urine sulfites. Consider trial of pyridoxine.

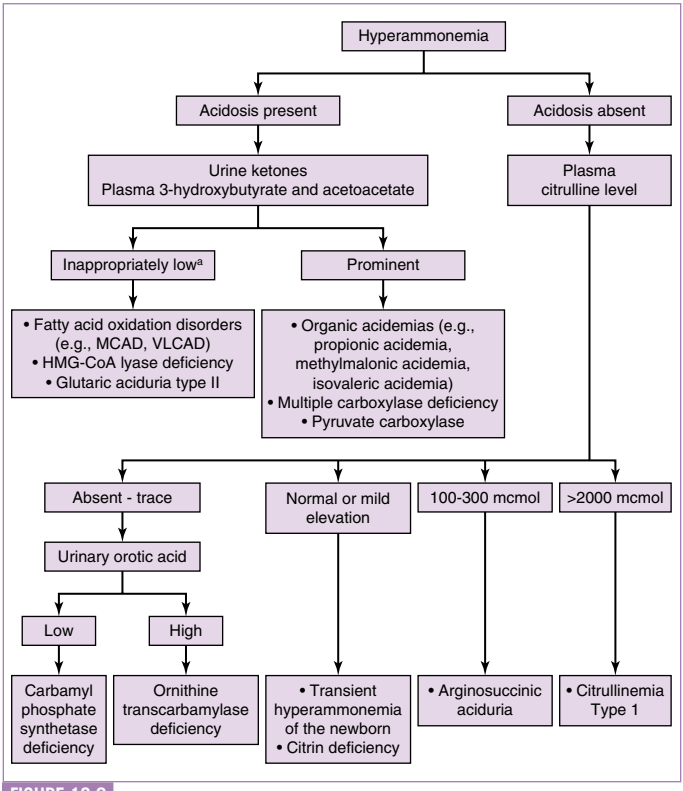

FIGURE 13.2

Evaluation of hyperammonemia.

Indicates inappropriately low urinary ketones in the setting of symptomatic hypoglycemia. *HMG-CoA*, Hydroxymethylglutaryl-CoA; *MCAD*, medium-chain acyl-CoA dehydrogenase; *VLCAD*, very-long-chain acyl-CoA dehydrogenase.

C. Categories of Metabolic Disorders

1. **Intoxication disorders** (Table 13.2)
2. **Disorders of reduced fasting tolerance** (Table 13.3)
3. **Disorders of complex molecules** (Table 13.4)
4. **Mitochondrial disorders** (Table 13.5)
5. **Neurotransmitter disorders** (Table 13.6)

D. Management of Metabolic Crisis

1. Specific acute management available in Tables 13.2–13.6.

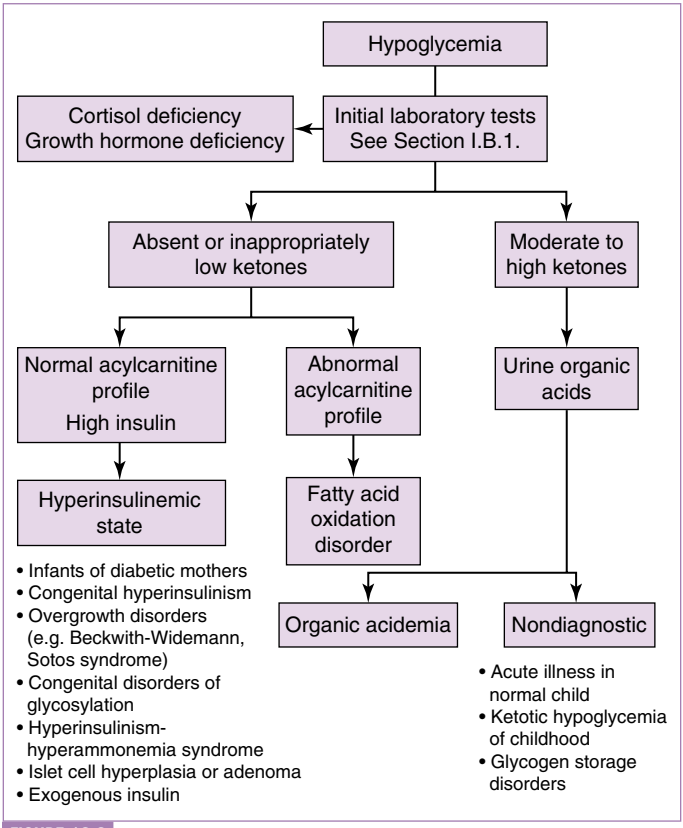

FIGURE 13.3

Evaluation of hypoglycemia. (Modified from Burton BK. Inborn errors of metabolism in infancy: a guide to diagnosis. *Pediatrics*. 1998;102:E69; and Cox GF. Diagnostic approaches to pediatric cardiomyopathy of metabolic genetic etiologies and their relation to therapy. *Prog Pediatr Cardiol*. 2007;24:15–25)

2. A general guiding principal is to provide hydration and enough glucose to meet the patient's caloric needs to stop catabolism.
   a. Use **D10% + electrolytes for age at 1.5 to 2 times maintenance rate.**
   b. Use caution in mitochondrial disorders (and do not use D10 in pyruvate dehydrogenase deficiency), because this may enhance lactic acidosis. If uncertain, measure lactate and acid-base status regularly.
3. For unknown/suspected metabolic disease, treatment should *not* be delayed during work-up.

TABLE 13.2

INTOXICATION DISORDERS[1-6]

Disorders With Selected Examples	Etiology, Clinical Presentation	Acute Management[a]	Chronic Management[a]	Diagnostic Testing[a]
Urea Cycle Disorders OTC Deficiency CPS I Deficiency Citrullinemia	Unable to metabolize proteins to energy Acute intoxication episodes of hyperammonemia, ± respiratory alkalosis	**Reversal of Catabolism** Bolus if dehydration D10 + ¼ NS to NS at 1.5–2× maintenance **Stop Intake of Offending Agents** Stop protein intake (NPO). Resume within 24–48 hrs to prevent deficiencies of essential nutrients **Toxin Removal** Removal of ammonia via sodium benzoate + sodium phenylacetate (Ammonul) with arginine IV or dialysis as indicated for ammonia >250 μmol/L	Protein-restricted diet Ammonia scavengers (e.g., sodium phenylbutyrate) Arginine supplementation (dependent on defect)	PAA Urine orotic acid Molecular testing OTC deficiency (most common, X-linked) and CPS I deficiency are not picked up on newborn **screening**
Organic Acidemias Propionic Acidemia Methylmalonic Acidemia Isovaleric Acidemia	Unable to metabolize certain amino acids and fats Acute intoxication episodes of hyperammonemia with metabolic acidosis Bone marrow suppression, cardiomyopathy	**Reversal of Catabolism,** as above **Stop Intake of Offending Agents,** as above **Toxin Removal** Carnitine in propionic, methylmalonic, and isovaleric acidemia. Glycine in isovaleric acidemia Bicarbonate if pH <7.1	Formula that restricts certain amino acids Carnitine	Acylcarnitine profile Quantitative (free and total) carnitine PAA UOA Molecular testing
Maple Syrup Urine Disease	Unable to metabolize branched-chain amino acids (BCAAs) Acute intoxication with high leucine leads to intracranial edema and coma Inappropriate urinary ketones	**Reversal of Catabolism,** as above **Stop Intake of Offending Agents** Stop protein from food and continue BCAA-free formula, valine, and isoleucine **Toxin Removal** Dialysis in extreme situations	Diet and formula that restricts BCAAs Supplementation with isoleucine and valine	PAA UOA Molecular testing

TABLE 13.2

INTOXICATION DISORDERS[1-6]—cont'd

Disorders With Selected Examples	Etiology, Clinical Presentation	Acute Management[a]	Chronic Management[a]	Diagnostic Testing[a]
Aminoacidopathies Phenylketonuria (PKU) Tyrosinemia (HT)	Unable to metabolize phenylalanine (PKU) or phenylalanine and tyrosine (HT) PKU: intellectual disability if untreated HT: liver failure, vomiting, pain crisis, hyponatremia, Fanconi syndrome	Supportive. Dextrose-based fluids are safe for use HT: Pain control and hydration during pain crisis	PKU: Phenylalanine-restricted diet; sapropterin effective in some HT: Tyrosine- and phenylalanine-restricted diet; Nitisinone	PAA HT: UOA for succinylacetone Molecular testing
Carbohydrate Disorders Galactosemia Hereditary Fructose Intolerance (HFI)	Unable to metabolize galactose (galactosemia) or fructose (HFI) Vomiting, diarrhea, liver failure, renal failure Galactosemia: risk of *Escherichia coli* sepsis	Supportive. Dextrose-based fluids are safe for use	Galactosemia: Avoidance of galactose (and lactose); Soy-based formulas HFI: Avoidance of fructose (and sucrose)	Urine reducing substances Galactosemia: erythrocyte gal-1-phosphate, galactose-1-phosphate uridyltransferase activity Molecular testing
Metal Disorders Menkes Wilson Disease Hemochromatosis	Defects in the uptake or excretion of metals Liver disease + neurologic involvement (Menkes, Wilson) + cardiomyopathy (Hemochromatosis)	Chelation therapy	Wilson: Copper avoidance, copper chelation Menkes: Copper supplementation Hemochromatosis: Phlebotomy, iron chelation	Serum copper Ceruloplasmin Iron Ferritin Transferrin Molecular Testing

[a]Management and testing should be in partnership with a genetics physician, as comprehensive details are beyond the scope of this resource.

CPS, Carbamoyl phosphate synthetase; *D10*, dextrose 10%; *IV*, intravenous; *NPO*, nil per os; *NS*, normal saline; *OTC*, ornithine transcarbamylase; *PAA*, plasma amino acids; *UOA*, urine organic acids.

TABLE 13.3

DISORDERS OF REDUCED FASTING TOLERANCE[1-6]

Disorders With Selected Examples	Etiology, Clinical Presentation	Acute Management[a]	Chronic Management[a]	Diagnostic Testing[a]
Fatty Acid Oxidation (FAO) Disorders VLCAD deficiency LCHAD deficiency MCAD deficiency	Disorders of fat metabolism Hypoketotic hypoglycemia in fasting. Can also present with rhabdomyolysis, cardiomyopathy, liver disease.	**Reversal of Fasting State** Bolus glucose if hypoglycemia D10 + ½ NS to NS at 1–1.5× maintenance **Stop Intake of Offending Agents** No IV lipids or long chain fats	Avoid prolonged fasting. Use of uncooked cornstarch for sustained anabolism. Nighttime feedings may be needed. For very-long-chain fatty acid disorders, limit intake of low-fat foods and supplement with medium-chain triglyceride oil.	Acylcarnitine profile Quantitative (free and total) carnitine UOA Urine acylglycines
Glycogen Storage Disorders GSD1a, 1b GSD II GSD III GSD IV GSD V GSD VI GSD IX	Multisystem disorders resulting from defects in the synthesis and catabolism of glycogen *Hepatic glycogenoses* (GSD Ia [von Gierke], GSD VI, GSD IX): Hepatomegaly, fasting ketotic hypoglycemia. ± hyperlipidemia, uremia, lactic acidosis *Muscle glycogenoses* (GSD V [McArdle], GSD II [Pompe]): Skeletal and cardiac muscle involvement resulting in fatigue, elevations in creatine kinase *Mixed* (GSD III [Cori], GSD IV): Fasting ketotic hypoglycemia with myopathy	**Reversal of Fasting State,** as above	Prevent long periods of fasting with use of cornstarch GSD II (Pompe): Enzyme replacement	Glucose Lactate Uric acid Lipid panel Transaminases CK Electrocardiogram Echocardiogram Enzyme activity Molecular testing

[a]Management and testing should be in partnership with a genetics physician, as comprehensive details are beyond the scope of this resource.

CK, Creatine kinase; *D10*, dextrose 10%; *GSD*, glycogen storage disease; *IV*, intravenous; *LCHAD*, long-chain L-3 hydroxyacyl-CoA dehydrogenase; *MCAD*, medium-chain acyl-CoA dehydrogenase; *NS*, normal saline; *UOA*, urine organic acids; *VLCAD*, very-long-chain acyl-CoA dehydrogenase.

TABLE 13.4

DISORDERS OF COMPLEX MOLECULES[1-6]

Disorders With Selected Examples	Etiology, Clinical Presentation	Management[a]	Diagnostic Testing[a]
Mucopolysaccharidoses MPS I (Hurler) MPS II (Hunter) MPS III (SanFillipo) MPS IV (Morquio) MPS VI (Maroteaux-Lamy)	Chronic, progressive, multisystem disorders from glycosaminoglycan accumulation Coarse facial features and organomegaly: MPS I Hurler, MPS II Hunter, MPS III SanFillipo Developmental Delay: MPS III SanFillipo Skeletal dysplasia: MPS IV Morquio	Acute management is supportive Stem cell transplantation: MPS I Enzyme replacement: MPS I, MPS II, MPS IV, MPS VI.	Skeletal survey for dysostosis multiplex Urine glycosaminoglycans Urine oligosaccharides Enzyme activity Molecular testing
Sphingolipidoses Gaucher Niemann-Pick Type A, B Tay-Sachs Krabbe Fabry	Impaired degradation of sphingolipids Progressive psychomotor retardation and neurologic problems (e.g., epilepsy, ataxia, and spasticity), hepatosplenomegaly Normal intellect: Gaucher (+ bone crises), Niemann-Pick B (+ lung disease), Fabry (+ acroparathesias, renal or cardiac disease)	Acute management is supportive Enzyme replacement: Gaucher, Fabry Stem cell transplant: Krabbe Substrate reduction with miglustat or eliglustat: Gaucher	Urine oligosaccharides Enzyme activity Molecular testing
Sterol Synthesis Disorders Smith-Lemli-Opitz Greenberg dysplasia	Multisystem disorders with dysmorphic features and variable skeletal dysplasia	Acute: Adrenal insufficiency may be present Chronic: Consider cholesterol supplementation and/or simvastatin for some disorders	Plasma sterols Serum cholesterol Molecular testing
Peroxisomal Disorders Zellweger Rhizomelic chondrodysplasia punctata (RCDP) X-Linked Adrenoleukodystrophy	Abnormal peroxisome function or synthesis Neurologic abnormalities such as hypotonia, encephalopathy, seizures, ocular findings Dysmorphic facial features: Zellweger Rhizomelia: RDCP Leukodystrophy: X-linked adrenoleukodystrophy	Acute: Stress dose corticosteroids if adrenal insufficiency Chronic: Stem cell transplant for X-linked adrenoleukodystrophy	Very-long-chain fatty acids including Phytanic and Pristanic Pipecolic acids Erythrocyte plasmalogen Molecular testing

[a]Management and testing should be in partnership with a genetics physician because comprehensive details are beyond the scope of this resource.

MPS, Mucopolysaccharidosis.

TABLE 13.5

MITOCHONDRIAL DISORDERS[1-6]

Disorders With Selected Examples	Clinical Presentation	Management[a]	Diagnostic Testing[a]
Mitochondrial Disorders MELAS MERRF Leigh Kearns-Sayre	Multisystemic disease which can include lactic acidosis, muscle weakness, cardiomyopathy, ataxia, ophthalmoplegia, neuropathy, chronic diarrhea	Acute: For MELAS, IV arginine may abort a neurologic crisis Chronic: Cocktail of antioxidants, vitamins, and cofactors	Serum & CSF lactate and pyruvate Plasma and CSF amino acids UOA Brain imaging Molecular testing Muscle biopsy

[a]Management and testing should be in partnership with a genetics physician, as comprehensive details are beyond the scope of this resource.
CSF, Cerebrospinal fluid; *IV*, intravenous; *MELAS*, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; *MERRF*, myoclonic epilepsy with ragged red fibers; *UOA*, urine organic acids.

TABLE 13.6

NEUROTRANSMITTER DISORDERS[1-6]

Disorders With Selected Examples	Clinical Presentation	Management[a]	Diagnostic Testing[a]
Neurotransmitter Disorders Nonketotic hyperglycinemia (NKH) Sulfite Oxidase Deficiency B6-dependent seizures GABA receptor mutations or metabolism defects	Infantile epileptic encephalopathy	Acute: Consider trial of pyridoxine +/- folinic acid	CSF neurotransmitters CSF glucose Urine sulfite PAA UOA Molecular testing
Dopamine Disorders Dopa-responsive dystonia Tyrosine hydroxylase deficiency	Dystonia, dyskinesia	Dopamine	CSF biogenic amines

[a]Management and testing should be in partnership with a genetics physician, as comprehensive details are beyond the scope of this resource.
CSF, Cerebrospinal fluid; *GABA*, γ-aminobutyric acid; *PAA*, plasma amino acid; *UOA*, urine organic acid.

E. Commonly Used Medications

1. Carnitine 50 mg/kg/dose intravenous (IV) every 6 hours when ill, or 100 mg/kg/day orally (PO) divided every 8 hours when well. For dosing in primary carnitine deficiency, see Formulary.
2. Sodium phenylacetate (10%) + sodium benzoate (10%) (Ammonul) should be combined with arginine HCl in a 25 to 35 mL/kg 10% dextrose solution and administered through a central venous catheter to treat acute hyperammonemia in a urea cycle patient.
   a. For a child less than 20 kg, the dose is 250 mg/kg sodium phenylacetate and 250 mg/kg sodium benzoate.
   b. For a child greater than 20 kg, the dose is 5.5 g/m^2 sodium phenylacetate and 5.5 g/m^2 sodium benzoate.

   c. The dose of arginine HCl is 200 to 600 mg/kg, depending on the diagnosis.
      (1) 200 mg/kg for carbamylphosphate synthase (CPS) deficiency and ornithine transcarbamylase (OTC) deficiency.
      (2) 600 mg/kg for citrullinemia and argininosuccinate lyase (ASL) deficiency.
   d. Administer as a loading dose over 90 to 120 minutes, followed by an equivalent dose as a maintenance infusion over 24 hours.
3. Arginine HCl for MELAS stroke-like episode: bolus of 0.5 g/kg given within 3 hours of symptom onset, followed by an additional 0.5 g/kg administered as a continuous infusion for 24 hours for the next 3 to 5 days.[9] (MELAS: mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes)
4. Sodium benzoate for nonketotic hyperglycinemia (NKH): start with 500 mg/kg/day added to a 24-hour supply of formula or divided at least 4 times daily and consult a biochemical geneticist.[10]

II. NEWBORN METABOLIC SCREENING[7]

A. Timing

1. First screen should be performed within the first 48 to 72 hours of life (at least 24 hours after initiation of feeding).
2. Second screen (requested in some states) should be performed after 7 days of age.
3. Preterm infants: Perform initial screen at birth (to collect sample before transfusions), another at age 48 to 72 hours, a third at age 7 days, and a final at age 28 days or before discharge (whichever comes first).

B. Abnormal Result

1. Requires immediate follow-up and confirmatory testing; consult a geneticist.
2. ACT Sheets and Confirmatory Algorithms are available for more information on how to proceed with specific abnormalities: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx (search ACT sheets).

C. Results Affected by Transfusion

Note: Repeat newborn metabolic screen 3 months after last transfusion.

1. Biotinidase enzyme activity
2. Galactose-1-phosphate uridyltransferase (GALT) activity
3. Hemoglobinopathy evaluation

III. DYSMORPHOLOGY[7,11-14]

A. History

Pertinent history includes pregnancy course, prenatal exposures, type of conception (natural or assisted), perinatal history, developmental milestones, and review of systems.

B. Family History

1. Three-generation pedigree focused on both medical and developmental histories (see Fig. EC 13.A).
2. Helpful mnemonics include:
   a. SIDE mnemonic[15]: Anything SIMILAR in the family? Anything INHERITED through the family? Any premature, unexplained DEATHS? Any EXTRAORDINARY events?
   b. SCREEN mnemonic[16]: SOME CONCERNS about conditions running in the family? REPRODUCTION—any issues with pregnancy infertility, or birth defects? EARLY disease, death, or disability? ETHNICITY? NONGENETIC—any other risk factors?
   c. Rule of Too/Two[13]:
      (1) Too: tall? short? many? few? early? young? different?
      (2) Two: cancers? generations? in the family? birth defects?
3. **Patterns of inheritance:** See Online Content for discussion of different patterns of inheritance.

C. Physical Examination

1. **Major anomalies:** Structural anomalies that are found in less than 5% of the population and may cause significant cosmetic or functional impairment, often requiring medical or surgical management.
2. **Minor anomalies**[11,12,14,17]: Structural anomalies that are found in greater than 5% of the population with little or no cosmetic or functional significance to the patient.
3. Examples of major and minor anomalies (Table 13.7). Three or more minor anomalies may be a nonspecific indicator of occult or major anomaly.

D. Work-up

1. **Imaging to evaluate for major anomalies**
   a. Head ultrasound (US) or brain magnetic resonance imaging (MRI)
   b. Echocardiogram
   c. Complete abdominal US
   d. Skeletal survey with radiographs composed of: AP views of skull, chest/ribs, upper extremities and hands, lower extremities and feet; lateral views of skull, complete spine, chest, and odontoid view.
2. **Dilated eye exam**
3. **Hearing evaluation**
4. **Genetic testing:** See Fig. 13.4 and Table 13.8. The patient should be referred to genetics for a dysmorphology evaluation and appropriate testing.

TABLE 13.7

EXAMPLES OF DYSMORPHOLOGY EXAM FINDINGS[11-14,17]

	Major Anomalies	Minor Anomalies
General	Growth <3rd percentile	Short or tall stature
Head	Structural brain abnormalities (e.g., holoprosencephaly, schizencephaly), craniosynostosis	Asymmetric head shape, micrognathia, prominent metopic ridge, widows peak
Eyes	Anophthalmia, cataracts, coloboma	Palpebral fissures, epicanthal folds, hypertelorism or hypotelorism, telecanthus, epicanthus, ptosis
Ears, Nose, Throat	Cleft lip/palate, tracheal-esophageal fistula	Periauricular pits/tags, overfolded helix, everted ears, low set ears, microtia, abnormal nasal bridge, branchial cleft cysts
Chest/Lungs	Congenital diaphragmatic hernia, situs inversus	Inverted nipples, accessory nipples, pectus excavatum or carinatum
Heart	Congenital heart defects (e.g., tetralogy of Fallot, coarctation of aorta, atrial or ventricular septal defects)	Patent ductus arteriosus, valvular abnormalities
Abdomen	Omphalocele, gastroschisis, intestinal atresia	Umbilical hernia
Genitourinary	Ambiguous genitalia, horseshoe kidney	Hypogonadism, pelvic kidney, shawl scrotum, labial hypoplasia
Musculoskeletal	Skeletal dysplasia, spina bifida	Clubfeet, bowing, syndactyly of two digits, post axial polydactyly, 5th finger clinodactyly, hypoplastic nails, short metacarpals or metatarsals
Skin	Cutis aplasia	Striae, café au lait spots, atypical skin creases, transverse palmar crease, nevus simplex, congenital dermal melanocytosis

IV. PATTERNS OF DYSMORPHOLOGIC CONDITIONS[11,14]

This section is not comprehensive; it covers some common reasons to seek a genetics consult. These conditions will often be managed by a multidisciplinary team.

A. Cardiac Disorders

1. **Congenital heart disease**: Investigation for co-occurring anomalies with abdominal US. Chromosome microarray testing indicated, including for 22q11 deletion syndrome. Table 13.9.
2. **Cardiomyopathy**: Can be from inborn errors of metabolism, channelopathies, mutations in genes important for sarcomere and desmosome production/function, or other single gene disorders.
3. **Long QT disorders**: Many single gene disorders.

B. Ciliopathies

1. **Nonmotile ciliopathies**: Defects in primary (nonmotile) ciliary function. Cystic renal disease, brain malformations (molar tooth sign), retinal

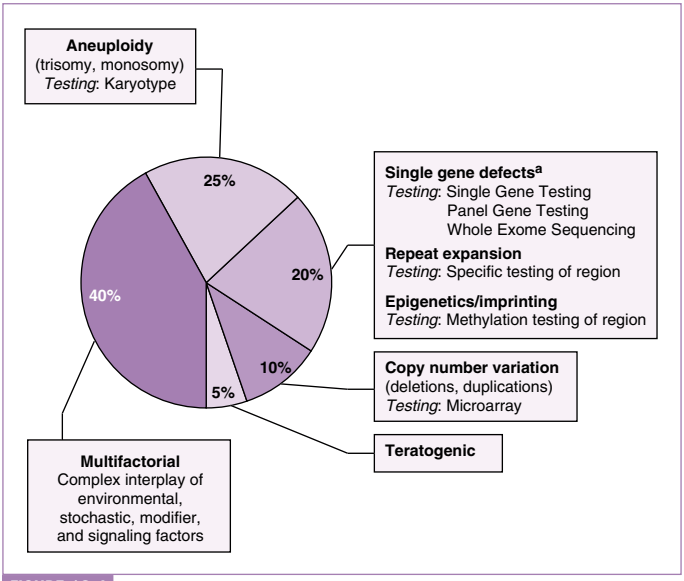

FIGURE 13.4

Etiologies of dysmorphic features.[29]

[a]Whole exome sequencing can only reliably detect single base pair changes and insertions/deletions of less than 20 base pairs.

degeneration, liver congenital hepatic fibrosis, polydactyly, skeletal dysplasia, obesity. **Examples**: Cystic kidneys as a result of heritable polycystic kidney disease; neurodevelopmental ciliopathies such as Joubert syndrome or Bardet-Biedl syndrome.

2. **Primary ciliary dyskinesias**: Defects in motile cilia. Recurrent respiratory infections (chronic sinopulmonary disease), infertility, situs inversus. **Examples**: More than 30 genes known to cause primary ciliary dyskinesia. When situs inversus is present, it is referred to as Kartagener syndrome.
3. **Evaluation**: Evaluation for potentially affected organ systems, including abdominal US, echocardiogram, brain MRI, and complete retinal evaluation with ophthalmology. Skeletal survey if limb defects. CMP to evaluate kidney and liver function. Unless a specific disorder suspected, broad genetic testing is appropriate.

C. Cleft Lip and Palate (CLP)

1. Can be isolated or part of a syndrome.
2. **Risk factors**: Maternal smoking, heavy alcohol use, systemic corticosteroid use, folic acid and cobalamin deficiency.[18]
3. Submucosal clefts may be indicated by a bifid uvula.
4. **Evaluation**: Children can have difficulties with feeding, speech, and hearing (chronic otitis or hearing loss as part of a syndrome). If not an isolated anomaly, may need further work-up with ophthalmology and echocardiogram.

TABLE 13.8

DIAGNOSTIC GENETIC TESTING AND CLINICAL CONSIDERATIONS

Genetic Testing Technology	Description of Technology	Turnaround Time	Able to Detect	Specific Indications
Karyotype	Systematically arranged photomicrograph of chromosomes	1–2 weeks	Aneuploidy, larger deletions/duplications (≥5kb), translocation or balanced rearrangements	Indicated for suspected aneuploidy, recurrent miscarriage, looking for a balanced translocation
Fluorescence in situ hybridization (FISH)	Mapping a segment of DNA by molecular hybridization of a fluorescent probe	<1 week	Presence or absence of a specific site or chromosome	Not indicated, except in family studies and for rapid diagnosis of a suspected trisomy[32]
Microarray (a.k.a. Array CGH, SNP or oligo chromosomal microarray)	Comparative genome hybridization using a high-density SNP profile or oligos (short segments of DNA) across the genome	2–4 weeks	Genomic gains or losses (copy number variation [CNV]), regions of homozygosity (consanguinity). Incidental findings unrelated to phenotype.	First-line cytogenetic test for all patients with unexplained global developmental delay, intellectual disability, autism, and/or congenital anomalies
Single gene testing	Nucleotide-by-nucleotide Sanger sequencing of a single gene	~1 month	Mutations in specific gene of interest	Indicated when there is a strong clinical suspicion of a specific single gene disorder
Targeted mutation analysis	Detection of previously identified familial mutation or common population mutation	<1 month	Whether the patient has (or does not have) only the specific mutation tested	Confirmation of clinical diagnosis, presymptomatic genetic diagnosis, identification of carrier status, preimplantation genetic diagnosis, prenatal testing
Repeat expansion testing	Southern blot or triplet-repeat primed PCR	<1 month	The quantity of repeats in the specific gene tested	Indicated when there is a strong clinical suspicion of a triplet repeat disorder
Methylation analysis	Methylation multiplex ligation-dependent probe amplification	<1 month	Whether the region tested has normal or abnormal methylation	Indicated when there is a strong clinical suspicion of a specific methylation defect (e.g., Prader-Willi)

Genetic Testing Technology	Description of Technology	Turnaround Time	Able to Detect	Specific Indications
Next-generation sequencing (multiple gene panels)	Massively parallel sequencing of specific genes	1–2 months	Simultaneously identifies if there are any variants in multiple genes of interest	Used for syndromes with heterogeneity (mutations in different genes can cause the same phenotype, or the phenotypes are hard to distinguish clinically)
Whole exome sequencing (WES)	Massively parallel sequencing of almost all exons	2–6 months	Simultaneously identifies if there are any variants in the coding portions of genes that match the patient's phenotype. Incidental findings unrelated to phenotype.	More comprehensive genomic test indicated in an otherwise negative workup, or when cost-benefit ratio of more targeted testing is in favor of WES
Whole genome sequencing (WGS)	Massively parallel sequencing of entire genome	Variable	More uniform coverage of exonic, intronic, and splice site mutations. Incidental findings unrelated to phenotype.	Not widely clinically available; used mostly in research studies

CGH, Comparative genomic hybridization; *DNA*, deoxyribonucleic acid; *PCR*, polymerase chain reaction; *Kb*, kilobases; *SNP*, single nucleotide polymorphism.

TABLE 13.9

GENETIC SYNDROMES ASSOCIATED WITH CARDIAC DEFECTS[11]

Genetic Syndrome	Cardiac Defect	Other Features	Diagnostic Evaluation
Noonan Syndrome[a]	Pulmonary valve stenosis, hypertrophic cardiomyopathy	Short stature, broad neck, lymphatic dysplasia, low ears and hypertelorism, coagulation defects	"Rasopathy" gene panel including *PTPN11*
Williams Syndrome (7q11.23 deletion)[a]	Supravalvular aortic stenosis	Periorbital fullness, broad nasal tip, large ears, thick lips, small teeth, hypercalcemia, renal artery stenosis, connective tissue abnormalities, overfriendliness	Microarray
Holt-Oram Syndrome	ASD	Upper limb malformation, cardiac conduction disease	*TBX5* sequencing
Down Syndrome[a]	VSD, AV canal defect	(See Section V)	Karyotype
Turner Syndrome[a]	Coarctation of aorta	(See Section V)	Karyotype
22q11.2 Deletion Syndrome[a]	Tetralogy of Fallot, interrupted aortic arch, VSD	(See Section V)	Microarray

[a]Published clinical management guidelines available.[20]

ASD, Atrial septal defect; *AV*, atrioventricular; *VSD*, ventricular septal defect.

5. **Examples**: Autosomal dominant inheritance seen in Van der Woude syndrome (associated with lip pits) and Stickler syndrome (can have retinal detachment, hearing loss).

D. Connective Tissue Disorders

1. Consider when a patient has velvety skin, hyperextensible joints, abnormal scarring, poor healing, striae, pectus deformities, tall stature, myopia, lens dislocations, arachnodactyly.
2. **Evaluation**: Some connective tissue disorders are associated with dilated aorta (echocardiogram), dysplastic vessels, or fragility of lens/retina (ophthalmology evaluation).
3. **Examples**: Dilated aorta with characteristic physical features in Marfan syndrome; vascular fragility in vascular Ehlers-Danlos (type IV); isolated hyperextensibility of joints in hypermobile Ehlers-Danlos (type III).

E. Developmental Delay, Intellectual Disability

1. All children should be offered genetic evaluation.
2. See Chapter 9 for information on evaluation.
3. **Examples:** Microarray is first tier test because it can detect microdeletion and microduplication syndromes, such as 1p36 deletion syndrome. *FMR1* repeat testing can detect fragile X syndrome and heterozygous females, who can also have developmental delays. Further testing may be indicated to detect monogenic causes, such as Kleefstra syndrome.

F. Deafness, Hard of Hearing

1. Approximately 60% of hearing loss is genetic. It can be syndromic or nonsyndromic.
2. Consider perinatal infectious causes (e.g., cytomegalovirus).
3. **Evaluation**: Consider connexin 26 and 30 gene testing as first step if nonsyndromic and/or broad gene panel testing. Individualize inner ear/brain imaging. Ophthalmology assessment, ECG, and renal US should be done for those with negative connexin testing.
4. **Examples**: Approximately half of nonsyndromic hearing loss is from *GJB2* (encodes connexin 26) gene mutations. Syndromic causes include Usher syndrome, which can also have gradual blindness.

G. Hypotonia

1. **Central**: Abnormalities of brain function, normal strength or axial weakness, preserved/persistent newborn reflexes, normal CK, normal muscle bulk.
   a. **Evaluation**: CK to differentiate. Evaluate for causes such as hypothyroidism (TSH); evaluate brain structure and function with MRI and EEG.
   b. **Examples**: Beckwith-Wiedemann syndrome, Prader-Willi syndrome, peroxisomal disorders.
2. **Peripheral**: Alert, profound weakness that is often appendicular, absent reflexes, feeding difficulties, normal or increased CK.
   a. **Evaluation**: Evaluate for causes such as hypothyroidism (TSH) or mitochondrial disease (lactate/pyruvate). Electromyography (EMG) to determine if muscle or nerve affected. Consider that cardiac muscle could be affected (echocardiogram).
   b. **Examples:** Spinal muscular atrophy, myotonic dystrophy, muscular dystrophies.

H. Limb and Stature Disorders

1. Can be defects in collagen formation, bone formation, or remodeling.
2. **Evaluation**: Radiographic skeletal survey of all bones to localize dysplasia. Some disorders, including achondroplasia, can have narrowing at the foramen magnum or cervical instability (flexion/extension C-spine films). There can be a risk of central or peripheral sleep apneas (sleep study). Karyotype for females with short stature to evaluate for Turner syndrome. Unless a specific disorder suspected, broad genetic testing is appropriate.
3. **Examples**: Rhizomelic limb shortening and narrow foramen magnum seen in achondroplasia. Cervical instability seen in *COL2A1* gene mutations (spondyloepiphyseal dysplasia congenita, Stickler syndrome). The presence of multiple congenital joint contractures is called arthrogryposis, which is seen in many disorders. Fractures can be seen in osteogenesis imperfecta and hypophosphatasia.

I. Liver Disease

1. Liver failure and/or direct and indirect hyperbilirubinemia can be a manifestation of a metabolic disorder or the result of a genetic syndrome.

2. **Evaluation**: Metabolic work-up including PAA, UOA, urine succinylacetone, very-long-chain fatty acids, urine reducing substances. Some syndromes have ocular features (ophthalmology evaluation). Unless a specific disorder suspected, broad genetic testing is appropriate.
3. **Examples**: Cholestasis found in progressive familial intrahepatic cholestasis (type 1, 2, and 3). Liver dysfunction can be seen in tyrosinemia. Indirect/unconjugated hyperbilirubinemia can be seen in Gilbert and Crigler-Najjar syndromes.

J. Oncologic Disorders[19]

1. Approximately 9% of pediatric oncology patients have a heritable cancer predisposition syndrome or germline mutation. This puts them and affected family members at risk for certain cancers and may affect their individualized treatments.
2. Obtain a thorough family history with specific cancer diagnoses and age of diagnosis.
3. **Evaluation:** Many cancers warrant referral. Genetic testing is tailored to each specific diagnosis. Examples include myelodysplastic syndrome, medulloblastoma, atypical teratoid rhabdoid tumor, sarcomas, pituitary blastoma, and many more.
4. **Examples:** Early onset of cancers in Li-Fraumeni syndrome (especially sarcoma) and von Hippel-Lindau syndrome (especially hemangioblastoma).

K. Overgrowth

1. Generalized overgrowth can result in macrosomia at birth or height and/or head circumference greater than the 98th percentile.
2. Hemihypertrophy of a limb may be the result of mosaicism from somatic changes.
3. Be aware that certain overgrowth syndromes have associated cancer risks and may require routine monitoring (e.g., abdominal US screening in Beckwith-Wiedemann syndrome).
4. **Evaluation**: Disorder-specific genetic testing based on exam findings; may require skin biopsy. In some disorders, internal organs can be affected (echocardiogram, ECG, renal US).
5. **Examples**: Generalized overgrowth with developmental delays can be the result of Sotos syndrome, Beckwith-Wiedemann syndrome, or others. Segmental overgrowth/hemihypertrophy can result from somatic *PIK3CA* mutations affecting the brain (MCAP syndrome) or a limb (Klippel-Trénaunay syndrome).

L. Seizure Disorders

1. Consider genetics especially with positive family history, intractable epilepsy, infantile onset, developmental regression, intellectual disability, dysmorphic features, autism, or brain malformations.
2. Can be the result of metabolic conditions or syndromic disorders.
3. Increased recurrence risk in families even if no genetic cause identified.
4. **Evaluation**: Consideration of microarray, epilepsy panels, or whole exome sequencing (particularly if dysmorphic features present);

consider biochemical testing for inborn errors of metabolism; physical exam with Wood's lamp for cutaneous manifestations (e.g., hypopigmented macules).

5. **Examples**: Sodium channel defects (*SCN1A* mutations) can lead to a broad spectrum of seizures. Accompanying dermatologic findings can be characteristic for neurocutaneous disorders, including neurofibromatosis type 1 and tuberous sclerosis.

M. Skin Pigmentation Alterations

1. Can be the result of post-zygotic mosaicism. As a result, genetic variants may only be detectable in affected skin and not in blood.
2. Skin and the central nervous system are derived from the same neural crest lineage; many skin pigmentation anomalies have associated central nervous system abnormalities, including malformations or seizures. Often referred to as neurocutaneous disorders.
3. **Evaluation**: Examination with a Wood's lamp, ophthalmology evaluation
4. **Examples**: Multiple café-au-lait macules seen in neurofibromatosis type 1 and Legius syndrome. Genetic mosaicism in skin can lead to a pigmentation pattern called hypomelanosis of Ito.

N. Vascular Anomalies

1. Can involve arterial, vascular, and lymphatic systems. Can be caused by germline mutations or postzygotic somatic changes (mosaicism). Some are associated with segmental overgrowth.
2. Vascular syndromes can cause clinically significant arteriovenous malformations and arteriovenous fistulas in the skin, internal organs, and brain/spine.
3. **Evaluation**: Examine mucosal membranes. Some disorders require evaluation for intraorganal arteriovenous malformations with abdominal US and/or MRI/magnetic resonance angiography (MRA) of brain and spine. Several disorders are autosomal dominant—obtain family history for vascular lesions.
4. **Examples**: Autosomal dominant history of multiple capillary malformations could be from *RASA1* mutations. Port-wine stains seen in Sturge-Weber syndrome. Telangiectasias on lips, nose, and hands seen in hereditary hemorrhagic telangiectasia.

V. ETIOLOGIES OF DYSMORPHIC FEATURES (FIG. 13.5)[11,14,29]

A. Aneuploidy

Abnormal number of chromosomes.

1. Aneuploidy syndromes are most commonly due to maternal nondisjunction and more rarely due to chromosomal translocation or mosaicism. Risk increases with maternal age.
2. The evaluation for aneuploidy often begins prenatally with a first trimester screen (nuchal translucency, nasal bone, free β-human chorionic gonadotropin [β-hCG], PAPP-A) or circulating cell-free fetal DNA analysis showing increased risk.

3. Prenatal diagnostic testing options include chorionic villus sampling in the first trimester or amniocentesis during or after the second trimester.
4. Fluorescence in situ hybridization (FISH) may be performed in the first 24 to 48 hours of life to indicate number of chromosomes but will not determine the morphology of the chromosomes (e.g., if a translocation is present). Therefore karyotype analysis is still indicated in aneuploidy syndromes, both to provide a diagnosis and to provide accurate genetic counseling.
5. **Specific aneuploidy syndromes:**
   a. **Down syndrome (Trisomy 21):**
      (1) **Features**: Hypotonia and characteristic facial features (brachycephaly, epicanthal folds, flat nasal bridge, upward-slanting palpebral fissures, Brushfield spots, small mouth and ears), excess skin at the nape of the neck, single transverse palmar crease, short fifth finger with clinodactyly, wide gap between the first and second toes. Intellectual disability present in all, but severity is variable.
      (2) Full health supervision guidelines from the American Academy of Pediatrics (AAP) are available (see Section VII).
      (3) In brief: In addition to karyotype, neonates should have echocardiogram to assess for congenital heart disease, ophthalmologic evaluation to assess for cataracts, hearing screen, complete blood count (CBC) to assess for transient myeloproliferative disease, thyroid studies to assess for hypothyroidism, and referral to early intervention services. Annual thyroid studies, CBC (add ferritin and CRP for any child at risk of iron deficiency), hearing and vision assessments. Cervical spine x-ray at age 3 years if asymptomatic (sooner imaging with immediate neurosurgical referral if symptomatic). Monitor for signs of obstructive sleep apnea and neurologic dysfunction.
   b. **Edwards syndrome (Trisomy 18):**
      (1) **Features**: Intrauterine growth restriction and polyhydramnios, small for gestational age at birth, clenched hands with overlapping fingers, hypoplastic nails, short sternum, prominent occiput, low-set and structurally abnormal ears, micrognathia, rocker-bottom feet, congenital heart disease, cystic and horseshoe kidneys, seizures, hypertonia, significant developmental and cognitive impairments.
      (2) Ninety percent die before 1 year of life.
   c. **Patau syndrome (Trisomy 13):**
      (1) **Features**: Defects of forebrain development (holoprosencephaly), severe developmental disability, low-set malformed ears, cleft lip and palate (CLP), microphthalmia, aplasia cutis congenita, polydactyly (most frequently of the postaxial type), narrow hyperconvex nails, apneic spells, cryptorchidism, congenital heart defects.
      (2) Ninety-five percent die before 6 months of life.

d. **Turner syndrome (45, X):**
   (1) **Features**: Short stature, gonadal dysgenesis with amenorrhea and lack of a pubertal growth spurt, broad chest with hypoplastic or inverted nipples, webbed neck. The diagnosis should be considered prenatally in a female fetus with hydrops, increased nuchal translucency, cystic hygroma, or lymphedema. Intelligence is usually normal, but patients are at risk for cognitive, behavioral, and social disabilities.
   (2) Full health supervision guidelines from the AAP are available (see Section VII).
   (3) In brief: Obtain baseline echocardiogram, renal US, ophthalmology and audiology evaluations. Routine thyroid testing, biochemical liver tests, HgbA1C, vitamin D, TTG and immunoglobulin A (IgA), audiology, skin examinations, bone mineral density, and skeletal assessments.

e. **Klinefelter syndrome (47, XXY; 48, XXYY; 48, XXXY; and 49, XXXXY):**
   (1) **Features**: Primary hypogonadism, which may present in infancy with hypospadias or cryptorchidism or in adolescence/adulthood with infertility, gynecomastia, and small testes. Children may have expressive language delay.
   (2) There is an increased risk of breast carcinoma in 47, XXY.
   (3) Testosterone therapy is indicated at puberty for hypergonadotropic hypogonadism.

B. Copy Number Variation (Deletions and Duplications)

Partial loss or additional copies of genetic material on part of a chromosome.

1. **22q11 Deletion syndrome (Velocardiofacial syndrome, DiGeorge syndrome)**
   a. **Features**: Congenital heart disease (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect [VSD], and truncus arteriosus most common), palatal abnormalities (velopharyngeal incompetence, cleft palate), characteristic facial features in approximately two-thirds, developmental delays, learning disabilities, immunodeficiency, hypocalcemia, feeding problems, renal anomalies, hearing loss, laryngotracheoesophageal anomalies, growth hormone deficiency, autoimmune disorders, seizures (with or without hypocalcemia), and psychiatric disorders.
   b. **Diagnostic evaluation**: Microarray; FISH is no longer recommended. Assessments should include serum calcium, absolute lymphocyte count, B- and T-cell subsets, renal US, chest x-ray, cardiac examination, and echocardiogram.
   c. **Health supervision**: Health supervision recommendations have been published. Hold live vaccines until immune function is assessed.
2. **5p– Syndrome (Cri-du-chat syndrome)**
   a. **Features**: High pitched cry, delayed development, intellectual disability, microcephaly, low birth weight, hypotonia, hypertelorism, low

set ears, small jaw, round face, congenital heart disease (VSD, atrial septal defect [ASD], PDA).
   b. **Diagnostic evaluation**: Can be detected on karyotype or microarray.
3. **1p36 Deletion syndrome**
   a. **Features**: Developmental delay, intellectual disability, delayed growth, hypotonia, seizures, speech delay, hearing and vision impairment, microcephaly, low ears with thick helices, congenital heart disease (structural defects or cardiomyopathy).
   b. **Diagnostic evaluation**: Microarray.

C. Disorders of Methylation/Epigenetics

Heritable changes that affect gene activity and expression.

1. **Prader-Willi syndrome**
   a. **Features**: Severe hypotonia and feeding difficulties in infancy, followed by an insatiable appetite in later infancy or early childhood. Developmental delays in motor and language abilities. All affected individuals have some degree of intellectual disability. Short stature is common; males and females have hypogonadism, and in most, infertility.
   b. **Diagnostic evaluation**: Results from missing *paternally* contributed region. Methylation testing can detect almost all individuals—whether due to abnormal paternal-specific imprinting, a paternal deletion, or maternal uniparental disomy within the Prader-Willi/Angelman critical region of 15q. Follow-up with further molecular testing.
   c. **Health supervision**: Full health supervision guidelines from the AAP are available (see Section VII). Monitor for feeding difficulties in infancy and close supervision beginning in childhood to prevent obesity. Evaluate for and treat hypothyroidism, sleep apnea (central and obstructive), central adrenal insufficiency,[21] and cryptorchidism.
   d. **Treatment**: Growth hormone can be beneficial, and hormone replacement therapy can aid in sexual development.
2. **Angelman syndrome**
   a. **Features**: Happy demeanor, hand-flapping, and fascination with water. Severe developmental delay, intellectual disability, severe speech impairment, gait ataxia, tremulous limbs, hypotonia, microcephaly, and seizures.
   b. **Diagnostic evaluation**: Results from missing *maternally* contributed region. Methylation testing can detect almost all individuals—whether due to abnormal maternal-specific imprinting, a maternal deletion, or paternal uniparental disomy within the Prader-Willi/Angelman critical region of 15q. Some individuals can be detected through *UBE3A* sequence analysis.
   c. **Health supervision**: Monitor for seizures, behavior problems, feeding issues, sleep disturbance, scoliosis, strabismus, constipation, and gastroesophageal reflux disease.

d. **Treatment**: Antiepileptic drugs for seizures; be careful not to overtreat, because Angelman syndrome also associated with movement abnormalities (*avoid* carbamazepine, vigabatrin, and tiagabine).[22] Speech therapy with a focus on nonverbal communication. Sedatives for nighttime wakefulness.

3. **Classic Rett syndrome**: X-linked disease present only in females because pathogenic *MECP2* variants are most often lethal in males who have only one X chromosome. Males who do survive with *MECP2* mutations have presentation different from Rett syndrome that often incudes neonatal encephalopathy.
   a. **Features**: Neurodevelopmental syndrome that presents after 6 to 18 months of typical development with acquired microcephaly, then developmental stagnation, followed by rapid regression. Gait ataxia or inability to ambulate, repetitive, stereotypical handwringing, fits of screaming or inconsolable crying, episodic breathing abnormalities (sighing, apnea, or hyperpnea), tremors, and generalized tonic-clonic seizures.
   b. **Diagnostic evaluation**: Molecular testing of *MECP2*.
   c. **Health Supervision**: Regular ECG to evaluate QT interval,[23] monitor for scoliosis.

D. Repeat Expansion

Pathogenic expansion of trinucleotide repeats during DNA replication.

1. **Fragile X syndrome**
   a. Most common cause of inherited intellectual disability.
   b. **Features**: Males have relative macrocephaly and prominent ears. Postpubertal macroorchidism and tall stature that slows in adolescence. Females have a range of intellectual disability due to the degree of X inactivation of the affected chromosome. Female premutation carriers (55 to 200 repeats) can develop primary ovarian insufficiency; males with 55 to 200 repeats can have a tremor/ataxia phenotype.
   c. **Diagnostic evaluation**: Repeat expansion testing of *FMR1* gene to assess number of CGG trinucleotide repeats (typically >200 in fragile X syndrome).
   d. **Health supervision**: Full health supervision guidelines from the AAP are available (see Section VII). Symptom and supportive psychopharmacologic medications.
2. Other examples include Huntington disease (CAG repeats), myotonic dystrophy (CTG repeats), and Friedrich ataxia (GAA repeats).

E. Mendelian/Single Gene Disorders

Mutation in a single gene causing a disorder.

1. **Marfan syndrome**
   a. **Features**: Myopia, ectopia lentis, aortic dilatation with predisposition to rupture, mitral valve prolapse, pneumothorax, bone overgrowth and joint laxity, pectus carinatum or excavatum, scoliosis, pes planus.

   b. **Diagnostic evaluation**: Clinical diagnosis based on the revised Ghent criteria (a "systemic score" system based on clinical features that can support a diagnosis if score is greater than or equal to 7). Molecular genetic testing of *FBN1* gene.
   c. **Health supervision**: Annual ophthalmologic examination; annual echocardiography; intermittent surveillance of the entire aorta with computed tomography (CT) or MRA scans beginning in young adulthood. Avoid contact sports, competitive sports, isometric exercise. Full health supervision guidelines from the AAP are available (see Section VII).
   d. **Treatment**: β-blocker (atenolol) and/or an angiotensin-II type 1 receptor blocker (losartan) is current standard of care. Valve-sparing surgery to replace aortic root when diameter exceeds ~4.5 cm in adults (or if rates of aortic dilation exceed ~0.5 cm/year) and significant aortic regurgitation is present.[24]
2. **Ehlers-Danlos syndrome (EDS)**
   a. **Features**: Smooth, velvety, hyperextensible skin, widened scars, poor healing, easy bruising, joint hypermobility with recurrent dislocations, chronic joint or limb pain, and a positive family history. The vascular-type EDS is distinct and involves translucent skin, characteristic facies (pinched nose), as well as risk for arterial, intestinal, and uterine fragility or rupture.
   b. **Diagnostic evaluation**: Clinical evaluation and family history. For classical and vascular types, echocardiogram and DNA testing. Vascular type additionally needs MRI/MRA imaging of aorta and iliac arteries. Joint hypermobility can be scored with Beighton criteria. No known genetic cause of hypermobile type.
   c. **Treatment**: Physical therapy to improve joint stability, low-resistance exercise, and pain medications as needed; treat gastroesophageal reflux. Vascular EDS requires management in a clinic specializing in connective tissue disorders.
3. **Achondroplasia**
   a. **Features**: Short arms and legs (especially rhizomelia); bowing of the lower legs; large head with characteristic facial features including frontal bossing and midface retrusion. Infantile hypotonia is typical, followed by delayed motor development. Gibbus deformity of the thoracolumbar spine leads to exaggerated lumbar lordosis. Rarely, children have hydrocephalus and restrictive pulmonary disease. Stenosis at the foramen magnum in infancy increases the risk of death; lumbar spinal stenosis may present in childhood but is more common in adulthood. Intelligence and lifespan are usually normal. Average adult height for males and females is approximately 4 feet.
   b. **Diagnostic evaluation**: Clinical diagnosis based on characteristic physical exam. *FGFR3* mutation testing available if diagnostic uncertainty.
   c. **Health supervision**: Full health supervision guidelines from the AAP are available (see Section VII). In brief: Use standard growth charts for achondroplasia. Baseline head CT including cervicomedullary junction in infancy, and precautions against uncontrolled head

movement or neck manipulation. Monitor for signs of obstructive sleep apnea, middle ear complications (e.g., otitis media), or spinal stenosis (more common in adults).

F. Teratogen Exposure (Table 13.10)

G. *In utero* Forces[25]

1. Uterine compression:
   a. Can be intrinsic (oligohydramnios, multiple fetuses, uterine deformities) or extrinsic (small pelvis).
   b. Results in deformations, including craniofacial (plagiocephaly, flattened facies, crumpled ear, craniosynostosis), extremities (dislocated hips, equinovarus or calcaneovalgus feet, tibial bowing, contractures), torticollis, lung hypoplasia, scoliosis.

TABLE 13.10

SELECTED TERATOGENS[11,30-31]

Exposure	Features
Intrauterine infections	See Chapter 17
Intrauterine substance exposure	Alcohol: Fetal alcohol spectrum disorder: microcephaly, small palpebral fissures with epicanthal folds, low nasal bridge with upturned nose, smooth philtrum and thin vermilion border, small chin, developmental delay, intellectual disability Cocaine: IUGR, developmental delay, learning disabilities, attention and behavioral challenges, occasional congenital anomalies
Intrauterine medication exposure *See Formulary for drug-specific information on risk in pregnancy*	Phenytoin: Fetal hydantoin syndrome: growth deficiency, hypertelorism, flat nasal bridge, cleft lip and palate, long philtrum and thin bowed upper lip, digitalized thumbs, hypoplasia of distal phalanges Warfarin: Nasal hypoplasia, epiphyseal stippling, hypoplastic distal phalanges, Peters anomaly, brain malformations Valproate: High forehead, broad nasal bridge, small mouth and chin, cardiac defects, long/thin phalanges, developmental delay Retinoic acid: Microtia, depressed nasal bridge, hypertelorism, cardiac defects, brain malformations, intellectual disability ACE inhibitors: Oligohydramnios, renal tubular dysgenesis, poor ossification of calvaria, cardiac defects, brain malformations Methotrexate: Microcephaly, growth restriction, hypoplasia of skull bones, micrognathia, low set ears, mesomelia, syndactyly
Maternal medical conditions	Diabetes mellitus: Polyhydramnios, macrosomia; variety of congenital anomalies including spina bifida, heart defects, skeletal anomalies, urinary/reproductive system anomalies Uncontrolled maternal PKU: Microcephaly, IUGR, hypertonia, cardiac defects, intellectual disability
Environmental exposures	High lead levels: Miscarriage, intrauterine growth restriction, learning and behavior problems High levels of radiation: Miscarriage, microcephaly, developmental delay; exposure of less than 5 rads (125 pelvic x-rays) not associated with increased risk of birth defects

This is not a comprehensive listing. Patient oriented resource for exposures during pregnancy and breastfeeding: mothertobaby.org.[31]

ACE, Angiotensin-converting enzyme; *IUGR*, intrauterine growth restriction; *PKU*, phenylketonuria.

2. Abnormal fetal muscular tone or posture can result in hyperextended knees, dislocated hips, contractures.
3. Placental compromise
4. Amniotic bands

VI. CONSENT AND DISCLOSURE OF GENETIC TESTING

A. Ethics of Genetic Testing in Pediatrics

Genetic testing in pediatric patients poses unique challenges given that children require proxies (most often parents) to give consent for testing. Several publications and statements have been made with regard to genetic testing in children, including the "Ethical Issues with Genetic Testing in Pediatrics" statement made by the AAP.[26] Important considerations include:

1. Testing and screening of a pediatric patient should be in his/her best interest and provide clear benefits.
2. If testing is performed for the interests of parents or other family members, it should not be to the detriment of the child.
3. Treatment and/or follow-up must be available after testing is sent.
4. Carrier testing or screening in children and adolescents is not broadly supported.
5. Predictive testing for late-onset disorders is discouraged until a patient is able to make an autonomous decision; in these cases, extensive pretest counseling is recommended.

B. Informed Consent

Pretest counseling and informed consent are important prior to sending any genome-wide testing and documentation of informed consent is recommended. Possible results from genetic testing include:

1. Positive—a causative/related variant is found.
2. Negative—either no causative/related variant is present, *or* the available technology or scope of the test methodology was unable to detect the causative/related variant. A negative result does not guarantee the condition does not have a genetic etiology.
3. Variant(s) of uncertain significance—variants for which the meaning is uncertain (could be variants without clinical significance or related to the patient's presentation but not previously reported).
4. Incidental finding(s)—variants anticipated to affect the patient's health that are unrelated to the indication for sending the test (and may be an adult-onset condition).
5. Discovery that parents are blood relatives and/or nonmaternity/nonpaternity.

C. Professional Disclosure of Familial Genetic Information

Pretest counseling should include the discussion that genetic testing may have implications for family members. With regard to disclosure of genetic testing results to at-risk family members when a patient or family member chooses not to disclose, the provider must weigh the duty to respect privacy and autonomy of the patient with the duty to prevent harm in another identifiable person. The ethical and legal duties of the physician are not well

defined. The American Society of Human Genetics released a statement on professional disclosure of familial genetic information which outlines "exceptional circumstances," which if all are present, disclosure may be permissible: (1) attempts to encourage disclosure by the patient have failed, (2) harm is "highly likely" to occur, (3) the harm is "serious and foreseeable," (4) either the disease is preventable/treatable, or early monitoring will reduce risks, (5) the at-risk relative(s) are identifiable, and (6) the harm of failure to disclose outweighs the harm that may result from disclosure.[27]

D. Disclosure of Incidental Findings

Patients are sometimes given the option to be informed of any incidental or secondary findings when they pursue genetic testing, but in general, it is recommended that incidental findings should be reported when there is strong evidence of benefit to the patient. The minimal list of reportable incidental findings may be found in the American College of Medical Genetics (ACMG) March 2013 statement and related updates.[28]

VII. WEB RESOURCES

A. Specific Genetic Disorders

1. Genetics Home Reference: http://ghr.nlm.nih.gov/. (Patient-friendly information)
2. GeneReviews: www.genereviews.org. (Expert-authored clinical descriptions including diagnosis and management recommendations)
3. National Organization for Rare Disorders: www.rarediseases.org
4. Online Mendelian Inheritance in Man (OMIM): http://omim.org (Curated primary literature, can be used to search for clinical features to build a differential)

B. Guidelines for Genetic Conditions

1. Patient Management Guidelines endorsed by AAP: https://www.aappublications.org/search/policy/policy [20]
2. Newborn screening ACT Sheets and Confirmatory Algorithms: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx

C. Molecular Testing Resources

1. Concert Genetics: www.concertgenetics.com
2. Genetics Testing Registry: https://www.ncbi.nlm.nih.gov/gtr

D. Teratogen Evaluation

1. LactMed: Drugs and lactation database available through the U.S. National Library of Medicine. www.toxnet.nlm.nih.gov.
2. Patient oriented information on exposures during pregnancy: www.mothertobaby.org [31]

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

VIII. ONLINE CONTENT

A. Patterns of Inheritance

1. **Autosomal dominant:**
   a. Disease manifestation with a variant in one allele of a gene; the other allele is normal.
   b. It can appear in multiple generations.
   c. An affected individual has a 50% risk of passing on the variant with *each* pregnancy.
2. **Autosomal recessive:**
   a. Disease manifestation requiring variants in both alleles of the gene.
   b. There can be multiple affected individuals in the same generation.
   c. An affected couple (each being a carrier) has a 25% chance of having an affected child, a 25% chance of having an *un*affected child, and a 50% chance of producing a carrier of the condition with *each* pregnancy.
3. **X-linked:**
   a. Because females have two X chromosomes and males have only one X chromosome, males are more commonly and more severely affected by X-linked conditions. Females can be unaffected or have a spectrum of manifestations. In carrier females, lyonization is the process of silencing one X chromosome in each cell and "unfavorable lionization" can result in a large proportion of cells that inactivated the normal X chromosome, and as a result clinical features are present.
   b. Females have a 50% chance of passing on an affected X to each male or female child. Males will pass on the affected X to all female children and will have *un*affected sons.
4. **Mitochondrial:**
   a. Classically a matrilineal inheritance pattern, caused by mitochondrial DNA inherited from one's mother that contributes to mitochondrial function. Sons will be affected but cannot pass the condition on to their offspring.
   b. There may be significant phenotypic variability due to "heteroplasmy," in which the relative proportion of affected and unaffected mitochondria may change as cells divide.
   c. Mitochondrial disease is currently known to be caused by either variants in mitochondrial DNA or by recessive variants in nuclear genes that code for proteins that function in the mitochondria.
5. **Genomic imprinting and uniparental disomy:**
   a. The two alleles of a gene may be functionally equivalent but may be expressed or silenced depending on the parent of origin of the chromosome. This is due to the presence of epigenetic machinery influencing the expression of genes and resulting in different methylation patterns.
   b. Uniparental disomy is a rare occurance in which offspring have inherited both copies of a chromosome from one parent. There are two types: (1) Uniparental isodisomy is an error in meiosis II, in

which the offspring receives two identical copies of a chromosome from one parent. This can result in autosomal recessive disorders because any variant on one parental allele could be present on both alleles of their offspring. (2) Uniparental heterodisomy is an error in meiosis I, in which the offspring receives both copies of a single parent's chromosome. This can result in disorders of imprinting because only one parent contributed to the epigenetic pattern of that chromosome.

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Chapter 14

Hematology

Jessica Calihan, MD

See additional content on Expert Consult

I. ANEMIA

A. Screening for Anemia

1. The American Academy of Pediatrics (AAP) recommends screening between 9 and 12 months with a repeat level in 6 months.
2. Screen yearly in high-risk children: history of prematurity or low birth weight, exposure to lead, exclusive breastfeeding without supplemental iron beyond 4 months, diet without iron-fortified cereals or foods naturally rich in iron, feeding problems, poor growth, inadequate nutrition.[1]

B. Definition of Anemia

1. Anemia is defined as a reduction in hemoglobin (Hb) two standard deviations below the mean, based on age-specific norms.
2. See Table 14.1 at the end of the chapter for age-specific blood cell indices.

C. Causes of Anemia

1. See Fig. 14.1 for approach to anemia based on red blood cell (RBC) production, as measured by reticulocyte count and cell size. Note that normal ranges for Hb and mean corpuscular volume (MCV) are age-dependent.
2. See Tables 14.2 and 14.3 for more details regarding specific causes of nonhemolytic and hemolytic anemia.

D. Evaluation of Anemia

1. Useful equations in the evaluation of anemia:
   a. Mentzer index[2] = MCV/RBC
      (1) Index >13 suggests iron deficiency anemia (IDA).
      (2) Index <13 suggests thalassemia trait.
      (3) Sensitivity: 62% for IDA, 86% for beta thalassemia trait. Specificity: 86% for IDA, 62% for thalassemia.
   b. Reticulocyte index = % reticulocytes × patient hematocrit/normal hematocrit[3]
      (1) >2 is indicative of increased RBC production in appropriate response to anemia.
      (2) <2 is evidence of hypoproliferative anemia.
2. Other useful indices and tests
   a. RBC distribution width (RDW):
      (1) Normal in thalassemia.
      (2) Increased in IDA and sideroblastic anemia.
   b. Mean cell hemoglobin concentration (MCHC): Hb/hematocrit (Hct):
      (1) Allows for classification of anemia as hypochromic, normochromic, or hyperchromic.

TABLE 14.2

NONHEMOLYTIC ANEMIA

NUTRITIONAL DEFICIENCY	
Iron deficiency anemia (IDA)	Causes: Poor intake, malnutrition, GI bleed, menstrual cycle, malabsorption (with celiac disease, *Helicobacter pylori*, IBD). Ferritin falls first. Low MCHC, elevated transferrin receptor, low reticulocyte Hb content. Usually normocytic; microcytic if severe or prolonged.
UNDERLYING DISEASE	
Anemia of chronic disease	Typically secondary to prolonged/frequent infections, autoimmune conditions (SLE, JIA, IBD), vasculitis.[3] Low iron, TIBC, transferrin. High ferritin, CRP, and ESR.
Renal disease	Impaired erythropoietin production.
Endocrine disease	Hypothyroidism, hyperthyroidism, panhypopituitarism, hyperparathyroidism (primary or secondary).
TOXINS	
Lead poisoning	Lead interferes with iron absorption and inhibits heme synthesis enzymes.
BONE MARROW	
Acquired Failure	
Primary red cell aplasia	Autoimmune disorder with autoantibody-mediated disruption of erythroid cell differentiation. Bone marrow shows absent erythroblasts, but is otherwise normal.
Secondary red cell aplasia	Causes: Infection (parvovirus B19, EBV, CMV, HHV-6, HIV, hepatitis), radiation, medications, collagen vascular disease. Variable RBC size, variable platelet and WBC counts. Aspirate bone marrow for evidence of dysfunction, neoplasm, infection.
Aplastic anemia	Causes: Infection (parvovirus B19, EBV, CMV), radiation, chemical exposure (benzene), medications (chloramphenicol, gold, NSAIDs), autoimmune conditions, idiopathic or immune-mediated. Hypocellular bone marrow and peripheral cytopenia. Severe: ANC $<500 \times 10^6$/L, platelet <20,000/μL, reticulocyte count $<60{,}000 \times 10^6$/L.
Vitamin B12 or folate deficiency	Typically secondary to malabsorption or inadequate intake.
Myelophthisic anemia	Bone marrow fibrosis and infiltration by abnormal tissue. Primary myelofibrosis: Clonal myeloproliferative disease with extramedullary hematopoiesis, ineffective erythropoiesis, bone marrow fibrosis, hepatosplenomegaly. Secondary causes: Lymphoma, multiple myeloma, infiltrating metastatic cancer, autoimmune disease, granulomatous disease (sarcoidosis), vitamin D deficiency, hypo-/hyperparathyroidism. Presentation: Pancytopenia
Inherited Causes with Pure Anemia	
Diamond-Blackfan Anemia	Autosomal dominant mutations in multiple ribosomal protein genes identified. Presentation: Infant (average 3 months) with RBC aplasia (sometimes with neutropenia and/or thrombocytosis) and congenital anomalies (30%–47% of patients): short stature, craniofacial abnormalities (cleft lip), skeletal (triphalangeal thumb, short stature), genitourinary, cardiac abnormalities.

Continued

TABLE 14.2

NONHEMOLYTIC ANEMIA—Cont'd.

Inherited Causes with Pancytopenia	
Fanconi anemia	Autosomal recessive or X-linked disorder. Presentation: Child with pancytopenia, radial and thumb abnormalities, renal anomalies, microcephaly, short stature, skin findings (hyperpigmentation, café au lait spots).
Shwachman-Diamond syndrome	Autosomal recessive mutation in *SBDS* gene. Presentation: Young child with neutropenia +/– thrombocytopenia and macrocytic anemia, exocrine pancreatic dysfunction, bony abnormalities.
Dyskeratosis congenita	Mutation in gene encoding telomerase complex components. Presentation: Anemia, thrombocytopenia, abnormal skin reticular hyperpigmentation, nail dystrophy, oral leukoplakia.

ANC, Absolute neutrophil count; *CMV*, cytomegalovirus; *CRP*, C-reactive protein; *EBV*, Epstein Barr virus; *ESR*, erythrocyte sedimentation rate; *GI*, gastroenterology; *Hb*, hemoglobin; *HHV-6*, human herpesvirus 6; *HIV*, human immunodeficiency virus; *IBD*, inflammatory bowel disease; *JIA*, juvenile idiopathic arthritis; *MCHC*, mean corpuscular hemoglobin concentration; *NSAID*, nonsteroidal anti-inflammatory drug; *RBC*, red blood cell; *SBDS*, Shwachman-Bodian-Diamond syndrome gene; *SLE*, systemic lupus erythematosus; *TIBC*, total iron binding capacity; *WBC*, white blood cell.

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TABLE 14.3

HEMOLYTIC ANEMIA

EXTRINSIC HEMOLYTIC ANEMIA	
DAT –	
Microangiopathic hemolytic anemia (MAHA): HUS, TTP, DIC	Anemia due to RBC shearing with passage through microthrombi in microvasculature. Diagnosis: Intravascular hemolysis, thrombocytopenia, schistocytes on peripheral smear.
Hemoglobin disorders: Sickle cell disease, unstable hemoglobin	Denaturation of hemoglobin causes precipitation in RBC and reduces deformability. Diagnosis: Smear with Heinz bodies, bite or blister cells.
DAT +	
Warm autoimmune hemolytic anemia	Diagnosis: Jaundice +/– splenomegaly, +anti-IgG and/or +anti-C3 autoantibodies. Treatment: Corticosteroids (first line; prednisone), splenectomy, rituximab. Transfuse for severe anemia with cardiovascular compromise (i.e., Hb <5 g/dL) or reticulocytopenia.
Cold autoimmune hemolytic anemia	Diagnosis: Acrocyanosis, hemoglobinuria, +anti-IgM autoantibodies. Treatment: Cold avoidance.

TABLE 14.3

HEMOLYTIC ANEMIA—Cont'd.	
Secondary autoimmune hemolytic anemia	Causes: Infections,[a] drug-associated,[b] malignancy (Hodgkin lymphoma), systemic lupus erythematosus, autoimmune lymphoproliferative syndrome, common variable immunodeficiency, posttransplant (stem cell or solid organ).
Transfusion reactions (ABO or Rh incompatibility)	See Table 14.18 for presentation of transfusion reactions.
INTRINSIC HEMOLYTIC ANEMIA	
Membrane Disorders	
Neonatal hemolytic disease	Maternal antibodies to incompatible fetal RBC antigens (Rh, A, B) causes hemolytic disease in utero and in neonatal period. Diagnosis: Mild anemia to hydrops fetalis, early jaundice. Treatment: Intensive phototherapy, exchange transfusion.
Hereditary spherocytosis	Inheritance: 75% AD. 25% spontaneous mutation or AR. Protein defect → membrane instability → RBC destruction via extravascular hemolysis. Diagnosis: Family history with clinical suspicion and spherocytes on smear, osmotic fragility test, EMA flow cytometry if unclear clinical picture. Treatment: Folate supplementation if moderate-severe hemolysis, anticipatory guidance, splenectomy (for severe disease), cholecystectomy if needed for symptomatic cholelithiasis.
Hereditary elliptocytosis	Inheritance: Typically AD. Diagnosis: Elliptocytes on smear. Treatment: Same as for hereditary spherocytosis.
Enzyme Deficiencies	
G6PD deficiency	Inheritance: X-linked disorder. Enzyme deficiency predisposes to intravascular hemolysis with oxidative stress (e.g., with infections/illness, fava beans, medications). Diagnosis: G6PD assay when well (may be falsely elevated immediately after hemolytic episode). Treatment: Avoid oxidative triggers (see drug/chemical list), transfuse for severe anemia.
Pyruvate kinase (PK) deficiency	Inheritance: AR disorder of *PKLR* or *PKM* genes causes chronic hemolysis. Diagnosis: Measure PK activity in RBC. Treatment: Transfuse if symptomatic. Consider splenectomy if severe transfusion-dependent anemia.

[a]Infections include EBV, CMV, mycoplasma, pneumococcus, parvovirus.

[b]Causative drugs include penicillin, cephalosporins, quinine/quinidine, amphotericin B, NSAIDs, procainamide, IVIG.

ABO, Blood type; *AD*, autosomal dominant; *AR*, autosomal recessive; *CMV*, cytomegalovirus; *DAT*, direct antiglobulin test; *DIC*, disseminated intravascular coagulation; *EBV*, Epstein-Barr virus; *EMA*, eosin-5-maleimide; *G6PD*, Glucose-6-phosphate dehydrogenase; *Hb*, hemoglobin; *HUS*, hemolytic uremic syndrome; *Ig*, immunoglobulin; *IVIG*, intravenous immunoglobulin; *NSAID*, nonsteroidal anti-inflammatory drug; *RBC*, red blood cell; *Rh*, rhesus factor; *TTP*, thrombotic thrombocytopenic purpura.

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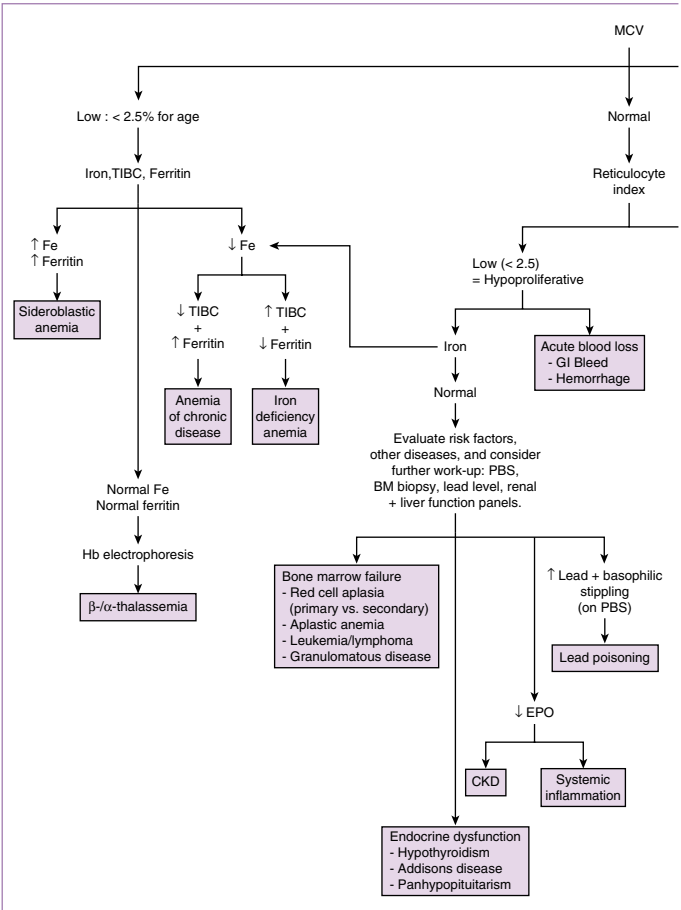

FIGURE 14.1

Approach to anemia. *AEDs*, Antiepileptic drugs; *BM*, bone marrow; *CKD*, chronic kidney disease; *DAT*, direct antiglobulin test; *EPO*, erythropoietin; Fe, iron; *G6PD*, Glucose-6-phosphate dehydrogenase; *GI*, gastrointestinal; *HUS*, hemolytic uremic syndrome; *LDH*, lactate dehydrogenase; *MAHA*, microangiopathic hemolytic anemia; *MCV*, mean corpuscular volume; *MMA*, methylmalonic acid; *PBS*, peripheral blood smear; *PK*, pyruvate kinase; *SC*, sickle cell; *SD*, standard deviation; *TIBC*, total iron binding capacity; *TTP*, thrombotic thrombocytopenic purpura. (Data from Wang, M. Iron deficiency and other types of anemia in infants and children. *Am Fam Physician*. 2016:93[4]:270–278; Orkin SH, Nathan DG, Ginsburg D, et al. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood*. 8th ed. Philadelphia: Saunders; 2015.)

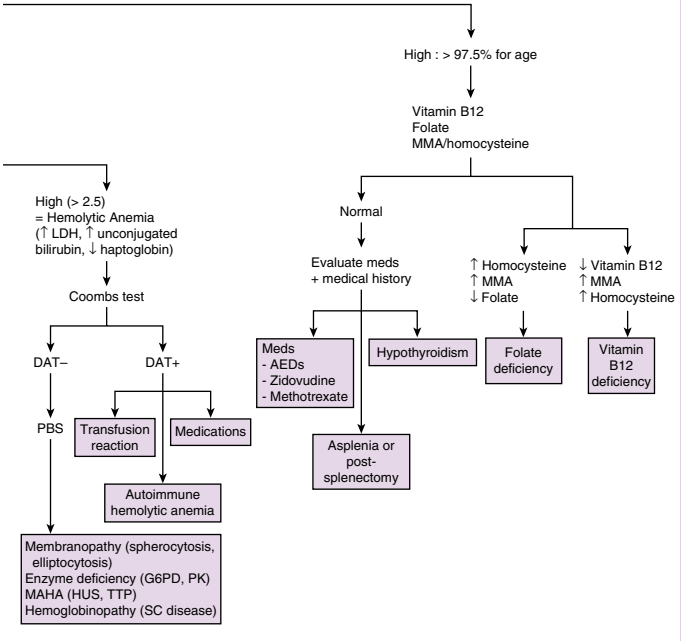

FIGURE 14.1–cont'd

(2) Low MCHC in iron deficiency and thalassemia.
(3) Elevated MCHC and spherocytes in hereditary spherocytosis and hemolytic disease of the newborn.

c. **Serum ferritin:**
(1) Reflects total body iron stores after 6 months of age.
(2) It is the first value to fall in early iron deficiency and is elevated with inflammation or infection.

d. **Coombs test:**[4]
(1) Direct (direct antiglobulin testing [DAT]): Detects antibody/complement bound to patient's RBCs by mixing prepared nonspecific antihuman globulin with patient's blood. RBC agglutination = positive test.
(2) Indirect (indirect antiglobulin testing): Detects antibodies to RBC antigens in patient's plasma by mixing reagent RBCs with patient's serum. RBC agglutination = positive test.

e. **Hemoglobin electrophoresis:**
(1) Involves separation of Hb variants based on molecular charge and size. All positive sickle preparations and solubility tests for sickle Hb (e.g., Sickledex) should be confirmed with electrophoresis or isoelectric focusing (component of mandatory newborn screening in many states).
(2) See Table 14.4 for neonatal Hb electrophoresis patterns.
(3) See Fig. 14.2 for changes in Hb polypeptide over time in a normal fetus/infant.

f. **Blood smear interpretation**[3]
(1) Howell-Jolly bodies = impaired splenic function, post-splenectomy
(2) Target cells = hemoglobinopathies, liver disease, post-splenectomy, thalassemia, HbSS, HbSC, HbC
(3) Bite cells, Heinz bodies = G6PD deficiency (during hemolysis)
(4) Toxic granulation of neutrophils, bandemia, atypical lymphocytes = infection
(5) Pencil poikilocytes = IDA, thalassemia
(6) Basophilic stippling = lead poisoning, sideroblastic anemia
(7) Pappenheimer bodies = sideroblastic anemia
(8) Hypersegmented neutrophils = Vitamin B12, folate deficiencies
(9) Blasts = leukemia, lymphoma
(10) Schistocytes (RBC fragments) = MAHA, burns, valve hemolysis
(11) Spherocytes = autoimmune hemolytic anemia, hereditary spherocytosis, ABO incompatibility/hemolytic disease of the newborn
(12) Elliptocytes = hereditary elliptocytosis, severe IDA
(13) Teardrop cells = myelofibrosis (and other BM infiltrating processes), thalassemia
(14) Echinocytes (Burr cells) = uremic patients
(15) Acanthocytes (Spur cells) = liver disease
(16) See Figs. EC 14.A to EC 14.L for examples of peripheral smears.

TABLE 14.4

NEONATAL HEMOGLOBIN ELECTROPHORESIS PATTERNS

FA	Fetal Hb and adult normal Hb; the normal newborn pattern.
FAV	Indicates presence of both HbF and HbA, but an anomalous band (V) is present that does not appear to be any of the common Hb variants.
FAS	Indicates fetal Hb, adult normal HbA, and HbS, consistent with benign sickle cell trait.
FS	Fetal and sickle HbS without detectable adult normal HbA. Consistent with clinically significant homozygous sickle Hb genotype (S/S) or sickle β^0-thalassemia, with manifestations of sickle cell disease during childhood.
FC[a]	Designates presence of HbC without adult normal HbA. Consistent with clinically significant homozygous HbC genotype (C/C), resulting in a mild hematologic disorder presenting during childhood.
FSC	HbS and HbC present. This heterozygous condition could lead to manifestations of sickle cell disease during childhood.
FAC	HbC and adult normal HbA present, consistent with benign HbC trait.
FSA	Heterozygous HbS/β^+-thalassemia, a clinically significant sickling disorder.
F[a]	Fetal HbF is present without adult normal HbA. May indicate delayed appearance of HbA, but is also consistent with homozygous β-thalassemia major or homozygous hereditary persistence of fetal HbF.
FV[a]	Fetal HbF and an anomalous Hb variant (V) are present.
AF	May indicate prior blood transfusion. Submit another filter paper blood specimen when infant is 4 months of age, at which time the transfused blood cells should have been cleared.

[a]Repeat blood specimen should be submitted to confirm original interpretation.

NOTE: HbA: $\alpha_2\beta_2$; HbF: $\alpha_2\gamma_2$; HbA_2: $\alpha_2\delta_2$.

Hemoglobin variants are reported in order of decreasing abundance; for example, FA indicates more fetal than adult hemoglobin.

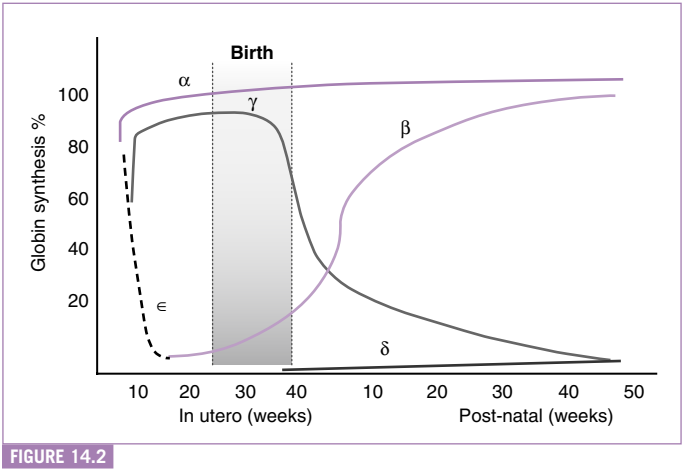

FIGURE 14.2

Neonatal hemoglobin electrophoresis patterns. (From Chandrakasan S, Kamat D. An overview of hemoglobinopathies and the interpretation of newborn screening results. *Pediatric Annals.* 2013:42[12]:502–508.)

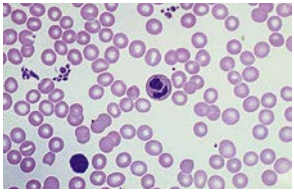

FIGURE EC 14.A
Normal smear. Round red blood cells with central pallor about one-third of the cell's diameter, scattered platelets, occasional white blood cells.

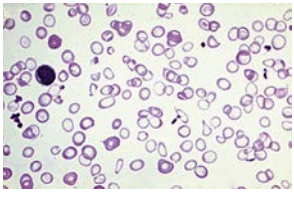

FIGURE EC 14.B
Iron deficiency. Hypochromic/microcytic red blood cells, poikilocytosis, plentiful platelets, occasional ovalocytes, and target cells.

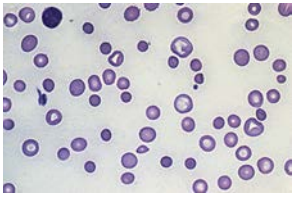

FIGURE EC 14.C
Spherocytosis. Microspherocytes (densely stained red blood cells with no central pallor) are a hallmark.

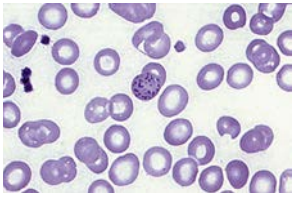

FIGURE EC 14.D
Basophilic stippling as a result of precipitated RNA throughout the cell; seen with heavy metal intoxication, thalassemia, iron deficiency, and other states of ineffective erythropoiesis.

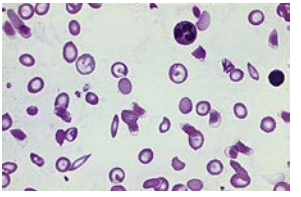

FIGURE EC 14.E
Sickle cell disease (hemoglobin SS) disease. Sickled cells, target cells, hypochromia, poikilocytosis, Howell–Jolly bodies; nucleated red blood cells common (not shown).

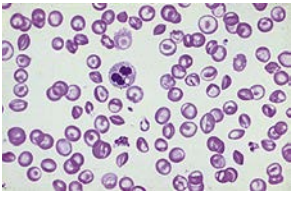

FIGURE EC 14.F
Sickle-hemoglobin C disease (hemoglobin SC) disease. Target cells, oat cells, poikilocytosis; sickle forms rarely seen.

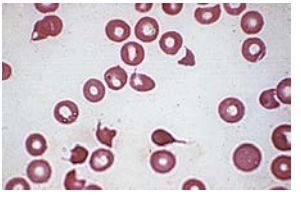

FIGURE EC 14.G
Microangiopathic hemolytic anemia. Red blood cell fragments, anisocytosis, polychromasia, decreased platelets.

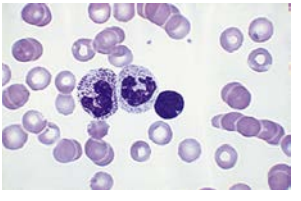

FIGURE EC 14.H
Toxic granulations. Prominent dark blue primary granules; commonly seen with infection and other toxic states (e.g., Kawasaki disease).

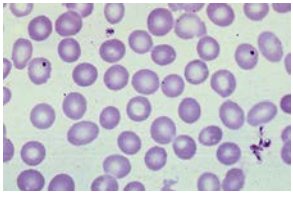

FIGURE EC 14.I
Howell–Jolly body. Small, dense nuclear remnant in a red blood cell; suggests splenic dysfunction or asplenia.

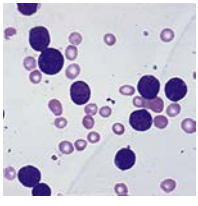

FIGURE EC 14.J
Leukemic blasts showing large nucleus-to-cytoplasm ratio.

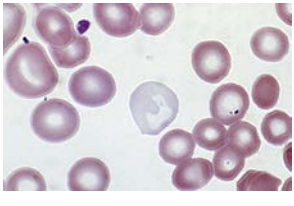

FIGURE EC 14.K
Polychromatophilia. Diffusely basophilic because of RNA staining; seen with early release of reticulocytes from the marrow.

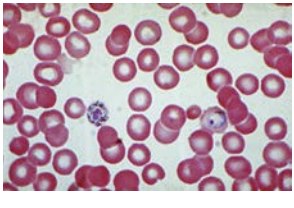

FIGURE EC 14.L
Malaria. Intraerythrocytic parasites.

E. Management of Anemia

1. **Iron deficiency anemia**
   a. Oral iron (ferrous sulfate)
      (1) Empirically treat children with microcytic anemia and history of poor dietary iron.[5]
      (2) In anemia of chronic disease, only use iron supplementation if evidence of absolute iron deficiency and ferritin <100 ng/mL.[5]
      (3) After initiation of iron supplementation, expect reticulocyte count to increase within the first week with a 1 g/dL increase in Hb in 4 weeks (if severe anemia with Hb <9 g/dL, a response should be seen in 2 weeks).[1]
   b. Iron transfusion (low molecular weight iron dextran[6] or iron sucrose[7]) is appropriate for children with iron malabsorption (PPI use, short bowel syndrome, primary malabsorption), poor response to oral iron therapy, inability to tolerate oral iron therapy, and hemodialysis-dependent patients receiving erythropoietin.
2. **Sickle cell anemia**
   a. **Etiology**: Caused by a genetic defect in β-globin that leads to polymerization and sickling with deoxygenation, leading to hemolysis, adherence to blood vessel endothelium, and vaso-occlusive ischemia.
   b. **Most common subtypes**: HbSS (sickle cell anemia) and HbSβ^0 (sickle-β^0-thalassemia) are most severe. HbSC (sickle-hemoglobin C disease) and HbSβ+ (sickle-β+-thalassemia) are often milder.
   c. **Diagnosis**: Often made on newborn screen with Hb electrophoresis. The sickle preparation and Sickledex are rapid tests that are positive in all sickle hemoglobinopathies. False-negative test results may be seen in neonates and other patients with a high percentage of fetal Hb.
   d. **Complications**: See Table 14.5. A hematologist should be consulted.
   e. **Acute management of anemia in sickle cell disease[8]:**
      (1) RBC exchange transfusions: Indicated for patients with symptomatic severe acute chest syndrome (ACS), stroke, intractable pain crisis, intrahepatic cholestasis, hepatic sequestration, refractory priapism, and multisystem organ failure. Also indicated for children with prior stroke or transcranial Doppler reading >200 cm/sec.[8] Replace with HbS-negative cells. Follow Hct carefully with goal Hct <30% to avoid hyperviscosity.[9]
      (2) Do not transfuse for asymptomatic anemia, acute kidney injury, or recurrent splenic sequestration.
   f. **Chronic management and health maintenance[8]:** See Table 14.6. Ongoing consultation and clinical involvement with a pediatric hematologist and/or sickle cell program are essential.
3. **Thalassemia**
   a. **Etiology**: Defects in α- or β-globin production leads to precipitation of excess chains, causing ineffective erythropoiesis and shortened survival of mature RBCs.

TABLE 14.5

SICKLE CELL DISEASE COMPLICATIONS

Complication	Presentation	Additional Testing	Disposition/Treatment
Fever	>101°F or 38.3°C	Blood cultures CXR Blood and urine cultures Throat and CSF cultures, if indicated	Admit if ill-appearing, temperature ≥40°C, infiltrate on CXR or abnormal SpO_2, WBC >30,000/μL or <5,000/μL, platelets <100,000/μL, Hb <5 g/dL, history of sepsis. Antibiotics: Ceftriaxone IV. Vancomycin if meningitis suspected or if severe illness. Clindamycin or levofloxacin if cephalosporin allergy.[34] Consider additional disease-specific coverage. If outpatient, return in 24 hr for second ceftriaxone dose.
Vaso-occlusive crisis	Dactylitis in <2 years old; unifocal or multifocal pain in >2 years old	Type and screen	Admit if signs of complications or pain not managed in outpatient setting. Recommendations for home pain control: • Mild-moderate pain: NSAIDs. • Moderate-severe pain: oxycodone, morphine, hydrocodone. Recommendations for emergency department or inpatient pain control: • Use IV opioids (morphine, hydromorphone). Use fentanyl if renal or hepatic dysfunction. • Use PCA and provide as needed doses for breakthrough pain. Schedule pain medication if not using PCA.[35] • Ketamine may be appropriate if poor response to opioids.[36] IV fluids as needed for dehydration. Evidence-based guidelines regarding amount or type of fluids are lacking.[37] Use incentive spirometry to reduce risk of ACS. Avoid transfusion unless other indication.
Acute chest syndrome	Fever, cough, chest pain, respiratory distress, hypoxia + new pulmonary infiltrate	CXR Type and screen Blood cultures	Admit. IV antibiotics: IV cephalosporin + oral macrolide. O_2 as needed for goal SpO_2 >95%, incentive spirometry. Analgesia, IV fluids (see above). Simple transfusion or partial exchange for moderate illness.[34] High-dose dexamethasone use is controversial.[38]

Splenic sequestration	Acutely enlarged spleen, Hb ≥2 g/dL below baseline	Type and screen	Admit for serial abdominal exams, IV fluid resuscitation. Simple transfusion if severe anemia. [a]Be cautious with transfused volume and use 5–10 mL/kg aliquots if hemodynamically stable as autotransfusion from spleen can cause rebound increase in Hb and viscosity.
Aplastic crisis	Acute illness (often viral, commonly parvovirus B19) + Hb < baseline, low reticulocyte count	Type and screen Parvovirus serology and PCR	Admit to isolated bed. IV fluids. Simple transfusion with RBCs.
Stroke	Focal neurologic signs May be precipitated by ACS, parvovirus, acute anemic events	MRI, TCD to detect increased velocities with stenosis	Emergency exchange transfusion preferable to simple transfusion, if possible.[39] Chronic transfusion to maintain sickle Hb to <30% in patients with abnormal TCD US findings or history of stroke.
Acute renal failure	Hematuria, proteinuria, hypertension	Urine spot protein, 24 hr collection	Monitor renal function. Avoid nephrotoxic drugs/contrast. Consult nephrology and initiate replacement therapy (hemodialysis) if necessary.
Avascular necrosis	Pain at site that worsens with activity, reduced range of motion. Hip most commonly involved, then shoulder and other joints.	XR of affected joint, MRI if necessary	Analgesics, physical therapy. Consult orthopedic surgery for assessment for possible decompression.
Priapism	Sustained painful erection lasting >4 hr	Not necessary	Oral and/or IV analgesia (as per VOC recommendations). Hydration with oral or IV fluids. Consider supplemental oxygen. Consult urology for possible aspiration and irrigation of corpus cavernosum (if does not self-resolve).

ACS, Acute chest syndrome; *CSF*, cerebrospinal fluid; *CXR*, chest x-ray; *Hb*, hemoglobin; *IV*, intravenous; *MRI*, magnetic resonance imaging; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *PCA*, patient-controlled analgesia; *PRN*, as needed; *PCR*, polymerase chain reaction test; *RBCs*, red blood cells; *SpO2*, peripheral oxygen saturation; *TCD*, transcranial Doppler; *VOC*, vaso-occlusive crisis; *WBC*, white blood cell; *XR*, X-ray.

National Heart, Lung, and Blood Institute. *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report*, 2014. National Heart, Lung, and Blood Institute; 2014.

TABLE 14.6

SICKLE CELL DISEASE HEALTH MAINTENANCE

Medications	Penicillin	Twice daily in children with HbSS and HbSβ0 under 5 years old.[a]
	Hydroxyurea[40]	Offer in children with HbSS or HbSβ0 >9 months.[b] Treatment goal: HbF >20%.[41] Maximum dose parameters: ANC ≥2000–4000/μL, Hb ≥8 g/dL without transfusion, platelet ≥80,000/μL, absolute reticulocyte count ≥80–100,000/μL. Continue in acute hospitalization or illness. Discontinue in pregnant and breast-feeding women.
	Hormonal contraception	Progestin-only contraception (pills, injection, implant), levonorgestrel IUDs, and barrier methods preferred over estrogen-containing methods due to increased risk of blood clots.
Immunizations[42]	Pneumococcal vaccine	13-valent conjugate vaccine per routine childhood schedule. 23-valent polysaccharide vaccine at 2 years old with second dose 5 years later.
	Meningococcal vaccine	Give MenACWY-CRM (Menveo) at 2, 4, 6, 12 months. If over 2 years old, administer 2-dose series of MenACWY-CRM or MenACWY-D. Give Meningococcal B vaccine in patients 10 years or older.
	Influenza vaccine	Yearly starting at 6 months. Give to all household members and close contacts.
Imaging and labs	Transcranial doppler	Screen annually from 2 to 16 years old in HbSS or HbSβ0. Not necessary to screen in HbSβ+ or HbSC.
	Spot urine test	Screen for proteinuria at age 10; repeat annually. Refer those with proteinuria (>300 mg in 24 hr) to nephrologist.
Other	Ophthalmology	Annual exam starting at age 10 to evaluate for retinopathy.

[a]Prophylaxis may be discontinued by age 5 years if patient has had no prior severe pneumococcal infections or splenectomy and has documented pneumococcal vaccinations, including second 23-valent vaccination. May be continued based on family preference. May be considered for children with HbSC/HbSβ+, especially after splenectomy.[8] Practice patterns vary.

[b]Increases levels of fetal Hb and decreases HbS polymerization in cells. Has been shown to significantly decrease episodes of vaso-occlusive crises, dactylitis, acute chest syndrome, number of transfusions, and hospitalizations. May decrease mortality in adults. Consider in HbSC/HbSβ+ if recurrent sickle cell-associated pain interfering with daily activities or quality of life.[40,43]

ANC, absolute neutrophil count; *HbF*, hemoglobin F level; *HbSβ+*, sickle cell beta thalassemia disease; *HbSS*, Homozygous sickle cell disease; *HbSC*, hemoglobin SC disease; *IUD*, intrauterine device.

National Heart, Lung, and Blood Institute. *Evidence-Based Management of Sickle Cell Disease: Expert Panel Report*, 2014. National Heart, Lung, and Blood Institute; 2014. Available at: http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/.

b. **α-Thalassemia**:
   (1) Silent carriers (α–/αα): Not anemic; Hb electrophoresis usually normal.
   (2) α-Thalassemia trait (α–/α–) or (αα/–): Causes mild microcytic anemia from birth; Hb electrophoresis usually normal. Hb Barts can be seen in infancy (e.g., on state newborn screens) in patients with α-thalassemia trait.
   (3) HbH disease (β_4) (α–/––): Causes moderately severe anemia from birth; HbH (β-tetramer) may be seen on newborn screen and subsequent electrophoresis.
   (4) Hb Bart/hydrops fetalis (––/––): Hb Barts (γ_4) cannot deliver oxygen; usually fatal *in utero* or in neonatal period.

c. **β-Thalassemia**: Ineffective erythropoiesis is more severe in β-thalassemia than α-thalassemia. Patients often develop more severe iron overload from increased enteral absorption and transfusions. Adult Hb electrophoresis with decreased Hb A, increased Hb A_2, and increased Hb F.
   (1) Thalassemia trait/thalassemia minor (β/β+) or (β/β0): Mildly decreased β-globin production. Usually asymptomatic with mild anemia.
   (2) Thalassemia intermedia (β+/β+): Markedly decreased β-globin production. Presents at about 2 years of age with moderate compensated anemia (Hb 7 to 10 g/dL). Wide variability in presentation that may include features noted as follows.
   (3) Thalassemia major/Cooley anemia (β0/β0, β+/β0, or β+/β+): Minimal to no β-globin production. Presence of anemia within first 6 months of life requiring regular transfusions. Overstimulation of bone marrow, ineffective erythropoiesis, and iron overload results in jaundice, growth failure, hypersplenism, gallstones, skeletal abnormalities, liver cirrhosis, and cardiac impairment.

d. **Management**[10]
   (1) Patients with thalassemia major are transfusion dependent. Patients with thalassemia intermedia may need occasional transfusions.
   (2) Transfuse every 3 to 5 weeks for goal pretransfusion Hb 9 to 10.5 mg/dL.
   (3) Goal posttransfusion Hb <14 to 15 g/dL due to risk of hyperviscosity and stroke.
   (4) Treat iron overload with chelation (deferoxamine), which should be initiated in thalassemia major after 10 to 20 transfusions or when ferritin >1000 μg/L.
   (5) Bone marrow transplant is curative.

II. NEUTROPENIA

A. Definition of Neutropenia

1. Neutropenia is defined as an absolute neutrophil count (ANC) <1500/μL. Severe neutropenia is defined as an ANC <500/μL.

2. See Table 14.7 at the end of the chapter for age-specific leukocyte differentials.
3. Repeat CBC 2 to 3 weeks later to determine if transient (e.g., secondary to a medication, infection) or persistent.[11]

B. Causes and Evaluation of Neutropenia[11]

1. CBC +/– blood smear should be obtained to evaluate neutrophil morphology and concurrent presence of anemia or thrombocytopenia.
2. If pancytopenic, obtain bone marrow aspiration and biopsy with cytogenetics.
3. If persistent neutropenia for more than 2 to 4 weeks, consider further workup based on potential etiologies (Table 14.8).

C. Management of Neutropenia

1. **Additional diagnostic testing:**[12]
   a. Repeat CBC 2×/week for 6 to 8 weeks for cyclic neutropenia.
   b. Reticulocyte Index to differentiate between destructive processes and marrow failure.
   c. Blood smear for morphologic abnormalities.
   d. Immunologic testing (Coombs test, anti-double-stranded DNA, anti-neutrophil antibody) for autoimmune or alloimmune processes.
   e. IgG, IgA, IgM, lymphocyte subtypes for immunodeficiency.
2. **Treatment:**
   a. Myeloid-specific cytokine granulocyte colony-stimulating factor (G-CSF; filgrastim).
      (1) Indications for continuous use: Severe congenital neutropenia, cyclic neutropenia, glycogen storage disease 1b, bone marrow failure (e.g., aplastic anemia, Schwachman Diamond-Oski syndrome).[12,13]
      (2) Indications for intermittent use: Life-threatening infection or history of recurrent or serious infections in patients with neutropenia.[12]
      (3) Side effects: Bone pain, headache, rashes.
   b. Stem cell transplant: Indicated for bone marrow failure (e.g., Fanconi anemia), poor response to G-CSF, severe congenital neutropenia with high risk of myelodysplasia or acute myeloid leukemia.[12]
3. **Complications**: See Chapter 22 for management of neutropenic fever and typhlitis.
4. **Anticipatory guidance:**[11]
   a. Maintain good oral hygiene and skin care to prevent local infections.
   b. Avoid rectal temperatures, rectal examinations, or rectal medications due to risk of mucosal trauma and bacteremia.
   c. No live or attenuated-live vaccines for patients with impaired T-/B-lymphocyte function. Otherwise follow usual vaccination schedule.
   d. If fever >38.4°C, seek emergent care for CBC, blood culture, and empiric antibiotics.
   e. Children with mild-moderate neutropenia can attend school/daycare, if they avoid obviously ill children.

TABLE 14.8

CAUSES OF NEUTROPENIA

	Cause	Mechanism	Presentation
ACQUIRED			
Infections	Viruses (EBV, CMV, parvovirus, HHV6, HIV, viral hepatitis). Bacteria (typhoid fever, Brucellosis). Protozoa (Leishmania, malaria), Rickettsial infections, etc.	Bone marrow suppression, viral-induced immune neutropenia, redistribution to marginated pools.	Occurs early in illness, persists 3–8 days and resolves spontaneously and/or with effective treatment of underlying illness.
Medications	Many: sulfasalazine, antipsychotics (clozapine, phenothiazines), thionamides, antimicrobials (TMP/SMX).	Direct marrow suppression (more common) or drug-induced immune-mediated destruction.	Hypersensitivity reaction: fever, lymphadenopathy, rash. May have +ANA.
Nutritional	Vitamin B12 deficiency Folic acid deficiency Copper deficiency	Ineffective hematopoiesis due to impaired DNA processing and nuclear maturation (with B12/folate deficiency).	Mostly seen in chronically ill children, especially with malabsorption. Hypersegmented neutrophils, megaloblastic anemia with B12/folate deficiency. High MMA and HcY in B12 deficiency vs. high HcY in folate deficiency.
Hypersplenism	Inflammation, neoplasm, storage disorder, hemolytic anemia.	Sequestration of WBCs in spleen.	Concurrent anemia, thrombocytopenia. Rarely associated with infections.

Continued

TABLE 14.8

CAUSES OF NEUTROPENIA—cont'd.

	Cause	Mechanism	Presentation
Autoimmune	Neonatal alloimmune neutropenia	Transfer of maternal IgG alloantibodies against fetus neutrophil antigens that were produced in response to fetal cells in maternal circulation.	Severe neutropenia with fever, infection. Transient, resolves after 6–8 weeks.
	Primary autoimmune neutropenia	Antineutrophil antibodies cross-react with antigen on neutrophil surface resulting in neutrophil destruction.	Typically 5–15 months old child without recurrent infections despite severe neutropenia. +ANA. Marrow with myeloid hyperplasia and normal to increased mature neutrophils.
	Secondary autoimmune neutropenia	Secondary to systemic disease: Systemic lupus erythematosus, Evans syndrome, rheumatoid arthritis/Felty syndrome, systemic sclerosis), infections (HIV, EBV).	Presents with signs/symptoms of systemic autoimmune disease.
	Pure white cell aplasia	Associated with thymoma, drug reactions, antiglomerular basement membrane antibody disease.	At risk of severe, recurrent infections. Disappearance of granulocytopoietic tissue from bone marrow. +Antibodies (e.g., GM- CFU inhibitory activity).
Acquired bone marrow disorders	Leukemia, lymphoma, solid tumor infiltration, myelofibrosis, granulomatous infections, aplastic anemia.	Impaired production of all cell lines due to bone marrow infiltration.	Typically associated with anemia +/or thrombocytopenia. Bone marrow biopsy diagnostic.

INHERITED[a]			
Severe congenital neutropenia	Severe congenital neutropenia	AD mutation in *ELANE* or *GFII* genes results in rapid apoptosis of myeloid precursors, arrest at promyelocyte development stage. Risk of myelodysplastic syndrome and acute myelogenous leukemia.	Recurrent infections: mouth ulcers, gingivitis, otitis media, respiratory infections, skin cellulitis, abscesses. Often with oncocytosis, eosinophilia, anemia, thrombocytosis. Bone marrow: myeloid maturation arrest, normal/increased promyelocytes.
	Kostmann syndrome	Severe form of SCN. AR mutation in *HAX1* gene results in absent myeloid progenitors.	Recurrent infections as above. Typically with monocytosis, eosinophilia.
Cyclic neutropenia		AD mutation in *ELANE* gene.	Periodic ~21-day cycles of neutropenia, typically associated with fever, oral ulcerations, +/– gingivitis, pharyngitis, skin infections.
Benign ethnic neutropenia		*DARC* gene polymorphism reducing Duffy antigen expression.	Mild neutropenia in patient of West Indian, Yemenite, African, Greek, or Arab descent without increased infection incidence or severity.
Bone marrow failure syndromes	Fanconi anemia	See section VII. Online content for description of bone marrow failure in anemia.	Pancytopenia.
	Diamond Blackfan anemia		

[a]This is not an exhaustive list of all inherited causes of neutropenia.

AD, autosomal dominant; *ANA*, antinuclear antibody; *AR*, autosomal recessive; *CMV*, cytomegalovirus; *DARC*, Duffy antigen/chemokine receptor; *EBV*, Epstein-Barr virus; *GM-CFU*, granulocyte-macrophage colony forming unit; *HcY*, homocysteine; *HHV6*, human herpes virus 6; *HIV*, human immunodeficiency virus; *MMA*, methylmalonic acid; *SCN*, severe congenital neutropenia; *TMP-SMX*, trimethoprim-sulfamethoxazole; *WBC*, white blood cell.

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III. THROMBOCYTOPENIA AND IMPAIRED PLATELET FUNCTION

A. Definition of Thrombocytopenia

1. Defined as platelet count <150,000/μL.
2. See Table 14.1 for age-specific values.

B. Bleeding Risk with Thrombocytopenia

1. Risk of clinically significant bleeding is related to both platelet function and number. Unlikely with platelet counts >30,000/μL in the absence of other complicating factors.[14]
2. Risk of severe bleeding (CNS hemorrhage, gross hematuria, melena/hematochezia, hematemesis) increases with platelet counts <10,000/μL.[14]

C. Evaluation of Thrombocytopenia[15,16]

1. Platelet size: Large = mean platelet volume (MPV) >11 fL, normal = MPV 7 to 11 fL, small = MPV <7 fL.
   a. Large platelets suggest increased marrow production in destructive processes (e.g., immune thrombocytopenia [ITP]) or some congenital disorders.
   b. Small platelets suggest production defects, typically seen in congenital disorders.
2. Peripheral blood smear: Confirm platelet count, evaluate size and morphology, and rule out artifact platelet aggregation (i.e., due to artificial clumping in EDTA tube).
3. Immature platelet fraction: Correlates with measure of reticulated platelets, which reflects thrombopoiesis. Increases with peripheral destruction; is normal/low with bone marrow failure.
4. Bone marrow aspiration: Obtain if systemic symptoms concerning for underlying malignancy, involvement other cell lines, and/or blasts on smear. Differentiates decreased production versus increased destruction.

D. Causes of Thrombocytopenia and Impaired Platelet Function

1. See Table 14.9 for an approach to the differential of thrombocytopenia.
2. See Table 14.10 for differential of abnormal platelet function.

E. Management of Thrombocytopenia

1. **ITP**[17]
   a. Pathophysiology: Immune-mediated destruction of circulating platelets.
   b. Presentation: Otherwise healthy 2- to 10-year-old child with sudden bruising or bleeding after recent mild illness or vaccination, isolated thrombocytopenia (platelets <100,000/μL), and peripheral smear with thrombocytopenia and reticulated large platelets.
   c. Diagnostic testing: No additional testing needed if presentation consistent with ITP. If persists >3 to 6 months, pursue further workup: Infection testing (human immunodeficiency virus, hepatitis C, *Helicobacter pylori* infection), antinuclear antibody, anticardiolipin

TABLE 14.9

APPROACH TO THROMBOCYTOPENIA

ACQUIRED		
Destructive • Smear: large platelets • Increased IPF • Bone marrow: normal-increased megakaryocytes	Immune-mediated	Immune thrombocytopenia (ITP) Evans Syndrome: ITP + autoimmune hemolytic anemia Autoimmune disorders (antiphospholipid antibody syndrome, systemic lupus erythematosus) Drug-induced thrombocytopenia (heparin-induced thrombocytopenia) Neonatal alloimmune thrombocytopenia[a] Neonatal autoimmune thrombocytopenia[a]
	Platelet consumption	Thrombotic microangiopathies (TMAs; e.g., HUS, TTP) Disseminated intravascular coagulation (DIC) Kasabach-Merritt syndrome (giant cavernous hemangioma, other vascular malformation) Major surgery/trauma/burn
	Mechanical destruction	Extracorporeal membrane oxygenation (ECMO) Hemodialysis
	Sequestration	Hypersplenism (sickle-cell disease, malaria)
Impaired platelet production • Smear: normal sized platelets • Low/normal IPF • Infiltration of bone marrow or reduced megakaryocytes	Infection	EBV, CMV, parvovirus, varicella, rickettsia, HIV, sepsis (DIC), congenital infection
	Nutritional deficiency	Folate, vitamin B12, iron deficiency
	Acquired bone marrow failure	Aplastic anemia, myelodysplastic syndromes, medications (chemotherapy), radiation
	Inherited bone marrow failure	Fanconi Anemia, Schwachman-Diamond syndrome
	Infiltrative bone marrow disease	Leukemia, lymphoma, infectious granulomas, storage diseases
CONGENITAL		
Impaired platelet production	Small platelets	Wiskott-Aldrich syndrome[b] X-linked Thrombocytopenia
	Large/giant platelets	Bernard-Soulier syndrome[b] Gray platelet syndrome[b] *MYH9*-related disorders[b] Type 2B von Willebrand disease[b] Paris-Trousseau-Jacobsen syndrome DiGeorge syndrome
	Normal platelets	Congenital amegakaryocytic thrombocytopenia (CAMT) Thrombocytopenia with absent radius (TAR) syndrome[b] Amegakaryocytic thrombocytopenia with radioulnar synostosis Autosomal dominant thrombocytopenia

[a]Neonatal alloimmune thrombocytopenia occurs when maternal IgG antiplatelet antibodies cross placenta and destroy fetal platelets expressing a "foreign" antigen inherited from father. Neonatal autoimmune thrombocytopenia occurs in children of mothers with antiplatelet antibodies, often related to autoimmune disorders (e.g., immune thrombocytopenic purpura or systemic lupus erythematosus).

[b]These disorders typically also have disordered platelet function.

CMV, Cytomegalovirus; *EBV*, Epstein-Barr virus; *HIV*, human immunodeficiency virus, *HUS*, hemolytic uremic syndrome; *TTP*, thrombotic thrombocytopenic purpura.

Buchanan GR. Thrombocytopenia during childhood: what the pediatrician needs to know. *Pediatr Rev.* 2005:26(11):401–409.

Israels SJ, Kahr WH, Blanchette VS, et al. Platelet disorders in children: a diagnostic approach. *Pediatr Blood Cancer.* 2011:56(6):975–983.

TABLE 14.10

CAUSES OF PLATELET DYSFUNCTION

Medications	NSAIDs, Beta-lactam antibiotics, SSRIs
Underlying disease	Uremia, myeloproliferative disorders, myelodysplastic disorders
Inherited disorders	Glanzmann thrombasthenia
	Von Willebrand disease
	Bernard-Soulier syndrome
	Storage pool diseases: Wiskott-Aldrich syndrome, Thrombocytopenia with Absent Radii syndrome, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome.

NSAIDs, Nonsteroidal anti-inflammatory drugs; *SSRIs*, selective serotonin reuptake inhibitors.

Israels SJ, Kahr WH, Blanchette VS, et al. Platelet disorders in children: a diagnostic approach. *Pediatr Blood Cancer.* 2011:56(6):975–983.

antibody and lupus anticoagulant (for antiphospholipid syndrome), serum immunoglobulins (IgG, IgA, IgM).[18]

d. Management: Observation if no or mild bleeding (e.g., skin manifestations). Treat if significant skin/mucosal bleeding with intravenous immunoglobulin (IVIG), steroids, *or* Anti-Rh (D) immune globulin in consultation with a hematologist.[18] Only transfuse platelets if life-threatening bleed, often with IVIG and high-dose steroids. May require emergent splenectomy.

2. **Thrombotic thrombocytopenic purpura (TTP)**[19]
   a. Pathophysiology: Decreased ADAMTS13 activity results in impaired processing of von Willebrand factor (vWF) multimers, which causes microthrombi.
   b. Presentation: Microangiopathic hemolytic anemia (MAHA), thrombocytopenia, acute kidney injury, fever, and neurologic symptoms (headache, hemiparesis, coma).
   c. Management: Early plasma exchange with fresh frozen plasma (FFP) and glucocorticoids. If high clinical suspicion, treat emergently before ADAMTS13 testing results.
3. **Hemolytic-uremic syndrome (HUS)**
   a. Pathophysiology: Due to Shiga toxin-producing *Escherichia coli* O157:H7 or *Shigella* diarrhea (sometimes *Streptococcus pneumoniae*, HIV).[20]
   b. Presentation: Early abdominal pain and bloody diarrhea, late thrombocytopenia and renal failure.
   c. Management: Supportive care with early/aggressive hydration, RBC/platelet transfusions as needed, antihypertensives, and neurologic monitoring.[21]
4. **Complement-mediated ("Atypical HUS")**
   a. Pathophysiology: Uncontrolled activation of complement on cell membranes.[21]
   b. Diagnostic testing: Complement panel, anti-CFH antibodies, consider genetic screening.
   c. Management: Eculizumab.

5. **Drug-induced thrombocytopenia**[22]
   a. Presentation: Lightheadedness, chills, fever, nausea/vomiting, purpura, petechiae ~7 days after starting medication (onset variable).
   b. Diagnostic testing for heparin-induced thrombocytopenia: +anti-PF4/heparin antibodies, +serotonin release assay.
   c. Management: Discontinue medication permanently, transfuse if severe thrombocytopenia to prevent intracranial or intrapulmonary hemorrhage.
6. **Neonatal alloimmune thrombocytopenia**[23]
   a. Pathophysiology: Maternal IgG antibodies (usually against paternally inherited PLA-1/HPA-1a) cross placenta and cause neonatal platelet destruction.
   b. Presentation: Severe thrombocytopenia, intracranial hemorrhage (ICH).
   c. Diagnostic testing: Identify antipaternal antibodies in infant circulation or maternal and infant platelet antigen typing.
   d. Management: Head ultrasound (US) to screen for ICH, transfuse platelets if <30,000/μL or signs of bleeding, consider IVIG if poor response to platelet transfusion.

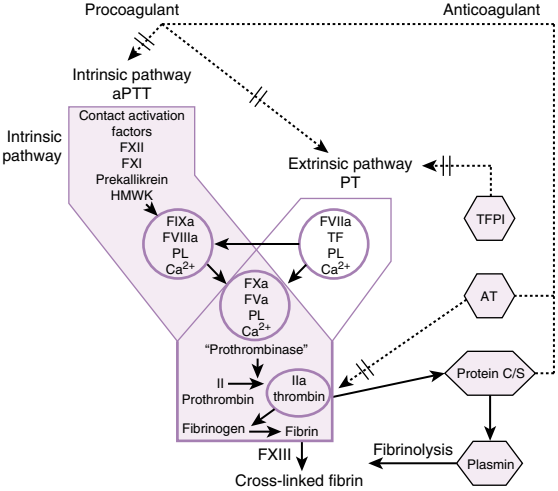
IV. COAGULATION

A. Evaluation of Coagulation and Platelet Function

1. Coagulation
   a. See Fig. 14.3 for coagulation cascade.
   b. **Activated partial thromboplastin time (aPTT)**: Measures intrinsic system and common pathway—Factors V, VIII, IX, X, XI, XII, fibrinogen, and prothrombin.
   c. **Prothrombin time (PT):** Measures extrinsic pathway and common pathway—Factors V, VII, X, fibrinogen, and prothrombin.
   d. **Thrombin time (TT):** Measures conversion of fibrinogen to fibrin. Prolonged with low or dysfunctional fibrinogen and anticoagulants (heparin, low molecular weight heparin, direct thrombin inhibitors), but not with common pathway abnormalities.
   e. **Reptilase time (RT):** Normal with heparin or direct thrombin inhibitors, but prolonged with fibrinogen abnormalities.
   f. **Mixing study:** Used in patients with abnormal clotting (i.e., prolonged PT, aPTT, or TT) to determine presence of factor deficiency (corrects with addition of normal plasma) or factor inhibitor (no correction would occur).
   g. **Dilute Russell viper venom time (dRVVT):** Russell viper activates factor X directly and is sensitive to inhibition by antiphospholipid antibodies. Prolonged dRVVT that corrects with addition of phospholipid to assay suggests presence of antiphospholipid antibodies (Lupus anticoagulants).[24]

Normal PT and PTT
- **von Willebrand disease (type 2B)**
- **Platelet dysfunction**
- **Thrombocytopenia**
- **Vascular abnormalities**
- **Factor XIII deficiency**
- **Fibrinolytic disorders**

Prolonged aPTT and normal PT
- **Factor VIII, IX, XI, XII deficiency or inhibitor**
- **Lupus anticoagulant**
- **von Willebrand disease**
- **Heparin**



Prolonged PT and aPTT
- **Normal TT:**
  - **Liver disease**
  - **Vitamin K deficiency (late)**
  - **Factor II/V/X deficiency or inhibitor**
  - **Combined factor deficiencies**
  - **Lupus anticoagulant**
- **Prolonged TT**
  - **DIC**
  - **Low fibrinogen**
  - **Dysfibrinogenemia**

Prolonged PT and normal aPTT
- **Factor VII deficiency or inhibitor**
- **Mild liver disease**
- **Vitamin K deficiency (early)**
- **Warfarin**

FIGURE 14.3

Coagulation cascade and differential diagnosis (DDX) of bleeding disorders. *aPTT*, Activated partial thromboplastin time; *DIC*, disseminated intravascular coagulation; *PT*, prothrombin time; *TT*, thrombin time. (Adapted from Rodriguez V. and Warad D, Pediatric coagulation disorders. *Pediatr Rev.* 2016:37[7]:279–290. Adaptation courtesy James Casella and Clifford Takemoto.)

h. **Fibrinogen:** Low levels (<50 to 100 mg/dL) causes impaired clot formation and prolongs PT and aPTT. Decreased in disseminated intravascular coagulation (DIC), liver disease, traumatic hemorrhage.
i. **D-dimer:** Fibrin degradation product increased with recent/ongoing fibrinolysis (e.g., deep vein thrombosis, pulmonary embolism, DIC, and many other clinical scenarios).
j. **Thromboelastography (TEG):** Whole blood test that rapidly measures time parameters of clot formation and overall clot strength, detects increased fibrinolysis. Useful for identification of coagulopathy and to guide transfusion in cardiac surgery and trauma.[25]

2. Platelet function[12]
   a. Always assess platelet number and use of platelet inhibitors (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) before platelet function testing.
   b. **Light transmission aggregometry (LTA):** Measures platelet aggregation *in vitro*.[16]
   c. **Platelet function analyzer-100 (PFA-100):** Measures primary hemostasis (platelet adhesion, activation, and aggregation) *in vitro*.[16]
   d. **Bleeding time (BT):** Evaluates clot formation, including platelet number/function and vWF, *in vivo*. Technically challenging to perform and has been largely replaced by above tests.

B. Definition of Abnormal Coagulation

1. An incorrect anticoagulant-to-blood ratio will give inaccurate results.
2. See Table 14.11 at end of chapter which lists normal hematologic values for coagulation testing.

C. Causes and Management of Coagulopathy

1. **Medications**
   a. Heparin affects aPTT, thrombin time, dRVVT, and mixing studies.
   b. Warfarin affects PT, may mildly affect aPTT, and interferes with dRVVT by reducing the activity of vitamin K–dependent factors (II, VII, IX, X, protein C and S).
2. **Disseminated intravascular coagulation**
   a. Tissue damage (e.g., due to sepsis, trauma, malignancy) results in tissue factor release and systemic activation of coagulation system, consumption of coagulation factors and platelets, increased fibrin formation and fibrinolysis, MAHA, bleeding, and microthromboses.[26]
   b. Diagnosis: Prolonged P T and aPTT, decreased fibrinogen, thrombocytopenia, increased D-Dimer, increased fibrin degradation products, and presence of schistocytes on peripheral smear.
   c. Treatment: Address underlying condition and supportive care. May require FFP, cryoprecipitate, and/or platelet transfusions if active bleeding or high bleeding risk.
3. **Liver disease**
   a. The liver is the major site of synthesis of factors V, VII, IX, X, XI, XII, XIII.
   b. It is also involved in the synthesis of prothrombin, plasminogen, fibrinogen, proteins C and S, and ATIII.

4. **Vitamin K deficiency**
   a. Often secondary to liver disease, pancreatic insufficiency, malabsorption, exclusive breastfeeding, prolonged antibiotic use, malignancy.
   b. Necessary for synthesis of factors II, VII, IX, X, protein C, and protein S.[12]
   c. Treatment: Parenteral vitamin K corrects PT in 2 to 6 hours. Oral form corrects in 6-8 hours.[27] Give FFP if evidence of severe bleeding. Prothrombin complex concentrate can be given in cases of life-threatening hemorrhage or ICH.
5. **Hemophilia A (Factor VIII deficiency) and Hemophilia B (Factor IX deficiency)[28]**
   a. Etiology: X-linked recessive disorders. Females can be symptomatic carriers.
   b. Diagnosis: Prolonged aPTT that corrects with mixing study, normal PT, low factor assays. Mild forms can have normal aPTT.
   c. Classification of disease severity:[28]
      (1) Severe: <1% activity; spontaneous bleed (hemarthrosis, hematoma) without trauma.
      (2) Moderate: 1% to 5% activity; bleeding after minor trauma.
      (3) Mild: 5% to 40% activity; bleeding with surgery or significant trauma.
   d. Bleeding prophylaxis:
      (1) Home prophylaxis: Intravenous (IV) factor replacement (per individualized protocols) to maintain factor level >1 IU/dL to prevent spontaneous bleeds and preserve joint function. Initiate before onset of frequent bleeding, typically in 1- to 3-year-olds.[29] Emicizumab-kxwh is a bispecific antibody that is delivered subcutaneously (SQ) and can be used for prophylaxis.
      (2) Surgical prophylaxis: Factor replacement for goal factor level 80 to 100 IU/dL (major procedure) or 50 to 80 IU/dL (minor procedure) preoperatively and through postoperative period of bleeding risk.[28] Consult hematologist before any diagnostic or therapeutic procedure, including dental, endoscopy with biopsy, arterial blood gas, etc.
   e. Treatment of acute bleeds:
      (1) Always remember: **"Factor first!"** Do not delay first dose for evaluation.
      (2) Bolus dose FVIII or FVIX concentrate. May require additional doses.
      (3) Consult hematologist for all major bleeding.
      (4) See Table 14.12 for desired factor replacement level and dosing.
      (5) Half-life of Factor VIII: 8 to 12 hours. Half-life Factor IX: 18 to 24 hours.[28]
      (6) If suspected intracranial bleed, replete 100% factor level immediately on presentation and **before** additional diagnostic testing (e.g., CT scan).
      (7) Alternative treatments for mild Hemophilia A: Desmopressin (DDAVP) and antifibrinolytic agents (tranexamic acid, aminocaproic acid).

TABLE 14.12

DESIRED FACTOR REPLACEMENT IN HEMOPHILIA

Bleeding Site	Desired Level (%)
Minor soft tissue bleeding	20–30
Joint	40–70
Simple dental extraction	50
Major soft tissue bleeding	80–100
Serious oral bleeding	80–100
Head injury	100+
Major surgery (dental, orthopedic, other)	100+

NOTE: A hematologist should be consulted for all major bleeding and before surgery.
Round to the nearest vial; do not exceed 200%.

Dose calculation:

1. Units of factor VIII needed = weight (kg) × desired % replacement × 0.5.

2. Units of factor IX needed = weight (kg) × desired % replacement × 1.0 or 1.2.

Dosing adapted from Nathan D, Oski FA. *Hematology of Infancy and Childhood.* Philadelphia: WB Saunders; 1998.

(8) Can use cryoprecipitate (for Hemophilia A, not for Hemophilia B) or FFP if no factor available.

f. Factor inhibitors: IgG antibodies that develop with repeat factor exposure and complicate treatment. Patients with severe hemophilia A are at the highest risk.
   (1) Screen for inhibitors with inhibitor assay if poor clinical response to factor. Consider screen during initiation of factor treatment and preoperatively.
   (2) In the presence of inhibitors, patients may require higher doses of factor, recombinant FVIIa, or activated prothrombin complex concentrates.

g. Healthcare maintenance
   (1) Vaccinations: Given per routine schedule. Give prophylactic factor for intramuscular vaccines or give vaccine SQ with smallest gauge needle without factor prophylaxis.[28]
   (2) Physical activity: Avoid high contact (e.g., soccer, hockey) and high velocity (e.g., skiing) activities.[28]
   (3) Medications to avoid: Aspirin, NSAIDs, anticoagulants.
   (4) Many younger children will need a central venous catheter for factor delivery and must therefore follow strict fever guidelines.

6. **Von Willebrand (vW) disease**

a. Pathophysiology: Most common inherited bleeding disorder. Abnormal platelet adhesion and aggregation, low factor VIII.[30]

b. Diagnosis: Low circulating vWF antigen (VWF:Ag) and/or low vWF function on ristocetin-based platelet aggregation study (VWF:RCo), low or normal factor VIII activity, prolonged PFA-100. May require additional evaluation.

c. Classification:[30]
   (1) Type 1 (75% to 80% cases): Partial quantitative deficiency.
   (2) Type 2 (20% to 25%): Qualitative dysfunction.

(3) Type 3 (rare): Absence or near absence of vWF + markedly low factor VIII activity (can resemble Hemophilia A patient on labs and presentation).

d. Treatment:[30]

(1) Desmopressin (DDAVP): Stimulates vWF release. Given IV or intranasal. May be used as prophylaxis for minor surgeries or treatment for mild bleeding. Ineffective in Type 3, variable effect in Type 2. Patients should be tested for DDAVP response before using as prophylaxis.

(2) VWF-containing concentrates (Humate-P, Alphanate, or Wilate): Replaces vWF and factor VIII and derived from blood donors. Recombinant vWF available (VONVENDI). Used for severe bleeding events and surgery.

(3) Cryoprecipitate only appropriate for life-threatening situations if vWF concentrate unavailable.

(4) Alternative therapies: IV or oral antifibrinolytic therapy (tranexamic acid and aminocaproic acid) can be used to prevent or treat mild mucocutaneous bleeding alone or in conjunction with other therapies.

D. Causes of Hypercoagulability

1. Most thrombotic events are due to an acquired condition; however, an inherited thrombophilia is more likely if there is a family history, an unusual thrombus location, absence of an inciting factor, and/or recurrent thromboses.
2. See Table 14.13 for etiologies and evaluation of hypercoagulable states.
3. Acquired conditions associated with venous thromboembolism include endothelial damage (vascular catheters, sepsis, smoking, diabetes, hypertension, surgery, hyperlipidemia), disturbed blood flow (central venous lines, congenital heart disease), hyperviscosity (macroglobulinemia, polycythemia, sickle cell disease), platelet activation (essential thrombocytosis, oral contraceptives, heparin-induced thrombocytopenia), malignancy, inflammatory bowel disease, parenteral nutrition, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria.

E. Thrombus Management

1. See Table 14.14 for anticoagulant use.
2. See Formulary for dosing and adjustment based on monitoring protocols.
3. Note: Children receiving anticoagulation therapy should be protected from trauma. Subcutaneous injections should be used when possible, and caution should be used with intramuscular injections. The use of antiplatelet agents and arterial punctures should be avoided.
4. See Table 14.15 for warfarin reversal guidelines.

V. BLOOD COMPONENT REPLACEMENT

A. Calculating Estimated Blood Volume (Table 14.16)

TABLE 14.13

HYPERCOAGULABLE STATES

Hypercoagulable Condition	Cause	Risk of VTE (Compared to General Population; Odds Radio)	Associated Test
Factor V Leiden (activated protein C resistance)	AD Factor V Leiden mutation.	3.77 (heterozygote)	1. Activated protein C resistance assay (screening test) 2. Factor V Leiden (DNA-based PCR assay)
Factor VIII, IX, XI abnormalities[a]	Inherited or acquired elevated factor levels.	6.7 (Factor VIII)	Factor VIII, IX, XI
Protein C and S deficiency[a]	AD. Homozygous more severe than heterozygous.	7.72 (protein C); 5.77 (protein S)	Protein C and S activity
Antithrombin III deficiency[a]	AD. Type I: low level and activity (homozygous not compatible with life). Type II: low activity or dysfunction.	9.44	Antithrombin III activity
Hyperhomocystinemia[a]	AR alteration in *MTFHR* gene.	1.27	1. Homocysteine level (fasting) 2. *MTHFR* genetic testing if homocysteine elevated
Prothrombin mutation	AD mutation in G20210A.	2.64 (heterozygote)	DNR-based PCR assay
Antiphospholipid antibodies[a]	Rarely inherited. Typically sporadic: spontaneous (primary) or secondary to autoimmune disorder (e.g., SLE) or infections.	High	Phospholipid-based clotting assays (aPTT, DRVVT) that correct with phospholipid addition ELISA assays: cardiolipin and β2-glycoprotein antibodies
High lipoprotein(a)	Levels determined by genetics and environment.	4.49	Lipoprotein(a) level
Plasminogen deficiency	Inherited hypoplasminogenemia (Type I) or dysplasminogenemia (Type II).		Plasminogen activity[b]

[a]These conditions may be inherited or acquired.

[b]Also consider testing tissue plasminogen activator (tPA) antigen and plasminogen activator inhibitor-1 (PAI-1) activity. Low tPA decreases fibrinolysis. Increased PAI-1 causes excess inhibition of tPA.

A hematologist should be consulted if initiating this workup.

AD, Autosomal dominant; *aPTT*, activated partial thromboplastin time; *AR*, autosomal recessive; *DRVVT*, dilute Russell's viper venom time; *ELISA*, enzyme-linked immunosorbent assay, *PCR*, polymerase chain reaction, *SLE*, systemic lupus erythematosus, *VTE*, venous thromboembolism.

Rodriguez V, Warad D. Pediatric coagulation disorders. *Pediatr Rev.* 2016;37(7):279–290.

Young G, Albisetti M, Bonduel M, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. *Circulation.* 2008;118(13):1373–1382.

TABLE 14.14

ANTICOAGULANTS

Medication	Indication	Contraindications and Adverse Effects	Monitoring	Reversal
Heparin/UFH (IV)	Acute treatment VTE, acute ischemic stroke (AIS), cerebral venous sinus thrombosis (CVST) without ICH. Prevention of thrombosis with cardiac catheterization, cardiopulmonary bypass surgery, extracorporeal circuits.	Heparin hypersensitivity, major active or high risk bleeding, platelets <50,000, known/suspected HIT, concurrent epidural therapy. Cautious use in patients with high bleeding risk or platelets <50,000/mm^3. Avoid IM injections and concurrent use drugs affecting platelet function (NSAIDs, aspirin, clopidogrel).	Anti-Xa level (goal 0.3–0.7 U/mL) or aPTT (1.5–2.5 times the control aPTT. The aPTT range in seconds (~50–80 sec) should be calibrated to anti-Xa of 0.3–0.7 U/mL.	Protamine sulfate
LMWH/enoxaparin (SQ)	Initial or ongoing therapy for VTE, CVST, AIS with cardioembolic source, recurrent AIS. Patients with history or risks for HIT.	HIT (lower risk than UFH) Chronic use (>6 months) use may decrease bone density.	Anti-Xa activity (goal 0.5–1 U/mL thrombosis, 0.1–0.3 U/mL for prophylaxis).	Protamine sulfate (partial neutralization)
Warfarin (PO)	Long-term anticoagulation after bridge from UFH or LMWH for VTE, CVST, AIS. Recurrent idiopathic VTE.	Interactions with diet and medications (see Table EC 14.A). Adjust dose in liver dysfunction, avoid in severe liver failure. Limited safety and efficacy data in newborns <3 months. Warfarin-induced skin necrosis has been reported in patients initiated without bridging anticoagulation. Teratogenic.	INR (2–3 with target 2.5, except with prosthetic cardiac valves) measured every 1–4 weeks.	Vitamin K (see Table 14.17)

DIRECT THROMBIN INHIBITORS				
Argatroban (IV)	Alternative to heparin in patients with HIT.	Avoid or alter dose in patients with hepatic impairment.	aPTT 1.5–2.5× baseline.	None
Bivalirudin (IV)	Inpatient treatment of VTE and prevention of thrombus during cardiac catheterization in patients with HIT.	Adjust dose with renal impairment.	aPTT 1.5–2.5× baseline.	None
Dabigatran (PO)[a]	Approved in adults to treat DVT/PE, reduce embolic risk in non-valvular AF.	*Studies ongoing for safety and efficacy in pediatric patients.*	None required.	Idarucizumab
FACTOR XA INHIBITORS				
Fondaparinux (SQ)[a]	Approved in adults to treat and prevent DVT/PE. Can be used in patients with HIT.	Adjust dose with renal impairment.	Anti-Xa level 0.5–1 mg/L.	None
Apixaban (PO)[a]	Approved in adults to treat and prevent DVT/ PE, reduction embolic risk in AF.	*Studies ongoing for safety and efficacy in pediatric patients.*	Can measure anti-Xa level.	Andexanet alfa
Rivaroxaban (PO)[a]	Approved in adults to treat and prevent recurrent DVT/PE, prevent non-valvular AF embolic complications.	*Studies ongoing for safety and efficacy in pediatric patients.*		

[a]These medications are undergoing Phase II/III trials for use in children and should not be used as first-line therapy.[44,45]

AF, Atrial fibrillation; *aPTT*, activated partial thromboplastin time; *DVT*, deep venous thrombosis; *HIT*, heparin-induced thrombocytopenia; *INR*, international normalized ratio; *IV*, intravenous; *LMWH*, low-molecular-weight heparin; *NSAID*, non-steroidal anti-inflammatory drug; *PE*, pulmonary embolism; *PO*, oral; *SQ*, subcutaneous; *UFH*, unfractionated heparin; *VTE*, venous thromboembolism.

Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *CHEST*. 2012;141(2):e737S–e801s.

Young G. Anticoagulation therapies in children. *Pediatr Clin North Am*. 2017;64(6):1257–1269.

TABLE 14.15

MANAGEMENT OF EXCESSIVE WARFARIN ANTICOAGULATION

INR and Bleeding	Intervention
INR 4–4.5 without serious bleeding	Hold or lower next warfarin dose. Recheck INR daily. For patients with high bleeding risk, consider standard dose of oral vitamin K.[a] When INR approaches therapeutic range, resume warfarin therapy.
INR ≥4.5 but <10 without serious bleeding	Hold warfarin. Recheck INR every 24 hr until <4. If high risk for bleeding, give standard dose of oral vitamin K[a]. When INR approaches therapeutic range, resume warfarin at a lower dose.
INR ≥10 without serious bleeding	Hold warfarin. Recheck INR every 12 hr. Give high dose oral vitamin K every 12–24 hr as necessary[b]. When INR approaches therapeutic range, resume warfarin at a lower dose.
Minor bleeding at any INR elevation	Hold warfarin. Monitor INR every 12–24 hr depending on bleeding severity. Give standard dose oral vitamin K and repeat as necessary if bleeding continues and INR not corrected at 24 hr[a]. Restart warfarin when INR approaches therapeutic range and when clinically appropriate at a lower dose.
Significant or life-threatening bleeding at any INR	Hold warfarin. Monitor INR every 4–6 hr. Administer high dose vitamin K IV, repeat as needed[b]. Transfusion of FFP (10–15 mL/kg IV), consider prothrombin complex concentrate; consult blood bank and/or hematology for dosing. Restart warfarin when INR approaches therapeutic range and when clinically appropriate at a lower dose.

[a]Standard dose Vitamin K: 0.03 mg/kg PO for patients <40 kg in weight; 1–2.5 mg PO for patients ≥40 kg. For rapid reversal, 0.5–2.5 mg IV slow infusion over 30 minutes. Expect INR reduction at 24–48 hr.

[b†]High dose Vitamin K: 0.06 mg/kg PO for patients <40 kg in weight; 5–10 mg for patients ≥40 kg. For emergent situations, 5–10 mg IV slow infusion over 30 minutes. Expect INR reduction at 12–14 hr.

NOTE: Always evaluate for bleeding risks and potential drug interactions. Do not give intramuscular Vitamin K to children on anticoagulants.

FFP, Fresh frozen plasma; *INR*, international normalized ratio; *IV*, intravenous; *PO*, by mouth.

The Johns Hopkins Hospital Children's Center pediatric policies, procedures, and protocols general care (Policy Number MDU043): Baltimore; 2019.

Adapted from: Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulation therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *CHEST*. 2012;141(2):e152S–e184S; Bolton-Maggs P, Brook L. The use of vitamin K for reversal of over-warfarinization in children. *Br J Haematol*. 2002;118:924–925.

TABLE 14.16

ESTIMATED BLOOD VOLUME

Age	Total Blood Volume (mL/kg)
Preterm infants	90–105
Term newborns	78–86
1–12 months	73–78
1–3 years	74–82
4–6 years	80–86
7–18 years	83–90
Adults	68–88

Data from Nathan D, Oski FA. *Hematology of Infancy and Childhood*. Philadelphia: WB Saunders; 1998.

B. Indications for and Expected Response Following Blood Transfusions

1. See Table 14.17 at the end of the chapter.
2. See Section VII. Online Content for information on directed donor transfusions.

C. Diagnosis and Management of Transfusion Reactions (Table 14.18)

D. Infectious Risks of Blood Transfusion

1. Transmission of infectious disease[31,32]
   a. Risk of HIV: 1 in 1,467,000.
   b. Human T-Lymphotropic virus (HTLV): 1 in 4,364,000.
   c. Hepatitis B: 1 in 765,000 to 1,006,000.
   d. Hepatitis C: 1 in 1,149,000.
   e. Parvovirus 1 in 10,000.
   f. Cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis A, parasites, tick-borne infections, and prior diseases may also be transmitted by blood products.
2. Sepsis related to bacterial contamination
   a. Risk of transmission of bacteria in RBCs is 1 in 5 million units.
   b. Risk of transmission in platelets is 1 in 100,000 units.
   c. Risk is higher in platelets because they are stored at room temperature.

VI. ADDITIONAL RESOURCES

A. Medications to avoid with G6PD Deficiency: http://g6pddeficiency.org/wp/living-with-g6pd-deficiency/drugs-to-avoid-list

B. Medications associated with thrombocytopenia: https://www.ouhsc.edu/platelets/ditp.html

C. Anemia Algorithm App: Created for adult patients, but provides useful framework for anemia differential.

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

TABLE 14.18

TRANSFUSION REACTIONS

Reaction	Timeline	Pathophysiology	Signs/Symptoms	Labs	Treatment
Acute hemolytic transfusion reaction	Immediate	Blood group incompatibility results in intravascular hemolysis, acute renal failure, DIC	Fevers, chills, flank pain, tachycardia, hypotension, shock, hematuria, bleeding	ABO, CBC Hemolysis labs: DAT, haptoglobin, LDH, bilirubin +/– DIC labs: PT/aPTT, fibrinogen, D-dimer Urinalysis (evaluate for hemoglobinuria)	Stop transfusion Notify blood bank Supportive measures: IV normal saline to achieve UOP >1 mL/kg/hr, vasopressors as needed, nephrology consult if necessary for acute renal failure
Febrile nonhemolytic reaction	1–6 hr	Either cytokines from donor WBCs in product or recipient anti-neutrophil or anti-HLA antibodies against WBCs in donor product.	Fever, chills, diaphoresis	Exclude alternative reactions (AHTR, sepsis)	Decreased incidence with leukoreduced products Stop transfusion Notify blood bank Antipyretics Consider future pre-medication with antipyretics (little evidence supporting practice)
Urticarial reaction	Immediate	Reaction to donor plasma proteins	Urticarial rash, respiratory distress	Possible formation IgE anti-IgA antibody	Stop transfusion Notify blood bank Epinephrine/steroids for respiratory compromise Antihistamines Resolved mild (cutaneous only) allergic reaction is the only time that a transfusion may be resumed with remainder of product

TABLE 14.18

TRANSFUSION REACTIONS—Cont'd.

Reaction	Timeline	Pathophysiology	Signs/Symptoms	Labs	Treatment
Delayed transfusion reaction	>24 hr post-transfusion (up to 30 days)	Minor blood group antigen incompatibility results in extravascular hemolysis	Fatigue, jaundice, dark urine	Anemia +DAT Evidence of hemolysis New RBC Abs	Monitor Hb level closely Supportive care

ABO, Blood type; *AHTR*, acute hemolytic transfusion reaction; *aPTT*, activated partial thromboplastin time; *CBC*, complete blood count; *DAT*, direct antiglobulin test; *DIC*, disseminated intravascular coagulation; *Hb*, hemoglobin; *HLA*, human leukocyte antigen; *IV*, intravenous; *LDH*, lactate dehydrogenase; *PRBCs*, packed red blood cells; *PT*, prothrombin time; *RBC*, red blood cell; *UOP*, urine output; *WBCs*, white blood cells.

Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet*. 2016;388(10061):2825–2836.

Bachowski G, Borge D, Brunker PAR, et al. *A Compendium of Transfusion Practice Guidelines*. 3rd ed. American Red Cross; 2017.

TABLE 14.1

AGE-SPECIFIC BLOOD CELL INDICES

Age	Hb (g/dL)[a]	HCT (%)[a]	MCV (fL)[a]	MCHC (g/dL RBC)[a]	Reticulocytes	WBCs (×10³/mL)[b]	Platelets (10³/mL)[b]
26–30 weeks gestation[c]	13.4 (11)	41.5 (34.9)	118.2 (106.7)	37.9 (30.6)	—	4.4 (2.7)	254 (180–327)
28 weeks	14.5	45	120	31.0	(5–10)	—	275
32 weeks	15.0	47	118	32.0	(3–10)	—	290
Term[d] (cord)	16.5 (13.5)	51 (42)	108 (98)	33.0 (30.0)	(3–7)	18.1 (9–30)[e]	290
1–3 days	18.5 (14.5)	56 (45)	108 (95)	33.0 (29.0)	(1.8–4.6)	18.9 (9.4–34)	192
2 weeks	16.6 (13.4)	53 (41)	105 (88)	31.4 (28.1)	—	11.4 (5–20)	252
1 month	13.9 (10.7)	44 (33)	101 (91)	31.8 (28.1)	(0.1–1.7)	10.8 (4–19.5)	—
2 months	11.2 (9.4)	35 (28)	95 (84)	31.8 (28.3)	—	—	—
6 months	12.6 (11.1)	36 (31)	76 (68)	35.0 (32.7)	(0.7–2.3)	11.9 (6–17.5)	—
6 months–2 years	12.0 (10.5)	36 (33)	78 (70)	33.0 (30.0)	—	10.6 (6–17)	(150–350)
2–6 years	12.5 (11.5)	37 (34)	81 (75)	34.0 (31.0)	(0.5–1.0)	8.5 (5–15.5)	(150–350)
6–12 years	13.5 (11.5)	40 (35)	86 (77)	34.0 (31.0)	(0.5–1.0)	8.1 (4.5–13.5)	(150–350)
12–18 YEARS							
Male	14.5 (13)	43 (36)	88 (78)	34.0 (31.0)	(0.5–1.0)	7.8 (4.5–13.5)	(150–350)
Female	14.0 (12)	41 (37)	90 (78)	34.0 (31.0)	(0.5–1.0)	7.8 (4.5–13.5)	(150–350)
ADULT							
Male	15.5 (13.5)	47 (41)	90 (80)	34.0 (31.0)	(0.8–2.5)	7.4 (4.5–11)	(150–350)
Female	14.0 (12)	41 (36)	90 (80)	34.0 (31.0)	(0.8–4.1)	7.4 (4.5–11)	(150–350)

[a]Data are mean (–2 SD).

[b]Data are mean (±2 SD).

[c]Values are from fetal samplings.

[d]1 month, capillary hemoglobin exceeds venous: 1 hour: 3.6-g difference; 5 day: 2.2-g difference; 3 weeks: 1.1-g difference.

[e]Mean (95% confidence limits).

Hb, Hemoglobin; *HCT*, hematocrit; *MCHC*, mean cell hemoglobin concentration; *MCV*, mean corpuscular volume; *RBC*, red blood cell; *WBC*, white blood cell.

Data from Forestier F, Dattos F, Galacteros F, et al. Hematologic values of 163 normal fetuses between 18 and 30 weeks of gestation. *Pediatr Res*. 1986;20:342; Oski FA, Naiman JL. *Hematological Problems in the Newborn Infant*. Philadelphia: WB Saunders; 1982; Nathan D, Oski FA. *Hematology of Infancy and Childhood*. Philadelphia: WB Saunders; 1998; Matoth Y, Zaizor K, Varsano I, et al. Postnatal changes in some red cell parameters. *Acta Paediatr Scand*. 1971;60:317; and Wintrobe MM. *Clinical Hematology*. Baltimore: Williams & Wilkins; 1999.

TABLE 14.7

AGE-SPECIFIC LEUKOCYTE DIFFERENTIAL

Age	Total Leukocytes[a]	Neutrophils[b]		Lymphocytes		Monocytes		Eosinophils	
	Mean (Range)	Mean (Range)	%	Mean (Range)	%	Mean	%	Mean	%
Birth	18.1 (9–30)	11 (6–26)	61	5.5 (2–11)	31	1.1	6	0.4	2
12 hr	22.8 (13–38)	15.5 (6–28)	68	5.5 (2–11)	24	1.2	5	0.5	2
24 hr	18.9 (9.4–34)	11.5 (5–21)	61	5.8 (2–11.5)	31	1.1	6	0.5	2
1 week	12.2 (5–21)	5.5 (1.5–10)	45	5.0 (2–17)	41	1.1	9	0.5	4
2 weeks	11.4 (5–20)	4.5 (1–9.5)	40	5.5 (2–17)	48	1.0	9	0.4	3
1 month	10.8 (5–19.5)	3.8 (1–8.5)	35	6.0 (2.5–16.5)	56	0.7	7	0.3	3
6 months	11.9 (6–17.5)	3.8 (1–8.5)	32	7.3 (4–13.5)	61	0.6	5	0.3	3
1 year	11.4 (6–17.5)	3.5 (1.5–8.5)	31	7.0 (4–10.5)	61	0.6	5	0.3	3
2 years	10.6 (6–17)	3.5 (1.5–8.5)	33	6.3 (3–9.5)	59	0.5	5	0.3	3
4 years	9.1 (5.5–15.5)	3.8 (1.5–8.5)	42	4.5 (2–8)	50	0.5	5	0.3	3
6 years	8.5 (5–14.5)	4.3 (1.5–8)	51	3.5 (1.5–7)	42	0.4	5	0.2	3
8 years	8.3 (4.5–13.5)	4.4 (1.5–8)	53	3.3 (1.5–6.8)	39	0.4	4	0.2	2
10 years	8.1 (4.5–13.5)	4.4 (1.5–8.5)	54	3.1 (1.5–6.5)	38	0.4	4	0.2	2
16 years	7.8 (4.5–13.0)	4.4 (1.8–8)	57	2.8 (1.2–5.2)	35	0.4	5	0.2	3
21 years	7.4 (4.5–11.0)	4.4 (1.8–7.7)	59	2.5 (1–4.8)	34	0.3	4	0.2	3

[a]Numbers of leukocytes are $\times 10^3/\mu L$; ranges are estimates of 95% confidence limits; percentages refer to differential counts.

[b]Neutrophils include band cells at all ages and a small number of metamyelocytes and myelocytes in the first few days of life.

Adapted from Cairo MS, Brauho F. Blood and blood-forming tissues. In: Randolph AM, ed. *Pediatrics*. 21st ed. New York: McGraw-Hill; 2003.

TABLE 14.11

AGE-SPECIFIC COAGULATION VALUES

Coagulation Test	Preterm Infant (30–36 Weeks), Day of Life 1[a]	Term Infant, Day of Life 1	Day of Life 3	1 Month–1 Year	1–5 Years	6–10 Years	11–16 Years	Adult
PT (s)	13.0 (10.6–16.2)	15.6 (14.4–16.4)	14.9 (13.5–16.4)	13.1 (11.5–15.3)	13.3 (12.1–14.5)	13.4 (11.7–15.1)	13.8 (12.7–16.1)	13.0 (11.5–14.5)
INR		1.26 (1.15–1.35)	1.20 (1.05–1.35)	1.00 (0.86–1.22)	1.03 (0.92–1.14)	1.04 (0.87–1.20)	1.08 (0.97–1.30)	1.00 (0.80–1.20)
aPTT (s)[b]	53.6 (27.5–79.4)	38.7 (34.3–44.8)	36.3 (29.5–42.2)	39.3 (35.1–46.3)	37.7 (33.6–43.8)	37.3 (31.8–43.7)	39.5 (33.9–46.1)	33.2 (28.6–38.2)
Fibrinogen (g/L)	2.43 (1.50–3.73)	2.80 (1.92–3.74)	3.30 (2.83–4.01)	2.42 (0.82–3.83)	2.82 (1.62–4.01)	3.04 (1.99–4.09)	3.15 (2.12–4.33)	3.1 (1.9–4.3)
Bleeding time (min)[a]					6 (2.5–10)	7 (2.5–13)	5 (3–8)	4 (1–7)
Thrombin time (s)	14 (11–17)	12 (10–16)[a]		17.1 (16.3–17.6)	17.5 (16.5–18.2)	17.1 (16.1–18.5)	16.9 (16.2–17.6)	16.6 (16.2–17.2)
Factor II (U/mL)	0.45 (0.20–0.77)	0.54 (0.41–0.69)	0.62 (0.50–0.73)	0.90 (0.62–1.03)	0.89 (0.70–1.09)	0.89 (0.67–1.10)	0.90 (0.61–1.07)	1.10 (0.78–1.38)
Factor V (U/mL)	0.88 (0.41–1.44)	0.81 (0.64–1.03)	1.22 (0.92–1.54)	1.13 (0.94–1.41)	0.97 (0.67–1.27)	0.99 (0.56–1.41)	0.89 (0.67–1.41)	1.18 (0.78–1.52)
Factor VII (U/mL)	0.67 (0.21–1.13)	0.70 (0.52–0.88)	0.86 (0.67–1.07)	1.28 (0.83–1.60)	1.11 (0.72–1.50)	1.13 (0.70–1.56)	1.18 (0.69–2.00)	1.29 (0.61–1.99)
Factor VIII (U/mL)	1.11 (0.50–2.13)	1.82 (1.05–3.29)	1.59 (0.83–2.74)	0.94 (0.54–1.45)	1.10 (0.36–1.85)	1.17 (0.52–1.82)	1.20 (0.59–2.00)	1.60 (0.52–2.90)
vWF (U/mL)[a]	1.36 (0.78–2.10)	1.53 (0.50–2.87)			0.82 (0.47–1.04)	0.95 (0.44–1.44)	1.00 (0.46–1.53)	0.92 (0.5–1.58)
Factor IX (U/mL)	0.35 (0.19–0.65)	0.48 (0.35–0.56)	0.72 (0.44–0.97)	0.71 (0.43–1.21)	0.85 (0.44–1.27)	0.96 (0.48–1.45)	1.11 (0.64–2.16)	1.30 (0.59–2.54)

TABLE 14.11

AGE-SPECIFIC COAGULATION VALUES—Cont'd.

Factor X (U/mL)	0.41 (0.11–0.71)	0.55 (0.46–0.67)	0.60 (0.46–0.75)	0.95 (0.77–1.22)	0.98 (0.72–1.25)	0.97 (0.68–1.25)	0.91 (0.53–1.22)	1.24 (0.96–1.71)
Factor XI (U/mL)	0.30 (0.08–0.52)	0.30 (0.07–0.41)	0.57 (0.24–0.79)	0.89 (0.62–1.25)	1.13 (0.65–1.62)	1.13 (0.65–1.62)	1.11 (0.65–1.39)	1.12 (0.67–1.96)
Factor XII (U/mL)	0.38 (0.10–0.66)	0.58 (0.43–0.80)	0.53 (0.14–0.80)	0.79 (0.20–1.35)	0.85 (0.36–1.35)	0.81 (0.26–1.37)	0.75 (0.14–1.17)	1.15 (0.35–2.07)
PK (U/mL)[a]	0.33 (0.09–0.57)	0.37 (0.18–0.69)			0.95 (0.65–1.30)	0.99 (0.66–1.31)	0.99 (0.53–1.45)	1.12 (0.62–1.62)
HMWK (U/mL)[a]	0.49 (0.09–0.89)	0.54 (0.06–1.02)			0.98 (0.64–1.32)	0.93 (0.60–1.30)	0.91 (0.63–1.19)	0.92 (0.50–1.36)
Factor XIIIa (U/mL)[a]	0.70 (0.32–1.08)	0.79 (0.27–1.31)			1.08 (0.72–1.43)	1.09 (0.65–1.51)	0.99 (0.57–1.40)	1.05 (0.55–1.55)
Factor XIIIs (U/mL)[a]	0.81 (0.35–1.27)	0.76 (0.30–1.22)			1.13 (0.69–1.56)	1.16 (0.77–1.54)	1.02 (0.60–1.43)	0.97 (0.57–1.37)
D-dimer		1.47 (0.41–2.47)	1.34 (0.58–2.74)	0.22 (0.11–0.42)	0.25 (0.09–0.53)	0.26 (0.10–0.56)	0.27 (0.16–0.39)	0.18 (0.05–0.42)
FDPs[a]								Borderline titer = 1:25–1:50 Positive titer <1:50

Continued

TABLE 14.11

AGE-SPECIFIC COAGULATION VALUES—cont'd.

Coagulation Test	Preterm Infant (30–36 Weeks), Day of Life 1[a]	Term Infant, Day of Life 1	Day of Life 3	1 Month–1 Year	1–5 Years	6–10 Years	11–16 Years	Adult
COAGULATION INHIBITORS								
ATIII (U/mL)[a]	0.38 (0.14–0.62)	0.63 (0.39–0.97)			1.11 (0.82–1.39)	1.11 (0.90–1.31)	1.05 (0.77–1.32)	1.0 (0.74–1.26)
α_2-M (U/mL)[a]	1.10 (0.56–1.82)	1.39 (0.95–1.83)			1.69 (1.14–2.23)	1.69 (1.28–2.09)	1.56 (0.98–2.12)	0.86 (0.52–1.20)
C1-Inh (U/mL)[a]	0.65 (0.31–0.99)	0.72 (0.36–1.08)			1.35 (0.85–1.83)	1.14 (0.88–1.54)	1.03 (0.68–1.50)	1.0 (0.71–1.31)
α_2-AT (U/mL)[a]	0.90 (0.36–1.44)	0.93 (0.49–1.37)			0.93 (0.39–1.47)	1.00 (0.69–1.30)	1.01 (0.65–1.37)	0.93 (0.55–1.30)
Protein C (U/mL)	0.28 (0.12–0.44)	0.32 (0.24–0.40)	0.33 (0.24–0.51)	0.77 (0.28–1.24)	0.94 (0.50–1.34)	0.94 (0.64–1.25)	0.88 (0.59–1.12)	1.03 (0.54–1.66)
Protein S (U/mL)	0.26 (0.14–0.38)	0.36 (0.28–0.47)	0.49 (0.33–0.67)	1.02 (0.29–1.62)	1.01 (0.67–1.36)	1.09 (0.64–1.54)	1.03 (0.65–1.40)	0.75 (0.54–1.03)
FIBRINOLYTIC SYSTEM[a]								
Plasminogen (U/mL)	1.70 (1.12–2.48)	1.95 (1.60–2.30)			0.98 (0.78–1.18)	0.92 (0.75–1.08)	0.86 (0.68–1.03)	0.99 (0.7–1.22)
TPA (ng/mL)					2.15 (1.0–4.5)	2.42 (1.0–5.0)	2.16 (1.0–4.0)	4.90 (1.40–8.40)
α_2-AP (U/mL)	0.78 (0.4–1.16)	0.85 (0.70–1.0)			1.05 (0.93–1.17)	0.99 (0.89–1.10)	0.98 (0.78–1.18)	1.02 (0.68–1.36)
PAI (U/mL)					5.42 (1.0–10.0)	6.79 (2.0–12.0)	6.07 (2.0–10.0)	3.60 (0–11.0)

[a]Data from Andrew M, Paes B, Milner R, et al. Development of the human anticoagulant system in the healthy premature infant. *Blood.* 1987;70:165–172; Andrew M, Paes B, Milner R, et al. Development of the human anticoagulant system in the healthy premature infant. *Blood.* 1988;72(5):1651–1657; and Andrew M, Vegh P, Johnston M, et al. Maturation of the hemostatic system during childhood. *Blood.* 1992;8:1998–2005.

[b]aPTT values may vary depending on reagent.

α_2-AP, α_2-Antiplasmin; *α_2-AT*, α_2-antitrypsin; *α_2-M*, α_2-macroglobulin; *aPTT*, activated partial thromboplastin time; *ATIII*, antithrombin III; *FDPs*, fibrin degradation products; *HMWK*, high-molecular-weight kininogen; *INR*, international normalized ratio; *PAI*, plasminogen activator inhibitor; *PK*, prekallikrein; *PT*, prothrombin time; *TPA*, tissue plasminogen activator; *VIII*, factor VIII procoagulant; *vWF*, von Willebrand factor.

Adapted from Monagle P, Barnes C, Ignjatovic, V, et al. Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost.* 2006;95;362–372.

TABLE 14.17

BLOOD PRODUCTS

Product	Contains	Indications	Dose	Volume of 1 Unit (U)	Change in blood count
PRBCs	Concentrated RBCs w/ Hct 55%–70%.	Generally Hb <7 gm/dL,[a] but consider clinical picture. Use typed and cross-matched products when possible. O− can be provided emergently without crossmatch if transfusion cannot be delayed. See Section VII. Online content for specific types of PRBCs.	10–15 mL/kg (at max 2–4 mL/kg/hr). RBCs must be transfused within 4 hours of leaving blood bank.	300–350 mL after processing	To determine volume necessary for desired Hct: PRBC volume (mL) = (EBV [mL] × [desired Hct − actual Hct])/Hct of PRBCs.[b]
Platelets		Severe (<10,000/μL) thrombocytopenia, symptomatic thrombocytopenia, to achieve platelets >50,000/μL before minor or >100,000/μL before major surgery or intracranial operation. Transfusion indications for neonates: Platelets <20,000/μL; platelets <30,000/μL + weight <1 kg, age <1 week, clinically unstable, history major bleed (e.g., IVH), current bleed, coagulopathy/DIC, preprocedure; platelets >50,000/μL only if significant bleed.	Children ≤30 kg[c]: 5–10 mL/kg or 1 equivalent unit per 5–10 kg. Children >30 kg: 1 apheresis unit. Transfuse as rapidly as able.	300 mL for 1 apheresis unit, 50 mL for 1 equivalent unit.	10 mL/kg increases platelets by 50,000/μL.
FFP	Physiologic quantities all coagulation factors[d]	Treat severe clotting factor deficiencies with active bleeding (DIC, Vitamin K deficiency with active bleeding, TTP) or before invasive procedure. Combine with vitamin K for emergency reversal warfarin.	15 mL/kg; repeat PRN.	250–300 mL	1 unit activity of all factors except V and VIII.

TABLE 14.17

BLOOD PRODUCTS—cont'd.

Product	Contains	Indications	Dose	Volume of 1 Unit (U)	Change in blood count
Cryoprecipitate	Enriched factors VIII and XIII, vWF, fibrinogen, fibronectin	For hypofibrinogenemia, dysfibrinogenemia.	Children <5 kg: 1 single donor unit. Children 5–50 kg: 1 unit per 5–10kg. Children >50 kg: 1–2 pools (5–10 units).	10–15 mL for 1 unit, 50–100 mL for a pool.	1units contains approximately 80 units factor VIII, 150 mg fibrinogen.[e]

[a]Restrictive transfusion protocol with Hb threshold 7 g/dL associated with fewer transfusions without differences in clinical outcomes.

[b]Hct of PRBCs is typically 55% to 70% depending on storage anticoagulant.

[c]1 unit of apheresis platelets is derived from a single donor and contains >3 x 10^{11} platelets/mL. 1 equivalent unit is ~1/5th-1/6th an apheresis unit. Single donor platelet concentrates are derived from a single donor and contain >5.5 x 10^{10} platelets in approximately 50 mL. 4-6 equivalent units or platelet concentrates can be pooled to make equivalent of 1 apheresis unit.

[d]FFP does not include platelets or fibrinogen. Does include anticoagulant factors (antithrombin III, proteins C/S). Note: FFP unlikely to have significant effect when INR ≤1.6.[46]

[e]This is an estimation. 1 unit of cryoprecipitate is derived from 500mL of blood from 1 donor. A pool is 5 individual donor units pooled together.

DIC, Disseminated intravascular coagulation; *EBV*, estimated blood volume; *FFP*, fresh frozen plasma; *Hct*, Hb/hematocrit; *PRBCs*, packed red blood cells; *PRN*, as needed; *RBCs*, red blood cells; *TTP*, thrombotic thrombocytopenic purpura; *vWF*, von Willebrand Factor.

Bachowski G, Borge D, Brunker PAR, et al. *A Compendium of Transfusion Practice Guidelines*. 3rd ed. American Red Cross; 2017

Behrman RE, Kliegman RM, Jenson AH. *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: Saunders; 2004.

TABLE EC 14.A

MEDICATIONS THAT INFLUENCE WARFARIN THERAPY

Significant Increase in INR	Significant Decrease in INR
Amiodarone	Amobarbital
Anabolic steroids	Aprepitant
Bactrim (TMP/SMZ)	Butabarbital
Chloramphenicol	Carbamazepine
Disulfiram	Dicloxacillin
Fluconazole	Griseofulvin
Isoniazid	Methimazole
Metronidazole	Phenobarbital
Miconazole	Phenytoin
Phenylbutazone	Primidone
Quinidine	Propylthiouracil
Sulfinpyrazone	Rifabutin
Sulfisoxazole	Rifampin
Tamoxifen	Secobarbital
Moderate Increase in INR	**Moderate Decrease in INR**
Cimetidine	Atazanavir
Ciprofloxacin	Efavirenz
Clarithromycin	Nafcillin
Delavirdine	Ritonavir
Efavirenz	
Itraconazole	
Lovastatin	
Omeprazole	
Propafenone	

Numerous medications not listed in this table can affect warfarin administration.
INR, International normalized ratio; *TMP/SMZ*, trimethoprim/sulfamethoxazole.

VII. ONLINE CONTENT

A. Specific PRBC Types

1. Leukoreduced RBCs: 99.9% white blood cells (WBCs) removed to reduce risks of pathogen transmission (e.g., CMV), HLA alloimmunization and febrile nonhemolytic transfusion reaction.
2. Washed RBCs: Removal of plasma proteins in products for recipients with history of anaphylactic transfusions reactions or complete IgA deficiency.
3. CMV-safe RBCs: Leukoreduced units likely comparable to low transmission risk with CMV-seronegative units (from donors with negative CMV serology). Preferred for vulnerable populations: CMV-negative bone marrow transplant or solid organ recipients, immunodeficient patients, premature or low birth weight infants, intrauterine transfusions, pregnant women.
4. Irradiated blood products: Inactivated donor lymphocytes capable of causing transfusion-associated graft versus host disease (GVHD).[33] Used for susceptible patients: leukemia, lymphoma, BMT, solid organ transplant, intensive chemotherapy, known/suspected immune deficiency, intrauterine transfusions, neonate transfusions, patients receiving T-cell suppressive therapy. Also necessary in directed donation from a relative.

B. Directed Donor Transfusions

1. When to consider directed donor:
   a. Chronic transfusion programs (e.g., "blood buddy" programs), where donors provide antigen-matched red cells repetitively for the same patient requiring frequent transfusions (e.g., thalassemia, sickle cell disease).
   b. NAIT, where maternal platelets lack causative antigens and represent optimal therapy.
2. Reasons to not consider directed donor:
   a. Practice not often feasible. Specific screening, donation, product testing, and processing causes delays (2 to 3 days or more) when compatible blood is often readily available.
   b. Directed donor may not be compatible: must be at least ABO/RhD compatible, and may require other RBC antigen compatibility if recipient has antibodies.
   c. Directed donors less likely to be truthful in donor screening, causing potential increased infection risk.
   d. Products from a relative require irradiation for increased risk of transfusion-related graft-versus-host disease (GVHD).
   e. If RBC donor is also a potential bone marrow transplant donor for recipient, donation increases risk of development of donor-directed human leukocyte antigen (HLA) antibodies in recipient, which may cause graft failure.

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Chapter 15

Immunology and Allergy

Carlos A. Salgado, MD

I. ALLERGIC RHINITIS[1–6]

A. Epidemiology

1. Most common pediatric chronic medical condition: Prevalence in children up to 40%.
2. Increases risk for recurrent otitis media, asthma, and acute and chronic sinusitis.
3. Risk factors: Atopic family history, serum immunoglobulin (Ig) E >100 IU/mL before age 6 years, higher socioeconomic status, and infant exposure to maternal smoking in utero and during early childhood.

B. Diagnosis

1. **History:**
   a. Allergen-driven mucosal inflammation leading to cyclical exacerbations or persistent symptoms.
   b. Symptoms: Nasal (congestion, rhinorrhea, and pruritus), ocular (pruritus and tearing), and postnasal drip (sore throat and cough).
   c. Patterns: Seasonal (depending on local allergens) versus perennial (with seasonal peaks)
   d. Coexisting atopic diseases common (eczema, asthma, and food allergy).
2. **Physical examination:**
   a. Allergic facies with shiners, mouth breathing, transverse nasal crease ("allergic salute"), and accentuated lines below lower eyelids (Dennie-Morgan lines).
   b. May have swollen nasal turbinates.
   c. Injected sclera with or without clear discharge, conjunctival cobblestoning.
3. **Diagnostic studies:**
   a. Diagnosis can be made on clinical grounds, however allergy with skin tests or allergen-specific IgE testing can identify specific allergic sensitivities.
   b. Total IgE, peripheral blood eosinophil count and imaging studies are not recommended due to poor specificity.

C. Differential Diagnosis

Vasomotor/nonallergic rhinitis (hypersensitivity to scents, alcohol, or changes in climate), infectious rhinitis, adenoid hypertrophy, rhinitis medicamentosa (rebound rhinitis from prolonged use of nasal vasoconstrictors), sinusitis, nonallergic rhinitis with eosinophilia syndrome, and nasal polyps.

D. Treatment

1. **Allergen avoidance:**
   a. Relies on identification of triggers, most common of which are pollens, fungi, dust mites, insects, and animals.
   b. HEPA filter may be useful when animal allergens are a concern.
   c. Thorough housecleaning and allergy-proof bed coverings can be useful.
2. **Oral antihistamines:**
   a. First-line treatment for mild or episodic symptoms or young patients who cannot tolerate or refuse nasal sprays.
   b. Second- and third-generation preparations preferable (loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine) due to reduced central nervous system (CNS) side effects.
   c. Adverse effects: Sedation and anticholinergic side effects (more prominent with first-generation agents).
3. **Intranasal corticosteroids** (fluticasone, mometasone, budesonide, flunisolide, ciclesonide, and triamcinolone):
   a. First-line for persistent or moderate-to-severe symptoms, as it is the most effective single maintenance therapy for nasal congestion and reduction of ocular symptoms.
   b. Maximal therapeutic benefit when used over several days or weeks. No effect with as-needed use.
   c. Adverse effects: Nasal irritation, sneezing, bleeding, and potential risk of reduction in growth velocity and adrenal suppression at high doses, especially in patients on multiple steroid preparations. Growth monitoring recommended.
   d. Administration: Clear mucus crusting, keep head pointed slightly down and avoid pointing medication at nasal septum.
4. **Leukotriene inhibitors** (montelukast):
   a. More effective in combination with antihistamines.
   b. Consider in patients with concomitant asthma.
5. **Intranasal antihistamines** (azelastine and olopatadine):
   a. Effective for acute symptoms; faster onset of action than glucocorticoid nasal spray.
   b. Adverse effects: Bitter taste, systemic absorption with potential for sedation.
6. **Intranasal combination agents** (azelastine/fluticasone): Useful for patients with moderate-to-severe allergic rhinitis.
7. **Immunotherapy:**
   a. Success rate is high when patients are chosen carefully and when performed by an allergy specialist.
   b. Consider when symptoms are inadequately controlled with medications and allergen avoidance.
   c. In addition to traditional subcutaneous immunotherapy, sublingual products have now been approved for several allergens.
   d. Not recommended for patients with poor adherence to therapy or those with poorly controlled asthma.

e. Not well studied in children younger than 5 years.
f. May reduce risk for future development of asthma, and treatment of allergic rhinitis may improve asthma control.

8. **Nasal irrigation with hypertonic saline:** Use distilled, sterile, or boiled water (at least 3 minutes) for homemade solutions.
9. **Ophthalmic agents:** Can be used to treat allergic conjunctivitis. Up to 60% of patients with allergic rhinitis have concomitant conjunctivitis. Avoid the use of steroids unless under the direction of an ophthalmologist.
   a. Mast cell stabilizers: Cromolyn sodium, lodoxamide-tromethamine, nedocromil, and pemirolast.
   b. H_1-antagonists and mast cell stabilizers: Alcaftadine, azelastine HCl, bepotastine, emedastine, epinastine, ketotifen fumarate, and olopatadine.

II. FOOD ALLERGY[7–12]

A. Epidemiology

1. Prevalence is 6% to 8% in young children and 3% to 4% in adolescence.
2. Most common allergens in children: Milk, eggs, peanuts, tree nuts (e.g., cashew, walnut), soy, fish, shellfish, and wheat.

B. Manifestations of Food Allergy

1. Often a combination of several syndromes; symptoms can occur within minutes to hours of ingesting food.
2. Diagnosis requires both sensitization (demonstration of allergen-specific IgE) and clinical symptoms after exposure to allergens.
3. **Anaphylaxis:** See Chapter 1.
4. **Skin syndromes:**
   a. **Urticaria/angioedema:**
      (1) Chronic urticaria is rarely related to food allergy.
      (2) Acute urticaria due to food allergy may be a risk factor for future anaphylaxis.
   b. **Atopic dermatitis/eczema:**
      (1) Food allergy is more common in patients with atopic dermatitis.
      (2) Even if not apparent by history, at least one-third of children with moderate to severe atopic dermatitis have IgE-mediated food allergies.
5. **Gastrointestinal syndromes:**
   a. **Oral allergy syndrome:**
      (1) Pollen-associated food allergy caused by cross-reactivity of antibodies to pollens (e.g., apple and tree pollen).
      (2) Pruritus of oral mucosa after ingestion of certain fresh fruits and vegetables in patients with pollen allergies. Rarely results in edema of oral mucosa, or progresses beyond mouth/throat.
      (3) Inciting antigens are usually denatured by cooking.

b. **Allergic eosinophilic gastroenteritis, esophagitis: see Chapter 12**
c. **Food protein induced enterocolitis syndrome (FPIES):**
   (1) Presents in infancy.
   (2) Vomiting and diarrhea (may contain blood); when severe, may lead to lethargy, dehydration, hypotension, acidosis.
   (3) Most commonly associated with milk and soy, but may occur with a wide variety of foods (e.g., rice, oat, fruits, and vegetables).
d. **Infantile proctocolitis:**
   (1) Confined to distal colon and can present with diarrhea or blood-streaked and mucous-containing stools.
   (2) Symptoms usually resolve within 72 hours of stopping offending agent; rarely leads to anemia.

C. Diagnosis of Food Allergy (Fig. 15.1)

1. **History and physical examination:**
   a. Identify specific foods and whether fresh vs. cooked.
   b. Establish timing and nature of reactions.
2. **Skin testing:**
   a. Skin prick test has poor positive predictive value, but very good negative predictive value.
   b. Patient must not be taking antihistamines.
   c. Widespread skin conditions (e.g., dermatographism, urticaria, severe eczema) may limit ability to perform skin tests.
3. **Measurement of allergen-specific IgE:**
   a. Similar to skin tests, it has poor positive predictive value and excellent negative predictive value.
   b. Levels above a certain range (variable amongst different antigens) have increasing positive predictive value.
   c. Useful in patients with dermatologic conditions that preclude skin testing.
   d. Component testing (measuring IgE to specific food proteins rather than crude extracts) may improve diagnostic accuracy for peanut and possibly other foods.
4. **Oral food challenges:**
   a. Can verify clinical reactivity to a specific food allergen or document that a food allergy has been outgrown.
   b. Must be performed under close medical supervision with emergency medications readily available.
   c. Patient must not be taking antihistamines.
   d. Most accurate when double-blinded using graded doses of disguised food.
5. **Trial elimination diet:**
   a. Helpful if improvement with removal of food from diet.
   b. Essential, especially in infants and for non-IgE-mediated food allergy.

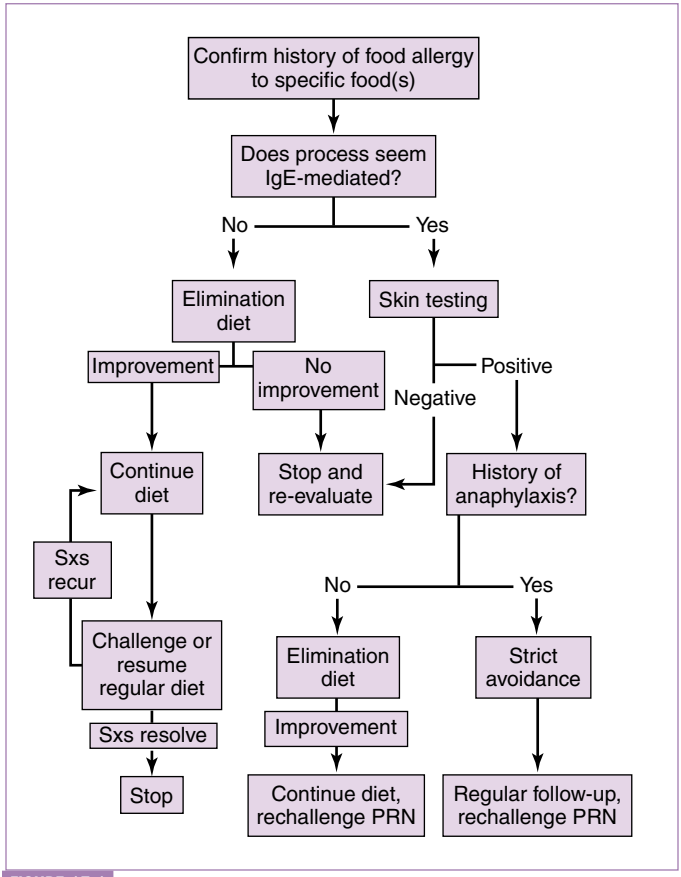

FIGURE 15.1

Evaluation and management of food allergy. *IgE*, Immunoglobulin E; *PRN*, as needed *Sxs*, symptoms. (Data from Wood RA. The natural history of food allergy. *Pediatrics*. 2003;111:1631–1637.)

D. Differential Diagnosis

1. **Food intolerance:** Nonimmunologic, based on toxins or other properties of foods leading to adverse effects.
2. **Malabsorption syndromes:**
   a. Cystic fibrosis, celiac disease (see Chapter 12), and lactase deficiency.
   b. Gastrointestinal malformations.

E. Treatment

1. **Allergen avoidance:**
   a. Most important intervention for all types of food allergy.
   b. Patients must pay close attention to food ingredients. Implement an *"If you can't read it, you can't eat it"* approach to avoid risky unlabeled foods.
   c. Nutritional counseling and regular growth monitoring are recommended.
2. **Nonanaphylactic angioedema/urticaria:**
   a. Antihistamines or corticosteroids, based on severity and duration of symptoms.
   b. Omalizumab used for chronic urticaria.
3. **Atopic dermatitis:** Symptomatic control (see Chapter 8).
4. **Anaphylaxis:**
   a. See Chapter 1 for management of anaphylaxis.
   b. Prescribe epinephrine auto-injector for all at-risk patients. Counsel to call 9-1-1 if using.
   c. Develop Anaphylaxis Action Plan indicating specific allergies, symptoms for which to observe, and medications to be administered.
   d. Counsel families to always have epinephrine auto-injector readily available.
   e. Make school aware of Anaphylaxis Action Plan and ensure they can administer lifesaving medications.
5. **Food-specific immunotherapy** is under investigation. It is used to induce clinical desensitization to specific allergens.

F. Natural History

1. About 50% of milk, egg, soy, and wheat allergies are outgrown by school age.
2. Peanut, tree nut, and shellfish allergies are outgrown only in 10% to 20%.
3. Skin tests and allergen-specific IgE may remain positive, even though symptoms resolve.

III. DRUG ALLERGY[13,14]

A. Definition

1. **Drug allergy:** Immunologically mediated response to an agent in a sensitized person.
2. **Drug intolerance:** Undesirable pharmacologic effect.
3. Although 10% of patients report penicillin allergy, after evaluation, about 90% of these individuals can tolerate penicillin.

B. Diagnosis

1. Cutaneous manifestations are the most common presentation for drug allergic reactions.
2. **Diagnostic studies:** Penicillin is the only drug for which standardized skin testing reagents and procedures have been validated. Skin testing or supervised graded dose challenge may be done with caution for other

medications, but the results must be carefully considered in the context of the clinical pictures, as both false positive and false negative results are common.

C. Management (Fig. 15.2)

1. **Avoidance**: When able, utilize alternative therapy.
2. **Desensitization:** Progressive administration of an allergenic substance to render immune system less reactive.

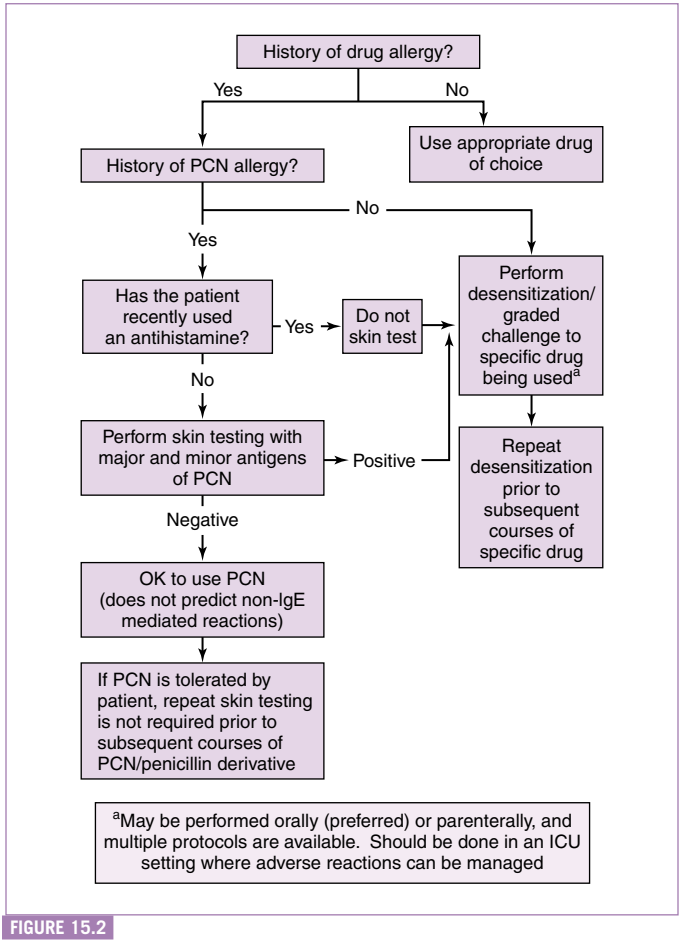

FIGURE 15.2

Evaluation and management of penicillin allergy. *ICU*, Intensive care unit; *IgE*, immunoglobulin E; *PCN*, penicillin. (Adapted from Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy*. 2015;45:300.)

TABLE 15.1

WHEN TO SUSPECT IMMUNODEFICIENCY

Recurrent Infections	Opportunistic Infections	Severe Infections	Other Conditions
Six or more new infections in 1 year Recurrent tissue or organ abscesses Two or more serious sinus infections in 1 year Two or more pneumonias in 1 year	*Pneumocystis jiroveci* pneumonia *Pseudomonas* sepsis Invasive infection with *Neisseria* spp.	Two or more months of antibiotics with little effect Sepsis in the absence of a known risk (e.g., indwelling vascular catheter, neutropenia) Bacterial meningitis Pneumonia with empyema Resistant superficial or oral candidiasis	Failure to gain weight or grow normally Family history of immunodeficiency or unexplained early deaths Lymphopenia in infancy Complications from a live vaccine Part of a syndrome complex (e.g., Wiskott-Aldrich [with thrombocytopenia, eczema], DiGeorge syndrome [with facial dysmorphism, congenital cardiac disease, hypoparathyroidism])

Adapted from Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameters for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol.* 2015;136(5):1186–1205; and Ballow M. Approach to the patient with recurrent infections. *Clinic Rev Allerg Immunol.* 2008;34:129.

3. **Graded challenge:** Administration of progressively increasing doses of a drug until full dose is reached; does not modify a patient's response to the drug, but is used to optimize safety when the history and test results are not completely reassuring.

IV. EVALUATION OF SUSPECTED IMMUNODEFICIENCY

See Tables 15.1 and 15.2.[15–21]

V. IMMUNOGLOBULIN THERAPY[22–25]

A. Intravenous Immunoglobulin (IVIG)

1. **Indications:**
   a. Replacement therapy for antibody-deficient disorders:
      (1) Children with severe hypogammaglobulinemia (<100 mg/dL) may benefit from a higher total *loading* dose in two separate doses a few days apart, followed by standard dosing every 3 to 4 weeks.
      (2) Useful in human immunodeficiency virus (HIV), antibody deficiency (IgG concentration <400 mg/dL from failure to form antibodies to common antigens), recurrent serious bacterial infections, or prior to measles prophylaxis.

TABLE 15.2

EVALUATION OF SUSPECTED IMMUNODEFICIENCY

Suspected Functional Abnormality	Clinical Findings	Initial Tests	More Advanced Tests
Humoral (e.g., common variable immunodeficiency, X-linked agammaglobulinemia, IgA deficiency)	Sinopulmonary and systemic infections (pyogenic bacteria) Enteric infections (enterovirus, other viruses, *Giardia* spp.) Autoimmune diseases (immune thrombocytopenia, hemolytic anemia, inflammatory bowel disease)	Immunoglobulin levels (IgG, IgM, IgA) Antibody levels to T-cell-dependent protein antigens (e.g., tetanus or pneumococcal conjugate vaccines) Antibody levels to T-cell-independent polysaccharide antigens in a child ≥2 years (e.g., pneumococcal polysaccharide vaccine, such as Pneumovax)	B-cell enumeration Immunofixation electrophoresis
Cell-mediated immunity (e.g., severe combined immunodeficiency, DiGeorge syndrome)	Pneumonia (pyogenic bacteria, fungi, *Pneumocystis jiroveci*, viruses)	TRECs newborn screening[a] Total lymphocyte counts HIV ELISA/Western blot/PCR	T-cell enumeration (CD3, CD4, CD8) In vitro T-cell proliferation to mitogens, antigens, or allogeneic cells Chromosomal Microarray or FISH 22q11 for DiGeorge deletion
Phagocytosis (e.g., chronic granulomatous disease (CGD), leukocyte adhesion deficiency, Chédiak-Higashi syndrome)	Cutaneous infections, abscesses, lymphadenitis (staphylococci, enteric bacteria, fungi, mycobacteria) Poor wound healing	WBC/neutrophil count and morphology	CGD: Nitroblue tetrazolium (NBT) test or dihydro-rhodamine (DHR) reduction test Chemotactic assay Phagocytic assay
Spleen	Bacteremia/hematogenous infection (pneumococcus, other streptococci, *Neisseria* spp.)	Peripheral blood smear for Howell-Jolly bodies Hemoglobin electrophoresis (HbSS)	Technetium-99 spleen scan or sonogram
Complement	Bacterial sepsis and other bloodborne infections (encapsulated bacteria, especially *Neisseria* spp.) Lupus, glomerulonephritis Angioedema	CH50 (total hemolytic complement)	Alternative pathway assay (AH50) Mannose-binding lectin level Individual complement component assays

[a]Newborn screening using TRECs has now been implemented in multiple states. TRECs identify lymphopenia in children and prompt further testing for SCID or other immunodeficiencies associated with lymphopenia.
ELISA, Enzyme-linked immunosorbent assay; *FISH*, fluorescent in situ hybridization; *HIV*, human immunodeficiency virus; *PCR*, polymerase chain reaction; *TRECs*, T-cell receptor excision circles; *WBC*, white blood cell.
From Lederman HM. Clinical presentation of primary immunodeficiency diseases. In: McMillan J, ed. *Oski's Pediatrics*. Philadelphia: Lippincott Williams & Wilkins; 2006:2441–2444.

b. Immune thrombocytopenic purpura (see Chapter 14):
   (1) Initially given on a single day or in divided doses over 2 to 5 consecutive days.
   (2) Maintenance dose given every 3 to 6 weeks based on clinical response and platelet count.
c. Bone marrow transplantation:
   (1) Adjust dosing to maintain trough IgG level of at least 400 mg/dL.
   (2) May decrease incidence of infection and death but not acute graft-versus-host disease.
d. Other indications:
   (1) Kawasaki disease (see Chapter 7).
   (2) Guillain-Barré syndrome.
   (3) Refractory dermatomyositis and polymyositis.
   (4) Chronic inflammatory demyelinating polyneuropathy.

2. **Precautions and adverse reactions:**
   a. Severe systemic symptoms (hemodynamic changes, respiratory difficulty, and anaphylaxis).
   b. Less-severe systemic reactions (headache, myalgia, fever, chills, nausea, and vomiting).
      (1) Decrease infusion rate and/or premedicate with intravenous corticosteroids, and/or antipyretics.
      (2) Can progress to aseptic meningitis syndrome.
   c. Acute renal failure (increased risk with preexisting renal insufficiency and with sucrose-containing IVIG).
   d. Acute venous thrombosis (increased risk with sucrose-containing IVIG).
   e. Use with caution in patients with confirmed undetectable IgA levels (e.g., patients with partial B-cell immunodeficiencies or familial IgA deficiency), as antibodies against IgA may trigger anaphylactic reaction.

B. Intramuscular Immunoglobulin (IMIG)

1. **Prophylaxis Indications:** Hepatitis A, measles, rubella, rabies, and varicella-zoster (see Chapter 16).
2. **Precautions and adverse reactions:**
   a. Similar to IVIG (discussed previously).
   b. Local reaction at injection site increases with repeated use.
   c. Intravenous or intradermal use of IMIG is absolutely contraindicated due to high risk for anaphylactoid reactions.
3. **Administration:**
   a. No more than 5 mL should be given at one site in large child/adolescent, and 1 to 3 mL for smaller children/infants.
   b. Administration of greater than 15 mL at one time is essentially never warranted.
   c. Peak serum levels achieved by 48 hours; immune effect lasts 3 to 4 weeks.

C. Subcutaneous Immunoglobulin

1. **Indication:** Replacement therapy for antibody deficiency.
2. **Dose:**
   a. See the Formulary for dosages and administration instructions.
   b. Larger doses can be given simultaneously in multiple sites or more frequently than once weekly.
   c. Using the same areas for injections improves tolerability.
3. **Precautions and adverse reactions:**
   a. Systemic side effects are rare because of the small volumes given and the slow absorption rate.
   b. Local redness and swelling are expected and generally decrease with every infusion.
4. **Considerations:** Does not require venous access or special nursing (parents can administer), but may require multiple needlesticks in larger children, depending on the volume to be infused.

D. Specific Immunoglobulins

1. **Hyperimmune globulins:**
   a. Prepared from donors with high titers of specific antibodies.
   b. Includes hepatitis B immune globulin, varicella-zoster immune globulin, cytomegalovirus immune globulin, Rho(D) immune globulin, botulism immune globulin, and others.
2. **Monoclonal antibody preparations** (rituximab, palivizumab, and others).

E. Vaccination Timing

See Chapter 16 for discussion of timing of routine vaccination after immunoglobulin administration.

VI. IMMUNOLOGIC REFERENCE VALUES

A. Serum IgG, IgM, IgA, and IgE Levels (Table 15.3)

B. Serum IgG, IgM, IgA, and IgE Levels for Low Birth Weight Preterm Infants (Table 15.4)

C. Lymphocyte Enumeration (Table 15.5)

D. Serum Complement Levels (Table 15.6)

TABLE 15.3

SERUM IMMUNOGLOBULIN LEVELS[a]

Age	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	IgE (IU/mL)
Cord blood (term)	1121 (636–1606)	13 (6.3–25)	2.3 (1.4–3.6)	0.22 (0.04–1.28)
1 month	503 (251–906)	45 (20–87)	13 (1.3–53)	
6 weeks				0.69 (0.08–6.12)
2 months	365 (206–601)	46 (17–105)	15 (2.8–47)	
3 months	334 (176–581)	49 (24–89)	17 (4.6–46)	0.82 (0.18–3.76)
4 months	343 (196–558)	55 (27–101)	23 (4.4–73)	
5 months	403 (172–814)	62 (33–108)	31 (8.1–84)	
6 months	407 (215–704)	62 (35–102)	25 (8.1–68)	2.68 (0.44–16.3)
7–9 months	475 (217–904)	80 (34–126)	36 (11–90)	2.36 (0.76–7.31)
10–12 months	594 (294–1069)	82 (41–149)	40 (16–84)	
1 year	679 (345–1213)	93 (43–173)	44 (14–106)	3.49 (0.80–15.2)
2 years	685 (424–1051)	95 (48–168)	47 (14–123)	3.03 (0.31–29.5)
3 years	728 (441–1135)	104 (47–200)	66 (22–159)	1.80 (0.19–16.9)
4–5 years	780 (463–1236)	99 (43–196)	68 (25–154)	8.58 (1.07–68.9)[b]
6–8 years	915 (633–1280)	107 (48–207)	90 (33–202)	12.89 (1.03–161.3)[c]
9–10 years	1007 (608–1572)	121 (52–242)	113 (45–236)	23.6 (0.98–570.6)[d]
14 years				20.07 (2.06–195.2)
Adult	994 (639–1349)	156 (56–352)	171 (70–312)	13.2 (1.53–114)

[a]Numbers in parentheses are the 95% confidence intervals (CIs).

[b]IgE data for 4 years.

[c]IgE data for 7 years.

[d]IgE data for 10 years.

Data from Kjellman NM, Johansson SG, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). *Clin Allergy.* 1976;6:51–59; Jolliff CR, Cost KM, Stivrins PC, et al. Reference intervals for serum IgG, IgA, IgM, C3, and C4 as determined by rate nephelometry. *Clin Chem.* 1982;28:126–128; and Zetterström O, Johansson SG. IgE concentrations measured by PRIST in serum of healthy adults and in patients with respiratory allergy: a diagnostic approach. *Allergy.* 1981;36:537–547.

TABLE 15.4

SERUM IMMUNOGLOBULIN LEVELS FOR LOW BIRTH WEIGHT PRETERM INFANTS

Age (months)	Plasma Ig Concentrations in 25- to 28-Weeks Gestation Infants			Plasma Ig Concentrations in 29- to 32-Weeks Gestation Infants		
	IgG (mg/dL)[a]	IgM (mg/dL)[a]	IgA (mg/dL)[a]	IgG (mg/dL)[a]	IgM (mg/dL)[a]	IgA (mg/dL)[a]
0.25	251 (114–552)	7.6 (1.3–43.3)	1.2 (0.07–20.8)	368 (186–728)	9.1 (2.1–39.4)	0.6 (0.04–1.0)
0.5	202 (91–446)	14.1 (3.5–56.1)	3.1 (0.09–10.7)	275 (119–637)	13.9 (4.7–41)	0.9 (0.01–7.5)
1.0	158 (57–437)	12.7 (3.0–53.3)	4.5 (0.65–30.9)	209 (97–452)	14.4 (6.3–33)	1.9 (0.3–12.0)
1.5	134 (59–307)	16.2 (4.4–59.2)	4.3 (0.9–20.9)	156 (69–352)	15.4 (5.5–43.2)	2.2 (0.7–6.5)
2.0	89 (58–136)	16.0 (5.3–48.9)	4.1 (1.5–11.1)	123 (64–237)	15.2 (4.9–46.7)	3.0 (1.1–8.3)
3	60 (23–156)	13.8 (5.3–36.1)	3.0 (0.6–15.6)	104 (41–268)	16.3 (7.1–37.2)	3.6 (0.8–15.4)
4	82 (32–210)	22.2 (11.2–43.9)	6.8 (1.0–47.8)	128 (39–425)	26.5 (7.7–91.2)	9.8 (2.5–39.3)
6	159 (56–455)	41.3 (8.3–205)	9.7 (3.0–31.2)	179 (51–634)	29.3 (10.5–81.5)	12.3 (2.7–57.1)
8–10	273 (94–794)	41.8 (31.1–56.1)	9.5 (0.9–98.6)	280 (140–561)	34.7 (17–70.8)	20.9 (8.3–53)

[a]Geometric mean (Numbers in parentheses are ±2 SD).

From Ballow M, Cates KL, Rowe JC, et al. Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. *Pediatr Res.* 1986;9:899–904.

TABLE 15.5

T AND B LYMPHOCYTES IN PERIPHERAL BLOOD

Age	CD3 (Total T Cell) Count[a] (%)[b]	CD4 Count[a] (%)[b]	CD8 Count[a] (%)[b]	CD19 (B Cell) Count[a] (%)[b]
0–3 months	2.50–5.50 (53–84)	1.60–4.00 (35–64)	0.56–1.70 (12–28)	0.30–2.00 (6–32)
3–6 months	2.50–5.60 (51–77)	1.80–4.00 (35–56)	0.59–1.60 (12–23)	0.43–3.00 (11–41)
6–12 months	1.90–5.90 (49–76)	1.40–4.30 (31–56)	0.50–1.70 (12–24)	0.61–2.60 (14–37)
1–2 years	2.10–6.20 (53–75)	1.30–3.40 (32–51)	0.62–2.00 (14–30)	0.72–2.60 (16–35)
2–6 years	1.40–3.70 (56–75)	0.70–2.20 (28–47)	0.49–1.30 (16–30)	0.39–1.40 (14–33)
6–12 years	1.20–2.60 (60–76)	0.65–1.50 (31–47)	0.37–1.10 (18–35)	0.27–0.86 (13–27)
12–18 years	1.00–2.20 (56–84)	0.53–1.30 (31–52)	0.33–0.92 (18–35)	0.11–0.57 (6–23)
Adult[c]	0.70–2.10 (55–83)	0.30–1.40 (28–57)	0.20–0.90 (10–39)	

[a]Absolute counts (number of cells per microliter $\times 10^{-3}$).

[b]Normal values (10th to 90th percentile).

[c]From Comans-Bitter WM, de Groot R, van den Beemd R, et al. Immunotyping of blood lymphocytes in childhood. Reference values for lymphocyte subpopulations. *J Pediatr.* 1997;130:388–393.

From Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the Pediatric AIDS Clinical Trials Group P1009 study. *J Allergy Clin Immunol.* 2003;112:973–980.

TABLE 15.6

SERUM COMPLEMENT LEVELS[a]

Age	C3 (mg/dL)	C4 (mg/dL)
Cord blood (term)	83 (57–116)	13 (6.6–23)
1 month	83 (53–124)	14 (7.0–25)
2 months	96 (59–149)	15 (7.4–28)
3 months	94 (64–131)	16 (8.7–27)
4 months	107 (62–175)	19 (8.3–38)
5 months	107 (64–167)	18 (7.1–36)
6 months	115 (74–171)	21 (8.6–42)
7–9 months	113 (75–166)	20 (9.5–37)
10–12 months	126 (73–180)	22 (12–39)
1 year	129 (84–174)	23 (12–40)
2 years	120 (81–170)	19 (9.2–34)
3 years	117 (77–171)	20 (9.7–36)
4–5 years	121 (86–166)	21 (13–32)
6–8 years	118 (88–155)	20 (12–32)
9–10 years	134 (89–195)	22 (10–40)
Adult	125 (83–177)	28 (15–45)

[a]Numbers in parentheses are the 95% confidence intervals (CIs).

Modified from Jolliff CR, Cost KM, Stivrins PC, et al. Reference intervals for serum IgG, IgA, IgM, C3, and C4 as determined by rate nephelometry. *Clin Chem.* 1982;28:126–128.

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Chapter 16

Immunoprophylaxis

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See additional content on Expert Consult

I. IMMUNIZATION SCHEDULES

A. Immunizations for Children Ages 0 to 18

1. Table 16.1: Routine Vaccines for Children and Adolescents in the United States[1]
2. All schedules: https://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html
   a. Comprehensive schedule
   b. By vaccine and age-group
   c. By medical indications
   d. Catch-up immunization schedule
3. Schedules updated annually and put forth by the Advisory Committee on Immunization Practices (ACIP)[2] and approved by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP), among others.

B. Nonroutine Vaccines Used in the United States[3]

1. For details on vaccines not routinely given in the United States, including bacille Calmette-Guérin (BCG; tuberculosis vaccine), Japanese encephalitis, rabies, typhoid, and yellow fever, see Table 16.2.
2. For information on other vaccines licensed but not routinely distributed, including anthrax and smallpox, see: http://emergency.cdc.gov/bioterrorism/.

II. IMMUNIZATION GUIDELINES

A. Vaccine Informed Consent

1. Vaccine Information Statements (VISs) can be found at: http://www.cdc.gov/vaccines/hcp/vis/current-vis.html.
2. The most recent VIS must be provided to the patient (nonminor) or parent/guardian, with documentation of version date and date of administration.
3. Multivaccine VISs for DTaP, *Haemophilus influenzae* type b (Hib), HepB, Polio, and PCV13 can be used when two or more of these vaccines are administered during the same visit.

B. Vaccine Administration

1. For information on vaccine storage, handling, and administration, see: http://www.cdc.gov/vaccines/hcp/admin/.
2. See Chapter 4 for details on intramuscular and subcutaneous administration procedures.

TABLE 16.1

ROUTINE VACCINES FOR CHILDREN AND ADOLESCENTS IN THE UNITED STATES

Disease	Vaccine Description	Dose and Administration	Side Effects[a]
Diphtheria, Tetanus, Pertussis	DTaP: Diphtheria and tetanus toxoids with acellular pertussis vaccine (preferred vaccine for children <7 years) DT: Diphtheria and tetanus toxoids without pertussis vaccine Td: Tetanus toxoid with reduced dose of diphtheria toxoid Tdap: Tetanus and diphtheria toxoids with acellular pertussis vaccine	0.5 mL IM × 5 doses (2, 4, 6, 15–18 months, and 4–6 years) • Dose #4 may be given as early as 12 months as long as it is 6 months after dose #3 • If dose #4 is inadvertently given ≥4 months but <6 months after dose #3 to a child ≥12 months, it does NOT need to be repeated Use DT for age <7 years if pertussis vaccine is contraindicated 0.5 mL IM × 1 dose at 11–12 years • May be administered regardless of interval since last tetanus and diphtheria toxoid-containing vaccine • 1 dose during each pregnancy (ideally 27–36 weeks gestation) Use Td for age ≥7 years if pertussis vaccine is contraindicated	Local reaction (common), fever ≥38.0°C (≤30%), drowsiness (≤50%), vomiting (4%–7%), crying ≥1 hr (1%–2%) Severe side effects of allergic reactions, persistent crying >3 hr, hypotonic-hyporesponsive episode, seizures, and body temperature >40.5°C that were more common with DTP vaccine are very rare with DTaP
Haemophilus influenzae type B (Hib)	Hib PRP-OMP: Capsular polysaccharide antigen conjugated to outer membrane protein of *Neisseria meningitidis* Hib PRP-T: Capsular polysaccharide antigen conjugated to tetanus toxoid	0.5 mL IM × 2–3 doses (2, 4, +/– 6 months), with booster at 12–15 months • 3 doses of PRP-T and 2 doses of PRP-OMP recommended • Should not be given prior to 6 weeks of age • No need to use same formulation for entire series • See Section IV.B.1 for children with high-risk conditions	Mild local pain, redness, swelling in 25% of recipients for <24 hr
Hepatitis A (HepA)	Inactivated virus purified from human fibroblast cultures	0.5 mL IM × 2 doses (12–23 months with 6–18-month interval between doses) Use 1 mL IM per dose if age ≥19 years International travel: • Age ≥12 months: 1 dose before departure • Age 6–11 months: give 1 dose before departure and revaccinate with 2 doses starting at 12 months	Mild injection site tenderness (≤37%) or redness (≤29%); irritability (42%), drowsiness (28%), fever (≤27%), headache (<9%)

Hepatitis B (HepB)	Produced by recombinant DNA technology; monovalent formulations may be used interchangeably	0.5 mL IM × 3 doses (Birth, 1–2 months, and 6–18 months) Use 1 mL IM per dose if age ≥ 20 years or giving 2-dose adolscent series (age 11-15 years). • 4 doses acceptable if combined vaccines used after birth dose • Monovalent HepB vaccine should be given to all term newborns within 24 hr of birth • See Section IV.C for details regarding preterm infants	Pain at injection site (3%–29%) or fever >37.7°C (1%–6%)
Human papilloma virus (HPV)	HPV9: Protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 HPV4: Protects against HPV types 6, 11, 16, and 18	0.5 mL IM × 2 doses (separated by 6–12 months) for age 11–12 years • Vaccination may be started at age 9; consider if history of sexual abuse or assault • If first dose at age ≥15 years or immunocompromised, give 3 doses at 0, 1–2, and 6 months	Pain, swelling, and erythema at injection site (≤90%, 48%, and 34%, respectively), headache (11%–15%), syncope Observation for syncope for 15 min after administration is recommended
Influenza NOTE: Influenza vaccine recommendations can change annually; see CDC for up-to-date recommendations[34]	LAIV4: Intranasal live, attenuated quadrivalent vaccine for healthy children age ≥2 years IIV4: Subvirion or purified surface-antigen quadrivalent vaccines for age ≥6 months ccIIV4: Cell culture-based quadrivalent vaccine for age ≥4 years RIV4: Recombinant quadrivalent vaccine for age ≥18 years	0.2 mL intranasally (0.1 mL per nare) 0.25–0.5 mL IM if age 6–35 months (see manufacturer recommendations) 0.5 mL IM if age ≥3 years • Give annually starting at age 6 months • Children ≤8 years who have not previously received ≥2 total doses (regardless of interval) should receive 2 doses separated by ≥ 4 weeks	Local reactions, fever within 24 hr after immunization in children <2 years (10%–35%) Possible association with GBS; however, the risk is rare (1–2 cases per million doses)
Measles, Mumps, Rubella (MMR)	Combination vaccine composed of live, attenuated viruses	0.5 mL SQ × 2 doses (12–15 months and 4–6 years) • Dose #2 may be given to age <4 years as long as there has been a 4-week interval International travel: • Age 6–11 months: Give 1 dose prior to departure, then revaccinate with 2 doses—dose #1 at 12–15 months, dose #2 ≥4 weeks later • Age ≥ 12 months (and unvaccinated): Give 2 doses at 4-week interval prior to departure	High fever (>39.4°C) in 5%–15%, usually 6–12 days after immunization, and may last ≤5 days; febrile seizures may occur 5–12 days after the first dose (rare) Other reactions include transient rash (5%), transient thrombocytopenia (1 in 22,000–40,000), encephalitis, and encephalopathy (<1 in 1 million)

Continued

TABLE 16.1—cont'd

ROUTINE VACCINES FOR CHILDREN AND ADOLESCENTS IN THE UNITED STATES

Disease	Vaccine Description	Dose and Administration	Side Effects[a]
N. meningitidis (Meningococcal)	MenACWY-D (Menactra): Quadrivalent (serogroups A, C, Y, W) polysaccharide diphtheria toxoid conjugate for age ≥9 months MenACWY-CRM (Menveo): Quadrivalent (serogroups A, C, Y, W) oligosaccharide diphtheria conjugate for age ≥2 months	0.5 mL IM at age 11–12 years with booster at age 16 years • See Section IV.B.2 for children with high-risk conditions	Mild localized tenderness (10%–41%) or erythema (11%–15%), irritability (18%–57%), sleepiness (14%–50%), headache (11%–30%)
	MenB-4C (Bexsero): Serogroup B vaccine for age 10–25 years MenB-FHbp (Trumenba): Serogroup B vaccine for age 10–25 years	0.5 mL IM x 2 doses • May be given at clinical discretion to adolescents 16–23 years (preferred age 16–18 years) who are not at increased risk • Dose interval for Bexsero is 1 month and for Trumenba is 6 months (vaccines are not interchangeable) • See Section IV.B.2 for children with high-risk conditions	Injection-site pain (85%), fatigue (35%–40%), headache (35%), and muscle pain (30%–48%)
Polio	IPV: Inactivated injectable vaccine containing 3 types of poliovirus Note: OPV, a live, attenuated oral vaccine, is no longer available in the United States; see Table 16.2	0.5 mL IM/SQ × 4 doses (2, 4, 6–18 months, and 4–6 years) • 4 or more doses of IPV can be administered before the 4th birthday when a combination vaccine containing IPV is used. However, a dose is still recommended after the 4th birthday and ≥ 6 months after the previous dose.	Local reactions (≤30%), irritability (≤65%), tiredness (≤61%), fever ≥39°C (≤4%)
Rotavirus	RotaTeq (RV5): Pentavalent live, attenuated oral vaccine containing five reassortant human and bovine rotavirus strains Rotarix (RV1): Monovalent live, attenuated oral vaccine	2 mL PO × 3 doses (2, 4, and 6 months) • If any dose RotaTeq or unknown, 3 doses should be given • First dose must be given before 15 weeks • Do NOT readminister if infant spits out or vomits dose 1 mL PO × 2 doses (2 and 4 months) • First dose must be given before 15 weeks • If the infant spits out or vomits a dose, 1 replacement dose can be given at same visit	Diarrhea (24%), vomiting (15%), otitis media (14.5%), nasopharyngitis (7%), and bronchospasm (1%); rates similar to placebo Small risk of intussusception (1 excess case per 30,000–100,000 vaccinated infants) usually within 1 week of vaccination

Streptococcus pneumoniae (Pneumococcal)	PCV13: Pneumococcal conjugate vaccine containing 13 purified capsular polysaccharides of *S. pneumoniae*, each coupled to a variant of diphtheria toxin: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) + additional serotypes (1, 3, 5, 6A, 7F, and 19A) for age ≥ 6 weeks PPSV23: Purified capsular polysaccharide from 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) for age ≥2 years	0.5 mL IM × 4 doses (2, 4, 6, 12–15 months) • See Section IV.B.3 for children with high-risk conditions • PCV13 and PPSV23 should not be administered during the same visit. 0.5 mL IM/SQ • See Section IV.B.3 for children with high-risk conditions • When both PCV13 and PPSV23 are indicated, administer PCV13 first.	Pain or erythema at injection site (>50%), irritability (20%–70%), decreased appetite (20%–40%), decreased sleep (≤40%), increased sleep (≤40%), fever (≤20%)
Varicella	Cell-free live, attenuated varicella virus vaccine for age ≥ 12 months	0.5 mL SQ × 2 doses (12–15 months and 4–6 years) • Dose #2 may be given to age <4 years as long as there has been a 3-month interval • A second dose given ≥4 weeks after the first is valid	Injection site reactions (20%–25%) and fever (10%–15%) Mild varicelliform rash within 5–26 days of vaccine administration (3%–5%) may occur, though not all postimmunization rashes are attributable to vaccine; vaccine rash is often mild, but patient may be infectious

[a]Unless otherwise indicated, side effect profiles for vaccines are derived from vaccine-specific package inserts. Available online at: http://www.immunize.org/fda/.[35]

DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *GBS*, Guillain-Barré syndrome; *Hib, Haemophilus influenzae* type b; *IIV,* inactivated influenza vaccine; *IM,* intramuscular; *IPV,* inactivated polio vaccine; *LAIV,* live, attenuated influenza vaccine; *OPV,* oral polio vaccine; *PCV13,* pneumococcal 13-valent conjugate vaccine; *PO,* per os; *PPSV23,* pneumococcal 23-valent polysaccharide vaccine; *SQ,* subcutaneous; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine.

TABLE 16.2

NONROUTINE VACCINES FOR CHILDREN AND ADOLESCENTS

Disease	Indication	Type	Dose and Administration	Side Effects[a]
Japanese encephalitis (JE)	≥1-month travel in endemic areas (most rural areas of Asia) during the JE season May also be considered for shorter-term travel with higher exposure risk (i.e., during epidemic or time outdoors in rural areas)	JE-VC: Inactivated cell culture–derived JE vaccine for age ≥2 months	0.25 mL IM if age 2 months to 2 years 0.5 mL IM ≥3 years 2 doses at 4-week interval, followed by annual boosters for persons age ≥17 years (if still indicated)	Fever (>10%–20%), irritability (>15%), and diarrhea (>10%) in young children; pain (>15%–25%) and headache (>20%) in adolescents and adults
Polio Oral polio vaccine (OPV) See Table 16.1 for IPV	Not used in the United States, but used worldwide Trivalent vaccine: Protective against all 3 poliovirus types in >95% of recipients In 2016, most countries switched to the bivalent vaccine	Trivalent (tOPV): Live, attenuated vaccine against wild types 1, 2, and 3 Bivalent (bOPV): Live, attenuated vaccine against wild types 1 and 3, but not 2	3 doses at minimum 4 week intervals starting at 6 weeks • Give additional OPV at birth in countries with endemic polio or high risk of importation • Give ≥1 IPV dose, starting at 14 weeks (can be coadministered with OPV)	Rare vaccine-associated paralytic poliomyelitis (VAPP) occurs for ~1 in 2.4 million doses.
Rabies	High-risk groups: Veterinarians, animal handlers, laboratory workers, children living in high-risk environments, those traveling to high-risk areas, spelunkers Postexposure prophylaxis (see Table 16.5)	HDCV: Inactivated virus cultured in human diploid cells PCECV: Inactivated virus cultured in purified chicken embryo cells	Preexposure: 1 mL IM × 3 doses (Days 0, 7, and 21 or 28) Postexposure: 1 mL IM × 4 doses (Days 0, 3, 7, and 14) • Do not administer in same part of body or in same syringe as RIG • Serum Ab titers should be followed at 6-month intervals for those at continuous risk and at 2-year intervals for those at risk of frequent exposure • Give booster doses only if titers are nonprotective	Uncommon in children; in adults, local reactions (≤25%), mild systemic reactions (≤20%) Arthus-like reaction (urticaria, arthralgia, angioedema, vomiting, fever, malaise) 2–21 days after immunization with HDCV is rare in primary series, but 6% after booster dose

Disease	Indication	Type	Dose and Administration	Side Effects[a]
Respiratory Syncytial Virus (RSV)[36]	Preterm infants: • Born <29 WGA and <12 months at the start of RSV season • Chronic lung disease of prematurity in first year of life or requiring ongoing medical support in second year of life Children <12 months with: • Anatomic pulmonary abnormality or neuromuscular disorder impairing upper airway clearance • Moderate-to-severe pulmonary hypertension • Hemodynamically significant heart disease (discuss with cardiologist) Children <2 years with: • Cardiac transplant • Profound immunocompromise	Palivizumab: Humanized mouse IgG1 monoclonal antibody to RSV	15 mg/kg IM Give every 28-30 days during RSV season for up to 5 doses • First dose should be given prior to the beginning of RSV season • Children who develop an RSV infection should discontinue use of Palivizumab	Fever and rash (local skin reaction)
Tuberculosis (TB)	1 dose of BCG should only be considered in the United States if a child is frequently and unavoidably exposed to contagious pulmonary TB that is untreated, ineffectively treated, or resistant to treatment, and the child cannot be given long-term primary preventive therapy (if nonresistant) Children should be HIV-negative and those ≥2 months should have a negative purified protein derivative (PPD)	BCG: Live, attenuated vaccine prepared from *Mycobacterium bovis*. Variable composition and efficacy worldwide, but ≤80% effective	Reconstitute 1 vial of vaccine (50 mg) in 1 mL sterile water (2 mL if age <1 month) Give 0.2–0.3 mL of reconstituted vaccine percutaneously with a multiple puncture device in the deltoid region	In 1%–2%, axillary or cervical lymphadenopathy and pustule formation at injection site can occur Rare complications are disseminated BCG infection or BCG osteitis (more common if immunocompromised)

Continued

TABLE 16.2—cont'd

NONROUTINE VACCINES FOR CHILDREN AND ADOLESCENTS

Disease	Indication	Type	Dose and Administration	Side Effects[a]
Typhoid	Travel to areas with risk of exposure to *Salmonella* serotype Typhi, people with frequent close contact with a documented carrier, laboratory workers in contact with *Salmonella* serotype Typhi, and people living in areas with endemic infection	ViCPS: Vi capsular polysaccharide vaccine for age ≥2 years Ty21a: Oral live, attenuated vaccine for age ≥6 years	0.5 mL IM Give 1 dose ≥2 weeks prior to exposure; booster every 2 years 1 dose by mouth every other day for a total of 4 doses ≥1 week prior to exposure; booster every 5 years	Local discomfort or erythema (up to 14%), subjective fever (3%), decreased activity (2%) Mild reactions including abdominal pain, nausea, diarrhea, vomiting, fever, or headache
Yellow fever	Travel to endemic areas including parts of sub-Saharan Africa and South America Required by some countries as a condition of entry	YF-Vax: Live, attenuated (17D strain) vaccine approved for age ≥9 months	0.5 mL SQ Give 1 dose ≥10 days prior to travel No booster doses indicated unless immunocompromised or at increased risk due to location or duration of exposure (e.g., prolonged travel or lab workers)	Rare viscerotropic disease (multiple-organ system failure) and neurotropic disease (encephalitis) Increased risk of adverse events in persons with thymic dysfunction; increased risk of postvaccine encephalitis in ages <9 months

[a]Unless otherwise indicated, side effect profiles for vaccines are derived from vaccine-specific package inserts. Available online at: http://www.immunize.org/fda/.[35]

Ab, Antibody; *BCG*, bacille Calmette-Guérin; *HDCV*, human diploid cell vaccine; *IgG1*, immunoglobulin G 1; *IM*, intramuscular; *IPV*, inactivated polio vaccine; *PCECV*, purified chick embryo cell vaccine; *RIG*, rabies immune globulin; *SQ*, subcutaneous; *WGA*, weeks gestational age.

3. Combination vaccines can reduce number of injections.
   a. MMR-Varicella (ProQuad)[4] can be used for children 12 months through 12 years of age. There is an increased risk of febrile seizures if given as first dose for ages 12 to 47 months.
   b. HepB-containing[5] combination vaccines should not be administered to infants <6 weeks because of the other components.
4. Simultaneous administration
   a. Routine childhood vaccines are safe and effective when administered simultaneously at different sites. There is no maximum number of vaccines that can be coadministered.
   b. If live vaccines are not given at the same visit, they should be separated by an interval of 28 days.

C. Live, Attenuated Vaccines

1. Certain vaccines have live components that must replicate to produce immunity: Influenza (intranasal), MMR, oral polio vaccine (OPV), BCG, typhoid (oral), varicella, yellow fever.
2. Systemic adverse reactions following these vaccines are usually mild, and usually occur 3 to 21 days after the vaccine is given.
3. Special consideration must be taken when administering these vaccines to patients with certain underlying medical conditions (see Section IV).

D. Timing and Spacing of Vaccine Doses

1. For information on recommended timing and spacing of vaccines, see: http://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
2. Combination vaccines
   a. Minimum age for administration is the oldest age for any of the individual components.
   b. Minimum interval between doses is equal to the greatest interval of any of the individual components.

E. Contraindications and Precautions[6]

1. Contraindication: A condition that increases the likelihood of a serious adverse reaction to a vaccine for a patient with that condition.
2. Precaution: A condition that may increase the likelihood or severity of an adverse reaction in a vaccine recipient, or may compromise the ability of the vaccine to produce immunity.
3. Table 16.3: Contraindications and precautions to select vaccines.
4. Table 16.4: Conditions incorrectly perceived as contraindications or precautions to vaccination (vaccines may be given under these conditions).
5. For full details, see: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

TABLE 16.3

CONTRAINDICATIONS AND PRECAUTIONS TO SELECT VACCINES[6,7,9]

Vaccine	Contraindication	Precaution
All vaccines	Severe (life-threatening) allergic reaction after 1 dose or to any vaccine component (see package inserts)	Moderate-severe acute illness (wait until after recovery if possible) Latex allergy: www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf
Live vaccines	Most forms of altered immunocompetence (see Section IV.A for exceptions) Solid organ transplant Pregnancy: Wait until after pregnancy; avoid becoming pregnant for ≥1 month after vaccine	Patients on corticosteroids: See Table 16.6 HSCT patients • Delay ≥3 months after immunosuppressive therapy has been discontinued • See Table EC 16.B Patients on biologic response modifier therapies: Contraindicated during therapy and for weeks to months after discontinuation Received other live vaccines in past 4 weeks
Diphtheria, Tetanus, Pertussis	Encephalopathy (including coma or status epilepticus) within 7 days of administration of prior dose of DTaP/Tdap not attributable to another identifiable cause	Evolving/progressive neurologic disorder, including uncontrolled seizures: Defer DTaP/Tdap temporarily; use DT or Td instead in children age ≥1 year, reconsider pertussis immunization at each visit (i.e., if condition stabilized) GBS within 6 weeks of previous dose History of Arthus-type hypersensitivity reaction (including severe pain or swelling) after tetanus or diphtheria toxoid-containing vaccine: Defer vaccination for 10 years after last administration DTaP/Tdap: Temp ≥40.5°C (104.8°F) within 48 hr of a previous dose
Hepatitis A	Anaphylaxis to aluminum hydroxyphosphate sulfate, aluminum hydroxide, or neomycin	
Hepatitis B	Anaphylaxis to yeast	Defer for infants <2,000 g if mother HBsAg negative; see Fig. 16.1 for details
HPV	Anaphylaxis to yeast	Pregnancy: Delay vaccination until after pregnancy.
Influenza (IIV)		History of GBS within 6 weeks after a previous dose Egg allergy other than hives (administer in a supervised medical setting)

Continued

TABLE 16.3—cont'd

Vaccine	Contraindication	Precaution
Influenza (LAIV)	Anaphylaxis to eggs or gelatin Contacts (including providers) of severely immunocompromised patients requiring care in protective environment Children <5 years with history of wheezing in past 12 months On aspirin or aspirin-containing products Use of influenza antiviral therapy in the past 48 hr (may interfere with immunogenicity)	History of GBS within 6 weeks after a previous dose Asthma or breathing problems in children ≥5 years Medical conditions that might be at higher risk of complications from influenza
Japanese Encephalitis	Anaphylaxis to protamine sulfate	
MMR	Anaphylaxis to neomycin or gelatin	History of thrombocytopenia or TTP Recent blood product administration (within 3–11 months, depending on product and dose). See Table EC 16.D Need for TB testing Other live vaccines in past 4 weeks Personal or family history of seizures (MMRV only)
Meningococcal (ACWY and B)	Anaphylaxis to tetanus or diphtheria toxoid	Pregnancy or breastfeeding: Not much information about potential risks; should be used only if clearly needed
Pneumococcal	PCV13: Anaphylaxis to any vaccine containing diphtheria toxoid	PPSV23 in Pregnancy: No evidence of harm, but avoid or give prior to pregnancy if possible
Polio	IPV: Anaphylaxis to neomycin, streptomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde OPV: Immunocompromised patients and close/household contacts	Pregnancy: No evidence of harm, but avoid or give prior to pregnancy if possible
Rabies	Anaphylaxis to gelatin (present in some vaccines, check package insert) Severe allergic reaction to prior dose (switch to PCECV if there is a reaction to HDCV)	
Rotavirus	SCID History of intussusception Severe allergic reaction to latex (RV1 only)	Concern for immunocompromise, preexisting chronic gastrointestinal disease, spina bifida, or bladder exstrophy Preterm infants: Defer initiation of routine vaccination if still hospitalized to prevent nosocomial spread
Tuberculosis (BCG)	HIV infection Burns or skin infections	

TABLE 16.3—cont'd

Vaccine	Contraindication	Precaution
Typhoid (Ty21a only)		Active gastrointestinal tract illness Certain antibiotics or antimalarials that would be active against *Salmonella* serovar Typhi or interfere with immunogenicity
Varicella[37]	Anaphylaxis to neomycin or gelatin	On aspirin or aspirin-containing products; avoid using salicylates for 6 weeks after vaccination Recent blood product administration (within 3–11 months, depending on product and dose, see Table EC 16.D) Tuberculosis or positive PPD Other live vaccines in past 4 weeks Receipt of antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hr before vaccination; avoid for 14 days after vaccination
Yellow fever[38]	Anaphylaxis to eggs or gelatin Symptomatic HIV infection or $CD4^+$ count <200/mm^3 (or <15% for age <6 years) Age <6 months Thymus disorder	Age 6–8 months: Risk of vaccine-associated encephalitis Pregnant or breastfeeding: Rare cases of in utero or breastfeeding transmission of the vaccine virus Asymptomatic HIV infection with $CD4^+$ count 200–499/mm^3 (or 15%–24% for age <6 year)

DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *GBS,* Guillain-Barré syndrome; *HDCV,* human diploid cell vaccine; *HIV,* human immunodeficiency virus; *HPV,* human papilloma virus; *HSCT,* hematopoietic stem cell transplant; *IIV,* inactivated influenza vaccine; *LAIV,* live, attenuated influenza vaccine; *MMR,* measles, mumps, rubella; *MMRV,* measles, mumps, rubella, varicella; *PCECV,* purified chick embryo cell vaccine; *PPD,* purified protein derivative; *SCID,* severe combined immunodeficiency; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine; *TTP,* thrombotic thrombocytopenic purpura.

Modified from Table 4.1, Centers for Disease Control and Prevention. "Contraindications and Precautions." Vaccine Recommendations and Guidelines of the ACIP. Last updated 14.09.2018. Available online at: http://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

TABLE 16.4

CONDITIONS INCORRECTLY PERCEIVED AS CONTRAINDICATIONS OR PRECAUTIONS TO VACCINATION[6,7,9]

Vaccine	NOT Contraindication/Precaution
All vaccines	Mild acute illness with or without fever Mild-moderate local reaction (i.e., swelling, redness, soreness); low-grade or moderate fever after previous dose Recent exposure to an infectious disease Current antimicrobial therapy (Exceptions: oral typhoid, varicella) Convalescent phase of illness Breastfeeding Preterm birth (Exception: hepatitis B vaccine in specific circumstances; see Fig. 16.1) History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy History of GBS (Exception: within 6 weeks of influenza or tetanus toxoid–containing vaccine)

TABLE 16.4—Cont'd

Vaccine	NOT Contraindication/Precaution
DTaP	Personal or family history of seizures, including seizures after previous dose of DTaP: Consider antipyretic use for 24 hr after vaccination. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hr of a previous dose Persistent, inconsolable crying lasting ≥3 hr within 48 hr of a previous dose Stable neurologic conditions (e.g., cerebral palsy, well-controlled seizures, or developmental delay)
Hepatitis B	Autoimmune disease (e.g., SLE or RA)
HPV	Evidence of active or prior HPV infection, such as abnormal Pap smear, history of genital warts, or positive HPV DNA test
Influenza (IIV)	Nonsevere allergy to egg or latex Pregnancy: Give regardless of trimester
Influenza (LAIV)	Contacts of persons with chronic disease or altered immunocompetence not requiring care in a protected environment Breastfeeding
MMR	Positive tuberculin skin test (PPD) Simultaneous PPD or interferon-γ release assay (IGRA) testing: may be done on the day of immunization but otherwise should be postponed 4–6 weeks Nonanaphylactic reactions to gelatin or neomycin or anaphylactic reaction to egg (consider observation for 90 min; skin testing not predictive)
Polio (IPV)	Previous receipt of ≥1 dose of OPV
PPSV23	History of invasive pneumococcal disease or pneumonia
Rotavirus	Prematurity (give at hospital discharge)
Varicella	Immunodeficient household contact (Exception: If patient experiences a presumed vaccine-related rash 7–25 days after vaccination, the person should avoid direct contact with immunocompromised persons for the duration of the rash) Humoral immunodeficiency (e.g., agammaglobulinemia)

DNA, Deoxyribonucleic acid; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *GBS,* Guillain-Barré syndrome; *HPV,* human papilloma virus; *IIV,* inactivated influenza vaccine; *IPV,* inactivated polio vaccine; *LAIV,* live, attenuated influenza vaccine; *OPV,* oral polio vaccine; *PPD,* purified protein derivative; *PPSV23,* pneumococcal 23-valent polysaccharide vaccine; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus.

Modified from Table 4.2, Centers for Disease Control and Prevention. "Contraindications and Precautions." Vaccine Recommendations and Guidelines of the ACIP. Last updated 14.09.2018. Available online at: http://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

III. POSTEXPOSURE PROPHYLAXIS (TABLE 16.5)

IV. SPECIAL PATIENT POPULATIONS[7]

A. Altered Immunocompetence[8,9]

1. For full details, see: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html.
2. **General principles**
   a. Primary immunodeficiency: Congenital and usually inherited conditions defined by an inherent absence or deficiency in cellular or humoral components that provide immunity.

TABLE EC 16.A

VACCINE INFORMATION FOR PATIENTS WITH IMMUNODEFICIENCIES[6-9]

Specific Immunodeficiency	Contraindicated Vaccines	Risk-Specific Recommended Vaccines	Effectiveness and Comments
B LYMPHOCYTE (HUMORAL)			
Severe antibody deficiencies (e.g., X-linked agammaglobulinemia, CVID)	OPV[a] Smallpox LAIV BCG Ty21a Yellow fever MMR MMRV	Pneumococcal Hib (ages 12–59 months)	The effectiveness of any vaccine is uncertain if it depends only on the humoral response
Less severe antibody deficiencies (e.g., IgA deficiency, IgG subclass deficiency)	OPV[a] BCG Yellow fever[5] Other live vaccines appear to be safe	Pneumococcal Hib (ages 12–59 months)	All vaccines likely effective; immune response might be attenuated
T LYMPHOCYTE (CELL MEDIATED AND HUMORAL)			
Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines[b]	Pneumococcal Hib (ages 12–59 months)	Vaccines likely to be effective
Partial defects (e.g., most DiGeorge syndrome patients, Wiskott-Aldrich)	All live vaccines[b]	Pneumococcal Meningococcal Hib (ages 12–59 months)	Effectiveness of any vaccine depends on degree of immune suppression
IFN-γ/ IL-12 axis deficiencies	All live bacterial vaccines (All live vaccines[b] contraindicated in IFN-γ or IFN-α deficiencies)	None	

Continued

TABLE EC 16.A—cont'd

Specific Immunodeficiency	Contraindicated Vaccines	Risk-Specific Recommended Vaccines	Effectiveness and Comments
COMPLEMENT			
Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal Hib (ages 12–59 months)	All routine vaccines likely effective
Eculizumab (Soliris) therapy	None	Meningococcal	
PHAGOCYTIC FUNCTION			
Chronic granulomatous disease	All live bacterial vaccines[b]	None	Live viral vaccines likely safe and effective
Phagocytic deficiencies that are undefined or accompanied by defects in T- and NK cell dysfunction (e.g., Chediak-Higashi syndrome, leukocyte adhesion deficiency)	All live vaccines[b]	Pneumococcal	All inactivated vaccines safe and likely effective
SECONDARY IMMUNODEFICIENCY			
HIV/AIDS	OPV[a] Smallpox BCG LAIV MMRV Withhold MMR, varicella, and zoster in severely immunocompromised persons Yellow fever vaccine may have a contraindication or precaution depending on clinical parameters of immune function (see CDC for details)	Pneumococcal Hib HepB	MMR and varicella vaccine in those with mild immunosuppression, rotavirus, and all inactivated vaccines, including IIV as per routine vaccination schedule, may be effective

Specific Immunodeficiency	Contraindicated Vaccines	Risk-Specific Recommended Vaccines	Effectiveness and Comments
Generalized malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial,[b] depending on immune status	Pneumococcal Hib	Effectiveness of any vaccine depends on degree of immune suppression
Asplenia	LAIV	Pneumococcal Meningococcal Hib	All routine vaccines likely effective
Chronic renal disease	LAIV	Pneumococcal HepB (indicated based on risk from dialysis-based bloodborne transmission)	All routine vaccines likely effective

[a]OPV is no longer available in the United States.

[b]Live bacterial vaccines: BCG, adenovirus, and oral Ty21a *Salmonella typhi* vaccine; Live viral vaccines: MMR, MMRV, OPV, LAIV, yellow fever, zoster, rotavirus, varicella, and vaccinia (smallpox). Nonemergency smallpox vaccination is not recommended for children <18 years old or the general public.

AIDS, Acquired immunodeficiency syndrome; *BCG*, bacille Calmette-Guérin; *CDC*, Centers for Disease Control and Prevention; *CVID*, common variable immunodeficiency; *HepB*, hepatitis B; *Hib*, *Haemophilus influenzae* type b; *HIV*, human immunodeficiency virus; *IFN*, interferon; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IL*, interleukin; *LAIV*, live, attenuated influenza vaccine; *MMR*, measles, mumps, rubella; *MMRV*, measles, mumps, rubella, varicella; *OPV*, oral polio vaccine; *SCID*, severe combined immunodeficiency.

Modified from Appendix A from Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. In: Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington, DC: Public Health Foundation; 2015. Available online at: www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/A/immuno-table.pdf.

b. Secondary immunodeficiency: Acquired loss or deficiency in cellular or humoral immune components as a consequence of a disease process or its therapy.
c. See Chapter 15 for specific information about immunodeficiencies.
d. See Table EC 16.A for specific vaccine recommendations and contraindications in patients with immunodeficiency.

3. **Primary immunodeficiency**
   a. Live vaccines generally contraindicated.
   b. Other vaccines should be given according to routine schedule. Immune response may vary.
   c. Increased incidence or severity of some vaccine-preventable diseases: recommendations for additional vaccination.
   d. Passive immunoprophylaxis with immunoglobulin therapy may be indicated.
      (1) See Chapter 15 for specific details.
      (2) See Table 16.5 for postexposure prophylaxis guidelines.
   e. Routine immunization of household contacts. Only exception is live, attenuated influenza vaccine (LAIV) if immunocompromise is severe (e.g., severe combined immunodeficiency [SCID]).
4. **Functional or anatomic asplenia (including sickle cell disease)**
   a. Penicillin prophylaxis: See Chapter 14 for details.
   b. See Section IV.B for Hib, meningococcal, and pneumococcal vaccination recommendations.
   c. Children ≥2 years undergoing elective splenectomy
      (1) Give pneumococcal and meningococcal vaccines ≥2 weeks before surgery for optimal immune response.
      (2) Consider another dose of Hib.
5. **Known or suspected human immunodeficiency virus (HIV) disease**
   a. See Section IV.B for Hib, meningococcal, and pneumococcal vaccination recommendations.
   b. Varicella: Administer when $CD4^+$ ≥15%.
   c. MMR: Give 2 doses to all HIV-infected children without evidence of severe immunosuppression (i.e., age ≤5 years with $CD4^+$ ≥15% for ≥6 months OR age >5 years with $CD4^+$ ≥15% and $CD4^+$ count ≥200 cells/mm for ≥6 months).
   d. Do not give MMR-Varicella combined vaccine.
   e. Do not administer LAIV.
   f. Do not administer OPV and BCG unless in areas where infection risk outweighs possibility of vaccine-associated disease.
   g. Consider passive immunoprophylaxis or chemoprophylaxis after exposures (see Table 16.5).
6. **Malignancy**
   a. Always consult with the patient's oncologist first. Recommendations vary based on the patient's specific treatment regimen.
   b. General strategies include the following
      (1) Presuming loss of immunity and revaccinating per CDC catch-up immunization schedule.

TABLE 16.5

POSTEXPOSURE PROPHYLAXIS (PEP)

Disease	Prophylaxis Type	Indication/Administration Details
Hepatitis A	Vaccine	Indicated for children ≥12 months if ≤2 weeks since exposure OR if >2 weeks since exposure and exposure ongoing
	IMIG	For children <12 months if ≤2 weeks since exposure Immunocompromised children with exposure Dosing: 0.1 mL/kg IM
Hepatitis B See Table 16.7 for details on percutaneous exposure to blood.	Vaccine	Give series to any previously unimmunized person with percutaneous blood exposure Give within 12 hr after birth to any infant with maternal HBsAg status positive/unknown
	HBIG: Prepared from plasma containing high-titer anti-HBsAg antibodies	Give within 12 hr after birth to infants with maternal HBsAg positive; see Fig. 16.1 for guidance when maternal HBsAg unknown Give to any previously unimmunized person or known nonresponder with percutaneous blood exposure to HBsAg positive blood Dosing: • 0.5 mL IM for infants <12 months • 0.06 mL/kg IM for children ≥12 months
Hib (invasive)	Vaccine	Invasive Hib ≤24 months: Initiate 1 month after acute illness and continue immunization series as if previously unimmunized Not required if invasive Hib disease develops in children >24 months Consider immunologic workup for any child with invasive Hib disease after completing immunization series
	Chemoprophylaxis	Exposure only: Rifampin prophylaxis recommended for household contacts in certain circumstances (see Table 3.11 of the 2018 Red Book for details[29])

Continued

TABLE 16.5—cont'd

Disease	Prophylaxis Type	Indication/Administration Details
Influenza NOTE: Recommendations vary by season; see CDC for up-to-date recommendations[34]	Chemoprophylaxis	Most commonly used: Neuraminidase inhibitors (e.g., oseltamivir) given the high resistance to adamantanes (e.g., amantadine) Indications: • Unimmunized high-risk children, including those for whom the vaccine is contraindicated or children immunized <2 weeks before exposure • Unimmunized individuals in close contact with high-risk individuals • Immunodeficient individuals unlikely to have protective response to vaccine • Control of outbreaks in a closed setting • Immunized high-risk individuals if vaccine strain different from circulating strain Delay for ≥2 weeks if LAIV has been given Not a substitute for immunization
Measles	Vaccine	Intervention of choice for measles outbreak; prevents or modifies disease if given within 72 hr of exposure
	IMIG	Indicated in children <1 year or nonimmune individuals who cannot receive the vaccine Prevents or modifies disease if given within 6 days of exposure
	IVIG	Recommended for nonimmune pregnant women and severely immunocompromised hosts (including HIV-infected children) regardless of immunization status Additional therapy not required if given within 3 weeks before exposure
Mumps	Vaccine	Persons ≥12 months who previously received ≤2 doses of MMR and are identified by public health authorities to be at increased risk during a mumps outbreak should receive 1 dose of MMR[39]
Meningococcal	Vaccine Chemoprophylaxis	Adjunct to chemoprophylaxis when an outbreak is caused by a vaccine-preventable serogroup Indications: • Direct exposure to an infected person's oral secretions (including unprotected healthcare workers) • Close contact in the 7 days prior to onset of disease (e.g., child care, preschool, and household contacts and passengers seated next to the index patient during airline flights ≥8 hr) Initiate within 24 hr of index patient diagnosis See Table 3.42 of the 2018 Red Book for details[29]

Disease	Prophylaxis Type	Indication/Administration Details
Pertussis	Vaccine Chemoprophylaxis	Immunize all unimmunized or partially immunized close contacts based on the recommended schedule Azithromycin, erythromycin, or clarithromycin recommended for household contacts and other close contacts. Alternatives include TMP-SMX (see Table 3.52 of the 2018 Red Book for details[29])
Rabies See Table 16.8 for details based on type of exposure Note: PEP indicated for bites, scratches, or contamination of open wound or mucous membrane with infectious material of potentially rabid animal or human	Vaccine RIG: Antirabies Ig prepared from plasma of donors hyperimmunized with rabies vaccine Other management	If unimmunized: give vaccine on days 0, 3, 7, and 14 with 1× RIG on day 0 If immunosuppressed, give a fifth dose on day 28 If RIG is unavailable, give vaccine alone If previously immunized: booster doses on days 0 and 3 If unimmunized: • Give 1× RIG on day 0 with vaccine • If no vaccine, give RIG alone • May be given within 7 days after initiating immunization Do not give RIG if previously immunized Dosing: 20 units/kg; infiltrate around the wound, give remainder IM Consider tetanus prophylaxis and antibiotics, if indicated General wound management: • Clean immediately with soap and water and flush thoroughly • Avoid suturing wound unless indicated for functional or cosmetic reasons Report all patients suspected of rabies infection to public health authorities
Rubella	Rubella Ig	Does not prevent infection or viremia For use in rubella-susceptible women exposed to confirmed rubella early in pregnancy when termination is not being considered.[40] Routine use of rubella Ig in early pregnancy is not recommended.
Tetanus	Vaccine TIG	See Table 16.9 for details Give to any child with HIV infection or other severe immunodeficiency for any tetanus-prone wound, regardless of vaccination status Dosing: 1× 250 units IM

Continued

TABLE 16.5—cont'd

Disease	Prophylaxis Type	Indication/Administration Details
Varicella See Fig. 3.12 of the 2018 Red Book for details[29]	Vaccine	Vaccinate immunocompetent, nonimmune people ≥12 months as soon as possible after exposure, preferably within 3 days Vaccination should still be given after this time for protection against subsequent exposures Do not give vaccine concurrently with or for 5 months after VariZIG Avoid antivirals for 21 days after vaccination
	VariZIG: Prepared from plasma containing high-titer antivaricella antibodies	Give for significant exposures in individuals with no immunity and a high likelihood of complications from infection including: • Immunocompromised • Pregnant women • Certain newborn infants Give as soon as possible within 10 days of exposure Dosing (Weight-based, IM, 125 units = 1 vial): • 62.5 units for ≤2 kg • 125 units for 2.1–10 kg • 250 units for 10.1–20 kg • 375 units for 20.1–30 kg • 500 units for 30.1–40 kg • 625 units for >40 kg
	IVIG	May be used if VariZIG is not available Dosing: 400 mg/kg IV
	Chemoprophylaxis	If VariZIG or IVIG are not available, consider prophylaxis with 7 days of acyclovir or valacyclovir beginning 7–10 days after exposure in immunocompromised, nonimmune patients

CDC, Centers for Disease Control and Prevention; *HBIG*, hepatitis B immune globulin; *HBsAg*, hepatitis B surface antigen; *Hib, Haemophilus influenzae* type b; *HIV*, human immunodeficiency virus; *Ig*, immunoglobulin; *IM*, intramuscular; *IMIG*, intramuscular immunoglobulin; *IVIG*, intravenous immunoglobulin; *LAIV*, live, attenuated influenza vaccine; *MMR*, measles, mumps, rubella; *PEP*, postexposure prophylaxis; *RIG*, rabies immune globulin; *TIG*, tetanus immune globulin; *TMP-SMX*, trimethoprim-sulfamethoxazole; *VariZIG*, varicella zoster immune globulin.

(2) Obtaining titers and revaccinating those with unprotective levels.

c. Timing of resumption of immunization varies based on the patient's specific treatment regimen (from 3 months to ≥24 months).
   (1) Inactivated vaccines are generally delayed until ≥6 months after the end of chemotherapy.
   (2) Live vaccines are generally delayed until ≥12 months after the end of chemotherapy.

d. Inactivated influenza vaccine (IIV) should be given annually, even during chemotherapy.

7. **Hematopoietic stem cell transplant (HSCT) recipients**
   a. After transplant, HSCT recipients are considered to have lost immunity to all vaccines. Reimmunize against all vaccine-preventable illnesses.
      (1) Inactivated vaccines are safe to administer 6 to 12 months after HSCT. Our center starts the pneumococcal series at 6 months and the remainder at 12 months.
      (2) IIV may be given as early at 6 months post-HSCT. Children ≤8 years should receive two doses. Do not administer LAIV. During a community outbreak, IIV may be given 3 to 4 months post-HSCT, with a second dose 4 weeks later regardless of age.
      (3) Avoid live vaccines during the first 24 months post transplant.
      (4) For specific vaccine recommendations, see Table EC 16.B.
   b. Consider passive immunoprophylaxis or chemoprophylaxis after exposures (see Table 16.5).
   c. Household contacts should receive routine immunizations. Only exception is LAIV if the HSCT recipient's level of immunocompromise is severe (e.g., HSCT in last 3 months). HSCT recipients should avoid contact with body fluids or skin eruptions of household contact who received rotavirus or varicella vaccines, respectively.
8. **Solid organ transplant recipients**
   a. See Section IV.B.3 for pneumococcal vaccination recommendations.
   b. Before transplant: Give all routinely recommended vaccines. Give live vaccines ≥4 weeks prior to transplantation.
      (1) Children 6 to 11 months can receive MMR if not immunosuppressed and if transplant is ≥4 weeks away.
      (2) Children 6 to 11 months (or without evidence of varicella immunity) can receive varicella vaccine if not immunosuppressed and if transplant is ≥4 weeks away.
   c. After transplant: Inactivated vaccines, including those indicated for immunocompromised hosts, should resume 2 to 6 months after transplant. Live vaccines are generally not given after transplant. For specific vaccine recommendations, see Table EC 16.C.
9. **Patients on corticosteroids**
   a. Only live vaccines are potentially contraindicated.
   b. See Table 16.6 for details.

TABLE EC 16.B

VACCINATIONS AFTER HSCT[41-44]

Vaccine	Timing Posttransplant (# of recommended doses)[c]
DTaP, DT, Td, Tdap	Age <7 years: 12 months (3 doses of DTaP) Age ≥7 years: 12 months (3 doses of DTaP OR 1 dose of Tdap, followed by 2 doses of either DT or Td)
HepA	12 months (2 doses)
HepB	12 months (3 doses)
Hib	12 months (3 doses)
HPV	Age 11–26 years: 6–12 months (3 doses)
IIV	6 months, or 4 months during outbreak (1 dose annually; 2 doses if age 6 months–8 years and receiving for first time or if given prior to 6 months post-HSCT)
IPV	12 months (3 doses)
LAIV[a]	Contraindicated
Meningococcal	Age 11–18 years: 12 months (2 doses; booster at 16–18 years if first post-transplant dose given at age 11–15 years)
MMR[a]	24 months (2 doses)[b]
PCV13	6 months (3 doses; a fourth dose should be added at 14 months instead of PPSV23 in patients with chronic GVHD)
PPSV23	14 months if no chronic GVHD
Rotavirus[a]	Contraindicated
Varicella[a]	24 months (2 doses)[b]

[a]Do not administer live vaccines to patients with active GVHD or ongoing immunosuppression.
[b]Should only be administered to patients without ongoing immunosuppression, no chronic GVHD, and 8–12 months after last dose of IVIG.
[c]Some variation in recommended timing of administration post-HSCT. These recommendations reflect our center's practice.
DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *GVHD,* graft versus host disease; *HepA,* hepatitis A; *HepB,* hepatitis B; *Hib, Haemophilus influenzae* type b; *HPV,* human papilloma virus; *IIV,* inactivated influenza vaccine; *IPV,* inactivated polio vaccine; *LAIV,* live, attenuated influenza vaccine; *MMR,* measles, mumps, rubella; *PCV13,* pneumococcal 13-valent conjugate vaccine; *PPSV23,* pneumococcal 23-valent polysaccharide vaccine; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine.

TABLE EC 16.C

VACCINATIONS AFTER SOLID ORGAN TRANSPLANT[43-46]

Vaccine	Administration Recommendations (Starting 2–6 Months Posttransplant)
DTaP, DT, Td, Tdap	Routine schedule
HepA	Routine schedule
HepB	Routine schedule
Hib	Routine schedule
HPV	Routine schedule
IIV	Routine schedule (can be administered ≥1 month after transplant during outbreak)
IPV	Routine schedule
LAIV	Contraindicated
Meningococcal	Routine schedule
MMR	Contraindicated
MMRV	Contraindicated
PCV13	Recommended, if not given pretransplant (high risk for pneumococcal disease)

TABLE EC 16.C—cont'd

Vaccine	Administration Recommendations (Starting 2–6 Months Posttransplant)
PPSV23	Recommended for age ≥2 years, if not given pretransplant (high risk for pneumococcal disease)
Rotavirus	Contraindicated
Varicella	Contraindicated[a]

[a]Exception: Select nonimmune patients with renal or liver transplant receiving minimal or no immunosuppression and without recent graft rejection.

NOTE: Vaccination should not be withheld because of concern about transplant rejection.

DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *HepA,* hepatitis A; *HepB,* hepatitis B; *Hib, Haemophilus influenzae* type b; *HPV,* human papilloma virus; *IIV,* inactivated influenza vaccine; *IPV,* inactivated polio vaccine; *LAIV,* live, attenuated influenza vaccine; *MMR,* measles, mumps, rubella; *MMRV,* measles, mumps, rubella, varicella; *PCV13,* pneumococcal 13-valent conjugate vaccine; *PPSV23,* pneumococcal 23-valent polysaccharide vaccine; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine.

TABLE 16.6

LIVE VACCINE IMMUNIZATION FOR PATIENTS RECEIVING CORTICOSTEROID THERAPY

Steroid Dose	Recommended Guidelines
Topical, inhaled, or local injection of steroids. Low-dose steroids (<2 mg/kg/day or <20 mg/day of prednisone equivalent[a]), including physiologic doses	Live vaccines can generally be given unless there is clinical evidence of immunosuppression.
High-dose steroids (≥2 mg/kg/day or ≥20 mg/day of prednisone equivalent[a]) duration of therapy <14 days	Live vaccines may be given immediately after cessation of therapy (but consider 2-week delay).
High-dose steroids (≥2 mg/kg/day or ≥20 mg/day of prednisone equivalent[a]) duration of therapy ≥14 days	Delay live vaccines until 4 weeks after discontinuation of therapy.
Systemic or local steroids in patients with underlying disease affecting immune response (e.g., lupus) or receiving other immunosuppressant medication	Do not administer live vaccines.

[a]20 mg/day cutoff for children weighing more than 10 kg.
Adapted from pages 84–85 of the 2018 Red Book.[29]

10. **Patients on biologic response modifiers**
    a. See Table 1.20 of the 2018 Red Book for details.[29]
    b. Antibodies to proinflammatory cytokines or proteins that bind to cytokine receptors (e.g., tumor necrosis factor [TNF]-α inhibitors) are considered highly immunosuppressive.
    c. Prior to initiating therapy:
        (1) Perform serologic testing for hepatitis B virus and vaccinate/revaccinate if hepatitis B surface antibody (HBsAb) is <10 mIU/mL.
        (2) Give inactivated vaccines (including IIV) ≥2 weeks prior to starting therapy.
        (3) Give live-virus vaccines ≥4 weeks prior, unless contraindicated by condition or other therapies.
    d. During/after therapy:
        (1) Live-virus vaccines: Contraindicated during therapy. Interval after therapy for safe administration has not been established.
        (2) Inactivated vaccines (including IIV): Give according to schedule.
11. **Patients treated with immunoglobulin or other blood products**
    See Table EC 16.D for suggested intervals between blood product and MMR or varicella administration.

B. Disease-Specific Considerations

1. **Children at high risk of Hib[10]**
    a. Indications: Functional or anatomic asplenia (including sickle cell disease), HIV infection, immunoglobulin deficiency, early component complement deficiency, or chemotherapy/radiation.

Table EC 16.D

RECOMMENDED INTERVALS BETWEEN ADMINISTRATION OF ANTIBODY-CONTAINING PRODUCTS AND MMR/VARICELLA VACCINES

Product/Indication (Dosing)	Interval (Months)
BLOOD TRANSFUSION (ALL 10 ML/KG IV)	
Washed RBCs	0
RBCs, adenine-saline added	3
Packed RBCs	6
Whole blood	6
Plasma/platelet products	7
INTRAMUSCULAR IMMUNOGLOBULIN	
Hepatitis A IgG (0.1–0.2 mL/kg IM)	3
Hepatitis B IgG (HBIG) (0.06 mL/kg IM)	3
Tetanus IgG (TIG) (250 units IM)	3
Rabies IgG (RIG) (20 units/kg IM)	4
Palivizumab (RSV monoclonal Ab) (15 mg/kg IM)	0
Varicella IgG (VariZIG) (125 units/10 kg IM; max 625 units)	5
Measles prophylaxis IgG (immunocompetent contacts; 0.5 mL/kg IM)	6
INTRAVENOUS IMMUNOGLOBULIN	
Cytomegalovirus IVIG (150 mg/kg max)	6
Botulinum IVIG (BabyBIG) (1.0 mL/kg IV)	6
IVIG	
• Replacement therapy for immune deficiencies (300-400 mg/kg)	8
• Postexposure measles prophylaxis (immunocompromised contacts) (400 mg/kg)	8
• Postexposure varicella prophylaxis (400 mg/kg)	8
• ITP treatment (400 mg/kg)	8
• ITP treatment (1000 mg/kg)	10
• Kawasaki disease (2 g/kg)	11

IM, Intramuscular; *ITP,* immune; *IV,* intravenous; *IVIG,* intravenous immunoglobulin; *RBCs,* red blood cells; *RSV,* respiratory syncytial virus.

Modified from Appendix A from Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* In: Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington, DC: Public Health Foundation; 2015. Available online at: www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/a/mmr_ig.pdf

b. Age <12 months: Give primary series.
c. Age 12 to 59 months:
   (1) Received 0 to 1 dose(s) before 12 months: Give 2 doses at 8-week intervals.
   (2) If ≥2 doses were received <12 months: Give 1 additional dose at least 8 weeks after previous dose.
d. Age ≥5 years and not fully immunized with asplenia or HIV: Give 1 dose at least 8 weeks after previous dose.

2. **Children at high risk of meningococcal disease**[11-13]
   a. Indications: Functional or anatomic asplenia, HIV infection, persistent complement deficiency (including Eculizumab use), travel to or residence in areas with hyperendemic or epidemic meningococcal disease, or residence in a community with a meningococcal outbreak.
   b. Age <2 years:
      (1) MenACWY-CRM (Menveo): If age 8 weeks to 6 months, give 4 doses at 2, 4, 6, and 12 months. If age 7 to 23 months and unvaccinated, give 2 doses with second dose ≥12 weeks after first dose and after first birthday.
      (2) MenACWY-D (Menactra): Can use for persistent complement component deficiency or travel, but not for anatomic/functional asplenia, sickle cell disease, or HIV infection before age 2 years. If age 9 to 23 months, give two doses 12 weeks apart (8-week interval acceptable if needed prior to travel).
   c. Age ≥2 year: Give two doses of Menactra or Menveo (min. 8-week interval). Only one dose is needed for children who are traveling, live in hyperendemic regions, or during an outbreak. Give Menactra ≥4 weeks after completing PCV13 series.
   d. Boosters:
      (1) Most recent dose given <7 years old: Give one booster dose 3 years after completion of the primary series, then every 5 years thereafter.
      (2) Most recent dose given ≥7 years old: Give one booster dose every 5 years.
   e. Age ≥10 years with asplenia or persistent complement deficiency:
      (1) Give two-dose MenB-4C (Bexsero) or three-dose MenB-FHbp (Trumenba) in addition to MCV4 series.
      (2) The two MenB vaccines are **not** interchangeable; use the same product for all doses in a series.

3. **Children at high risk for pneumococcal disease**[14,15]
   a. Indications:
      (1) Immunocompromised: Functional or anatomic asplenia (including sickle cell disease), primary immunodeficiencies, HIV infection, malignancy, immunosuppressive or radiation therapy, solid organ transplant, chronic renal failure or nephrotic syndrome

(2) Other chronic conditions: Chronic heart disease, chronic lung disease, diabetes mellitus, CSF leak, cochlear implant, chronic liver disease, or alcoholism

b. All recommended doses of PCV13 should be given prior to PPSV23, if possible.
c. Age <6 years at high risk: Complete primary series with PCV13.
d. Age ≥2 years at high risk: Give one dose of PPSV23 ≥8 weeks after last PCV13 dose.
e. Age ≥6 years with immunocompromise, CSF leak, or cochlear implant with no history of PCV13: Give one dose of PCV13 ≥8 weeks after any prior PPSV23. Wait ≥8 weeks before giving PPSV23 if patient has never received PPSV23.
f. Age ≥6 years with immunocompromise: Give one PPSV23 booster dose 5 years after the first dose (do not repeat).

C. Preterm Infants

1. **Immunize according to chronologic age, using regular vaccine dose.** Defer risk of rotavirus vaccine until hospital discharge.
2. **Hepatitis B**:
   a. For infants <2 kg born to hepatitis B surface antigen (HBsAg) negative mothers, delay first vaccine dose until 1 month of age or hospital discharge (whichever is first).
   b. For management of preterm and low-birth-weight infants of mothers with positive or unknown HepB status, see Fig. 16.1.
3. See Table 16.2 for indications for respiratory syncytial virus (RSV) immunoprophylaxis.

D. Pregnant Women

1. **Tdap (tetanus, diphtheria, acellular pertussis)**: Give during each pregnancy, preferably at 27 to 36 weeks gestation, regardless of prior immunization status.
2. **Give IIV** regardless of trimester. Do not give LAIV.
3. **Other inactivated vaccines**: Considered precautionary and generally deferred until after the pregnancy.
4. **Live vaccines**: Generally contraindicated during pregnancy.

E. Immigration, Emigration, and Travel

1. **Travelers**:
   a. See CDC's Travelers' Health site for destination-specific recommendations: http://www.cdc.gov/travel/destinations/list.
   b. Consider referral to a travel clinic.
2. **Immigrants from outside the United States.**
   See CDC's Immigrant and Refugee Health site for recommendations for immigrants, refugees, and international adoptees: http://www.cdc.gov/immigrantrefugeehealth/.

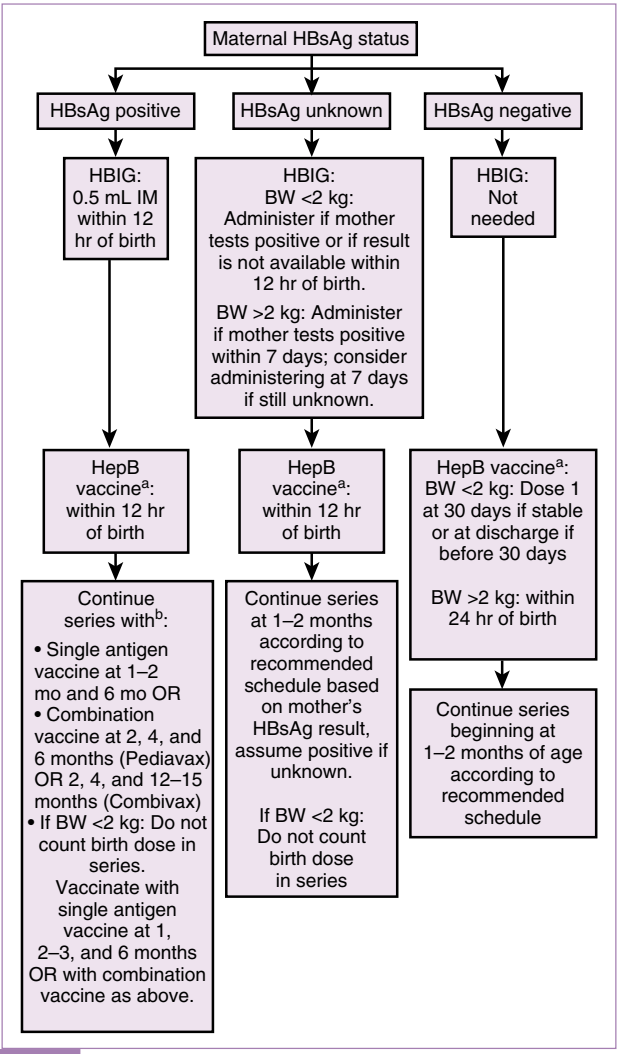

FIGURE 16.1

Management of neonates born to mothers with unknown or positive hepatitis B surface antigen *(HBsAg)* status. [a]Only single antigen vaccine should be used. [b]Reimmunization may be required based on anti-HBs; test for HBsAg and anti-HBs at age 9 to 12 months or 1 to 2 months after completion of HepB series if delayed. HBsAg-negative infants with anti-HBs levels ≥10 mIU/mL are protected. HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be reimmunized with a fourth dose and retested. If still <10 mIU/mL, two additional doses should be given. If after six doses the levels are <10 mIU/mL, no additional doses of HepB vaccine are indicated. *BW,* birth weight; *HBIG,* hepatitis B immune globulin; *HepB,* hepatitis B. (Modified from American Academy of Pediatrics. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Elk Grove Village, IL: AAP; 2018.)

V. COUNSELING AND COMMUNICATION ABOUT VACCINES[16-26]

A. Vaccine Hesitancy

1. **Definition**: Delay in the acceptance or refusal to vaccinate despite the availability of vaccine services. Not a dichotomous behavior, but a continuum. Vaccine-hesitant parents may accept all vaccines but remain concerned, accept some vaccines and refuse others, or refuse all vaccines. Approximately 3% of parents in the United States refuse all vaccines.[20]
2. The AAP recommends continued engagement with vaccine-hesitant parents while providing other health services and attempting to modify opposition to vaccines.
3. **Determinants of vaccine acceptance**
   a. The 3C Model: Confidence, Complacency, Convenience. Key determinants of vaccine acceptance in global populations as determined by the World Health Organization (WHO) SAGE Working Group on Vaccine Hesitancy. See Online Content for more details.
   b. Parental concerns about vaccines (Box 16.1)

BOX 16.1

PARENTAL CONCERNS ABOUT VACCINES

Vaccine Safety
Too many vaccines
Development of autism
Vaccine additives (thimerosal, aluminum)
Overload of the immune system
Serious adverse reactions
Potential for long-term adverse events
Inadequate research performed before licensure
May cause pain to the child
May make the child sick
Necessity of Vaccines
Disease is more "natural" than vaccine
Parents do not believe diseases being prevented are serious
Vaccine-preventable diseases have disappeared
Not all vaccines are needed
Vaccines do not work
Freedom of Choice
Parents have the right to choose whether to immunize their child
Parents know what's best for their child
Believe that the risks outweigh the benefits of vaccine
Do not trust organized medicine, public health
Do not trust government health authorities
Do not trust pharmaceutical companies
Ethical, moral, or religious reasons

Adapted from Table 2 of Edwards KM, Hackell JM, AAP Committee on Infectious Diseases, The Committee on Practice and Ambulatory Medicine. Countering vaccine hesitancy. *Pediatrics*. 2016;138(3):e20162146.

TABLE 16.7

HEPATITIS B VIRUS PROPHYLAXIS AFTER PERCUTANEOUS EXPOSURE TO BLOOD

Exposed Person	HBsAg Status of Source of Blood: Positive	Negative	Unknown
Unimmunized	HBIG and HBV series	HBV series	HBV series
PREVIOUSLY IMMUNIZED			
Known responder	No treatment	No treatment	No treatment
Known nonresponder	HBIG and HBV series (or HBIG ×2 at 1-month interval if already received two HBV series without response)	No treatment	Treat as if positive if known high-risk source
Response unknown	Test exposed person for anti-HBs[a]: If adequate, no treatment If inadequate, HBIG ×1 and HBV booster	No treatment	Test exposed person for anti-HBs[a]: If adequate, no treatment If inadequate, HBV booster dose and recheck titer in 1–2 months

[a]Adequate anti-HBs is ≥10 mIU/mL.

Anti-HBs, hepatitis B surface antibody; *HBIG,* hepatitis B immune globulin; *HBV,* hepatitis B vaccine.

Adapted from Table 3.23 of the 2018 Red Book.[29]

TABLE 16.8

RABIES POSTEXPOSURE PROPHYLAXIS BASED ON ANIMAL

Animal Type	Evaluation and Disposition of Animal	Postexposure Prophylaxis Recommendations
Dog, cat, ferret	Healthy and available for 10 days' observation	Do not begin prophylaxis unless animal develops signs of rabies
	Rabid or suspected rabid: euthanize animal and test brain	Provide immediate immunization and RIG[b]
	Unknown (escaped)	Consult public health officials
Skunk, raccoon, bat,[a] fox, woodchuck, most other carnivores	Regard as rabid unless geographic area is known to be free of rabies or until animal is euthanized and proven negative by testing	Provide immediate immunization and RIG[b]
Livestock, rodents, rabbit, other mammals	Consider individually	Consult public health officials; these bites rarely require treatment

[a]In the case of direct contact between a human and a bat, consider prophylaxis even if a bite, scratch, or mucous membrane exposure is not apparent.

[b]Treatment may be discontinued if animal fluorescent antibody is negative.

RIG, Rabies immune globulin.

Adapted from Table 3.63 of the 2018 Red Book.[29]

TABLE 16.9

INDICATIONS FOR TETANUS PROPHYLAXIS

Prior Tetanus Toxoid Doses	Clean, Minor Wounds		All Other Wounds	
	Tetanus Vaccine[a]	TIG	Tetanus Vaccine[a]	TIG
Unknown or <3	Yes	No	Yes	Yes
≥3, last <5 years ago	No	No	No	No
≥3, last 5–10 years ago	No	No	Yes	No
≥3, last ≥10 years ago	Yes	No	Yes	No

[a]DTaP preferred under age 7 years; Tdap preferred over age 7 years. DT or Td if pertussis is contraindicated.
DT, Diphtheria and tetanus vaccine; *DTaP,* diphtheria, tetanus, acellular pertussis vaccine; *Td,* tetanus and diphtheria vaccine; *Tdap,* tetanus, diphtheria, acellular pertussis vaccine; *TIG,* tetanus immune globulin.
Adapted from Table 3.78 of the 2018 Red Book.[29]

B. Countering Vaccine Hesitancy

1. Parent and/or patient-specific concerns should be acknowledged and addressed while correcting misconceptions in a nonconfrontational manner.
2. Relationship with primary care provider/pediatrician is a strong influence on decision to vaccinate. Mutual desire to do what is best for the child should be emphasized.
3. See Section VII: Online Content, for more information on specific communication strategies and interventions, as well as online provider resources.

VI. WEB RESOURCES[27-33]

- **Advisory Committee on Immunization Practices (ACIP) Vaccine Recommendations and Guidelines**: www.cdc.gov/vaccines/hcp/acip-recs/index.html
- **Epidemiology and Prevention of Vaccine-Preventable Diseases (Pink Book)**: www.cdc.gov/vaccines/pubs/pinkbook/index.html
- **AAP Report of the Committee on Infectious Diseases (Red Book)**: http://redbook.solutions.aap.org/
- **CHOP Vaccine Education Center**: http://www.chop.edu/centers-programs/vaccine-education-center
- **WHO Immunization, Vaccines and Biologicals**: www.who.int/immunization/
- **VaxView**: www.cdc.gov/vaccines/vaxview/index.html
  Data for ACIP-recommended vaccine coverage across the United States.
- **Vaccine Adverse Event Report System (VAERS)**: http://vaers.hhs.gov/
  National vaccine safety surveillance program run by the CDC and U.S. Food and Drug Administration (FDA) that collects information about post-vaccination adverse events.
- **Vaccines for Children (VFC) Program**: www.cdc.gov/vaccines/programs/vfc/about/index.html
  Provides vaccines to children who parents/guardians may not be able to afford them.
- **Centers for Disease Control and Prevention (CDC) Vaccine Shortages and Delays**: www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

VII. ONLINE CONTENT

A. Additional Vaccine Recommendations

1. Vaccine Information for Patients with Immunodeficiencies (Table EC 16.A)
2. Vaccinations After HSCT (Table EC 16.B)
3. Vaccinations After Solid Organ Transplant (Table EC 16.C)
4. Recommended Intervals Between Administration of Antibody-Containing Products and MMR/Varicella Vaccines (Table EC 16.D)

B. The 3C Model: Key Barriers to Vaccine Use Worldwide[16]

1. Confidence: Trust in healthcare professionals, vaccines, and their effectiveness. Includes concerns regarding vaccine safety, quality of interactions with healthcare providers, religious beliefs, and media influence.
2. Complacency: Low awareness of the risks of vaccine-preventable diseases and the importance of vaccines. Includes resistance to introduction of new vaccines, resistance to mode of vaccine delivery, and lack of knowledge about the risks of now uncommon diseases.
3. Convenience: Availability of and accessibility to vaccines and healthcare services (rural areas, low-middle income countries). Includes vaccine supply issues, lack of education or medical literacy, geographic barriers, political conflicts and instability, and immigration.

C. Strategies to Address Vaccine Hesitancy[18-19,22-26]

1. Communication
   a. Studies have found that parents want more information than they are getting, want balanced information about potential benefits and harms, struggle to find unbiased, trustworthy sources of information, and view healthcare workers as an important source of information.
   b. Consider the timing for making vaccination information available to parents, the settings where information is available, the provision of impartial and clear information tailored to parental needs, and parents' perceptions of health workers and the information provided.
   c. AAP Communication Highlights (Box EC 16.A)
2. Interventions
   a. SAGE Working Group assessed systematic reviews and meta-analyses of worldwide strategies to address vaccine hesitancy. No convincing evidence that any specific intervention to address parental vaccine hesitancy/refusal is effective across populations.
   b. Most effective interventions were tailored to specific populations and addressing specific concerns, pointing to the importance of understanding the drivers of vaccine hesitancy to inform the interventions.
   c. Most successful interventions were multicomponent strategies that directly targeted unvaccinated/under vaccinated populations, aimed to increase vaccine knowledge and awareness, improved convenience and access to vaccination, mandated vaccination, and engaged religious or other influential leaders to promote vaccination.

BOX EC 16.A

VACCINE COMMUNICATION HIGHLIGHTS

Vaccines are safe and effective, and serious disease can occur if your child and family are not immunized.

Vaccine-hesitant individuals are a heterogeneous group, and their individual concerns should be respected and addressed.

Vaccines are tested thoroughly before licensure, and vaccine safety assessment networks exist to monitor vaccine safety after licensure.

Nonmedical vaccine exemptions increase rates of unvaccinated children.

Unvaccinated children put vaccinated children and medically exempt children who live in that same area at risk.

Pediatricians and other healthcare providers play a major role in educating parents about the safety and effectiveness of vaccines.

Strong provider commitment to vaccination can influence hesitant or resistant parents. Personalizing vaccine acceptance is often an effective approach.

The majority of parents accepted the provider's vaccine recommendations when they were presented as required immunizations to maintain optimal disease prevention.

The current vaccine schedule is the only one recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP). Alternative schedules have not been evaluated.

Adapted from Table 4 of Edwards KM, Hackell JM, AAP Committee on Infectious Diseases, The Committee on Practice and Ambulatory Medicine. Countering vaccine hesitancy. *Pediatrics*. 2016;138(3):e20162146.

D. Provider Resources for Vaccine Communication

1. WHO guide to addressing vaccine hesitancy: www.who.int/immunization/programmes_systems/vaccine_hesitancy/en
2. CDC resources for effective communication with parents regarding vaccines
   a. Vaccine conversations with parents: https://www.cdc.gov/vaccines/hcp/conversations/conv-materials.html
   b. List of public health, policy, and clinical studies for helping providers increase vaccination rates in their communities: www.cdc.gov/vaccines/hcp/admin/reminder-sys.html
3. The Community Guide: www.thecommunityguide.org/topic/vaccination Regularly publishes evidence-based recommendations on interventions intended to improve routine delivery of universally recommended vaccinations in the United States (in collaboration with the CDC).
4. AAP Tools
   a. AAP refusal to vaccinate form: https://www.aap.org/en-us/Documents/immunization_refusaltovaccinate.pdf
   b. Risk communication videos: https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/vaccine-hesitant-parents.aspx#Video

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Chapter 17

Microbiology and Infectious Disease

Kevin Klembczyk, MD and Samuel McAleese, MD

I. COMMON NEONATAL AND PEDIATRIC INFECTIONS: GUIDELINES FOR DIAGNOSIS AND INITIAL MANAGEMENT

Tables 17.1–17.6 and Figs. 17.1–17.3 present the most common neonatal and pediatric infections, organized by site of infection or by organism, when applicable. These recommendations are based on national guidelines and recent literature. They are not meant to replace clinical judgment.

For recommendations on preliminary identification of bacteria and antibiotic selection based on spectrum of activity for commonly used antibiotics, please see Sections II–III. Please note that local resistance pattern should guide antibiotic selection. Follow published institutional guidelines and culture results for individual patients and infections. When possible, always use the agent with the narrowest spectrum of activity, particularly when organism susceptibilities are known.

A. Congenital, Perinatal, and Neonatal Infections (Table 17.1)

B. Pediatric Infections by System (Table 17.2)

C. Pediatric Viral Illnesses (Table 17.3)

D. Pediatric Tick-Borne Diseases (Table 17.4)

E. Tuberculosis: Diagnosis and Treatment (Boxes 17.1 and 17.2)[1,2]

1. Diagnosis
   a. See Box 17.1 for screening guidelines and Box 17.2 for information on interpretation of tuberculin skin tests (TSTs) and interferon gamma release assays (IGRAs).
   b. If positive screening test, obtain chest X-ray.
   c. If symptoms indicate active tuberculosis (TB) disease, determine source.
      (1) Consider pediatric protocol chest CT over X-ray when available.
      (2) Specimen sources include sputum, bronchial washings, gastric aspirates (morning aspirate before feeding/ambulation x 3 specimens), pleural fluid, cerebrospinal fluid, urine, tissue biopsy.
      (3) Acid-fast smear and/or nucleic acid amplification testing may provide rapid diagnosis. The latter may also detect rifampin resistance. Solid media culture can take as long as 10 weeks, liquid media 1 to 6 weeks.
   d. Lumbar puncture is recommended in children less than 12 months with confirmed TB and should be considered in children 12 to 24 months. (Cont'd on pg. 433.)

TABLE 17.1

CONGENITAL, PERINATAL, AND NEONATAL INFECTIONS

	Presentation	Etiology	Diagnosis	Treatment
CONGENITAL AND PERINATAL INFECTIONS				
Cytomegalovirus[1]	**Congenital**: 90% asymptomatic at birth. IUGR, jaundice, thrombocytopenia, petechiae, hepatosplenomegaly, transaminitis, microcephaly, intracranial calcifications, sensorineural hearing loss, and retinitis. **Perinatal**: sepsis, pneumonitis, hepatosplenomegaly, transaminitis	Herpes virus. Congenital infection is transmitted in utero. Perinatal infection may be transmitted via birth canal or breastmilk.	PCR or rapid viral culture of saliva, urine, blood, sputum, or CSF. Variable practice of screening infants (urine or saliva). May target those who fail newborn hearing screen or with low birth weight.	Congenital: PO valganciclovir for 6 months if symptomatic. Affected infants should have hearing tested at regular intervals. Perinatal: IV ganciclovir for 2–3 weeks. Follow CMV serum viral load.
Group B Strep[3,48]	Early-onset: 0–6 days, typically within 24 hr. Most commonly pneumonia, bacteremia, or meningitis. Late-onset: 7–89 days, typically 3–4 weeks. Most commonly bacteremia or meningitis. Also septic arthritis, osteomyelitis, UTI, and cellulitis.	Transmitted by mother with genitourinary GBS colonization OR in setting of maternal infection (bacteremia, endometritis, chorioamnionitis). Intrapartum antibiotics decrease transmission (at least 1 dose ≥4 hr prior to delivery).	Multiple accepted approaches for risk assessment among infants born >35 weeks of gestation. Example of common, categorical approach shown in Fig. 17.1. Newer, multivariate risk assessment (Neonatal Early-Onset Sepsis Calculator) is available at: https://neonatalsepsiscalculator.kaiserpermanente.org. Diagnosis made by culture.	Penicillin G. Presumptive early-onset GBS sepsis: ampicillin and gentamicin. Empiric treatment for late-onset GBS meningitis: ampicillin and cefotaxime. Ceftriaxone if >30 days. Consider inclusion of vancomycin for *Streptococcus pneumoniae* meningitis.
Hepatitis B[1]	90% of infants infected perinatally or in first year of life develop chronic HBV infection, leading to: 1. Chronic low-grade hepatitis 2. Progression to cirrhosis and HCC 3. Risk of reactivation acute hepatitis	Hepadnavirus usually transmitted perinatally (rather than in utero), from mother with acute or active chronic infection. 95% of transmission prevented with appropriate immunoprophylaxis at birth.[4]	If mother HBsAg-positive, test infant for HBsAg and anti-HBsAg between 9 and 12 months (or 1–2 months after final HBV vaccine). Monitor HBV DNA and ALT in chronic HBV. Infection cleared at ~1% per year. See Table 17.5 for interpretation of serologies.	See Chapter 16 for immunoprophylaxis with HBV vaccine and HBIG. Breastfeeding is safe. Refer for treatment if active HBV replication with elevated ALT for 6 months.

Continued

TABLE 17.1—cont'd

CONGENITAL, PERINATAL, AND NEONATAL INFECTIONS

	Presentation	Etiology	Diagnosis	Treatment
Hepatitis C[1]	80% of acute infections become chronic. Syndrome less pronounced than in hepatitis B.	Flavivirus transmitted in utero or perinatally from about 5% of infected (RNA-positive) mothers.	HCV antibody at 18 months (maternal HCV antibodies persist 12+ months). Monitor ALT.	Rapidly evolving field. New oral antiviral regimens approved for 12+ years. Breastfeeding safe.
Herpes simplex virus[1]	Presents within first 4 weeks as: 1. Localized to skin, eyes, and mouth (45%) 2. Localized CNS (30%) 3. Disseminated (25%) with sepsis, pneumonitis, hepatitis, consumptive coagulopathy, and CNS involvement.	Herpes virus transmitted most commonly via maternal genital tract with active HSV lesions. Less commonly ascending (in utero) and postnatal (via caregivers) transmission.	Surface culture or PCR from active vesicles, mouth, nasopharynx, conjunctivae, and anus. PCR or culture of blood and CSF. Viremia can be seen in nondisseminated disease.	IV acyclovir: 14 days for skin, eye, and mouth disease; 21 days for CNS or disseminated disease. CSF clearance must be proven. Treat eye involvement with additional topical antiviral. All types receive 6 months PO prophylaxis.
Rubella[1]	IUGR, cataracts, glaucoma, cardiac anomalies (PDA and PPS), deafness, "blueberry muffin rash."	Togavirus transmitted via primary maternal infection (85% chance of transmission if maternal infection before 12 weeks gestation).	IgM at birth. Level typically would increase within first 6 months of life. Diagnosis can be confirmed by stable or increasing IgG level over first 7 to 11 months. RNA PCR and viral culture also used.	Supportive care, with evaluation by ophthalmology and cardiology.
Syphilis[1]	May be asymptomatic at birth. Oro/nasophraryngeal secretions ("snuffles"), mucocutaneous lesions, maculopapular rash, hepatosplenomegaly, hemolytic anemia, thrombocytopenia. If untreated, CNS, bones/joints/teeth, eyes, and skin affected by late disease.	*Treponema pallidum* is a spirochete transmitted in utero at any stage of maternal syphilis.	If maternal nontreponemal serology positive (RPR or VDRL), obtain maternal treponemal test (STT) and screen infant nontreponemal tests. Reverse sequence testing is also practiced. Full evaluation includes: CBC, transaminases, CSF analysis, long-bone x-rays, adnominal US neuro-imaging, ophtho exam, ABR testing.	Full evaluation and treatment indicated for infants at high risk: Abnormal exam or infant RPR or VDRL titer fourfold greater than maternal or mother inadequately treated. Full treatment: IV aqueous penicillin G or IM procaine penicillin G for 10 days. If less likely (normal exam, RPR/VDRL ≤ fourfold maternal titer, and mother

			Refer to Red Book for interpretation of screening tests, diagnostic approach, and treatment algorithms.	treated during pregnancy >4 weeks before delivery): benzathine penicillin G single dose. If unlikely (normal exam, RPR/VDRL ≤ fourfold maternal titer, mother treated before pregnancy, and maternal titer low and stable before and throughout pregnancy): ensure titer returns to negative. Some experts give benzathine penicillin G single dose.
Toxoplasmosis[1]	May be asymptomatic at birth. Major: chorioretinitis, cerebral calcifications, hydrocephalus. Other: IUGR, microcephaly, seizures, hearing loss, strabismus, maculopapular rash, cytopenias.	Intracellular parasite transmitted via primary infection during pregnancy (contracted from cat feces or undercooked meat).	Serologies and PCR. Positive IgM after 5 days or IgA after 10 days is diagnostic. Positive PCR in CSF, blood, or urine is diagnostic. Eye exam for chorioretinitis. CT is most sensitive for cerebral calcifications.	Pyrimethamine + sulfadiazine with folinic acid for at least 12 months.
Varicella[1]	Congenital infection → varicella embryopathy = limb hypoplasia, cutaneous scarring, eye/CNS damage. Maternal disease onset at 5 days pre-through 2 days postpartum confers high risk of disseminated infection in infant, with high mortality, due to lack of sufficient maternal antibodies.	Herpes virus transmitted via primary maternal infection, most commonly during 1st or early 2nd trimester. Also via active lesions peripartum.	PCR of vesicle or scab swab is gold standard. PCR of saliva less sensitive.	Acyclovir 10 days in disseminated disease. Immunoprophylaxis with VariZIG (or IVIG): 1. Mother develops primary varicella between 5 days pre- and 2 days postpartum. 2. Hospitalized preterm infants with known exposure.[5]

Continued

TABLE 17.1—cont'd

CONGENITAL, PERINATAL, AND NEONATAL INFECTIONS

	Presentation	Etiology	Diagnosis	Treatment
Zika virus[6]	Microcephaly, CNS or ocular anomalies, deafness, congenital contractures.	Flavivirus transmitted in utero after primary maternal infection.	Workup: RNA PCR of blood/urine, IgM in serum, and neuroimaging. Test if: 1. Clinical findings with possible maternal infection in pregnancy based on stay in endemic areas. 2. Lab-proven maternal infection in pregnancy, even without clinical findings.	Supportive. Head ultrasound, audiology evaluation, and full ophthalmologic exam by 1 month. See Red Book and latest WHO/CDC algorithms.
NEONATAL INFECTIONS				
Fever in infant[7,8]	Serious bacterial infections (UTI, bacteremia, meningitis) are common in febrile infants. Risk is significant even if well-appearing without a clear source. Unimmunized infants, premature infants, or infants who received antibiotics recently are at higher risk for serious bacterial infection.	0–28 days: *Escherichia coli, Klebsiella pneumoniae, GBS.* Rarely, *Listeria.* 29+ days: The marked decline in invasive infections due to *Haemophilus influenzae type b* and *S. pneumoniae* since introduction of conjugate vaccines has reduced the likelihood of serious bacterial infection in this age group. In neonates under 90 days, vast majority of bacterial infections are UTIs.	Ill-appearing infant or <28 days, require full sepsis workup and admission. Goal with well-appearing infants >28 days is identifying those who can be safely discharged and monitored as outpatient with or without antibiotics. Well-established algorithms often rely on the Rochester, Philadelphia, and Boston criteria. Step-by-Step approach is a newer model that is also generally accepted. Our approach is outlined in Fig. 17.2.	Empiric therapy: 0–28 days: ampicillin + gentamicin or cefotaxime when meningitis is suspected. Add acyclovir as clinically indicated. 29+ days: ceftriaxone In well-appearing infants with negative cultures, treatment and admission can be shortened to 24–36 hr (blood cultures positive by 24 hr in 91% of cases of bacteremia[7]). Macrolide antibiotic if confirmed chlamydia pneumonia.

Neonatal exudative conjunctivitis[1,9]	*Neisseria gonorrhoeae* Onset 2–5 days. *Chlamydia trachomatis* Onset 5–12 days.	Culture is gold standard. DFA is FDA-approved. NAAT often used. Culture secretions. Gonococcal ophthalmia should prompt hospitalization and evaluation for disseminated disease.	Gonorrhea: ceftriaxone or cefotaxime single dose. Chlamydia: oral azithromycin × 3 days or erythromycin × 14 days. Saline irrigation.

ABR, Auditory brainstem response; *ALT*, alanine aminotransferase; *CBC*, complete blood count; *CDC*, Centers for Disease Control; *CMV*, cytomegalovirus; *CNS*, central nervous system; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *DFA*, direct fluorescent antibody; *DNA*, deoxyribonucleic acid; *FDA*, Food and Drug Administration; *GBS*, group B streptococcus; *HBIG*, hepatitis B immunoglobulin; *HBsAg*, hepatitis B surface antigen; *HBV*, hepatitis B virus; *HCC*, hepatocellular carcinoma; *HCV*, hepatitis C virus; *HSV*, herpes simplex virus; *Ig*, immunoglobulin; *IM*, intramuscular; *IUGR*, intrauterine growth restriction; *IV*, intravenous; *IVIG*, intravenous immunoglobulin; *NAAT*, nucleic acid amplification test; *PCR*, polymerase chain reaction; *PDA*, patent ductus arteriosus; *PO*, by mouth; *PPS*, peripheral pulmonic stenosis; *RNA*, ribonucleic acid; *RPR*, rapid plasma regain; *SNHL*, sensorineural hearing loss; *UTI*, urinary tract infection; *VDRL*, venereal disease research laboratory test; *WHO*, World Health Organization.

TABLE 17.2

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
CENTRAL NERVOUS SYSTEM				
Meningitis[11,12]	Infant: ill-appearing, fever, hypothermia, lethargy, vomiting, poor feeding, seizures, bulging fontanelle. Child and adolescent: fever, headache, altered mental status, nuchal rigidity, photophobia, nausea, vomiting. Can be progressive or acute and fulminant.	<1 month: *Group B Streptococcus, Escherichia coli, Klebsiella, Listeria* 1–23 months: *Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae* (GBS), *Haemophilus influenzae.* 2+ years: *S. pneumoniae, N. meningitidis.* Brain abscess: *Streptococcus* spp., anaerobes, *Staphylococcus aureus*	Indication for head CT prior to LP: immunocompromised, known CNS disease, papilledema, focal neurologic deficit (not including CN VI/VII palsy). LP for Gram stain, culture, and analysis. See Table 17.6.	If hemodynamically unstable, do not delay antibiotics for head CT or LP. <1 month: ampicillin + cefotaxime. 1+ month: vancomycin + ceftriaxone Adjunctive dexamethasone may reduce hearing loss in children >6 weeks with *H. influenzae* type B meningitis. Brain abscess: vancomycin + ceftriaxone + metronidazole.
VP shunt infection[11]	Similar to meningitis.	*Staphylococcus epidermidis, S. aureus,* Gram-negative bacilli, *Cutibacterium acnes.*	MRI with gadolinium. CSF analysis and culture (shunt sampling/tap or LP).	Vancomycin and cefepime. Removal of infected hardware and shunt externalization.
HEAD AND NECK				
Conjunctivitis[12]	Foreign body sensation, itching, burning, photophobia, hyperemia.	Viruses (~80% of cases, especially adenovirus), *S. pneumoniae, H. influenzae,* *Neisseria gonorrhoeae, Chlamydia trachomatis.* Noninfectious: allergic, toxic, inflammatory, dry eyes.	Clinical diagnosis is nonspecific, and individual symptoms are unreliable. Allergic: watery, pruritic. Viral: fever, bilateral conjunctivitis, lymphadenopathy. Bacterial: fever, purulent discharge, pain.	Viral: supportive care. Bacterial: ophthalmic polymyxin B/TMP drops for bacterial infection. Ointments preferred in young children. Ophthalmology consult if photophobia, vision loss, severe pain, recurrent episodes, or suspected gonorrhea.

Acute otitis media[13]	Nonspecific symptoms and signs, including fever, irritability, apathy, poor feeding, vomiting, and diarrhea. May have ear pain and/or rubbing.	*S. pneumoniae, H. influenzae, Moraxella catarrhalis.*	Moderate-to-severe bulging of the tympanic membrane, mild bulging with signs of inflammation, or new-onset otorrhea.	High-dose amoxicillin × 10 days. If amoxicillin in past 30 days, give amoxicillin/clavulanate. Consider watchful waiting if: 6–23 months—unilateral AOM without otorrhea or severe symptoms.[a] 24+ months—unilateral or bilateral AOM without otorrhea or severe symptoms.[a] [a](Toxic-appearing, T ≥39°C, otalgia >48 hr.) If treatment failure after 48–72 hr: amoxicillin-clavulanate × 10 days or IM ceftriaxone × 1–3 days.
Mastoiditis[14]	Complication of AOM. Tender mastoid, protruding auricle.	*S. pneumoniae, Streptococcus pyogenes, H. influenzae.*	Clinical. Contrast CT or MRI if complications suspected (CNS signs, ill-appearing, treatment failure).	Empiric ceftriaxone and vancomycin. Often requires surgical management.
Otitis externa[15]	Ear pain, pruritus, discharge, auricle and tragus tenderness and erythema.	*Pseudomonas, S. aureus.*	Culture in severe cases.	Otic drops × 7 days: ciprofloxacin or polymyxin-neomycin. Wick if outer canal swollen.
Group A strep pharyngitis[16]	Classic signs: fever, tonsillar exudates, lymphadenopathy, absence of cough. Higher concern between age 3 and 15. Scarlet fever (from exotoxin production) involves diffuse, finely papular, erythematous rash 24–48 hr after onset of symptoms.	Group A strep.	Rapid antigen detection test. If negative, confirm with culture. IDSA recommends testing if 3+ years old, without viral symptoms (cough, rhinorrhea, hoarseness, oral ulcers).	Amoxicillin × 10 days or benzathine penicillin IM × 1 dose. Nonsevere PCN allergy: cephalexin × 10 days. PCN-allergic: clindamycin × 10 days. Second line: azithromycin × 5 days.

Continued

TABLE 17.2—cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Peritonsillar abscess[17,18]	Sore throat, trismus, uvular deviation. Can be bilateral. Most common in adolescents.	Often polymicrobial: *S. pyogenes,* viridians group streptococci, *S. aureus,* oral anaerobes.	Clinical. Consider imaging if diagnosis unclear.	Ampicillin/sulbactam or ceftriaxone/cefotaxime + clindamycin. Often requires aspiration or I&D.
Retropharyngeal/parapharyngeal abscess[17,18]	Sore throat, fever, dysphagia, neck stiffness, medial deviation of wall of oropharynx (parapharyngeal abscess). Most common at age 2–4 years.	Often polymicrobial: *S. pyogenes,* viridians group streptococci, *S. aureus,* oral anaerobes.	Clinical. Consider imaging if diagnosis unclear.	Ampicillin/sulbactam or ceftriaxone/cefotaxime + clindamycin. If no airway compromise, can trial antibiotics × 48–72 hr, prior to obtaining CT and surgical management.
Ludwig angina (submandibular cellulitis)[19]	Rapidly progressive, bilateral cellulitis, often originating as dental infection. Causes elevation of the tongue, risk of airway compromise.	Often polymicrobial: viridians group streptococci, oral anaerobes.	Clinical. Consider imaging if diagnosis unclear.	(Ampicillin/sulbactam or aqueous penicillin) + metronidazole. Consider surgical drainage.
Lemierre syndrome[20]	Thrombophlebitis of internal jugular vein seeded from primary oropharyngeal infection, bacteremia, or distant site(s) of infection. High grade fever (>39.5), neck swelling/tenderness, exudative tonsillitis, or grayish pseudomembranes.	*Fusobacterium necrophorum*, *Bacteroides*, nongroup A streptococci.	WBC count, CRP, and ESR often are markedly elevated. CT with contrast is most useful imaging. An unremarkable oropharyngeal appearance at the time of septicemia does not rule out Lemierre syndrome.	Aqueous penicillin G AND metronidazole. Surgical management often required.
Preseptal cellulitis[21]	May follow external trauma, spread from sinuses or hematogenous infection.	*S. aureus, Streptococcus spp.*	Clinical.	Amoxicillin/clavulanate × 7 days.
Orbital cellulitis[21]	Proptosis, ophthalmoplegia, pain on extraocular movements, and blurred vision.	*Streptococcus spp, S. aureus, H. influenzae, M. catarrhalis.* Most commonly extension of rhinosinusitis.	CT with contrast; ophthalmology and ENT consultation.	(Ampicillin/sulbactam or ceftriaxone or cefotaxime) + vancomycin. Often requires abscess drainage.

Sinusitis (bacterial)[22]	Rhinorrhea, inflammation of septum and turbinates, tenderness over sinuses.	*S. pneumoniae, H. influenzae* (nontypeable), *M. catarrhalis*. If chronic, also *S. aureus,* anaerobes.	Clinical: persistent sinusitis 10+ days without improvement, worsening course after initial improvement, or severe symptoms (purulent discharge, fever ≥39°C) for 3+ days.	Amoxicillin/clavulanate × 10–14 days. If uncomplicated and persistent >10 days, can opt to observe with close follow-up. In chronic sinusitis, consider culture to guide antibiotics.
Cervical lymphadenitis[1,23]	Distinguished from reactive lymphadenopathy by fluctuance, warmth, overlying erythema.	Acute (<2 weeks) - Unilateral: most commonly *S. aureus, S. pyogenes*. Bilateral: consider EBV, CMV. Chronic (>2 weeks) - Consider *Bartonella henselae* (cat scratch disease), atypical mycobacteria, Toxoplasmosis, HIV, TB.	Consider ultrasound if diagnosis unclear. Consider FNA and culture if no improvement in 48–72 hr. If >2 weeks, consider tuberculin skin test.	PO cephalexin or amoxicillin/clavulanate or clindamycin × 7 days. IV ampicillin/sulbactam, or cefazolin or clindamycin. Azithromycin × 5 days shown to have mild effect on cat scratch disease.
Oral candidiasis (thrush)	White plaques on tongue, buccal mucosa, and/or palate.	*Candida albicans* is most common.	Clinical.	Nystatin swish and swallow or clotrimazole troches for 7-14 days. Nystatin for infants.
PULMONARY				
Community-acquired pneumonia[24]	Fever, respiratory distress, cough. On exam, tachypnea, hypoxia, diminished breath sounds, crackles asymmetric breath sounds.	Bacterial: *S. pneumoniae,* nontypeable *H. influenzae, M. catarrhalis.* *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* may be considered in subacute presentations. Viral: influenza, parainfluenza, human metapneumovirus, adenovirus.	Clinical diagnosis for mild disease. Chest x-ray if hypoxic, respiratory distress, or hospitalized. CBC or inflammatory markers (CRP, ESR, procalcitonin) are not reliable to differentiate bacterial vs viral pneumonia. Blood culture not required for mild disease.	Outpatient: high-dose amoxicillin × 5 days. Inpatient: ampicillin × 5 days. ICU: ceftriaxone plus TMP/SMX. Small parapneumonic effusions treated with antibiotics alone.

Continued

TABLE 17.2—cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Pertussis[1]	Mild URI symptoms (catarrhal stage). Progresses to whooping cough (paroxysmal stage). Duration 6–10 weeks. Atypical presentation in neonates with cyanosis, gasping and posttussive emesis.	*Bordetella pertussis*. Droplet transmission. Incubation 7–10 days.	NAAT performed on posterior nasopharynx specimen. Sensitivity is not significantly affected by antibiotic treatment.	Azithromycin × 5 days. Alt: TMP-SMX. Treatment during paroxysmal stage unlikely to affect clinical course but reduces transmission. Postexposure prophylaxis recommended for household and other close contacts (including children in daycare).
Tuberculosis	See Section 17.I.E.			
GASTROINTESTINAL				
Appendicitis[25]	Right lower quadrant pain, anorexia, fever. More difficult to diagnose in females or those <3 years of age.	Enteric pathogens + anaerobes.	Clinical diagnosis. Imaging now standard (ultrasound if available, otherwise CT with contrast or MRI).	Ceftriaxone + metronidazole + source control. Nonoperative management only considered if symptoms <48 hr and no abscess or fecalith.
Gastroenteritis[1,26]	Typically mild disease that does not require hospitalization. Worrisome signs include: age <2 months, underlying disease, persistent vomiting, high output diarrhea (>8×/day), family reported signs of severe dehydration.	Etiologies without treatment: toxin-mediated *S. aureus*, *Bacillus cereus*, *Clostridium perfringens*; viral: norovirus, rotavirus, astrovirus, adenovirus.	If suspect inflammatory bacterial enteritis: stool culture or bacterial NAAT panel. Depending on exposures and chronicity, consider stool for ova and parasites.	Enteral rehydration is preferred to intravenous regardless of etiology.
		Nontyphoid *Salmonella* spp.		If <3 months, immunocompromised, hemoglobinopathy, or severe disease, treat with ceftriaxone x 2-5 days or azithromycin x 3 days. For invasive infection, evaluate for focal infection to guide duration of treatment.

		Shigella spp. *Campylobacter* spp. *E. coli*		If <3 months, immunocompromised, or severe disease, treat with ceftriaxone x 2-5 days, azithromycin x 3 days, or ciprofloxacin x 3 days. If severe disease, age <3 months, relapse, immunocompromised: azithromycin × 3 days or ciprofloxacin × 5 days. In most cases there is no need for antibiotics. Azithromycin × 3 days or ciprofloxacin × 3 days if severe or prolonged (>7 days); no antibiotics for STEC O157:H7, as antibiotics increase risk of hemolytic uremic syndrome.[27]
Clostridium difficile colitis[28]	Diarrhea, pseudomembranous colitis with fever and abdominal pain. Severe disease present with shock, ileus, or megacolon. Asymptomatic colonization is common through 12 months of age.		Stool *C. difficile* toxin gene NAAT. Do not test unless ≥3 unformed stools within 24 hr. Make sure patient is not receiving laxatives.	Discontinue antibiotics if possible. Nonsevere: PO metronidazole or PO vancomycin. Severe (shock, ileus, or toxic megacolon): PO vancomycin + IV metronidazole.
Giardia[1]	Intermittent cramps, watery diarrhea, anorexia. Can be asymptomatic, acute, or chronic.	Flagellate protozoan. Fecal-oral transmission of cysts. Incubation period 1–3 weeks.	Stool EIA or DFA. Stool NAAT panel if available.	Metronidazole × 5–7 days. Alternatives: nitazoxanide × 3 days or tinidazole × 1 dose.

Continued

TABLE 17.2—cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Helicobacter pylori[29]	Chronic gastritis, duodenal ulcer. Can often be asymptomatic. Warning signs include severe chronic abdominal pain, anorexia and failure to thrive, or persistent vomiting. Sequelae: iron deficiency anemia, short stature, and chronic immune thrombocytopenia.	Fecal-oral transmission. Up to 80% prevalent in resource-poor countries.	Diagnosis should aim to find the underlying cause of symptoms and not solely look for *H. pylori* infection. Diagnostic testing for *H. pylori* not recommended in children with functional abdominal pain. Gold standard: gastric biopsy with culture (also yields susceptibilities). Test of cure (stool EIA or urea breath test) 4–6 weeks after treatment.	Triple therapy: PPI + amoxicillin + clarithromycin × 14 days. Subsequent regimens should be guided by susceptibilities. If none are available, PPI + amoxicillin + metronidazole +/− bismuth × 14 days.
GENITOURINARY				
Cystitis (UTI)[30]	Dysuria, urgency, fever of unknown source. Foul smelling urine is not sensitive for UTI. Risk factors for infants less than 2 years: Nonblack Temp >39°C Uncircumcised Fever >2 days Young age (<12 mo if female, <6 mo if male)	*E. coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*. The following are not considered pathogens in healthy children: *Lactobacillus spp*, coagulase-negative staphylococci, and *Corynebacterium spp*.	Diagnosis requires pyuria (≥10 WBCs/hpf or positive leukocyte esterase) and culture of ≥50,000 colony forming units for infants and children and ≥100,000 for adolescents. In infants, bagged urine specimen can be used for screening urinalysis, and if positive, should send catheterized sample for culture and repeat urinalysis.	PO cephalexin or nitrofurantoin: 3 days (7 days if <2 years). In young (<2 years) patients with 1st time UTI: renal bladder ultrasound; VCUG if abnormal. There is controversy around the timing of VCUG. AAP guidelines support waiting until second UTI. AAP Section on urology (based on RIVUR study) supports VCUG after 1st febrile UTI.[31]

Pyelonephritis[30]	Symptoms of cystitis, plus fever or flank pain (costovertebral angle tenderness). All neonatal UTIs are considered pyelonephritis.		Diagnosis of cystitis (see above), PLUS fever, flank pain, or ill appearance.	If tolerating PO, cephalexin or cefadroxil. If not tolerating PO, cefazolin or ceftriaxone. Cefepime if history of pseudomonas or catheter-dependent. Duration: 7 days. Longer treatment up to 14 days can be considered if not improving after 3 days. Transition to oral antibiotics once clinically improving.
Sexually transmitted infections	See Chapter 5.			
OSTEOARTICULAR				
Osteomyelitis[32]	Majority in long bones: pain, limping, swelling, erythema, fever. Spinal infection in infants involving the discs: gradual irritability, refusal to crawl/sit. Spinal infection involving vertebra (more common in adolescents): back pain.	Hematogenous spread. *S. aureus* (>80% cases), GAS, *S. pneumoniae*, GBS (<3 months), *Kingella kingae (<5 years), Salmonella* spp. (if history of sickle cell disease).	Blood cultures, consider bone cultures. Inflammatory markers: CRP and ESR. Imaging: X-ray, MRI.	Consider empiric coverage based on local resistance patterns. For children <5 years: cefazolin or oxacillin ± TMP/SMX. For children >5 years: cefazolin or oxacillin or clindamycin or TMP/SMX. (Clindamycin monotherapy is ineffective for *K. kingae*. In unstable or ill-appearing, IV vancomycin. Switch to oral therapy when clinically improved. Duration 3-4 weeks for acute infection.

Continued

TABLE 17.2—cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Hardware-associated bone infection[32]	Pain, limping, swelling, erythema, fever.	Coagulase-negative *Staphylococci, S. aureus, C. acnes,* Gram-negative bacilli including *Pseudomonas* spp.	Same as osteomyelitis plus deep tissue/bone sample.	Cefepime and vancomycin; add rifampin if *S. aureus*. Prolonged duration of treatment.
Septic arthritis[1,33]	Pain, swelling of joint, inability to bear weight, gait abnormality, fever.	*S. aureus* (>80% cases). GAS, *S. pneumoniae, K. kingae* (<5 years), *Salmonella* (if history of sickle cell disease). *Borrelia burgdorferi* (Lyme disease; if subacute presentation involving large joint). *Neisseria gonorrhoeae* (adolescents with migratory arthritis).	Kocher criteria used to differentiate septic joint from transient synovitis. Designed for hips, but often applied to knee/ankle. If 3 of 4 criteria met, 93% chance of septic joint: 1. Non–weight bearing 2. Fever 3. ESR >40 mm/hr 4. WBC >12,000/mm^3 If criteria met or high-risk: Knee—X-ray Hip—ultrasound. Joint aspiration suggests septic arthritis if >50,000 WBC/mm^3. For Lyme disease: two-tier test with serology and confirmation western blot and/or PCR from joint fluid.	Early drainage relieves discomfort, prevents synovial damage. Consider empiric coverage based on local resistance patterns. For children <5 years: cefazolin or oxacillin ± TMP/SMX. For children >5 years: cefazolin or oxacillin or clindamycin or TMP/SMX. If unstable or ill-appearing, IV vancomycin. Duration 3-4 weeks for acute infection. Lyme disease is treated empirically with ceftriaxone or doxycycline. *N. gonorrhea* is treated with ceftriaxone. Should also treat for chlamydia and test for other STIs.
SKIN AND SOFT TISSUE				
Nonpurulent cellulitis/erysipelas[34]	Intact skin, erythema, warmth, swelling, tenderness, nonpurulent.	Beta-hemolytic *streptococci*. Less common *S. aureus*.	Clinical. Blood or wound culture not routinely recommended.	Cephalexin × 5 days.

Purulent cellulitis/abscess[34]	Erythema, warmth, fever, tenderness, fluctuance, induration, history of purulent drainage.	*S. aureus*	Clinical. Ultrasound can confirm drainable collection. Wound cultures for hospitalized or immunocompromised children.	Mild/moderate: I&D Add TMP/SMX if any of the following: Abscess >2 cm, extensive cellulitis, fever, hypotension, septic phlebitis, immunocompromised. Severe: I&D + vancomycin.
Animal/human bites[34]	Higher risk injury with puncture wounds.	Often polymicrobial: *S. aureus,* Streptococci, *Pasteurella multocida* (animal), *Capnocytophaga* spp., oral anaerobes, *Eikenella corrodens* (human).	Clinical: puncture vs. nonpuncture.	Antibiotic prophylaxis is indicated if moderate/severe wound especially of hand or face, immunocompromise, possible penetration of periosteum or joint capsule, or edema of the area. Prophylaxis: amoxicillin/clavulanate x 5 days. See Chapter 2 for additional management. See Chapter 16 for post-exposure prophylaxis recommendations for tetanus and rabies.

Continued

TABLE 17.2—Cont'd

PEDIATRIC INFECTIONS BY SYSTEM

	Presentation	Etiology	Diagnosis	Treatment
Dermatophyte (tinea) infections[1]	Tinea capitis - Multiple scaly patches with alopecia and patches of alopecia with black dots at follicular orifices that represent broken hairs. May also present with widespread scaling, kerion, or favus. Tinea pedis (athlete's foot) - Interdigital hyperkeratotic or vesiculobullous eruption. Tinea cruris (jock itch) - Involving the inguinal fold. Tinea corporis - Dermatophyte infection occurring in sites other than feet, groin, face, or hand.	Dermatophytes	Tinea capitis, pedis, cruris, corporis: Clinical. Can confirm with skin scrapings in 10% potassium hydroxide (KOH).	Tinea capitis: Oral griseofulvin or terbinafine × 4–8 weeks or 2 weeks after clinical resolution. Fungal shedding decreased with selenium sulfide or ketoconazole shampoo. Tinea pedis, cruris, corporis: Topical antifungal. Tinea pedis: 2–4 weeks. Tinea cruris: 4–6 weeks. Tinea corporis: 4 weeks.
	Tinea unguium (onychomycosis) - White or yellow discoloration of finger- or toe-nail, often with thickening, splitting, or deformity.		Tinea unguium: Confirm with nail clippings in 10% KOH or culture.	Topical ciclopirox 8% once daily for 4–8 weeks preferred (no lab monitoring). Alternative: oral terbinafine 6 weeks if fingernail; 12 weeks if toenail.
BLOODSTREAM				
Catheter-related bloodstream infections[35]	Fever, erythema around catheter site; pain with infusion.	*S. aureus*, Gram-negative bacilli, Coagulase-negative *Staphylococci* (usually requires two positive cultures to exclude contaminant), *Enterococcus* species.	Two sets of cultures (one peripheral, one from suspected catheter) prior to antibiotics. If unable to draw peripheral culture, draw two sets from same line several minutes apart.	Vancomycin and cefepime. Remove line whenever possible.

Malaria[1]	Paroxysmal fevers and malaise. Severe malaria: 5+% parasitemia, CNS involvement, shock, hypoglycemia, anemia, thrombocytopenia, acidosis.	*Plasmodium falciparum, vivax, ovale.* *P. vivax* and *ovale* form hypnozoites in liver, difficult to eradicate. Incubation period 7 days to months.	Thick and thin blood smears. If high suspicion with negative smears, repeat every 12–24 hr for 72 hr. Rapid antigen detection tests exist. Speciation is performed by microscopy, with confirmation by PCR in specialized labs.	Severe: IV artesunate complemented by either artemether-lumefantrine, clindamycin, or doxycycline. Non-severe (chloroquine-resistant or unknown resistance): artemether-lumefantrine x 3 days. Alternative: quinine + (clindamycin or doxycycline). Non-severe (chloroquine-sensitive): chloroquine or hydroxychloroquine. *P. vivax* or *ovale*: add primaquine × 14 days. Travel prophylaxis varies by region due to chloroquine resistance. See CDC Yellow Book for resistance info and specific regimens.
Other				
Fever of unknown origin[36]	Defined as temperature greater than 38.3 for at least 2 weeks. Often an uncommon presentation of a common disease.	Localized or systemic infections are most commonly identified etiology.	No specific guidelines exist; stepwise approach is recommended.	Consider discontinuing all nonessential medications to aid in diagnosis.

Continued

TABLE 17.2—Cont'd

PEDIATRIC INFECTIONS BY SYSTEM

Presentation	Etiology	Diagnosis	Treatment
	Other etiologies include: rheumatologic, neoplastic, collagen vascular disease (e.g., juvenile idiopathic arthritis), drug fever, and Kawasaki disease.	First line: blood count, peripheral smear, renal/hepatic function tests, lactate dehydrogenase, inflammatory markers, blood cultures, urinalysis, chest x-ray. Second line: TB testing, CMV, EBV, echocardiogram. Third line: abdominal/pelvis CT, ANA, C3/C4, HIV, thyroid studies.	Treatment depends on etiology identified.

AAP, American Academy of Pediatrics; *ANA*, antinuclear antibody; *AOM*, acute otitis media; *AUA*, American Urologic Association; *CBC*, complete blood count; *CDC*, Centers for Disease Control; *CMV*, cytomegalovirus; *CN*, cranial nerve; *CNS*, central nervous system; *CRP*, C-reactive protein; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *DFA*, direct fluorescent antibody; *EBV*, Epstein-Barr virus; *EIA*, enzyme immunoassay; *ENT*, ear-nose-throat physician (otolaryngologist), *ESR*, erythrocyte sedimentation rate; *FNA*, fine needle aspiration; *GBS*, group B streptococcus; *HIV*, human immunodeficiency virus; *hpf*, high-power field; *ICU*, intensive care unit; *I&D*, incision and drainage; *IDSA*, Infectious Disease Society of America; *IM*, intramuscular; *IV*, intravenous; *LP*, lumbar puncture; *MRI*, magnetic resonance imaging; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *NAAT*, nucleic acid amplification test; *PCN*, penicillin; *PCR*, polymerase chain reaction; *PO*, by mouth; *RIVUR*, randomized intervention for children with vesicoureteral reflux; *STEC*, Shiga toxin–producing *Escherichia coli*; *T*, temperature; *TB*, tuberculosis; *TMP*, trimethoprim; *TMP/SMX*, trimethoprim sulfamethoxazole; *URI*, upper respiratory infection; *UTI*, urinary tract infection; *VCUG*, voiding cystourethrography; *VP*, ventriculoperitoneal, *WBC*, white blood cell.

TABLE 17.3

PEDIATRIC VIRAL ILLNESSES

	Presentation	Transmission and Incubation	Diagnosis	Treatment
Cytomegalovirus (CMV)[1]	Infectious mononucleosis-like syndrome with fever and hepatitis. Immunocompromised: pneumonia, retinitis, colitis, leukopenia, thrombocytopenia. See Table 17.1 for congenital CMV.	Primary infection from respiratory droplets or vertical transmission. Persists after primary infection with intermittent shedding.	PCR for CMV DNA, histopathology for definitive diagnosis of tissue invasive disease. Gold standard is CMV culture in affected organ system. Quantitative CMV DNA and pp65 antigen are used in immunocompromised, and to monitor response to treatment. IgG to screen for risk of reactivation (e.g., organ transplant donors and recipients).	Ganciclovir or valganciclovir for disseminated or organ-specific CMV (typically immunosuppressed), serodiscordant transplant recipients, and CMV retinitis. Alternative antiviral: foscarnet (nephrotoxic).
Dengue[1]	Febrile phase (2–7 days) with myalgias, arthralgias, retro-orbital headache. Critical phase (24–48 hr) follows defervescence with increased vascular permeability. Convalescent phase with gradual improvement. Severe dengue (hemorrhagic fever): severe abdominal pain, bleeding, shock.	Four virus subtypes; severe dengue more common with second or subsequent infections. Transmitted by *Aedes* mosquitoes. Incubation period 3–14 days.	RT-PCR or anti-dengue virus IgM EIA.	Supportive. Avoid NSAIDs (bleeding risk).

Continued

TABLE 17.3—cont'd

PEDIATRIC VIRAL ILLNESSES

	Presentation	Transmission and Incubation	Diagnosis	Treatment
Epstein-Barr virus (EBV)[1]	Infectious mononucleosis: fever, pharyngitis with petechiae or exudates, hepatosplenomegaly, atypical lymphocytosis. Variable presentation in young children. Associated with post-transplant lymphoproliferative disease, Burkitt lymphoma, nasopharyngeal carcinoma, and other malignancies.	Transmitted via oral secretions or sexual contact. Incubation period 30–50 days.	Heterophile antibody positive by 2 weeks postexposure; though low sensitivity in children under 4 years. IgM/IgG to viral capsid antigen if heterophile negative and suspicion high. See Fig. 17.3.	Supportive. No strenuous activity or contact sports × 21 days, or until symptoms and splenomegaly resolve. Steroids if tonsillar swelling threatens airway, massive splenomegaly, myocarditis, hemolytic anemia, or HLH.
Human immunodeficiency virus (HIV)	See Section 17.I.F.			
Influenza[1]	Often abrupt onset of systemic symptoms (fever, myalgias, chills, headache, malaise, anorexia) with URI, croup, bronchiolitis, pneumonia. Complications include AOM, secondary bacterial pneumonia (especially *Staphylococcus aureus* and *Streptococcus pneumoniae*); rarely myositis, myocarditis, or CNS complications, including encephalitis, myelitis, Guillain-Barre syndrome.	Incubation 1–4 days.	Clinical diagnosis; lab confirmation not required for treatment. Multiple rapid antigen and PCR tests exist.	Oseltamivir for 5 days. Alternatives include inhaled zanamivir, IV peramivir, and PO baloxavir. Most effective within 48 hr of onset of symptoms. Treat all patients who are hospitalized, have severe illness, or are at high risk for complications. Consider treating patients who could transmit to elderly or unvaccinated contacts. Counsel families on influenza vaccination. Recommendations change yearly. See http://www.cdc.gov/flu.

Measles[1]	Fever, cough, coryza, conjunctivitis, Koplik spots, descending maculopapular rash. At risk for acute encephalitis and subacute sclerosing panencephalitis.	Droplet and airborne precautions. Incubation period 8–12 days.	RT-PCR from throat swab or urine or serum IgM.	Supportive. Counsel families on measles vaccination. Vitamin A reduces morbidity and mortality.
Mumps[1]	Swelling of 1+ salivary glands, often parotid. Orchitis more common after puberty.	Droplet precautions until 5 days after onset of parotid swelling. Incubation period 12–25 days.	RT-PCR from buccal swab or serum IgM.	Supportive.
Parvovirus B19 (Fifth disease)[1]	Mild viral syndrome followed by slapped cheek rash with circumoral pallor. Symmetric, macular, reticular rash on trunk, spreads peripherally. Polyarthropathy. Transient aplastic crisis. Can cause chronic infection and anemia in immunocompromised.	Droplet precautions. Incubation period 4–14 days.	Serum IgM. PCR required if immunocompromised.	Supportive. RBC transfusion in aplastic crisis. IVIG used in chronic infections of immunodeficient patients.
Rubella[1]	Descending, erythematous, maculopapular rash. See Table 17.1 for congenital rubella.	Droplet precautions until 7 days after onset of the rash. Incubation period 14–21 days.	Serum IgM.	Supportive.
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2)	Most children with SARS-CoV-2 may be asymptomatic or with mild to moderate symptoms including fever, cough and pharyngeal erythema. Less often GI symptoms.[48] In contrast with infected adults, most infected children appear to have a milder clinical course, although infants may have more severe disease.[49]	Respiratory transmission, likely droplet. Shedding can start 1-2 days prior to symptoms and continue >2 weeks. Incubation period: 5 days (2-14). Virus detected in stool with implications for fecal-oral transmission.[50] Perinatal transmission has not been reported.	Nasopharyngeal swab for PCR per CDC criteria.[51] Serological tests are being developed. Although imaging is often not performed, CT shows patchy peripheral ground glass opacities.[52,53]	Supportive care. No current FDA-approved directed therapies. Therapeutics being considered: remdesivir, lopinavir/ritonavir, hydroxychloroquine, nitazoxamine, tocilizumab, and others.

Continued

TABLE 17.3—cont'd

PEDIATRIC VIRAL ILLNESSES

	Presentation	Transmission and Incubation	Diagnosis	Treatment
Varicella zoster virus (VZV)[1]	Primary varicella (chickenpox): pruritic macules that progress to vesicles, plus fever and malaise. Herpes zoster: painful, vesicular, dermatomal rash. See Table 17.1 for congenital VZV.	Airborne spread or direct contact. Incubation period 10–21 days. Reactivation of latent VZV from sensory ganglia.	Clinical. PCR of vesicular fluid.	Supportive care if healthy host. Treat with acyclovir/valacyclovir if chronic skin or lung disease, unvaccinated and 12+ years old, or immunocompromised. Acyclovir/valacyclovir reduce duration and risk of postherpetic neuralgia.

DNA, Deoxyribonucleic acid; *EIA*, enzyme immunoassay; *HLH*, hemophagocytic lymphohistiocytosis; *Ig*, immunoglobulin; *IVIG*, intravenous immunoglobulin; *NSAIDs*, nonsteroidal antiinflammatory drugs; *RBC*, red blood cell; *RT-PCR*, reverse-transcriptase polymerase chain reaction.

TABLE 17.4

PEDIATRIC TICK-BORNE DISEASES

	Presentation	Etiology	Diagnosis	Treatment
Lyme disease[1]	Early localized: <1 month after tick bite. Erythema migrans. Early disseminated: 3–10 weeks after bite. Secondary erythema migrans with multiple smaller target lesions, cranioneuropathy (especially facial nerve palsy), systemic symptoms, rarely carditis with heart block or aseptic meningitis. Late disease: 2–12 months after bite. Pauciarticular arthritis of large joints, peripheral neuropathy, encephalopathy.	Spirochete *Borrelia burgdorferi* (*B. afzelii* and *B. garinii* in Europe and Asia). Requires 24–48 hr of tick attachment. Incubation 3–32 days (median 11 days). Most common in New England and Mid-Atlantic. Less common in Upper Midwest and Northwest.	Early: Clinical. No testing indicated. Early disseminated and late disease: EIA or IFA for antibodies. If positive, Western blot to confirm. IgM detectable for first 30 days. IgG detectable by week 4–6. False positives occur with viral infections, other spirochetes, and autoimmune disease. Perform LP as clinically indicated for CNS involvement.	Early localized: amoxicillin (14 days) or cefuroxime (14 days) or doxycycline (10 days). Early disseminated: any of above x 14 days. Late disease: any of above x 28 days. Doxycycline relatively contraindicated in children < 8 years. If cranioneuropathy, doxycycline preferred (any age). For meningitis, use ceftriaxone. In high-risk areas, can consider one-time dose of prophylactic doxycycline following removal of engorged tick for children > 8 years.
Rocky Mountain spotted fever[1]	Rash initially erythematous and macular, progresses to maculopapular and petechial. Classically spreads proximally from ankles and wrists, with involvement of palms and soles.	*Rickettsia rickettsii.* Incubation 3–12 days. Widespread; most common in South Atlantic, Southeastern, and South Central United States.	Clinical, with lab confirmation. Gold standard is indirect fluorescent antibody; IgG and IgM increase around 7–10 days. Serum PCR if available. Negative result (PCR or antibody testing) does not rule out the diagnosis.	Doxycycline recommended for children of any age. Should be started as soon as the diagnosis is suspected. Duration: continue until patient is afebrile for ≥3 days, with clinical improvement.

Continued

TABLE 17.4—cont'd

PEDIATRIC TICK-BORNE DISEASES

	Presentation	Etiology	Diagnosis	Treatment
Ehrlichiosis[1]	Systemic febrile illness. More severe disease: pulmonary infiltrates, bone marrow hypoplasia, respiratory failure, encephalopathy, meningitis, DIC, spontaneous hemorrhage, and renal failure.	*Ehrlichia chaffeensis* and *Ehrlichia ewingii*. Incubation period 5–14 days. Southeastern, South Central, East Coast, and Midwestern United States.	Identification of DNA by PCR from whole blood is highly sensitive and specific. Isolation in culture must be done at CDC specialty labs from samples prior to initiation of antibiotics.	Doxycycline for at least 3 days after defervescence, for a minimum total course of 7 days.
Anaplasmosis[1]	Same as *Ehrlichia*.	*Anaplasma phagocytophilum*. Incubation 5–21 days. Upper Midwest and Northeastern United States, Northern California.	Same as *Ehrlichia*.	Same as *Ehrlichia*.

CDC, Centers for Disease Control and Prevention; *CNS*, central nervous system; *DIC*, disseminated intravascular coagulation; *DNA*, deoxyribonucleic acid; *EIA*, enzyme immunoassay; *Hr*, hour; *IFA*, immunofluorescent assay; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *LP*, lumbar puncture; *PCN*, penicillin; *PCR*, polymerase chain reaction.

TABLE 17.5

INTERPRETATION OF THE SEROLOGIC MARKERS OF HEPATITIS B IN COMMON SITUATIONS

Serologic Marker				
HB*s*Ag	**Total HB*c*Ab**	**IgM HB*c*Ab**	**HB*s*Ab**	**Interpretation**
–	–	–	–	No prior infection, not immune.
–	–	–	+	Immune after hepatitis B vaccination (if concentration ≥10 IU/mL) or passive immunization from HBIG administration.
–	+	–	+	Immune after recovery from HBV infection.
+	+	+	–	Acute HBV infection.
+	+	–	–	Chronic HBV infection.

HBsAg, Hepatitis B surface antigen; *HBcAb*, antibody to hepatitis B core antigen; *HBsAb*, antibody to hepatitis B surface antigen; *HBIG*, hepatitis B immune globulin; *HBV*, hepatitis B virus; *IgM*, immunoglobulin M.
From Davis AR, Rosenthal P. Hepatitis B in Children. *Pediatr Rev.* 2008;29(4);111–120.

TABLE 17.6

CEREBROSPINAL FLUID ANALYSIS IN SUSPECTED MENINGTITIS

	Bacterial meningitis	**Viral meningitis**	**No CNS infection**
WBC (cells/mm^3)	>10; typically >100, but wide range	10–100	<10
Cell type	PMN predominance (80+%)	Mononuclear	Mononuclear
Protein (mg/dL)	>100	60–100	<60
Glucose (mg/dL)	<40	40–80	40–80

CNS, Central nervous system; *PMN*, polymorphonuclear neutrophil; *WBC*, white blood cell.
Adapted from Tunkel 2004. Analysis of cerebrospinal fluid is necessary to differentiate various types of meningitis. Initial studies such as cell counts and gram stain can be helpful, but culture of cerebrospinal fluid remains diagnostic. Opening pressure is generally in the range of 200 to 500 mm H_2O, although values may be lower in neonates, infants, and children with acute bacterial meningitis.

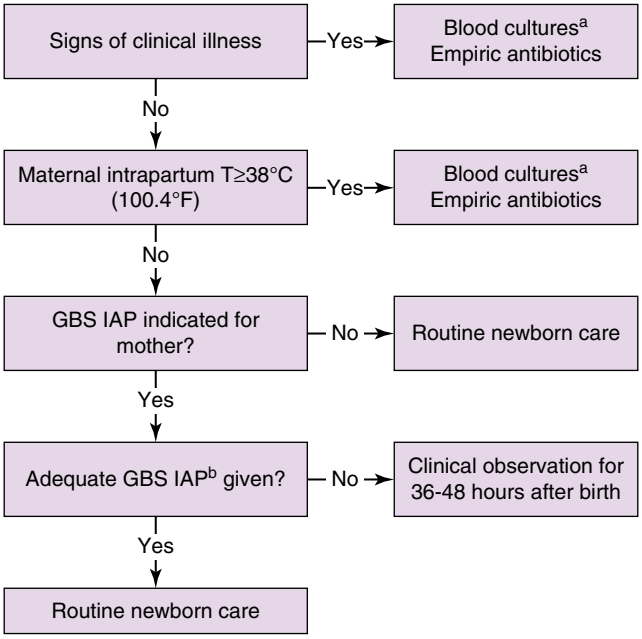
2. Treatment of latent TB infection (Cont'd from pg. 408)
   a. Rule out active TB.
   b. Treatment regimens
      (1) 12 weeks of weekly isoniazid and rifapentine if above 2 years.
      (2) 9 months of isoniazid daily.
      (3) Rifampin daily for 4 months (preferred regimen if isoniazid-resistant).
   c. If young (<4 years) or immunocompromised, treat recent contacts of people with active TB, even if testing (TST/IGRA) is negative. Some experts would discontinue treatment if repeat testing is negative at 8-12 weeks.
3. Treatment of active TB
   a. High rates of resistance in endemic countries. Treatment should be initiated in consultation with an infectious disease specialist.

b. Pulmonary TB: 6-month regimen, including 2 months RIPE (rifampin, isoniazid, pyrazinamide, ethambutol), followed by 4 months of rifampin/isoniazid.
c. Extra-pulmonary or drug-resistant TB: Consult infectious disease specialist.
d. Pyridoxine supplementation if breastfed, meat-/milk-deficient diet, symptomatic HIV, or pregnant.

F. Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Please see the National Institutes of Health (NIH) guidelines on the diagnosis and management of children with HIV infection at www.aidsinfo.nih.gov/ for the most up-to-date recommendations.

1. Diagnosis
   a. Perinatal: See Table 17.8 for diagnosis in perinatal period.[37]
   b. Infants and children[38]: HIV nucleic acid testing must be used under 18 months to avoid confounding from maternal antibodies. Antigen/antibody testing can be performed after 18 months. If concern for breastmilk exposure, test immediately, then at 4 to 6 weeks, 3 months, and 6 months after stopping breastfeeding.
   c. Adolescents[39]: HIV screening with fourth-generation antigen/antibody assay with opt-out consent as part of routine clinical care. If positive, confirm with HIV-1/HIV-2 immunoassay; if indeterminate, HIV-1 nucleic acid testing.
2. Management[37–40]
   a. See Table 17.7 for management during perinatal period.
   b. Initiation of therapy for all children with HIV is recommended by the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents and the World Health Organization (WHO).
   c. Therapy: Combination antiretroviral therapy (ART) of at least three drugs from at least two different classes. Go to http://www.aidsinfo.nih.gov/ for most current therapy recommendations.
3. Monitoring[38]
   a. At diagnosis: CD4 count, plasma HIV RNA viral load, genotype resistance. If starting therapy, HLA-B*5701 (screening for hypersensitivity to abacavir) and hepatitis B serology.
   b. Follow-up not on ART: Every 3 to 4 months, CD4 count, plasma HIV RNA viral load, CBC with differential, complete metabolic panel with glucose, renal function, albumin, transaminases, lipid panel. Every 6 to 12 months, obtain urinalysis to evaluate for nephropathy.
   c. Follow-up on ART: At 2 to 4 weeks after initiation or switching therapy, CD4, viral load, and labs according to possible toxicities of ART. Then similar testing as above every 3 to 4 months.
   d. Once viral suppression achieved, CD4 improved, good adherence, and otherwise stable for 2 to 3 years, can space labs to every 6 to 12 months.
   e. Latent TB skin testing starting at age 3 to 12 months, and then annually.



[a] Consider lumbar puncture and CSF culture before initiation of empiric antibiotics for infants who are at the highest risk of infection, especially those with critical illness. Lumbar puncture should not be performed if the infant's clinical condition would be compromised, and antibiotics should be administered promptly and not deferred because of procedure delays.

[b] Adequate GBS IAP is defined as the administration of penicillin G, ampicillin, or cefazolin ≥4 hours before delivery.

FIGURE 17.1

Example of categorical risk factor assessment for infants ≥35 weeks gestation. The risk of infection is highly variable among the newborn infants depending on the gestational age, duration of ROM, and timing and content of administered intrapartum antibiotics. This approach likely results in empirical treatment of many relatively low-risk infants. Newer, multivariate approaches are available online. (From Puopolo KM, Lynfield R, Cummings JJ, COMMITTEE ON INFECTIOUS DISEASES. Management of Infants at Risk for Group B Streptococcal Disease. *Pediatrics*. 2019 Aug 1;144(2):e20191881)

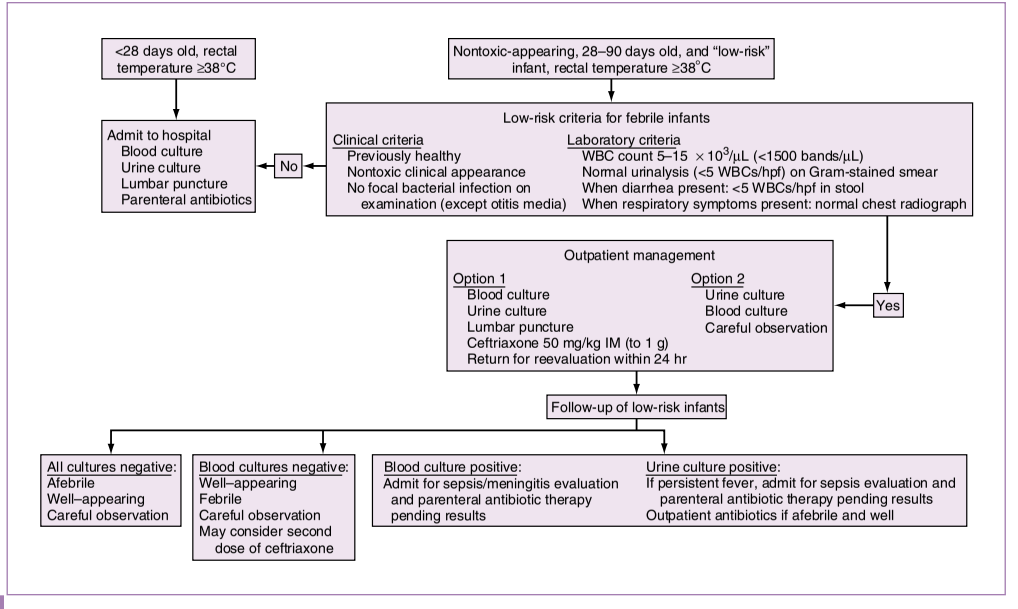


FIGURE 17.2

Algorithm for management of a previously healthy infant aged ≤90 days with a fever without localizing signs. This algorithm is a suggested but not exhaustive approach. *hpf*, High-power field. (Modified from Baraff LJ. Management of fever without source in infants and children. *Ann Emerg Med.* 2000;36:602–614; and Baraff LJ. Management of infants and young children with fever without source. *Pediatr Ann.* 2008;37:673–679.)

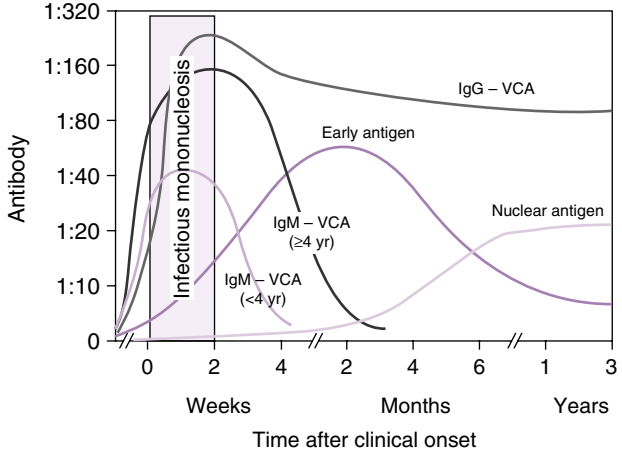


FIGURE 17.3

Graphic representation of the development of antibodies to Epstein–Barr virus antigens as a function of time from infection. Antibody titers are calculated as geometric mean values expressed as reciprocals of the serum dilution. The immunoglobulin M *(IgM)* response to viral capsid antigen *(VCA)* varies according to age of the patient. *IgG*, Immunoglobulin G. (From Jenson HB. Epstein-Barr Virus. In: Kliegman RE, Stanton B, St Geme J, et al., eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016.)

BOX 17.1

TUBERCULOSIS SCREENING GUIDELINES[1,41]

The American Academy of Pediatrics recommends treatment for at-risk individuals. Clinicians should complete at-risk assessment questionnaire at first well-child visit, then every 6 months in 1st year of life, and then routine care (at least annually). Screening questions include:

- Born outside the United States in countries with endemic infection
- Traveled outside United States in countries with endemic infection
- Family member with positive tuberculin skin test (TST)
- Exposed to someone who had tuberculosis disease
- Special populations including children with HIV, organ transplant, and those on immunosuppressive therapies including tumor necrosis factor blockers/antagonists

f. Vaccines[1] (see Chapter 16 and Red Book for details):
   (1) Meningococcal conjugate ACWY (can start at 2 months; 2 or 4 doses depending on age).
   (2) 23-valent polysaccharide pneumococcal vaccine at 2 years.
   (3) MMR can be given if CD4 >15% (any age) and CD4 count > 200 lymphocytes/mm^3 (if >5 years).
   (4) Some experts would consider monovalent varicella vaccine for children >12 months with CD4 >15%. Combined MMRV should not be given.

BOX 17.2

DEFINITIONS OF POSITIVE TUBERCULIN SKIN TESTING[1]

Induration ≥5 mm

- Children in close contact with known or suspected contagious cases of tuberculosis
- Children suspected to have tuberculosis based on clinical or radiographic findings
- Children on immunosuppressive therapy or with immunosuppressive conditions (including HIV infection)

Induration ≥10 mm

- Children at increased risk for dissemination based on young age (<4 years) or with other medical conditions (cancer, diabetes mellitus, chronic renal failure, or malnutrition)
- Children with increased exposure: Those born in or whose parents were born in endemic countries; those with travel to endemic countries; those exposed to HIV-infected adults, homeless persons, illicit drug users, nursing home residents, or incarcerated or institutionalized persons

Induration ≥15 mm

- Children ≥4 years without any risk factors

A tuberculin skin testing **(TST)** should be read in 48 to 72 hours. The measles vaccine can suppress TST reactivity for 4 to 6 weeks. An **interferon gamma release assay (IGRA)** can be used instead of TST in children older than 2 years. It has a higher specificity than TST because antigens used are not found in Bacillus Calmette-Guérin (BCG) vaccine or most pathogenic nontuberculous mycobacteria.

4. Pre-exposure prophylaxis (PrEP)[7]
   a. Common indications
      (1) Men who have sex with men: HIV-positive partner, bacterial STI (gonorrhea, chlamydia, syphilis) in past 6 months, history of inconsistent or condomless anal intercourse with an unknown status or nonmonogamous partner, commercial (or exchange) sex, history of high number of sex partners
      (2) Heterosexual men and women: HIV-positive partner, bacterial STI (gonorrhea, syphilis) in past 6 months, history of inconsistent condom use, commercial (or exchange) sex, history of high number of sex partners, living in a high HIV prevalence setting.
   b. Initiating
      (1) Labs: fourth generation HIV test, syphilis, gonorrhea, chlamydia, HBV, HCV (if ever used IV drugs), and renal function. Pregnancy test if indicated. Counsel on condom use.
      (2) Use emtricitabine/tenofovir alafenamide (Descovy) for biological males. Effective only after 7 days. Emtricitabine/tenofovir disoproxil (Truvada) for biological females. Effective only after 21 days. Consult infectious disease expert for initiation of PrEP unless provider has extensive experience.

TABLE 17.7

DIAGNOSIS AND MANAGEMENT FOR INFANTS WITH *IN UTERO* HIV EXPOSURE

Age	Laboratory Tests[a]	Next Steps
Prenatal/Labor	Opt-out testing of all pregnant women. HIV antibody testing in third trimester, before 36 weeks gestation preferred. Rapid HIV testing with confirmation if unknown HIV status during labor.	Start ART in mother. If viral load RNA >1000 copies/mL or unknown at labor, start IV zidovudine (ZDV) and consider cesarean section if greater than 38 weeks gestation.
Newborn	HIV nucleic acid test (DNA or RNA) if maternal status unknown, or high risk of infection. Baseline CBC with differential.	Start ZDV within 6–12 hr of delivery. If low-risk, continue ZDV for 4 weeks. If maternal viral load detectable and <1000 copies/mL near delivery, give nevirapine x 3 doses (within 48hr of birth, 48hr after first dose, 96hr after second dose). Continue zidovudine for 6 weeks. Some experts add lamivudine for 1 week. If mother did not receive antepartum ART or has acute/primary HIV in the 3rd trimester or has viral load >1000 copies/mL near delivery, start empiric ART with zidovudine, lamivudine, and either nevirapine or raltegravir.
2–3 weeks	HIV nucleic acid test (DNA or RNA). CBC with differential.	Check ZDV dosing and administration. Assess psychosocial needs, consider case management referral.
4–6 weeks	HIV nucleic acid test (DNA or RNA). CBC with differential.	Discontinue ZDV monotherapy regardless of PCR result (ZDV monotherapy is used during first 6 weeks for prophylaxis only). If positive, start ART according to guidelines. Presumptively exclude HIV infection if results of ≥2 weeks PCR and ≥4 weeks PCR both negative. No TMP-SMX needed. If PCR results not yet known, begin *Pneumocystis jirovecii* pneumonia prophylaxis, such as TMP-SMX.
2 months		Discontinue TMP-SMX if DNA or RNA testing negative.
4–6 months	HIV nucleic acid test (DNA or RNA).	Definitively exclude HIV infection: two negative PCRs at ≥1 month and ≥4 months, as long as no signs/symptoms of HIV infection.
18–24 months	Antibody testing may be performed to confirm clearance of maternal HIV antibodies. If present, need to use nucleic acid testing.	

[a]Any abnormal result requires prompt pediatric HIV specialist consultation.

ART, Antiretroviral therapy; *CBC*, complete blood cell count; *DNA*, deoxyribonucleic acid; *HIV*, human immunodeficiency virus; *IV*, intravenous; *PCR*, polymerase chain reaction; *RNA*, ribonucleic acid; *TMP-SMX*, trimethoprim–sulfamethoxazole; *ZDV*, zidovudine.

Modified from Department of Health and Human Services guidelines for pediatric and perinatal HIV infection (see www.aidsinfo.nih.gov for more detailed information). National Perinatal HIV Hotline: 1-888-448-8765.

(3) Descovy and Truvada are FDA-approved for adolescents > 35kg. Descovy is not approved to prevent transmission via vaginal sex.

c. Follow-up

(1) Every 3 months: HIV test and syphilis/gonorrhea/chlamydia if patient is symptomatic, engaging in anal intercourse, has prior history of STIs, or has multiple partners. Counsel on condom use at every visit.

(2) Every 6 months: Same as above, plus routine STI screening (including oral and/or anal testing, if applicable) and renal function.

5. Post-exposure prophylaxis (PEP)[42,43]

a. Indications for occupational PEP: Consider with percutaneous, mucosal, or skin exposure to blood or bodily fluids from a patient with known HIV or in whom there is high suspicion. See Section IV. for further non-HIV details.

b. Indications for nonoccupational (nPEP): Unprotected vaginal/anal intercourse, oral sex with ejaculation or blood exposure, needle sharing, or injuries with blood exposure from an individual with known HIV or unknown status.

c. Labs: 4th-generation HIV test, HBV surface antigen and antibody, HCV antibody. Depending on exposure, consider tetanus prophylaxis and STI testing.

d. Regimen: Initiate as soon as possible (lower likelihood of efficacy at greater than 72 hours); three-drug (or more) ART regimen for 28 days. Regimen: tenofovir and emtricitabine with raltegravir. For nPEP, dolutegravir may be used instead of raltegravir. Consult infectious disease expert for any initiation of PEP.

e. Follow-up testing can occur at 6 weeks, 12 weeks, and 6 months; for occupational exposures, if 4th-generation testing available, follow-up testing can be done at 6 weeks and 4 months.

f. Clinicians' PEP Line: 1-888-448-4911.

II. MICROBIOLOGY

A. Collection of Specimens for Blood Culture

1. Preparation: To minimize contamination, clean venipuncture site with 70% isopropyl ethyl alcohol. Apply tincture of iodine or 10% povidone-iodine and allow skin to dry for at least 1 minute, or scrub site with 2% chlorhexidine for 30 seconds and allow skin to dry for 30 seconds. Clean blood culture bottle injection site with alcohol only.
2. Collection: Two sets of cultures from two different sites of equal blood volume should be obtained for each febrile episode, based on patient weight: less than 8 kg, 1 to 3 mL; 8 to 13 kg, 4 to 5 mL; 14 to 25 kg, 5 to 6 mL; greater than 25 kg, 10 mL. Peripheral sites preferred. If concern for central line infection, collect one from central access site, second from peripheral. Consider anaerobe blood cultures if concern for the following: head and neck infections, intra-abdominal infections, immunodeficiency, trauma or pressure sore.[44,45]

B. Rapid Microbiologic Identification of Common Aerobic Bacteria (Fig. 17.4) and Anaerobic Bacteria (Fig. 17.5)

Note: Molecular assays for identification of bacteria and antibiotic resistance are increasingly available.

III. SPECTRA OF ACTIVITY FOR COMMONLY USED ANTIBIOTICS (FIG. 17.6)

IV. EXPOSURES TO BLOOD BORNE PATHOGENS AND PROPHYLAXIS

A. General Practice[46]

1. Regardless of status of patient, if you experience a needlestick or splash exposure, immediately wash with soap/water, irrigate, report to supervisor, and seek medical assistance.
2. There is an increased risk of transmission with larger volume of blood, prolonged exposure, high viral titer, deep injury, or if patient has advanced disease.
3. Source should be tested for HIV, hepatitis C antibody, and hepatitis B surface antigen. Exposed person should be tested for HIV, hepatitis C antibody, hepatitis B surface antibody, and hepatitis B surface antigen.

B. Disease-Specific Post-Exposure Management

1. Hepatitis B[47]: High risk of transmission if surface antigen and e-antigen positive. Lower risk of transmission if surface antigen positive, e-antigen negative. Post-exposure management includes hepatitis B immune globulin and initiation of hepatitis B vaccine series, depending on immune status. For details, see Chapter 16.
2. Hepatitis C[47]: Lower risk of transmission. No preventative therapy is currently recommended, but this is an evolving field. Follow-up testing essential.
3. See Section I.F for information on post-exposure management for HIV.

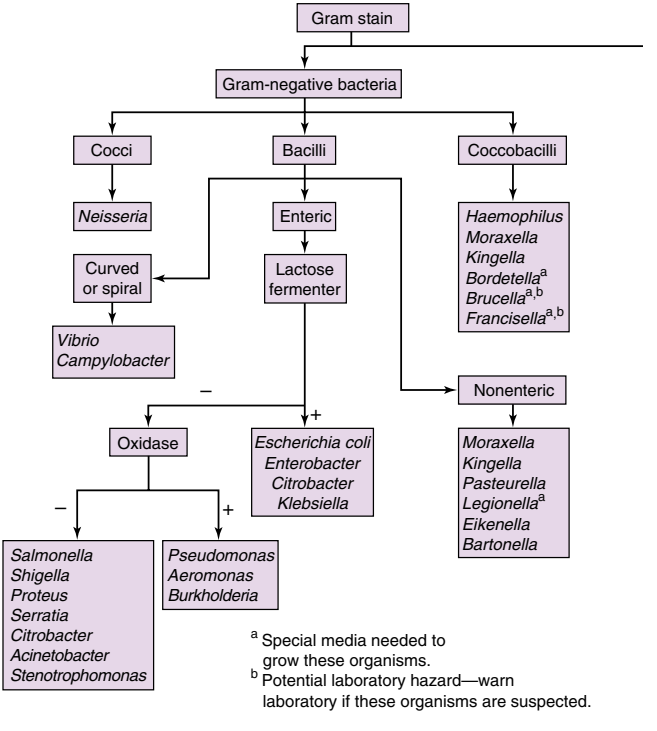
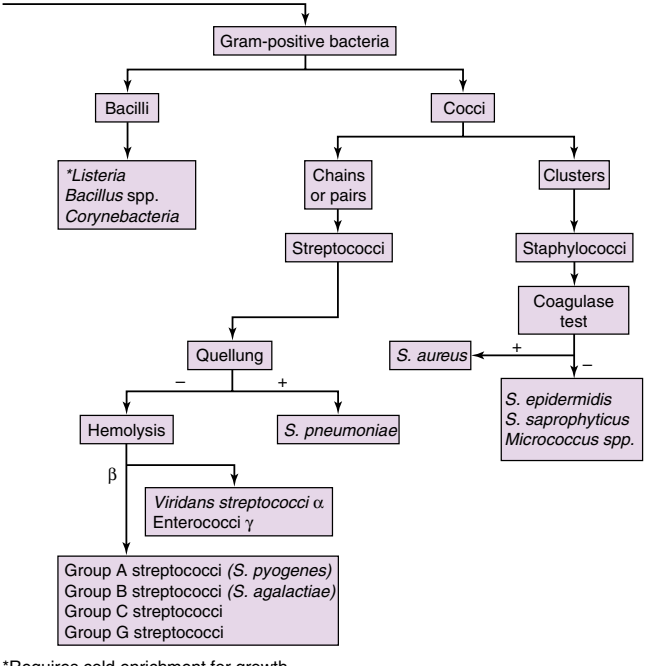


FIGURE 17.4
Algorithm demonstrating identification of aerobic bacteria.



*Requires cold enrichment for growth.

FIGURE 17.4, cont'd

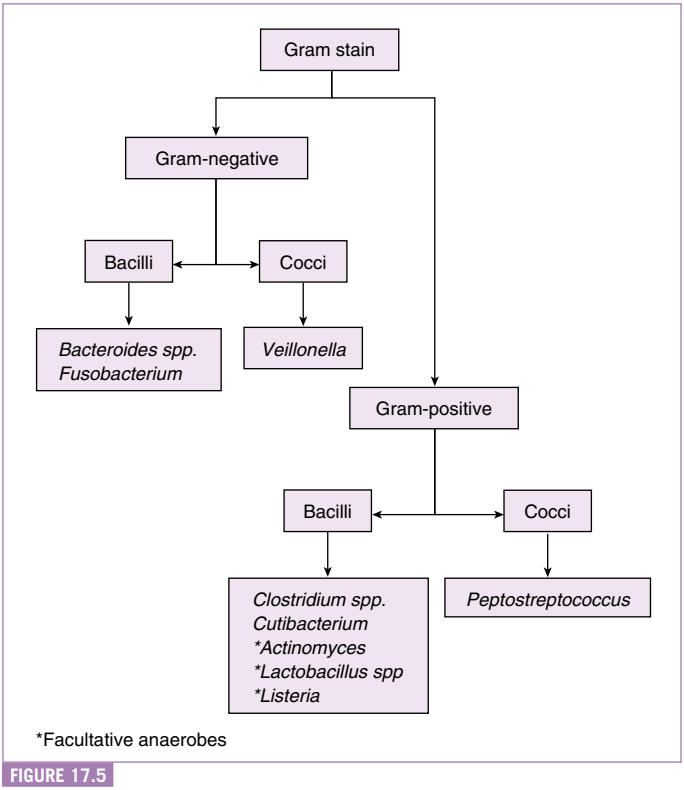


FIGURE 17.5
Algorithm demonstrating identification of anaerobic bacteria.

FIGURE 17.6

Approximation for the spectrum of activity for commonly used antibiotics and common pediatric infections. Exact sensitivities will change with different local resistance patterns. For antibiotic recommendations for specific infections, refer to relevant part of Section I.

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Chapter 18

Neonatology

Niana Carter, MD and Bethany Sharpless Chalk, PharmD

See additional content on Expert Consult

I. NEWBORN RESUSCITATION

A. Algorithm for Neonatal Resuscitation (Fig. 18.1)

1. Essential functional equipment: Radiant warmer, prewarmed blankets, hat, bag-mask/NeoPIP ventilator, appropriately sized laryngoscope, appropriately sized endotracheal tube (ETT) +/–stylet, suction device and bulb syringe, emergency medications, and vascular access supplies.
2. Meconium stained fluids: Per Neonatal Resuscitation Program (NRP) 7th edition, routine intrapartum oropharyngeal/nasopharyngeal suctioning and endotracheal intubation are not recommended.[2]
3. Cord clamping should be delayed for at least 30 to 60 seconds for vigorous term and preterm infants, given no maternal or fetal indications for immediate clamping.[3] See Box EC 18.A for exclusions. There is insufficient evidence to support or refute use of umbilical cord milking.

B. Endotracheal Tube Size and Depth of Insertion (Table 18.1)

1. **Quick estimations:**
   a. ETT size: 2.5 mm for infants <30 weeks gestational age (wGA); 3.0 mm for 30 to 34 wGA; 3.5 mm for >35 wGA.
   b. ETT depth: Infant's weight (kg) + 6 cm

C. Vascular Access (See Chapter 4 for Umbilical Venous/Artery Catheter Placement)

NOTE: During the initial resuscitation, an umbilical venous catheter (UVC) should be inserted just far enough to obtain blood return; no measurement or verified placement is needed.

II. ROUTINE NEWBORN CARE OF A TERM INFANT

A. General Care for the Full-Term Healthy Newborn with Uncomplicated Delivery

NOTE: Protocols vary by hospital.

1. Drying, removal of wet blankets. Then, preferably skin-to-skin contact with mother[4] or otherwise placed under warmer.
2. Feeding: Preferably breastfeeding soon after birth and on demand thereafter. Breastfed newborns should feed 8 to 12 times daily. Formula-fed newborns should be offered a bottle soon after birth.

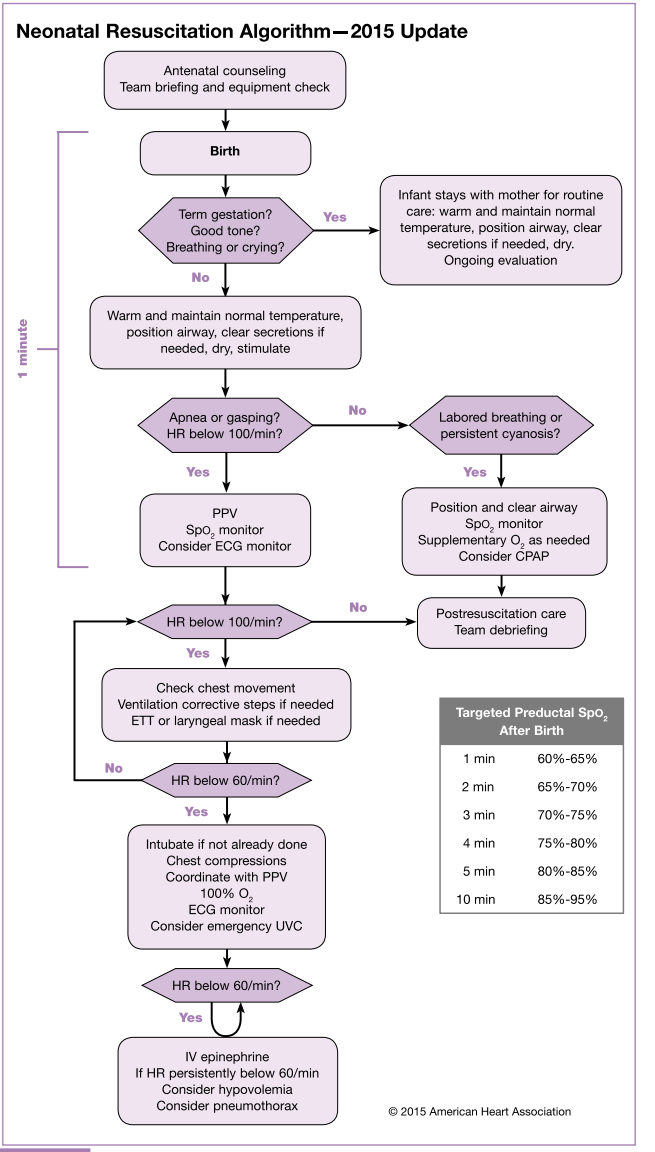


FIGURE 18.1

Overview of resuscitation in the delivery room. *CPAP*, Continuous positive airway pressure; *HR*, heart rate; *IV*, intravenous; *PPV*, positive pressure ventilations; *SpO_2*, oxygen saturation by pulse oximetry. (From Wykoff M, Aziz K, Escobedo M. et al. Part 15: neonatal resuscitation: 2015 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132(2):S543–560.)

BOX EC 18.A

EXCLUSION CRITERIA FOR DELAYED CORD CLAMPING

Absolute Exclusions Prior to Birth[2,3]

Fetal

- Monochorionic twins
- Discordant twins >25%
- IUGR <3rd percentile with reversed end-diastolic flow
- Poorly controlled maternal diabetes
- Congenital diaphragmatic hernia
- Abdominal wall defects
- Infant requiring immediate resuscitation

Maternal

- Known carrier of G6PD
- Placental abruption
- Velamentous cord insertion
- Incision through placenta
- Uterine rupture
- Placental delivery prior to infant

Individualized Considerations—Not Absolute Exclusions

- Hydrops fetalis
- RBC alloimmunization
- History of sibling with double volume exchange transfusion

Note: Presence of meconium-stained amniotic fluid does not automatically exclude delayed cord clamping.

G6PD, Glucose-6-phosphate dehydrogenase; *IUGR*, intrauterine growth retardation; *RBC*, red blood cell

TABLE 18.1

PREDICTED ENDOTRACHEAL TUBE SIZE AND DEPTH BY BIRTH WEIGHT AND GESTATIONAL AGE

Gestational Age (weeks)	Weight (g)	ETT Size (mm)	ETT Depth of Insertion (cm from Upper Lip)
23–24	500–600	2.5	5.5
25–26	700–800	2.5	6
27–29	900–1000	2.5	6.5
30–32	1100–1400	2.5–3.0	7
33–34	1500–1800	3.0	7.5
35–37	1900–2400	3.0–3.5	8
38–40	2500–3100	3.5	8.5

ETT, Endotracheal tube.

Data from Peterson J, Johnson N, Deakins K, et al. Accuracy of the 7-8-9 rule for endotracheal tube placement in the neonate. *J Perinatol.* 2006;26:333–336.

3. Vitamin K injection for prevention of hemorrhagic disease of the newborn.
4. Antibiotic ophthalmic ointment for prophylaxis against gonococcal infection.
5. Monitor clinically for jaundice, accounting for newborn's risk factors for hyperbilirubinemia. Transcutaneous bilirubin monitoring may be useful as a screening tool but does not replace plasma level.[5] Obtain plasma bilirubin level if warranted. See Section IX for more information and management.
6. Consider blood glucose monitoring if infant is at increased risk or is symptomatic of hypoglycemia (see Fig. 18.2 for management).
7. Monitor for stool/urine output. Most infants should have 1 void and 1 meconium stool within first 24 hours.[6]
8. Monitor for excessive weight loss.

B. Prior to Discharge[7]

1. Newborn metabolic screening: First screen typically performed within first 72 hours of life, at least 24 hours after initiation of feeding (see Chapter 13).
2. Vaccinations: Hepatitis B vaccine (see Chapter 16).
3. Critical congenital heart disease screening: Measure pre- and/or post-ductal oxygen saturation (see Chapter 7).
4. Newborn hearing screening.
5. Document red reflex.
6. Establish primary care.

III. NEWBORN ASSESSMENT

A. Vital Signs and Birth Weight

1. **Mean arterial blood pressure:** Related to birth weight, gestational age.

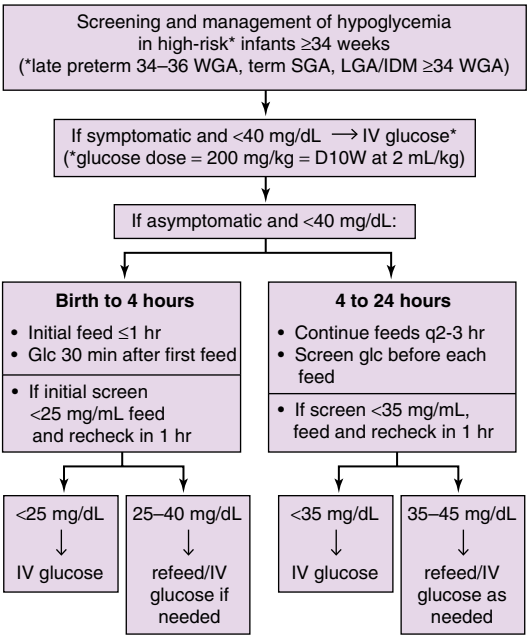


FIGURE 18.2

Screening for and management of postnatal glucose homeostasis. *D10W*, 10% dextrose in water; *glc*, glucose; *IDM*, infant of diabetic mother; *IV*, intravenous; *LGA*, large for gestational age; *SGA*, small for gestational age; *WGA*, weeks gestational age (Modified from Adamkin D, Committee on the Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127:575–579.)

2. **Birth weight:**
   a. Extremely low birth weight (ELBW): <1000 g, very low birth weight (VLBW): <1500 g, low birth weight (LBW): <2500 g.
   b. Small for gestational age (SGA): <10% for gestational age, large for gestational age (LGA): >90% for gestational age.

B. APGAR Scores (Table 18.2)

Assess at 1 and 5 minutes. Repeat at 5-minute intervals if score at 5 minutes is <7.[8]

C. Gestational Age Estimation

The Ballard Score is most accurate between the age of 12 and 20 hours, and approximates gestational age based on neuromuscular and physical maturity ratings (Fig. EC 18.A).

TABLE 18.2

APGAR SCORES

Score	0	1	2
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent, irregular	Slow, crying	Good
Muscle tone	Limp	Some flexion of extremities	Active motion
Reflex irritability (nose suction)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Acrocyanosis	Completely pink

Data from Apgar V. Proposal for a new method of evaluation of the newborn infant. *Anesth Analg.* 1953;32:260.

1. Posture: Observe infant quiet and supine. Score 0 for arms, legs extended; 1 for starting to flex hips and knees, arms extended; 2 for stronger flexion of legs, arms extended; 3 for arms slightly flexed, legs flexed and abducted; and 4 for full flexion of arms and legs.
2. Square window: Flex hand on forearm enough to obtain fullest possible flexion without wrist rotation. Measure angle between hypothenar eminence and ventral aspect of forearm.
3. Arm recoil: With infant supine, flex forearms for 5 seconds, fully extend by pulling on hands, then release. Measure the angle of elbow flexion to which arms recoil.
4. Popliteal angle: Hold infant supine with pelvis flat, thigh held in knee-chest position. Extend leg by gentle pressure and measure popliteal angle.
5. Scarf sign: With baby supine, pull infant's hand across the neck toward opposite shoulder. Determine how far elbow will reach across. Score 0 if elbow reaches opposite axillary line, 1 if past midaxillary line, 2 if past midline, and 3 if elbow unable to reach midline.
6. Heel-to-ear maneuver: With baby supine, draw foot as near to head as possible without forcing it. Observe distance between foot and head and degree of extension at knee.

D. Birth Trauma

1. **Extradural fluid collections:** See Table 18.3 and Fig. 18.3.
2. **Fractured clavicle:** Possible crepitus/deformity/decreased movement on day 1 ± swelling/discomfort on day 2.
3. **Brachial plexus injuries:** See Section XI.

E. Selected Anomalies, Syndromes, and Malformations (see Chapter 13 for genetic disorders)

1. **VACTERL association: V**ertebral defects, **A**nal atresia, **C**ardiac defects, **T**racheo-**E**sophageal fistula, **R**enal anomalies, and **L**imb abnormalities.
2. **CHARGE syndrome**: **C**oloboma, **H**eart disease, choanal **A**tresia, **R**etarded growth and development (may include central nervous system anomalies), **G**enital anomalies (may include hypogonadism), and **E**ar abnormalities or deafness.
3. **Infant of a diabetic mother:** Increased risk of hypoglycemia, polycythemia, transient tachypnea of the newborn (TTN), sacral agenesis,

Neuromuscular maturity

Neuromuscular maturity sign	Score							Record score here
	–1	0	1	2	3	4	5	
Posture								
Square window (wrist)	> 90°	90°	60°	45°	30°	0°		
Arm recoil		180°	140–180°	110–140°	90–110°	<90°		
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°	
Scarf sign								
Heel to ear								
							TOTAL NEUROMUSCULAR MATURITY SCORE	

Physical maturity

Physical maturity sign	Score							Record score here
	–1	0	1	2	3	4	5	
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled	
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald		
Plantar surface	Heel-toe: 40–50 mm: –1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior two thirds	Creases over entire sole		
Breast	Imper-ceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud		
Eye/ear	Lids fused: loosely: –1 tightly: –2	Lids open, pinna flat, stays folded	Sl. curved pinna, soft, slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff		
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae		
Genitals (female)	Clitoris prominent and labia flat	Prominent clitoris and small labia minora	Prominent clitoris and enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora		
							TOTAL PHYSICAL MATURITY SCORE	

Score
Neuromuscular_____
Physical_____
Total_____

Maturity rating														
Score	–10	–5	0	5	10	15	20	25	30	35	40	45	50
Weeks	20	22	24	26	28	30	32	34	36	38	40	42	44

Gestational age (weeks)
By dates_____
By ultrasound_____
By exam_____

FIG. EC 18.A

Neuromuscular and physical maturity (New Ballard Score). (Modified from Ballard JL et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr*. 1991;119:417–423.)

TABLE 18.3

BIRTH-RELATED EXTRADURAL FLUID COLLECTIONS

	Caput Succedaneum	Cephalohematoma	Subgaleal Hemorrhage
Location	At point of contact; can extend across sutures	Usually over parietal bones; does not cross sutures	Beneath epicranial aponeurosis; may extend to orbits or nape of neck
Findings	Vaguely demarcated; pitting edema, shifts with gravity	Distinct margins; initially firm, more fluctuant after 48 hr	Firm to fluctuant, ill-defined borders; may have crepitus or fluid waves
Timing	Maximal size/firmness at birth; resolves in 48–72 hr	Increases after birth for 12–24 hr; resolution over weeks	Progressive after birth; resolution over weeks
Severity	Minimal	Rarely severe	May be severe, especially in the setting of associated coagulopathy

Data from DJ Davis. Neonatal subgaleal hemorrhage: diagnosis and management. *CMAJ.* 2001;164:1452.

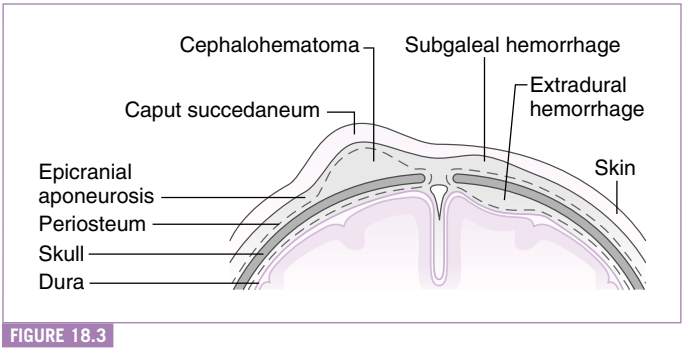


FIGURE 18.3

Types of extradural fluid collections seen in newborn infants.

femoral hypoplasia, cardiac defects, cleft palate/lip, preaxial radial defects, microtia, microphthalmos, holoprosencephaly, microcephaly, anencephaly, spina bifida, hemivertebrae, urinary tract defects, and polydactyly.

4. **Fetal alcohol syndrome:** SGA, short palpebral fissures, epicanthal folds, flat nasal bridge, long philtrum, thin upper lip, small hypoplastic nails. May be associated with cardiac defects.

IV. FLUIDS, ELECTROLYTES, AND NUTRITION

A. Fluids

1. **Fluid requirements of newborns** (Table 18.4)
2. **Insensible water loss in preterm infants** (Table EC 18.A)

TABLE 18.4

ESTIMATED MAINTENANCE FLUID REQUIREMENTS OF NEWBORNS

Birth Weight (g)	Fluid Requirements (mL/kg/24 hr) by Age			
	Day 1	Day 2	Day 3–6	Days 7+
<750	100–140	120–160	140–200	140–160
750–1000	100–120	100–140	130–180	140–160
1000–1500	80–100	100–120	120–160	150
>1500	60–80	80–120	120–160	150

Data from Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn.* 10th ed. Philadelphia: Elsevier; 2018.

B. Glucose

1. **Glucose infusion rate (GIR):** Preterm neonates require approximately 5 to 6 mg/kg/min of glucose (40 to 100 mg/dL).[9] Term neonates require approximately 3 to 5 mg/kg/min of glucose. Calculate as follows:

$$\text{GIR (mg/kg/min)} = 0.167 \times [\,\%\ \text{dextrose concentration}] \left[\text{infusion rate} \left(\frac{\text{mL}}{\text{hr}}\right)\right] / [\text{Weight (kg)}]$$

2. **Management of hyperglycemia and hypoglycemia:** Table 18.5 and Fig. 18.2 (see Chapters 1 and 10).

C. Electrolytes, Minerals, and Vitamins

1. **Electrolyte requirements** (Table 18.6)
2. **Mineral and vitamin requirements:**
   a. Infants born at <34 weeks gestation have higher calcium, phosphorus, sodium, iron, and vitamin D requirements and require breastmilk fortifier or special preterm formulas with iron. Fortifier is generally added to breast milk after the 2nd week of life.
   b. Iron: Preterm infants tolerating full enteral feeds require an elemental iron supplementation of 2 to 4 mg/kg/day. Timing of initiation remains controversial, generally after age 2 weeks.
   c. Vitamin D: Infants fed breast milk without fortifier require 400 IU daily. Infants fed preterm formula require 200 IU/day. Infants fed full term formula should be supplemented 400 IU/day until consuming 1 liter daily.
   d. ADEK: Indicated for infants with malabsorption and/or cholestasis tolerating full enteral feeds.

D. Nutrition

1. **Growth and caloric requirements: Table 18.7**
2. **Total parenteral nutrition (see Chapter 21)**

TABLE EC 18.A

INSENSIBLE WATER LOSS IN PRETERM INFANTS

Body Weight (g)	Insensible Water Loss (mL/kg/day)
<1000	60–70
1000–1250	60–65
1251–1500	30–45
1501–1750	15–30
1751–2000	15–20

Estimates of insensible water loss at different body weights during the first few days of life
Data from Veille JC. Management of preterm premature rupture of membranes. *Clin Perinatol.* 1988;15:851–862.

TABLE 18.5

MANAGEMENT OF HYPERGLYCEMIA AND HYPOGLYCEMIA

	Hypoglycemia	Hyperglycemia
Definition	Serum glucose <40 mg/dL in term and late preterm infants	Serum glucose >125 mg/dL in term infants, >150 mg/dL in preterm infants
Differential diagnosis	Insufficient glucose delivery Decreased glycogen stores Increased circulating insulin (e.g., infant of a diabetic mother, maternal drugs, Beckwith-Wiedemann syndrome, tumors) Endocrine and metabolic disorders Sepsis or shock Hypothermia, polycythemia, or asphyxia	Excess glucose administration Sepsis Hypoxia Hyperosmolar formula Neonatal diabetes mellitus Medications
Evaluation	Assess for symptoms and calculate glucose delivery to infant. Confirm bedside glucose with laboratory serum glucose. Consider other laboratory evaluations: Complete blood cell count with differential; electrolytes; blood, urine, ±cerebrospinal fluid cultures; urinalysis; insulin and C-peptide levels.	
Management	See Fig. 18.3. If glucose <40 and symptomatic, treat with intravenous glucose (dose = 200 mg/kg, which is equivalent to dextrose 10% at 2 mL/kg). Change dextrose infusion rates gradually. Generally, no more than 2 mg/kg/min in a 2-hr interval (see Chapter 1) . Monitor glucose levels every 30–60 min until normal.	Gradually decrease glucose infusion rate if receiving >5 mg/kg/min Monitor glucosuria. Consider insulin infusion for persistent hyperglycemia.

TABLE 18.6

ELECTROLYTE REQUIREMENTS

	Before 24 hr of Life	Transitional, After 24 hr of Life[a]	Growing Premature Infant	Growing Term Infant
Sodium (mEq/kg/day)	0–1	2–5	3–5	2–4
Potassium (mEq/kg/day)	0	0–2	2–3	2–3

[a]Pending postnatal diuresis has been established. Period to physiologic and metabolic stability, generally occurring between 2 and 7 days.

TABLE 18.7

AVERAGE CALORIC REQUIREMENTS AND GROWTH FOR PRETERM AND TERM INFANTS

	Preterm Infant	Term Infant
Caloric requirements (kcal/kg/day) [Parental/Enteral]	PN: 85–110 EN: 105–130 *Up to 150 for infants with cardiac conditions or BPD	PN: 90–100 EN: 100–120
Growth after 10 days of life	<2 kg: 15–20 g/kg/day >2 kg: 25–35 g/day	20–30 g/day

*Signifies an exception for infants with cardiac conditions or BPD.

V. CYANOSIS IN THE NEWBORN

A. Differential Diagnosis

1. **General:** Hypothermia, hypoglycemia, sepsis
2. **Cardiac:** Congestive heart failure, congenital cyanotic heart disease
3. **Respiratory:** Persistent pulmonary hypertension of the newborn (PPHN), diaphragmatic hernia, pulmonary hypoplasia, choanal atresia, pneumothorax, respiratory distress syndrome (RDS), TTN, pneumonia, meconium aspiration
4. **Neurologic:** Central apnea, central hypoventilation, intraventricular hemorrhage (IVH), meningitis
5. **Hematologic:** Polycythemia, methemoglobinemia
6. **Medications:** Respiratory depression from maternal medications (e.g., magnesium sulfate, narcotics, general anesthesia)

B. Evaluation

1. **Physical examination:** Note central vs. peripheral and persistent vs. intermittent cyanosis, respiratory effort, single vs. split S_2, presence of heart murmur. Acrocyanosis is often a normal finding in newborns.
2. **Clinical tests:** Hyperoxia test (see Chapter 7) , preductal/postductal arterial blood gases or pulse oximetry to assess for right-to-left shunt, and transillumination of chest for possible pneumothorax.
3. **Other data:** Complete blood cell count (CBC) with differential, serum glucose, chest radiograph, electrocardiogram (ECG), echocardiography. Consider blood, urine, and cerebrospinal fluid cultures if sepsis is suspected and methemoglobin level if cyanosis is out of proportion to hypoxemia.

VI. RESPIRATORY DISEASES

A. General Respiratory Considerations

1. **Exogenous surfactant therapy:**
   a. Indications: RDS in preterm infants, meconium aspiration, pneumonia, persistent pulmonary hypertension.
   b. Administration: If infant is ≤26 weeks gestation, first dose is typically given in delivery room or as soon as stabilized; repeat dosing can be considered based on ongoing oxygen requirements and level of respiratory support.
   c. Complications: Pneumothorax, pulmonary hemorrhage.
2. **Supplemental O_2:** Adjust inspired oxygen to maintain O_2 saturation. Ideal target oxygen saturations vary based on factors such as gestational age, chronologic age, and underlying conditions, and aims to minimize adverse outcomes from hypoxemia and hyperoxemia. Higher targets (>94%) can be used when the retinas are mature (see Section XIII) and in cases of pulmonary hypertension.[10]

B. Respiratory Distress Syndrome

1. **Etiology:** Deficiency of pulmonary surfactant resulting in increased surface tension and alveolar collapse. Surfactant is produced in increasing quantities after 32 weeks gestation.

TABLE 18.8

INCIDENCE OF RESPIRATORY DISTRESS SYNDROME BY GESTATIONAL AGE AND ANTENATAL STEROID ADMINISTRATION[11-14]

Gestational Age (week)	Antenatal Steroids Administered	Antenatal Steroids Not Administered
<30	35%	60%
30–34	10%	25%
34–36	1.4%[a]; 5.5%	2.3%[a]; 6.4%
>37	2.6%	5.4%

[a]Neonates with severe respiratory distress syndrome.

Note: The use of antenatal corticosteroids in >34 weeks gestational age is controversial due to inconsistent data regarding efficacy and limited data regarding long-term effects.

2. **Prevention:**
   a. Antenatal maternal administration of steroids >24 hours and <7 days prior to delivery, has been shown to decrease neonatal morbidity and mortality.[11-14]
      (1) Generally, either two doses of betamethasone administered 24 hours apart or four doses of dexamethasone given every 12 hours.
      (2) A single repeat course considered in women <34 weeks gestation and whose previous steroid course was administered >14 days prior. Serial courses not currently recommended.
   b. Other factors that accelerate lung maturity include maternal hypertension, sickle cell disease, narcotic addiction, intrauterine growth retardation, prolonged rupture of the membranes, and fetal stress.
3. **Incidence:** Table 18.8
4. **Risk factors:** Prematurity, maternal diabetes, cesarean section without antecedent labor, perinatal asphyxia, second twin, previous infant with RDS.
5. **Clinical presentation:**
   a. Respiratory distress worsens during first few hours of life, progresses over 48 to 72 hours, and subsequently improves.
   b. Recovery is accompanied by brisk diuresis.
   c. See Chapter 26 for imaging findings.
6. **Management:**
   a. Ventilatory and oxygenation support
   b. Surfactant therapy

C. Persistent Pulmonary Hypertension of the Newborn

1. **Etiology:** Idiopathic or secondary to conditions leading to increased pulmonary vascular resistance. PPHN is most commonly seen in term or postterm infants, infants born by cesarean section, and infants with a history of fetal distress and low APGAR scores. It usually presents within 12 to 24 hours of birth:
   a. Vasoconstriction secondary to hypoxemia and acidosis
   b. Interstitial pulmonary disease (meconium aspiration syndrome, pneumonia)
   c. Hyperviscosity syndrome (polycythemia)

d. Pulmonary hypoplasia, either primary or secondary to congenital diaphragmatic hernia or renal agenesis

2. **Diagnostic features:**
   a. Severe hypoxemia (Pao_2 <35 to 45 mmHg in 100% O_2) disproportionate to radiologic changes.
   b. Structurally normal heart with right-to-left shunt at foramen ovale and/or ductus arteriosus; pre/postductal oxygenation gradient (≥7 to 15 mmHg is significant).
   c. Must be distinguished from cyanotic heart disease. Infants with cyanotic heart disease will have an abnormal cardiac examination and show little to no improvement in oxygen therapy or hyperventilation. See Chapter 7 for interpretation of hyperoxia test.
3. **Principles of therapy:**
   a. **Improve oxygenation:** Supplemental oxygen administration and optimization of oxygen-carrying capacity with blood transfusions as indicated.
   b. **Minimize pulmonary vasoconstriction:**
      (1) Minimal handling of infant or noxious procedures. Sedation and occasionally paralysis of intubated neonates may be necessary.
      (2) Avoid severe hyperventilation associated hypocarbia (PCO_2 <30 mmHg), which can be associated with myocardial ischemia and decreased cerebral blood flow. Hyperventilation may result in barotrauma and predispose to chronic lung disease. Consider high-frequency ventilation.
   c. **Maintenance of systemic blood pressure and perfusion:** Reversal of right-to-left shunt through volume expanders and/or inotropes.
   d. **Consider pulmonary vasodilator therapy: see Chapter 1**
      (1) Inhaled nitric oxide (NO): Reduces pulmonary vascular resistance (PVR). Typical starting dose is 20 parts per million (ppm). Unlikely to have additional benefit at >40 ppm. Complications include methemoglobinemia (reduce NO dose for methemoglobin >4%), NO_2 poisoning (reduce NO dose for NO_2 concentration >1 to 2 ppm).
      (2) Prostacyclin analog (e.g., epoprostenol): Pulmonary vasodilator, normally produced by lung when lung vessels are constricted.
      (3) Sildenafil: Cyclic cGMP-specific phosphodiesterase type 5 (PDE5) inhibitor; results in pulmonary vasodilation.
   e. **Broad-spectrum antibiotics:** Sepsis is a common underlying cause of PPHN.
   f. **Consider extracorporeal membrane oxygenation (ECMO):** Reserved for cases of severe cardiovascular instability, oxygenation index (OI) >40 for >3 hour, or alveolar-arterial gradient ($A\text{-}aO_2$) ≥610 for 8 hours (see Chapter 1 for OI and A-a gradient equations). Infants typically need to be >2000 g and at >34 weeks gestation to be ECMO candidates. Obtain head ultrasound and consider EEG before initiating ECMO.
4. **Mortality depends on underlying diagnosis:** Mortality rates are generally lower for RDS and meconium aspiration, but higher in sepsis and diaphragmatic hernia.

D. Transient Tachypnea of the Newborn

1. **Etiology:** Incomplete or delayed resorption of amniotic fluid from the lungs.
   a. Immaturity of respiratory epithelial Na^+ transport.
2. **Risk factors:** Birth by cesarean section, male sex, macrosomia, lower gestational age, maternal diabetes, maternal asthma, maternal smoking.
3. **Diagnostic features:**
   a. Symptoms present within first 6 hours of delivery and resolve within first postnatal week, usually within 72 hours.
   b. Tachypnea: greater than 60 breaths/min, often in the range of 80 to 100 breaths/min.
   c. Retractions, grunting, or nasal flaring may be present. Cyanosis and hypoxia rare.
   d. CXR consistent with retained fluid: congestion, perihilar streaking, fluid in the interlobar fissure.
   e. Exclusion of other diagnoses, i.e. pneumonia, aspiration, congenital malformations, subarachnoid hemorrhage, hypoxic-ischemic encephalopathy (HIE), pneumothorax, acidosis, RDS.
4. **Management:**
   a. NPO with gavage feedings or 10% dextrose-containing fluids via IV.
   b. Supplemental oxygen and/or CPAP as indicated.
   c. No proven benefit of adjuncts including diuretics or racemic epinephrine.

E. Pneumothorax

1. Seen in 1% to 2% of normal newborns.
2. Associated with use of high ventilatory pressures and underlying diseases such as RDS, meconium aspiration, and pneumonia.
3. Consider monitoring in a neonatal intensive care unit (NICU).
4. Consider needle thoracostomy or chest tube placement (see Chapter 4).

VII. APNEA AND BRADYCARDIA

A. Apnea[15]

1. **Definition:** Respiratory pause >20 seconds or a shorter pause associated with cyanosis, pallor, hypotonia, or bradycardia <100 bpm. May be central (no diaphragmatic activity), obstructive (upper airway obstruction), or mixed.
2. **Etiology:** See Fig. 18.4. Apnea of prematurity occurs in most infants born at <28 weeks gestation, ~50% of infants born at 30 to 32 weeks gestation, and <7% of infants born at 34 to 35 weeks gestation. Usually resolves by 34 to 36 weeks postmenstrual age, but may persist after term in infants born at <25 weeks gestation.
3. **Management:**
   a. Consider pathologic causes for apnea (e.g., meningitis, seizures).
   b. Pharmacotherapy with caffeine or other stimulants.

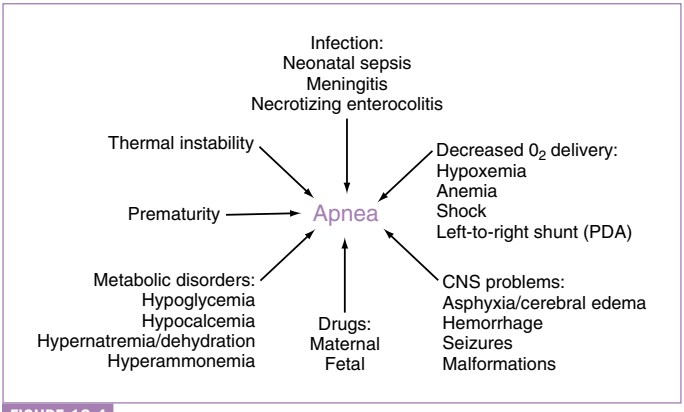


FIGURE 18.4

Causes of apnea in the newborn. *CNS*, Central nervous system; *PDA*, patent ductus arteriosus. (From Klaus MH, Fanaroff AA. *Care of the High-Risk Neonate*. 5th ed. Philadelphia: WB Saunders; 2001:268.)

c. Continuous positive airway pressure or mechanical ventilation (see Chapter 1).

B. Bradycardia without Central Apnea

Etiologies include obstructive apnea, mechanical airway obstruction, gastroesophageal reflux, increased intracranial pressure, increased vagal tone (defecation, yawning, rectal stimulation, and placement of nasogastric [NG] tube), electrolyte abnormalities, heart block.

VIII. CARDIAC DISEASES

A. Patent Ductus Arteriosus

1. **Definition:** Failure of ductus arteriosus to close in first 72 hours of life or reopening after functional closure. Typically results in left-to-right shunting of blood once PVR has decreased. If PVR remains high, blood may be shunted right to left, resulting in hypoxemia (see Section VI.C).
2. **Epidemiology:** Up to 60% in preterm infants weighing <1500 g and higher in those weighing <1000 g. Female-to-male ratio is 2:1.
3. **Diagnosis:**
   a. Examination: Systolic murmur may be continuous and best heard at the left upper sternal border or left infraclavicular area. Bounding peripheral pulses with widened pulse pressure if large shunt. Hyperactive precordium and palmar pulses may be present.
   b. ECG: Normal or left ventricular hypertrophy in small to moderate patent ductus arteriosus (PDA); biventricular hypertrophy in large PDA.
   c. Chest radiograph: May show cardiomegaly and increased pulmonary vascular markings, depending on size of shunt.

d. Echocardiogram

4. **Management:**
   a. Indications for treatment, timing of intervention, and best management strategy remain controversial.[16,17]
   b. Indomethacin/Ibuprofen: Prostaglandin synthetase inhibitor; 80% closure rate in preterm infants
      (1) Ibuprofen is as effective as indomethacin but fewer renal adverse effects.[18]
      (2) Complications[16-18]: Transient decrease in glomerular filtration rate and decreased urine output, transient gastrointestinal bleeding (no increased incidence of necrotizing enterocolitis [NEC]), prolonged bleeding time, and disturbed platelet function for 7 to 9 days independent of platelet count (no increased incidence of intracranial hemorrhage). Spontaneous isolated intestinal perforations are seen with indomethacin use. Rates are higher with concomitant hydrocortisone use.
   c. Acetaminophen[19-22]: Insufficient evidence but thought to be as effective as indomethacin/ibuprofen without effects on the kidneys and platelets.
   d. Surgical ligation of the duct.

B. Cyanotic Heart Disease (See Chapter 7)

IX. HEMATOLOGIC DISEASES

A. Unconjugated Hyperbilirubinemia in the Newborn[23]

1. **Overview:**
   a. During first 3 to 4 days of life, total serum bilirubin (TSB) increases to 6.5 ± 2.5 mg/dL.
   b. Maximum rate of bilirubin increase for normal infants with nonhemolytic hyperbilirubinemia: 5 mg/dL/24 hr or 0.2 mg/dL/hr.
   c. Always consider clinical jaundice or TSB >5 mg/dL on first day of life pathologic.
   d. Risk factors: Birth weight <2500 g, exclusive breastfeeding, prematurity, ABO incompatibility, cephalohematoma or significant bruising, predischarge bilirubin in high-risk zone, observed jaundice in first 24 hours, gestational age 35 to 36 weeks, infant of a diabetic mother, previous sibling requiring phototherapy, low albumin, infection, race.
2. **Evaluation:**
   a. Maternal prenatal testing: ABO and Rh (D) typing and serum screen for isoimmune antibodies.
   b. Infant or cord blood: Blood and Rh typing (if maternal blood type is O, Rh negative, or prenatal blood typing was not performed). Consider hemoglobin, blood smear, glucose-6-phosphate dehydrogenase (GPD) testing, direct Coombs test.

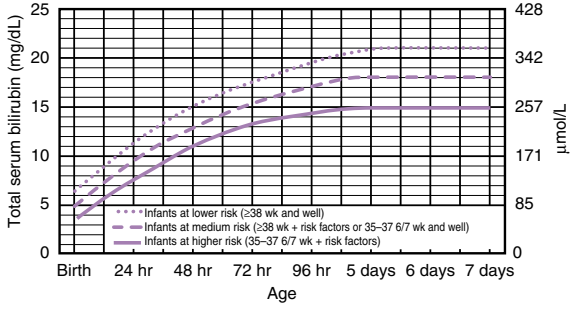
3. **Management:**
   a. Phototherapy: Ideally, intensive phototherapy should produce a TSB decline of 1 to 2 mg/dL within 4 to 6 hours, with further subsequent decline. Guidelines:
      (1) Preterm newborn (Table 18.9)
      (2) Term newborn (Fig. 18.5)
   b. Intravenous immunoglobulin (IVIG) (>35 weeks gestational age): In isoimmune hemolytic disease, IVIG administration (0.5 to 1 g/kg over 2 hours) is recommended if TSB is rising despite intensive phototherapy or TSB is within 2 to 3 mg/dL of exchange transfusion level (see Chapter 15 for discussion of IVIG).

TABLE 18.9

GUIDELINES FOR MANAGEMENT OF HYPERBILIRUBINEMIA IN PRETERM INFANTS AGED <1 WEEK

Gestational age (weeks)	Phototherapy (mg/dL)	Consider Exchange Transfusion (mg/dL)
<28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18

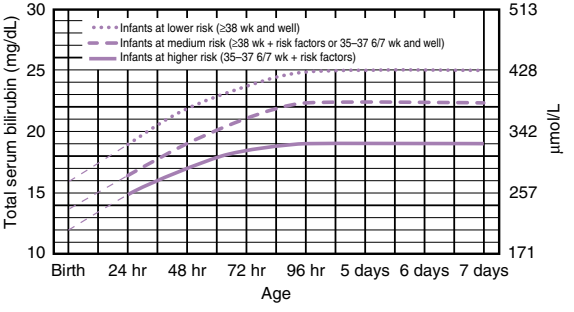
Data from Maisels MJ, Watchko JF, Bhutani V. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. *J Perinatol*. 2012;32(9):660–4.



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured)
- For well infants 35–37 6/7 wk, can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wk and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2–3 mg/dL (35–50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

FIGURE 18.5

Guidelines for phototherapy in infants born at 35 weeks of gestation or more. *G6PD*, Glucose-6-phosphate dehydrogenase; *TSB*, total serum bilirubin.



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TBS is ≥5 mg/dL (85 μmol/L) above these lines.
- Risk factors: Isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35–37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

FIGURE 18.6

Guidelines for exchange transfusion in infants born at 35 weeks of gestation or more. *B/A*, Bilirubin/albumin; *G6PD*, glucose-6-phosphate dehydrogenase; *TSB*, total serum bilirubin.

c. Neonatal double-volume exchange transfusion (see Table 18.9 and Fig. 18.6):
   (1) Volume: 160 mL/kg for full-term infant, 160 to 200 mL/kg for preterm infant.
   (2) Route: During exchange, blood is removed through umbilical arterial catheter (UAC) and an equal volume is infused through UVC. If UAC is unavailable, use a single venous catheter.
   (3) Procedure: Replaces up to 85% of infant's circulation. Exchange in 15-mL aliquots for full-term infants. Exchange at 2 to 3 mL/kg/min in premature/less stable infants to avoid hemolysis.
   (4) Complications: Emboli, thromboses, hemodynamic instability, electrolyte disturbances, coagulopathy, infection, death.

NOTE: CBC, reticulocyte count, peripheral smear, bilirubin, Ca^{2+}, glucose, total protein, infant blood type, Coombs test, and newborn screen should be performed on a preexchange sample of blood; they are of no diagnostic value with postexchange blood. **If indicated, save preexchange blood for serologic or genetic studies.**

B. Conjugated Hyperbilirubinemia (See Chapter 12)

1. **Definition:** Direct bilirubin >2.0 mg/dL and >10% of TSB.

2. **Etiology:** Biliary obstruction/atresia, choledochal cyst, hyperalimentation, α_1-antitrypsin deficiency, hepatitis, sepsis, infections (especially urinary tract infections), hypothyroidism, inborn errors of metabolism, cystic fibrosis, red blood cell abnormalities.
3. **Management:** Ursodiol for infants on full feeds; consider supplementation with fat-soluble vitamins (A, D, E, K); otherwise depends on etiology. Phototherapy is not contraindicated but poses the risk for "bronze baby" syndrome.

C. Polycythemia

1. **Definition:** Venous hematocrit >65% confirmed on two consecutive samples. May be falsely elevated when obtained by heel stick or falsely lower when obtained by arterial stick.
2. **Etiologies:** Delayed cord clamping, twin-twin transfusion, maternal-fetal transfusion, intrauterine hypoxia, Beckwith-Wiedemann syndrome, maternal diabetes, neonatal thyrotoxicosis, congenital adrenal hyperplasia, trisomies.
3. **Clinical findings:** Plethora, respiratory distress, cardiac failure, tachypnea, hypoglycemia, irritability, lethargy, seizures, apnea, jitteriness, poor feeding, thrombocytopenia, hyperbilirubinemia.
4. **Complications:** Hyperviscosity predisposes to venous thrombosis and CNS injury. Hypoglycemia may result from increased erythrocyte utilization of glucose.
5. **Management:** Partial exchange transfusion for symptomatic infants, with isovolemic replacement of blood with isotonic fluid. Blood is exchanged in 10- to 20-mL increments to reduce hematocrit to <55%.

$$\text{Estimated blood volume} = \text{birth weight (kg)} \times 90 \text{ mL/kg}$$

X. GASTROINTESTINAL DISEASES

A. Necrotizing Enterocolitis

1. **Definition:** Serious intestinal inflammation and injury thought to be secondary to bowel ischemia, immaturity, and infection. Occurs principally in infants who have been fed.
2. **Risk factors:** Prematurity, asphyxia, African American race, hypotension, polycythemia–hyperviscosity syndrome, umbilical vessel catheterization, exchange transfusion, bacterial and viral pathogens, enteral feeds, PDA, congestive heart failure, cyanotic heart disease, RDS, intrauterine cocaine exposure.
3. **Clinical findings:** See Table EC 18.B.
   a. Systemic: Temperature instability, apnea, bradycardia, metabolic acidosis, hypotension, disseminated intravascular coagulopathy.
   b. Intestinal: Blood in stool, absent bowel sounds, and/or abdominal tenderness or mass. Elevated pregavage residuals in the absence of other clinical symptoms rarely raise a suspicion of NEC.
   c. Radiologic: Ileus, intestinal pneumatosis, portal vein gas, ascites, pneumoperitoneum (see Chapter 26).

TABLE EC 18.B

MODIFIED BELL'S STAGING SYSTEM FOR NECROTIZING ENTEROCOLITIS

Stage	Findings
IA (NEC suspected)	Temperature instability, apnea, bradycardia, lethargy, mild abdominal distention, gastric residuals, poor feeding, bilious emesis, occult blood in stool, x-ray findings: normal to mild ileus
IB (NEC suspected)	As for Stage IA, but with gross blood in stool
IIA (definite NEC, mildly ill)	As for stage IB with pneumatosis intestinalis, absent bowel sounds ± abdominal tenderness
IIB (definite NEC, moderately ill)	As for Stage IIA with metabolic acidosis, mild thrombocytopenia; definite abdominal tenderness; ± abdominal cellulitis or right lower quadrant mass; ± ascites or portal venous gas
IIIA (advanced NEC, severely ill infant, bowel intact)	As for stage IIB, but with hypotension, bradycardia, apnea, metabolic and respiratory acidosis, neutropenia, disseminated intravascular coagulation, peritonitis, abdominal distention and tenderness, abdominal erythema; definite ascites
IIIB (severely ill, perforated bowel)	As for Stage IIIA with pneumoperitoneum

NEC, Necrotizing enterocolitis.

Modified from Kleigman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification and spectrum of illness. *Curr Prob Pediatr.* 1987;17(4):219–288.

4. **Management:** Nothing by mouth, NG tube decompression, maintain adequate hydration and perfusion, broad spectrum antibiotics for 7 to 10 days based on hospital antibiogram, surgical consultation. Surgery is performed for signs of perforation or necrotic bowel.
5. **Minimizing risk of NEC:**
   a. Several studies link the use of probiotics and a decreased risk of NEC.[24] However, variations among formulations of probiotics, dosing, and lack of long-term studies on outcome have prevented the standard use of probiotics in the NICU.[25]
   b. There have been additional studies on supplements including L-arginine and lactoferrin.[26-28] Data remains insufficient to support a practice recommendation.[29]
   c. The exclusive use of human milk, including donor breast milk, has been shown to decrease the risk of NEC and associated mortality.[30]

B. Bilious Emesis

See Table EC 18.C and Chapter 12.

1. **Mechanical:** Annular pancreas, intestinal atresia/duplication/malrotation/obstruction (including adjacent organomegaly), meconium plug or ileus, Hirschsprung disease, imperforate anus.
2. **Functional (i.e., poor motility):** NEC, electrolyte abnormalities, sepsis.

NOTE: Must eliminate malrotation as an etiology because volvulus is a surgical emergency.

C. Abdominal Wall Defects (Table EC 18.D)

D. Gastroesophageal Reflux Disease (See Chapter 12)

XI. NEUROLOGIC DISEASES

A. Neonatal Hypoxic-Ischemic Encephalopathy:

1. **Initial Management**[31]
2. **Hypothermia protocol:** Infants with evidence of HIE shortly after birth who are >36 weeks gestation should be considered for hypothermia. Protocol should be initiated within 6 hours of delivery.
3. **Criteria for hypothermia vary by center but typically include one or more of the following:**
   a. Cord gas or blood gas in the first hour of life with a pH of <7.0 or base deficit of >16. For infants with a pH of 7.01 to 7.15 or base deficit of 10 to 15.9, additional criteria should be met (e.g., significant perinatal event).
   b. 10-minute APGAR ≤5.
   c. Evidence of moderate to severe encephalopathy.
   d. Need for assisted ventilation at birth for at least 10 minutes.
4. Severity and outcome of HIE in full-term neonate: Table 18.10.

B. Intraventricular Hemorrhage

1. **Definition:** IVH usually arises in the germinal matrix and periventricular regions of the brain.

TABLE EC 18.C

CONSIDERATIONS IN BILIOUS EMESIS

	Proximal Intestinal Obstruction	Distal Intestinal Obstruction
Differential diagnosis	Duodenal atresia Annular pancreas Malrotation with or without volvulus Jejunal obstruction/atresia	Ileal atresia Meconium ileus Colonic atresia Meconium plug—hypoplastic left colon syndrome Hirschsprung disease
Physical exam	Abdominal distention not prominent	Abdominal distention
Diagnosis	Abdominal X-ray: "Double bubble" Upper gastrointestinal series	Abdominal x-ray: Dilated loops of bowel Contrast enema Sweat test Mucosal rectal biopsy

Modified data from: Shields TM and Lightdale JR. Vomiting in children. *Pediatr Rev.* 2018;39:342–358.

TABLE EC 18.D

DIFFERENCES BETWEEN OMPHALOCELE AND GASTROSCHISIS

	Omphalocele	Gastroschisis
Position	Central abdominal	Right paraumbilical
Hernia sac	Present	Absent
Umbilical ring	Absent	Present
Umbilical cord insertion	At the vertex of the sac	Normal
Herniation of other viscera	Common	Rare
Extraintestinal anomalies	Frequent	Rare
Intestinal infarction, atresia	Less frequent	More frequent

BOX 18.1

SIGNS AND SYMPTOMS OF OPIOID WITHDRAWAL

W	Wakefulness
I	Irritability, insomnia
T	Tremors, temperature variation, tachypnea, twitching (jitteriness)
H	Hyperactivity, high-pitched cry, hiccups, hyperreflexia, hypertonia
D	Diarrhea (explosive), diaphoresis, disorganized suck
R	Rub marks, respiratory distress, rhinorrhea, regurgitation
A	Apnea, autonomic dysfunction
W	Weight loss
A	Alkalosis (respiratory)
L	Lacrimation (photophobia), lethargy
S	Seizures, sneezing, stuffy nose, sweating, sucking (nonproductive)

TABLE 18.10

SEVERITY AND OUTCOME OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN FULL-TERM NEONATE

	Mild	Moderate	Severe
Level of consciousness	Increased irritability, hyperalert	Lethargic	Stupor or coma
Seizures	Rare	Common	Uncommon
Primitive reflexes	Exaggerated	Suppressed	Absent
Brain stem dysfunction	Rare	Rare	Common
Elevated intracranial pressure	Rare	Rare	Variable
Duration	<24 hr	>24 hr (variable)	>5 days
Poor outcome (%)[a]	0	20–40	100

[a]Poor outcome is defined by presence of intellectual disability, cerebral palsy, or seizures.

Data from MacDonald M, Mullett, M. Severity and outcome of hypoxic-ischemic encephalopathy in full term neonate. In: *Avery's Neonatology.* 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

2. **Incidence:**
   a. 30% to 40% of infants <1500 g; 50% to 60% of infants <1000 g
   b. Highest incidence within first 72 hours of life: 60% within 24 hours, 85% within 72 hours, and <5% after 1 week of age
3. **Diagnosis and classification:**
   a. Ultrasonography; grade is based on maximum amount of hemorrhage seen by age 2 weeks:
      (1) Grade I: Hemorrhage in germinal matrix only
      (2) Grade II: IVH without ventricular dilation
      (3) Grade III: IVH with ventricular dilation
      (4) Grade IV: Periventricular hemorrhagic infarct with or without IVH.

   NOTE: Many institutions use descriptive data (as opposed to the grading system) to denote severity of IVH.
4. **Screening:** Indicated in infants <32 weeks gestational age within 72 hours of life; repeat in 1 to 2 weeks.
5. **Outcome:** Infants with grade III and intraparenchymal hemorrhages have an increased risk for neurodevelopmental disabilities and posthemorrhagic hydrocephalus.

TABLE 18.11

BRACHIAL PLEXUS INJURIES

Plexus Injury	Spinal Level Involved	Clinical Features
Erb-Duchenne palsy (90% of cases)	C5–C6 Occasionally involves C4	Adduction and internal rotation of arm. Forearm is pronated; wrist is flexed. Diaphragm paralysis may occur if C4 is involved.
Total palsy (8%–9% of cases)	C5–T1 Occasionally involves C4	Upper arm, lower arm, and hand involved. Horner syndrome (ptosis, anhidrosis, and miosis) exists if T1 is involved.
Klumpke paralysis (<2% of cases)	C7–T1	Hand flaccid with little control. Horner syndrome if T1 is involved.

C. Periventricular White Matter Injury

1. **Definition and ultrasound findings:** Ischemic necrosis of periventricular white matter, characterized by CNS depression within first week of life and later findings of cysts on ultrasound with or without ventricular enlargement (caused by cerebral atrophy) or noncystic white matter injury visualized by MRI.
2. **Incidence:** More common in preterm infants but also occurs in term infants.
3. **Etiology:** Primarily ischemia-reperfusion injury, hypoxia, acidosis, hypoglycemia, acute hypotension, low cerebral blood flow.
4. **Outcome:** Commonly associated with cerebral palsy with or without sensory and cognitive deficits.

D. Neonatal Seizures (See **Chapter 20**)

E. Neonatal Abstinence Syndrome

1. Onset of symptoms usually occurs within first 24 to 72 hours of life (methadone may delay symptoms until 96 hours or later). Symptoms may last weeks to months. Box 18.1 shows signs and symptoms of opioid withdrawal.
2. Increasing evidence supports benefit of nonpharmacologic management,[32] including rooming in, breastfeeding, skin-to-skin, swaddling, and environmental controls such as decreased disruptions.

F. Peripheral Nerve Injuries

1. **Etiology:** Result from lateral traction on shoulder (vertex deliveries) or head (breech deliveries).
2. **Clinical features** (Table 18.11).
3. **Management:** Evaluate for associated trauma (clavicular and humeral fractures, shoulder dislocation, facial nerve injury, cord injuries). Full recovery is seen in 85% to 95% of cases in first year of life.

XII. UROLOGIC DISORDERS

A. Lower Urinary Tract Obstruction

1. **Definition:** Rare birth defect caused by partial or complete blockage of the urethra. Common causes include posterior urethral valves (PUV), urethral atresia, and triad syndrome (constricted narrowing in midportion of urethra). More common in males.

2. **Diagnosis and Evaluation:** Fetal anatomy ultrasound (18 to 24 weeks) with visualization of markedly distended bladder, often with a thickened wall (greater than 2 mm).[33] A "keyhole" sign representing dilation of the posterior urethral valve proximal to the obstruction may be seen, but is not specific.
   a. Other tests include comprehensive anatomic survey or fetal MRI, echocardiogram, and karyotype to rule out co-existing abnormalities and determine gender. More than 10% of cases are associated with Trisomy 13, 18, or 21.
   b. Vesicocentesis can evaluate renal function by serially assessing urine electrolytes at 24 to 48 hour intervals.
3. **Clinical findings:** Ureterectasis, caliectasis, hydronephrosis, pulmonary hypoplasia, renal dysplasia, oligohydramnios, clubfeet, Potter facies.
4. **Management:** Fetal vesicoamniotic shunting or cystoscopy. Consultation with pediatric urology and nephrology to review postnatal course including dialysis, vesicostomy, and transplantation. Elective termination or expectant management should be offered for fetuses with poor prognostic profiles (Table EC 18.E).

B. Bladder Exstrophy-Epispadias-Cloacal Exstrophy Complex

1. **Definition:** Anomalies involving urinary tract eversion; with genitourinary, musculoskeletal, and occasionally gastrointestinal malformations. See Table EC 18.F for comparison.
2. **Diagnosis:** Fetal anatomy ultrasound showing abnormality of bladder filling, low-set umbilical cord, abdominal mass that increases in size throughout pregnancy, separation of pubic bones and small genitals.
3. **Management:** Reconstructive surgery that aims to establish bladder continence, preserve renal function, repair epispadias and genitalia, and close the pelvic bones.

XIII. RETINOPATHY OF PREMATURITY[34]

A. Definition

Interruption of normal progression of retinal vascularization.

B. Etiology

Exposure of the immature retina to high oxygen concentrations can result in vasoconstriction and obliteration of the retinal capillary network, followed by vasoproliferation. Risk is correlated to degree of prematurity.

C. Diagnosis

Dilated funduscopic examination should be performed in the following patients:

1. All infants born ≤30 weeks gestation
2. Infants born >30 weeks gestation with unstable clinical course, including those requiring cardiorespiratory support
3. Any infant with a birth weight ≤1500 g

D. Timing[35]

1. All infants born ≤27 weeks gestation, initial retinopathy of prematurity (ROP) screening examination performed at 31 weeks postmenstrual age.

TABLE EC 18.E

PROGNOSTIC CRITERIA BASED ON FETAL URINE

Urinary Component	Favorable
Sodium (Na)	Less than 100 mEq/L
Chloride (Cl)	Less than 90 mEq/L
Osmolarity (Osm)	Less than 210 mEq/L
Calcium (Ca)	Less than 2 mmol/L
Beta-2 microglobulin	Less than 2 mg/L

Data from Glick PL, Harrison MR, Golbus MS, et al. Management of the fetus with congenital hydronephrosis II: Prognostic criteria and selection for treatment. *J Pediatr Surg*. 1985;20:376–87.

TABLE EC 18.F

COMPARISON OF BLADDER EXSTROPHY-EPISPADIAS-CLOACAL EXSTROPHY COMPLEX DISORDERS

	Epispadias	Bladder Exstrophy	Cloacal Exstrophy
Severity	Mild, least severe	Intermediate	Most severe
Definition/ symptoms	Defect/opening in the urethra only Males: Urethra is short and split with meatus present on dorsum of penis. Females: Urethra develops too anteriorly with opening located between split clitoris and labia minora.	Defect in the urethra and the bladder. The posterior vesical wall everts through an opening in abdominal wall.	Defect in the urethra, bladder and rectum. Bladder divided in two halves with penis split in two halves in males, or clitoris divided in two halves in females.
Incidence	Males: 1 in 112,000 births. Females: 1 in 400,00 births.	1 in 10,000 to 1 in 50,000 births. Males affected 2–3 times more than females.	1 in 400,000 births.
Associations		Vesicoureteral reflux, urinary incontinence, widening of pubic bones, displacement of umbilicus.	Omphalocele, imperforate anus, spinal abnormalities, (OEIS).

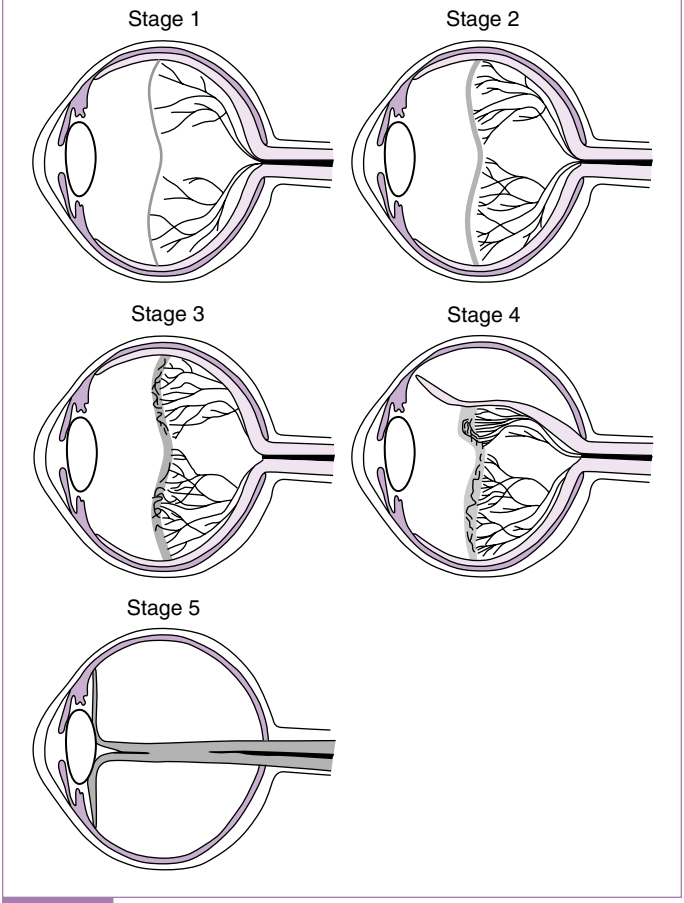


FIGURE 18.7

Retinopathy of prematurity: Stages and plus disease. (From Ann Hellström, Lois EH Smith, Olaf Dammann. Retinopathy of prematurity. *Lancet.* 2013;382(9902):1445–1457, Copyright © 2013 Elsevier Ltd.)

2. All infants born ≥28 weeks gestation, initial ROP screening examination performed at 4 weeks chronologic age.
3. Infants born before 25 weeks gestation, consider earlier screening at 6 weeks chronologic age (even if before 31 weeks postmenstrual age) based on the severity of comorbidities to enable earlier detection and treatment of aggressive posterior ROP (a severe form of rapidly progressive ROP).

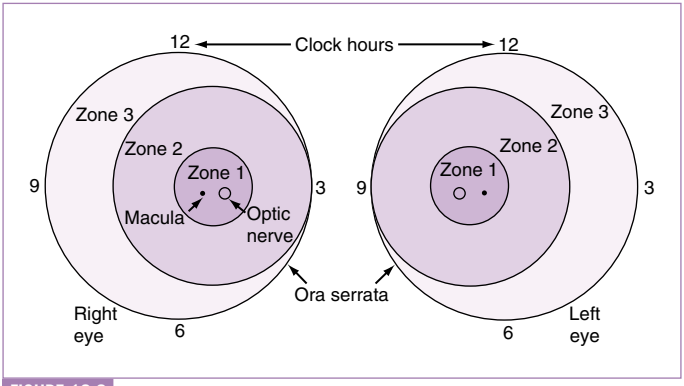


FIGURE 18.8

Zones of the retina. (From American Academy of Pediatrics. Screening examination of premature infants for retinopathy of prematurity, AAP policy statement. *Pediatrics.* 2018(6);142:1–9.)

E. Classification

1. **Stage** (Fig. 18.7)
   a. Stage 1: Demarcation line separates avascular from vascularized retina
   b. Stage 2: Ridge forms along demarcation line
   c. Stage 3: Extraretinal, fibrovascular proliferation tissue forms on ridge
   d. Stage 4: Partial retinal detachment
   e. Stage 5: Total retinal detachment
2. **Zone** (Fig. 18.8)
3. **Plus disease:** Abnormal dilation and tortuosity of posterior retinal blood vessels in two or more quadrants of retina; may be present at any stage
4. **Number of clock hours or 30-degree sectors involved**

F. Management[34-35]

1. **Type 1 ROP:** Peripheral retinal ablation should be considered. Anti-VEGF treatment may be as effective for Zone I disease. Type 1 ROP classified as:
   a. Zone I: Any stage ROP with plus disease
   b. Zone I: Stage 3 ROP without plus disease
   c. Zone II: Stage 2 or 3 ROP with plus disease
2. **Type 2 ROP:** Serial examinations rather than retinal ablation should be considered. Type 2 ROP classified as:
   a. Zone I: Stage 1 or 2 ROP without plus disease
   b. Zone II: Stage 3 ROP without plus disease
3. Follow-up (Table EC 18.G)

XIV. COMMONLY USED MEDICATIONS IN THE NEONATAL INTENSIVE CARE UNIT

See Table 18.12. For neonatal specific drug dosing, refer to Formulary.

TABLE EC 18.G

SUGGESTED SCHEDULE FOR FOLLOW-UP OPHTHALMOLOGIC EXAMINATION IN RETINOPATHY OF PREMATURITY

≤1 Week	1–2 Weeks	2 Weeks	2–3 Weeks
Zone I: stage 1 or 2 ROP Zone II: stage 3 ROP	Zone II: stage 2 ROP	Zone II: stage 1 ROP	Zone III: stage 1 or 2 ROP
Zone I: immature vascularization, no ROP	Posterior zone II: immature vascularization	Zone II: no ROP, immature vascularization	Zone III: regressing ROP
Immature retina extends into posterior zone II near boundary of zone I	Zone I: unequivocally regressing ROP	Zone II: unequivocally regressing ROP	
Suspected presence of aggressive posterior ROP			

NOTE: The presence of plus disease in zone I or II indicates that peripheral ablation rather than observation is appropriate.

ROP, Retinopathy of prematurity.

From American Academy of Pediatrics. Screening examination of premature infants for retinopathy of prematurity, AAP policy statement. *Pediatrics*. 2018;142(6):1–9.

TABLE 18.12

DOSING OF COMMONLY USED ANTIMICROBIALS IN THE NEONATAL INTENSIVE CARE UNIT, BASED ON POSTMENSTRUAL AND POSTNATAL AGE

Drug	Dosing (IV)
Acyclovir	HSV infection: 20 mg/kg/dose
Ampicillin	Typical dosing: 25–50 mg/kg/dose; GBS meningitis: ≤7 postnatal days: 300 mg/kg/day divided Q8H ≥8 postnatal days: 300 mg/kg/day divided Q6H
Cefotaxime	Sepsis/meningitis: 50 mg/kg/dose Gonococcal infections: 25 mg/kg/dose
Ceftazidime	Sepsis/Meningitis: 30–50 mg/kg/dose Consider use of ceftazidime for neonatal sepsis in the absence of cefotaxime due to drug shortages, and in whom ceftriaxone is contraindicated.
Fluconazole[b]	Invasive candidiasis: Loading 12–25 mg/kg/dose; maintenance 6–12 mg/kg/dose
Gentamicin	See chart below See Formulary for recommendations for therapeutic monitoring.
Metronidazole	Loading dose: 15 mg/kg/dose; maintenance dose: See chart below
Oxacillin	25–50 mg/kg/dose; use higher dose for meningitis
Piperacillin/ Tazobactam	100 mg/kg/dose
Vancomycin	Bacteremia: 10 mg/kg/dose; meningitis: 15 mg/kg/dose See Formulary for recommendations for therapeutic monitoring.

Dosing Interval Chart: Ampicillin, Oxacillin

PMA (Weeks)	Postnatal (Days)	Interval (Hours)
≤29[a]	0–28	12
	>28	8
30–36	0–14	12
	>14	8
37–44	0–7	12
	>7	8
≥45	All	6

Dosing Interval Chart: Vancomycin

PMA (Weeks)	Postnatal (Days)	Interval (Hours)
≤29	0–14	18
	>14	12
30–36	0–14	12
	>14	8
37–44	0–7	12
	>7	8
≥45	All	6

Dosing Interval Chart: Metronidazole

PMA (Weeks)	Maintenance Dose (mg/kg)	Interval (Hours)
24–25	7.5	24
26–27	10	24
28–33	7.5	12
34–40	7.5	8
>40	7.5	6

Dosing Interval Chart: Gentamicin

PMA (Weeks)	Postnatal (Days)	Dose (mg/kg)	Interval (Hours)
≤29	0–7	5	48
	8–28	4	36
	≥29	4	24
30–34	0–7	4.5	36
	≥8	4	24
≥35	All	4	24[e]

Dosing Interval Chart: Fluconazole

Gest. Age (Weeks)	Postnatal (Days)	Interval (Hours)
≤29	0–14	48
	>14	24
≥30	0–7	48
	>7	24

Dosing Interval Chart: Acyclovir

PMA (Weeks)	Postnatal (Days)	Interval (Hours)
	All	
<30		8–12
≥30	All	8

TABLE 18.12

DOSING OF COMMONLY USED ANTIMICROBIALS IN THE NEONATAL INTENSIVE CARE UNIT, BASED ON POSTMENSTRUAL AND POSTNATAL AGE

Dosing Interval Chart: Piperacillin/Tazobactam, Ceftazidime

PMA (weeks)	Postnatal (Days)	Interval (Hr)
≤29	0–28	12
	>28	8
30–36	0–14	12
	>14	8
37–44	0–7	12
	>7	8
≥45	All	8

Dosing Interval Chart: Cefotaxime

	Sepsis		Meningitis[c,d]	
GA (Weeks)	Postnatal (Days)	Interval (Hr)	Postnatal (Days)	Interval (Hr)
All weeks	<7	12	0–7	8–12
<32	≥7	8	>7	6–8
≥32	≥7	6		

[a]Or significant asphyxia, PDA, or treatment with indomethacin

[b]Thrush = 6 mg/kg/dose on day 1, then 3 mg/kg/dose orally (PO) Q24 hr, regardless of gestational or postnatal age.

[c]Consider smaller doses and longer intervals for very low–birth weight neonates (less than 2 kg).

[d]Usual dose same for bone and joint, genitourinary, intra-abdominal, lower respiratory tract, or skin and skin structure infections.

[e]Use every 36 hr dosing for patients undergoing therapeutic hypothermia.

See Online NeoFax: http://neofax.micromedexsolutions.com/neofax/neofax.php?strTitle=NeoFax&area=1&subarea=0

GBS, Group B *Streptococcus; GC*, gonococcus; *GA*, gestational age; *IV*, intravenous; *PDA*, patent ductus arteriosus; *PMA*, postmenstrual age.

XV. WEB RESOURCES

- Educational resource: www.nicuniversity.org
- Outcomes calculator: http://www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/pages/epbo_case.aspx
- Neonatal dermatology: http://www.adhb.govt.nz/newborn/TeachingResources/Dermatology/Dermatology.htm
- Premature growth chart and calculator: http://peditools.org/fenton2013
- Bilitool: https://bilitool.org
- NeoFax: https://neofax.micromedexsolutions.com/neofax
- Neonatal Sepsis Calculator: https://neonatalsepsiscalculator.kaiserpermanente.org/
- 7th Edition of the Neonatal Resuscitation Program (NRP): https://www.aap.org/en-us/continuing-medical-education/life-support/NRP/Pages/NRP.aspx

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A complete list of references can be found online at www.expertconsult.com.

XVI. ONLINE CONTENT

I. PRENATAL ASSESSMENT OF FETAL HEALTH

A. Fetal Anomaly Screening

1. **Fetal screening:**
   a. Chorionic villus sampling (CVS): Segment of placenta obtained either at 8 to 11 weeks gestation. Detects chromosomal abnormalities and metabolic disorders; however, it cannot detect neural tube defects or measure α-fetoprotein (AFP). Complications include pregnancy loss (0.7% to 2%), maternal infection, increased risk for feto-maternal hemorrhage, and fetal limb and jaw malformations.
   b. Amniocentesis: 20 to 30 mL of amniotic fluid is withdrawn under ultrasound guidance after 16 to 18 weeks gestation. Detects chromosomal abnormalities, metabolic disorders, and neural tube defects. Complications include pregnancy loss (0.06% to 1.0%), leakage of amniotic fluid (1.7%), chorioamnionitis, vertical transmission to infant in mothers with chronic viral infections, and fetal scarring or dimpling of the skin.
   c. Cell free DNA is a noninvasive prenatal screening test available for common trisomies and fetal sex determination. However, there are still limitations to this testing and further diagnostic testing is typically recommended for positive results.[1]
2. **Anatomy ultrasound:** Performed at 18 to 20 weeks gestation.
3. **Maternal AFP:** (Box EC 18.B)

B. Fetal Health

1. **Amniotic fluid volume estimation and amniotic fluid index (AFI):** (Box EC 18.C). AFI is calculated using ultrasound by adding together width of amniotic fluid pockets in four quadrants
2. **Biophysical profile test:** (Table EC 18.H)
3. **Intrapartum Fetal Heart Rate (FHR) Monitoring:**
   a. **Normal baseline FHR:** 120 to 160 beats/min (bpm). Mild bradycardia is 100 to 120 bpm. Severe bradycardia is <90 bpm.
   b. **Normal beat-to-beat variability:** Deviation from baseline of >6 bpm. Absence of variability is <2 bpm from baseline and is a sign of potential fetal distress, particularly when combined with variable or late decelerations.
   c. **Accelerations:** Associated with fetal movements, are benign, and indicate fetal well-being.
   d. **Decelerations:**
      (1) Early decelerations: Begin with onset of contractions. Heart rate reaches nadir at peak of contraction and returns to baseline as contraction ends. Early decelerations occur secondary to changes in vagal tone after brief hypoxic episodes or head compression and are benign.
      (2) Variable decelerations: Represent umbilical cord compression and have no uniform temporal relationship to the onset of a contraction. Variable decelerations are considered severe when

BOX EC 18.B

MATERNAL α-FETOPROTEIN ASSOCIATIONS

Elevated (>2.5 multiples of the median)	Low (<0.75 multiples of the median)
Incorrect gestational dating	Underestimation of gestational age
Neural tube defects	Intrauterine growth retardation
Anencephaly	Trisomy 13
Multiple pregnancy	Trisomy 18
Turner syndrome	Trisomy 21
Omphalocele	
Cystic hygroma	
Epidermolysis bullosa	
Renal agenesis	

Data from Cunningham FG, Leveno KJ, et al. Prenatal diagnosis. In: *Williams Obstetrics*. 25th ed. USA, McGraw-Hill Education; 2018.

BOX EC 18.C

AMNIOTIC FLUID VOLUME ESTIMATION AND AMNIOTIC FLUID INDEX

Oligohydramnios (<500 mL)/(AFI <5)	Polyhydramnios (>2L)/(AFI >25)

• Renal and urologic anomalies:
  • Potter syndrome
  • Lung hypoplasia
• Limb deformities
• Premature rupture of membranes
• Placental insufficiency
	• GI anomalies: Gastroschisis, duodenal atresia, tracheoesophageal fistula, diaphragmatic hernia, esophageal atresia ± tracheoesophageal fistula
	• CNS anomalies: those associated with impaired swallowing (anencephaly, holoprosencephaly), neuromuscular disorders such as myotonic dystrophy, spinomuscular atrophy (SMA, Werdnig-Hoffman disease)
	• Chromosomal trisomies
	• Maternal diabetes
	• Cystic adenomatoid malformation of the lung

AFI, Amniotic fluid index; *CNS*, central nervous system; *GI*, gastrointestinal.
Data from Cunningham FG, Leveno KJ, et al. Amniotic fluid. In: *Williams Obstetrics*. 25th ed. USA, McGraw-Hill Education; 2018.

heart rate drops to <60 bpm for about 60 seconds, with a slow recovery to baseline.

(3) Late decelerations: Occur after peak of contraction, persist after contraction stops, and show a slow return to baseline. Late decelerations result from uteroplacental insufficiency and indicate fetal distress.

C. Estimation of Gestational Age

1. **Last menstrual period (LMP).** Naegele rule gives most accurate determination of gestational age

   Estimation due date = (LMP − 3 months) + 7 days

2. **Ultrasound:** Crown-rump length obtained between 6 and 12 weeks gestation predicts gestational age ± 3 to 4 days. After 12 weeks,

TABLE EC 18.H

THE BIOPHYSICAL PROFILE

Biophysical Variable	Normal (Score = 2)	Abnormal (Score = 0)
Fetal breathing movements	1 or more episodes of ≥20 sec within 30 min	Absent or no episode of ≥20 sec within 30 min
Gross body movements	2 or more discrete body/limb movements within 30 min (episodes of active continuous movement considered as a single movement)	<2 episodes of body/limb movements within 30 min
Fetal tone	1 or more episodes of active extension with return to flexion of fetal limb(s) or trunk (opening and closing of hand considered normal tone)	Slow extension with return to partial flexion, movement of limb in full extension, absent fetal movement, or partially open fetal hand
Reactive fetal heart rate	2 or more episodes of acceleration of ≥5 bpm and of >15 sec associated with fetal movement within 20 min	1 or more episodes of acceleration of fetal heart rate or acceleration of <15 bpm within 20 min
Qualitative amniotic fluid volume	1 or more pockets of fluid measuring ≥2 cm in vertical axis	Either no pockets or largest pocket <2 cm in vertical axis

bpm, Beats per minute.

Adapted from Gearhart et al. Biophysical profile, ultrasound. Emedicine. www.emedicine.com.

the biparietal diameter is accurate within 10 days; beyond 26 weeks, accuracy diminishes to ± 3 weeks.

3. **Postmenstrual age:** Gestational age + chronological age in weeks. Used in perinatal period during hospitalization and until 2 years of age.

D. Expected Birth Weight by Gestational Age (see Table 18.1)

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Chapter 19

Nephrology

Paul M. Gallo, MD, PhD

I. URINALYSIS[1]: TABLE 19.1

A. Common indications include: Infectious workup (urinary tract infection [UTI], pyelonephritis), abdominal trauma, suspected diabetes or renal disease, rhabdomyolysis, edema, failure to thrive.
B. Best if urine specimen is evaluated within 1 hour of voiding, otherwise should be kept at 4°C.
C. Annual screening UAs are not recommended by the American Academy of Pediatrics (AAP) unless patient is at high risk of chronic kidney disease.

II. KIDNEY FUNCTION TESTS

A. Tests of Glomerular Function

1. **Glomerulogenesis is complete at 36 weeks gestation.** Glomerular filtration rate (GFR) increases over the first two years of life related to glomerular maturation.
2. **Normal GFR values**, as measured by inulin clearance (gold standard), are shown in Table 19.2.
3. **Creatinine clearance (CCr):**
   Closely approximates inulin clearance in the normal range of GFR. When GFR is low, CCr overestimates GFR. May be inaccurate in children with obstructive uropathy or problems with bladder emptying secondary to challenges getting complete timed urine collections.

$$\text{CCr (mL/min/1.73 m}^2\text{)} = [U \times (V/P)] \times 1.73/\text{BSA},$$

   where U (mg/dL) = urinary creatinine concentration; V (mL/min)= total urine volume (mL) divided by the duration of the collection (min) (24 hours = 1440 minutes); P (mg/dL) = serum creatinine concentration (may average two levels); and BSA (m^2) = body surface area.
4. **Estimated GFR (eGFR) from plasma creatinine:** Varies related to body size/muscle mass. If body habitus is markedly abnormal or a precise measurement of GFR is needed, consider other methods. Creatinine must be in steady state to estimate GFR; use caution in the setting of acute kidney injury. Three methods to calculate estimated GFR:

TABLE 19.1

URINALYSIS COMPONENTS

Test	Purpose	Normal Findings	Special Notes
Appearance	General impression	Colorless to amber. Cloudy/turbid urine can be normal.	Causes of turbid urine: • Uric acid crystals in acidic urine • Phosphate crystals in alkaline urine • Cellular and infectious material Causes of red/orange urine: Foods, drugs (propofol, chlorpromazine, thioridzine, rifampin), hemoglobinuria, porphyrias
Specific Gravity	Correlates with kidney's ability to concentrate urine; surrogate of osmolality and hydration status	Between 1.003 and 1.030	Isosthenuria: Urine with osmolality equal to plasma (specific gravity of 1.010). May indicate disease affecting ability to concentrate/dilute urine. Falsely elevated by: Glucose, high protein, iodine-based contrast, ketoacids
pH	Evaluate renal tubule hydrogen ion maintenance	pH 4.5–8, average range of 5–6	Influenced by serum pH Alkaline urine may indicate UTI with urea-splitting organisms or certain types of stones
Protein	Evaluate for proteinuria	**Dipstick values:** Negative Trace 1+ (~30 mg/dL) 2+ (~100 mg/dL) 3+ (~300 mg/dL) 4+ (>1000 mg/dL)	Confirm and quantify significant proteinuria with random urine protein/creatinine ratio or 24-hr urine collection Evaluate for postural proteinuria with first morning void Concentrated urine can lead to false positive result
Glucose	Detect glucose in urine	Glucosuria is always abnormal	Glucosuria typically seen when blood glucose >160–180 mg/dL Consider diabetes mellitus, proximal renal tubular disease, pregnancy Dipstick only measures glucose; reduction tests (Clinitest) will detect other sugars for suspected inborn errors of metabolism
Ketones	Detect breakdown of fatty acids	Negative to trace	Suggests diabetes mellitus or starvation-induced catabolism Neonatal ketoacidosis may indicate inborn error of metabolism
Nitrite	Detect gram-negative bacterial metabolism	Negative	Specific (90%–100%), but not sensitive (15%–82%) for UTI False positive from phenazopyridine

Test	Purpose	Normal Findings	Special Notes
Leukocyte Esterase	Detect presence of WBCs	Negative	Indicates pyuria Sensitive (67%–84%), but less specific (64%–92%) for UTI
Hemoglobin	Detects presence of RBCs or hemoglobin	Negative	Indicates hematuria or hemoglobinuria False positive on dipstick: Myoglobin (crush injury, rhabdomyolysis, vigorous exercise, etc.), contamination with blood outside the urinary tract
Bilirubin, Urobilinogen	Evaluate for hyperbilirubinemia	Negative	Positive with indirect hyperbilirubinemia Urobilinogen may be present in low amounts; increased in all cases of hyperbilirubinemia
Red Blood Cells	Differentiate hemoglobinuria from intact RBCs	Centrifuged urine normally contains <5 RBC/hpf	RBC morphology suggest location of bleeding; dysmorphic RBCs suggest a glomerular origin, normal RBCs suggest lower tract bleeding
White Blood Cells	Detect inflammation/infection	Centrifuged urine normally contains <5 WBC/hpf	Consider UTI, sterile pyuria, inflammatory disorders (e.g., Kawasaki)
Epithelial Cells	Index of possible contamination	<5 squamous epithelial cells/hpf	15–20 squamous epithelial cells/hpf suggests contamination, although any amount may indicate contamination
Sediment	Investigate for formed elements: casts, cells, crystals	None	Hyaline casts: may be normal (e.g., dehydration)

RBC, Red blood cell; *UTI*, urinary tract infection; *WBC*, white blood cell

TABLE 19.2

NORMAL VALUES OF GLOMERULAR FILTRATION RATE

Age (Sex)	Mean GFR ± SD (mL/min/1.73 m^2)
1 week (M and F)	41 ± 15
2–8 weeks (M and F)	66 ± 25
>8 weeks (M and F)	96 ± 22
2–12 years (M and F)	133 ± 27
13–21 years (M)	140 ± 30
13–21 years (F)	126 ± 22

F, Female; *M*, male; *SD*, standard deviation.

Adapted from: Hogg RJ, Furth S, Lemley KV, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease in Children and Adolescents: Evaluation, Classification, and Stratification. *Pediatrics*. 2003;111:1416.

TABLE 19.3

PROPORTIONALITY CONSTANT FOR CALCULATING GLOMERULAR FILTRATION RATE

Age	*k*-Values
Low birth weight during first year of life	0.33
Term AGA during first year of life	0.45
Children and adolescent girls	0.55
Adolescent boys	0.70

AGA, Appropriate for gestational age.

Data from Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am.* 1987;34:571.

a. **Bedside Chronic Kidney Disease in Children (CKiD) cohort**: Only applicable if creatinine measured by enzymatic assay. Recommended for eGFR determination in children aged 1 to 16 years. Estimated GFRs of ≥75 mL/min/1.73 m^2 determined by this equation likely represent normal kidney function; clinical correlation is recommended with GFR estimation.[2]

$$\text{eGFR}(\text{mL}/\text{min}/1.73\ \text{m}^2) = 0.413\times (\text{L}/\text{Pcr}),$$

where *0.413* is the proportionality constant, *L* = height (cm), and *Pcr* = plasma creatinine (mg/dL).

b. **Schwartz equation**: Historical equation for eGFR in children. However, laboratories are increasingly shifting to enzymatic assays to determine creatinine; use of enzymatically determined creatinine (vs Jaffe method) with the Schwartz equation leads to overestimation of GFR and should be considered when applying clinically:

$$\text{eGFR}(\text{mL}/\text{min}/1.73\ \text{m}^2) = \text{kL}/\text{Pcr},$$

where *k* = proportionality constant (Table 19.3); *L* = height (cm); and *Pcr* = plasma creatinine (mg/dL).

c. **Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI):** Used to calculate GFR in those >18 years old. Available at NKDEP website (see Section XII).

5. **Other measurements of GFR:** May be used when more precise determination of GFR is needed (e.g., dosing of chemotherapy). These methods include iothalamate, DTPA, and iohexol. Cystatin C is a low molecular protein that can also be used to estimate GFR and is more accurate than serum creatinine in individuals with conditions that significantly impact muscle mass, the source of creatinine.

B. Tests of Kidney Tubular Function

1. **Proximal tubule and solute handling:**
   a. **Proximal tubule reabsorption:** Proximal tubule is responsible for reabsorption of electrolytes, glucose, and amino acids. Studies to evaluate

proximal tubular function compare urine and blood levels of specific compounds, arriving at a percentage of tubular reabsorption (Tx):

$$Tx = 1 - [(Ux / Px)/(UCr / PCr)] \times 100\,\%,$$

where *Ux* = concentration of compound in urine; *Px* = concentration of compound in plasma; *Ucr* = concentration of creatinine in urine; and *Pcr* = concentration of creatinine in plasma. This formula can be used for amino acids, electrolytes, calcium, and phosphorus. It is commonly used to calculate tubular reabsorption of phosphate (TRP). In a patient with hypophosphatemia and preserved proximal tubular function, the tubular reabsorption of phosphate would be expected to be near 100%.

b. **Fractional excretion of sodium (FENa)[3]:** Commonly used to assess tubular function. Must consider sodium and volume status. May be inaccurate with recent diuretic use.

$$FENa = [(UNa / PNa) / (UCr / PCr)] \times 100\,\%,$$

where *UNa* = concentration of sodium in urine; and *PNa* = concentration of sodium in plasma. FENa is usually <1% in prerenal azotemia or glomerulonephritis, and >1% (usually >3%) in acute tubular necrosis (ATN) or postrenal azotemia. Infants have diminished ability to reabsorb sodium; FENa in volume-depleted infants is <3%.

c. **Fractional excretion of urea (FEurea):** May be useful in certain clinical scenarios, including patients on diuretics. Use FENa equation above, substituting urea for sodium. FEurea is usually <35% in prerenal azotemia and >50% in ATN.[3]

d. **Fractional excretion of bicarbonate ($FHCO_3$)**: May help differentiate the types of renal tubular acidosis (RTA). The majority of bicarb reabsorption occurs in proximal tubule.

$$FeHCO_3 = [(UHCO_3 / PHCO_3) / (UCr / PCr)] \times 100\,\%,$$

Normal $FEHCO_3$ is <5%. Distal RTA is usually <5%. >15% suggests proximal (Type II) RTA.

2. **Distal tubule and pH balance:**

a. **Urine anion gap (UAG):** Used as an indirect measure of ammonium production in the distal nephron.

$$UAG = UNa + UK - UCl,$$

where *UNa* = concentration of sodium in urine; *UK* = concentration of potassium in urine; and *UCl* = concentration of chloride in urine. Positive UAG (usually >20) suggests a distal RTA. Negative UAG (usually <–20) suggests high urinary NH4+ (e.g., secondary to diarrhea).

b. **Urine pH:** A urine acidification defect (distal RTA) should be suspected when random urine pH values are >6 in the presence of moderate systemic metabolic acidosis. Confirm acidification defects by simultaneous venous or arterial pH, plasma bicarbonate concentration, and determination of the pH of fresh urine.

c. **Urine osmolality:** Urine is concentrated distally in the kidney tubules. Urine osmolality, ideally on a first morning urine specimen, may be

TABLE 19.4

AGE-ADJUSTED CALCIUM/CREATININE RATIOS

Age	Ca^{2+}/Cr Ratio (mg/mg) (95th Percentile for Age)
<7 months	0.86
7–18 months	0.60
19 months to 6 years	0.42
Adults	0.22

From Sargent JD, Stukel TA, Kresel J, et al. Normal values for random urinary calcium-to-creatinine ratios in infancy. *J Pediatr.* 1993;123:393.

used to evaluate capacity to concentrate urine. If osmolality is >600 mOsm/L, then tubular dysfunction, including disease states such as diabetes insipidus leading to inappropriate water loss, is unlikely. For more formal testing, see the water deprivation test in Chapter 10.

d. **Urine calcium**: Hypercalciuria may be seen with distal RTA, vitamin D intoxication, hyperparathyroidism, immobilization, excessive calcium intake, use of steroids or loop diuretics, or an idiopathic cause. Diagnosis is as follows:
   (1). 24-hour urine: Calcium >4 mg/kg/24 hr (gold standard)
   (2). Spot urine: Determine calcium/creatinine (Ca/Cr) ratio. Normal urine Ca/Cr ratio does not rule out hypercalciuria. Correlate clinically and follow elevated spot urine Ca/Cr ratio with a 24-hr urine calcium determination if indicated (Table 19.4).[4]

III. CHRONIC HYPERTENSION[5-7]

Note: See Chapter 1 for the management of acute hypertension and Chapter 7 for normal blood pressure (BP) parameters.

A. Definition

Hypertension is defined as the sustained elevation of BP at or above the 95th percentile for those <13 years or ≥130/80 for those ≥13 years. Any BP that is >90th percentile or ≥120/80 should be repeated at a clinic visit; if persistently elevated when confirmed by manual auscultation, the child should return for a repeat measurement for confirmation (see Section III.E).

B. Measurement of Blood Pressure in Children

1. All children ≥3 years should have BP measured annually. Children ≥3 years should have BP measured at **all** visits if at increased risk for hypertension: obesity, taking medications known to increase BP, renal disease, history of aortic arch obstruction/coarctation, diabetes.
2. Children aged <3 years with risk factors should have BP measured at all well-child care visits. Risk factors include history of prematurity <32 weeks gestation or small for gestational age, very low birth weight, congenital heart disease, kidney/urologic disease or family history of

TABLE 19.5

CAUSES OF HYPERTENSION BY AGE GROUP

Age	Most Common	Less Common
Neonates/infants	Renal artery thrombosis after umbilical artery catheterization Coarctation of aorta Renal artery stenosis	Bronchopulmonary dysplasia Medications Patent ductus arteriosus Intraventricular hemorrhage
1–10 years	Renal parenchymal disease Coarctation of aorta	Renal artery stenosis Hypercalcemia Neurofibromatosis Neurogenic tumors Pheochromocytoma Mineralocorticoid excess Hyperthyroidism Transient hypertension Immobilization-induced Sleep apnea Essential hypertension Medications
11 years to adolescence	Renal parenchymal disease Essential hypertension	All diagnoses listed in this table

Modified from Sinaiko A. Hypertension in children. *N Engl J Med.* 1996;335:26.

kidney disease, recurrent UTIs, malignancy, solid organ or bone marrow transplant, taking medications known to increase BP, systemic illness associated with hypertension, and evidence of increased intracranial pressure.

3. BP should be measured in a seated position in an upper extremity after 5 minutes of rest with feet/back/arm supported and mid-cuff at heart level; auscultation is preferred. Appropriate cuff size has a bladder width at least 40% of upper arm circumference at midway point. Bladder length should cover 80% to 100% of arm circumference. Cuffs that are too small may result in falsely elevated BPs. Choose a larger-sized cuff if there is a choice between two.

C. Etiologies of Hypertension in Neonates, Infants, and Children (Table 19.5)

Drugs causing hypertension include glucocorticoids, calcineurin inhibitors, sympathomimetics, oral contraceptives, stimulants (methylphenidate), ephedrine, erythropoietin, NSAIDs, caffeine, tobacco, ethanol, cocaine, amphetamines.

D. Evaluation of Chronic Hypertension

1. Rule out factitious causes of hypertension (improper cuff size or measurement technique [e.g., manual vs. oscillometric]), non-pathologic causes of hypertension (e.g., fever, pain, anxiety, muscle spasm), and iatrogenic mechanisms (e.g., medications, excessive fluid administration).

2. **History:** Headache, blurred vision, dyspnea on exertion, edema, obstructive sleep apnea symptoms (including poor sleep quality or duration), endocrine symptoms (diaphoresis, flushing, constipation, weakness, etc.), history of neonatal intensive care unit stay, rule out pregnancy, history of UTIs, history of medications and supplements, illicit drug use, or any family history of kidney dysfunction or hypertension.
3. **Physical examination:** Four-extremity pulses and BPs, endocrine disease stigmata, edema, hypertrophied tonsils, skin lesions, abdominal mass, or abdominal bruit.
4. **Clinical evaluation of confirmed hypertension:**
   a. Laboratory studies:
      (1) All patients: Urinalysis (UA), serum electrolytes, creatinine, blood urea nitrogen (BUN), lipid profile
      (2) Obese patients: Hgb A1c, AST/ALT, fasting lipid panel
      (3) Consider on basis of history and exam: Fasting serum glucose, thyroid stimulating hormone, drug screen, polysomnography, complete blood count
   b. Clinical practice guidelines recommend 24-hour ambulatory blood pressure monitoring (ABPM) be conducted in all children with persistently elevated blood pressure to confirm the diagnosis of hypertension. Other at-risk populations (e.g., coarctation of the aorta status–post repair, CKD, history of hypertension) should also have this monitoring done yearly regardless of clinic blood pressure.
   c. Imaging:
      (1) Renal ultrasound in patients <6 years old or those with abnormal UA or renal function.
      (2) Echocardiography to evaluate for left ventricular hypertrophy if pharmacologic treatment considered.
      (3) Consider renovascular imaging if renal artery stenosis is suspected.
   d. Patients ≥6 years of age do not require extensive evaluation for secondary causes if they have a strong family history of hypertension (HTN), are overweight, and do not have any evidence of secondary causes on history and physical exam.

E. Classification and Treatment of Hypertension (Table 19.6)

Target: SBP and DBP to <90th percentile and <130/80 mmHg in adolescents ≥13 years old. Consider target 50th percentile in those with CKD.

1. **Nonpharmacologic:** Aerobic exercise, sodium restriction, smoking cessation, and weight loss indicated in all patients with hypertension. Reevaluate BP after lifestyle interventions, and begin pharmacologic therapy if hypertension persists.
2. **Pharmacologic:** Indications include secondary hypertension, symptomatic hypertension, stage 2 hypertension without a clearly modifiable factor (e.g., obesity), diabetes mellitus, and persistent hypertension despite nonpharmacologic measures.

TABLE 19.6

CLASSIFICATION OF HYPERTENSION IN CHILDREN AND ADOLESCENTS AND MANAGEMENT RECOMMENDATIONS

	Ages 1–13 Years	Ages ≥13 Years	Frequency of BP Measurement	Pharmacologic Therapy (in Addition to Lifestyle Modifications)
Normal BP	<90th percentile	<120/<80	Annually (or sooner if at increased risk; see Section III.B)	None
Elevated BP	90th to <95th percentile *OR* 120/80 to <95th percentile, whichever is lower	120/<80 to 129/<80	Recheck in 6 months; if persistent over 2 additional visits, conduct ABPM and diagnostic evaluation	None, unless compelling indications: CKD, DM
Stage 1 Hypertension	95th to 95th percentile plus 12 mmHg *OR* 130/80 to 139/89, whichever is lower	130/80 to 139/89	Recheck in 1–2 weeks; if persistently elevated over 2 additional visits, conduct ABPM and diagnostic evaluation	Initiate therapy, especially if symptomatic, end-organ damage is present, CKD, DM, persistent hypertension despite nonpharmacologic measures
Stage 2 Hypertension	≥95th percentile plus 12 mmHg *OR* ≥140/90, whichever is lower	≥140/90	Evaluate and refer within 1 week, or immediately if the patient is symptomatic	Initiate therapy

All blood pressures expressed in mmHg.

ABPM, Ambulatory blood pressure monitoring; *CKD*, chronic kidney disease; *DBP*, diastolic blood pressure; *DM*, diabetes mellitus; *SBP*, systolic blood pressure.

Modified from Flynn JT, Kaelber DC, Baker-Smith CM, et al., and AAP Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.

3. **Treatment monitoring:** Repeat echocardiogram every 6 to 12 months in those with cardiac end organ damage or those at high risk. Repeated 24-hour ABPM can be used to assess treatment effectiveness as needed.

F. Antihypertensive Drugs for Outpatient Management of Primary Hypertension in Children 1 to 17 Years of Age

Clinical guidelines recommend angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, thiazide diuretics, or long-acting calcium channel blockers as first-line medications for management of chronic hypertension in children.[6] Medication choice may be impacted by underlying comorbidities, contraindications, and side effects. Providers should familiarize themselves with existing guidelines, medication contraindications, and side effects. A list of medications and common side effects is found in Table 19.7.

TABLE 19.7

ANTIHYPERTENSIVE DRUGS FOR OUTPATIENT MANAGEMENT OF HYPERTENSION IN CHILDREN 1–17 YEARS OF AGE

Class	Drug	Comments
Angiotensin-converting enzyme (ACE) inhibitor	Benazepril Captopril Enalapril Fosinopril Lisinopril Ramipril Quinapril	Blocks conversion of angiotensin I to angiotensin II Decreases proteinuria while preserving renal function **Contraindicated**: Pregnancy, compromised renal perfusion (e.g., renal artery stenosis) Check serum potassium and creatinine periodically to monitor for hyperkalemia and uremia Monitor for cough and angioedema
Angiotensin-II receptor blocker (ARB)	Candesartan Irbesartan Losartan Olmesartan Valsartan	**Contraindicated**: Pregnancy Check serum potassium and creatinine periodically to monitor for hyperkalemia and uremia
α- and β-Blockers	Labetalol Carvedilol	Cause decreased peripheral resistance and decreased heart rate **Contraindications**: Asthma, heart failure, insulin-dependent diabetes Heart rate is dose-limiting May impair athletic performance
β-Blocker	Atenolol Esmolol Metoprolol Propranolol	Decreases heart rate, cardiac output, and renin release Noncardioselective agents (e.g., propranolol) are contraindicated in asthma and heart failure Metoprolol and atenolol are β_1 selective Heart rate is dose-limiting May impair athletic performance Should not be used in insulin-dependent diabetics
Calcium channel blocker	Amlodipine Felodipine Isradipine Extended-release nifedipine	Acts on vascular smooth muscles Renal perfusion/function is minimally affected; generally few side effects Amlodipine and isradipine can be compounded into suspensions May cause tachycardia

Class	Drug	Comments
Central α-agonist	Clonidine	Stimulates brainstem α_2 receptors and decreases peripheral adrenergic drive May cause dry mouth and/or sedation (↓ opiate withdrawal) Transdermal preparation also available Sudden cessation of therapy can lead to severe rebound hypertension
Loop diuretics	Furosemide Bumetanide	Side effects are hyponatremia, hypokalemia, and ototoxicity
Thiazide diuretics	Hydrochlorothiazide Chlorthalidone Chlorothiazide	Side effects are hypokalemia, hypercalcemia, hyperuricemia, and hyperlipidemia
Potassium-sparing diuretics	Spironolactone Triamterene Amiloride	Useful as add-on therapy in patients being treated with drugs from other drug classes Potassium-sparing diuretics are modest antihypertensives. They may cause severe hyperkalemia, especially if given with ACE inhibitor or ARB
Peripheral α-antagonist	Doxazosin Prazosin Terazosin	May cause hypotension and syncope, especially after first dose
Vasodilator	Hydralazine	Directly acts on vascular smooth muscle and is very potent Tachycardia, sodium retention, and water retention are common side effects
	Minoxidil	Used in combination with diuretics or β-blockers Minoxidil is usually reserved for patients with hypertension resistant to multiple drugs

Modified from Flynn JT, Kaelber DC, Baker-Smith CM, et al., and AAP Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904.

IV. URINARY TRACT INFECTIONS[8-13]

A. History

Highly dependent on patient age. Inquire about fever, dysuria, frequency, urgency, and back/abdominal pain. Obtain voiding history (stool, urine), stream characteristics in toilet-trained children, sexual activity, sexual abuse, circumcision status, prolonged/bubble baths or swimming, evaluation of growth curve, recent antibiotic use, and family history of vesicoureteral reflux (VUR), recurrent UTIs, or chronic kidney disease.

B. Physical Examination

Vital signs, abdominal examination for tenderness, flank masses, bowel distention, evidence of impaction, meatal stenosis or circumcision in males, vulvovaginitis or labial adhesions in females, neurologic examination of lower extremities, perineal sensation and reflexes, and rectal and sacral examination (for anteriorly placed anus).

C. Risk Factors

2011 AAP guidelines,[8] reaffirmed in 2016,[9] for children 2 to 24 months provide resources to help clinicians stratify the risk of UTI in the absence of another source of infection in a febrile child.

1. Females are at higher risk for UTI than males.
2. Uncircumcised males are at higher risk than circumcised males.
3. Other risk factors include non-black race, fever ≥39°C, and fever >1 to 2 days.

D. Methods of Urine Collection

1. **If a child is 2 months to 2 years old, has a fever, and appears sufficiently ill to warrant immediate antibiotics**, obtain UA and urine culture by transurethral catheterization. **Suprapubic percutaneous aspiration** may be useful in critically ill children, is generally very safe, and is similar to bladder catheterization in sensitivity and specificity.
2. **If a child is 2 months to 2 years old, has a fever, and does not appear ill enough to warrant immediate antibiotics**, obtain urine by catheterization or the most convenient method available. **Bag or absorbent pad** may be helpful when UTI is unlikely (to rule out infection), but both have very high false positive rates (>75% of cultures positive) and should not be sent for culture.[8] If UA does not suggest UTI, it is reasonable to avoid antimicrobial therapy. If UA does suggest UTI, urine culture should be obtained by catheterization.
3. **If a child is >2 years old and toilet trained**, may provide midstream clean-catch urine specimen.

E. Diagnosis

To establish the diagnosis of UTI, both UA results suggestive of infection and positive urine culture are recommended.

1. Nitrite test:
   a. Detects products of reduction of dietary nitrates by urinary gram-negative bacterial species (especially *Escherichia coli*, *Klebsiella*, and *Proteus*).
   b. Sensitivity 15% to 82% and specificity 90% to 100% for UTI.[8]
   c. Special circumstances: False-negative (low sensitivity) results commonly occur with insufficient time (<4 hours) for conversion of urinary nitrates to nitrites (age-dependent voiding frequency) and inability of bacteria to reduce nitrates to nitrites (many gram-positive organisms such as *Enterococcus*, *Mycobacterium* spp., and fungi).
2. Leukocyte esterase test:
   a. Detects esterase released from leukocyte lysis.
   b. Sensitivity 67% to 84% and specificity 64% to 92% for UTI.[8]
3. Pyuria is defined at a threshold of ≥5 WBCs/hpf. Absence of pyuria is rare if a true UTI is present.
4. Urine culture:
   a. Transurethral catheterization or suprapubic aspiration: >50,000 colony-forming units (CFU) per mL diagnostic of UTI. Some sources suggest >10,000 CFU/mL in the presence of fever, symptoms, and pyuria may also be diagnostic.[10]

b. Clean catch: >100,000 CFU/mL necessary to diagnose a UTI.
c. Bagged specimen: Should not be used to collect urine culture.
d. Catheter-associated (indwelling urethral or suprapubic): No specific data for pediatric patients. Adult Infectious Diseases Society of America guidelines define it as presence of symptoms and signs compatible with UTI and >1000 CFU/mL of one or more bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose catheter has been removed within previous 48 hours.[11]

F. Classification

Pyelonephritis (upper UTI), rather than cystitis (lower UTI), is suggested by fever ≥38.5°C (especially if lasting >48 hours after initiating appropriate antibiotics), systemic symptoms, costovertebral angle tenderness, elevated CRP, leukocytosis.

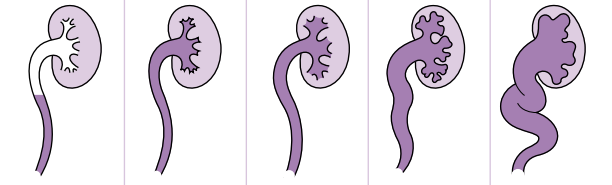
G. Imaging

1. **Renal and bladder ultrasound (RBUS):** Evaluates for anatomic abnormalities and abscesses. Indications include children 2 to 24 months with first UTI, recurrent or atypical UTIs, or if no response to treatment within 48 hours. If there is clinical improvement <48 hours and follow up is reliable, should be done after full recovery. If there is no response to treatment or follow up is uncertain, then RBUS during illness is indicated.
2. **Voiding cystourethrography (VCUG):** Evaluates bladder anatomy, emptying, and looks for signs of vesicoureteral reflux (VUR). Should not be obtained routinely after first febrile UTI. Indications include children 2 to 24 months with abnormal RBUS findings (hydronephrosis, scarring, or other findings suggestive of either high-grade VUR or obstructive uropathy), complicated or recurrent pyelonephritis.[8] Consider if family history of VUR. Optimal time is 2 to 6 weeks after infection.

H. Treatment of Culture-Positive Urinary Tract Infection

For empiric therapy, see Chapter 17.

1. **Organisms:**
   a. *E. coli* is the most common cause of pediatric UTI.
   b. Other common pathogens: *Klebsiella, Proteus* spp., *Staphylococcus saprophyticus,* and *Staphylococcus aureus.*
   c. Neonatal UTI: Group B streptococci and other bloodborne pathogens.
   d. *Enterococcus* and *Pseudomonas* are more prevalent in abnormal hosts (e.g., recurrent UTI, abnormal anatomy, neurogenic bladder, hospitalized patients, or those with frequent bladder catheterizations). Consider blood cultures if urine grows uncommon organism or *Staphylococcus.*
2. **Treatment considerations and duration:**
   a. Route: Parenteral antibiotics for children who are toxic, dehydrated, or unable to tolerate oral medication due to vomiting or noncompliance.



Grade I	Grade II	Grade III	Grade IV	Grade V
Ureter only	Ureter, pelvis, calyces; no dilatation, normal calyceal fornices	Mild or moderate dilatation and/or tortuosity of ureter; mild or moderate dilatation of the pelvis, but no or slight blunting of the fornices	Moderate dilatation and/or tortuosity of the ureter; mild dilatation of renal pelvis and calyces; complete obliteration of sharp angle of fornices, but maintenance of papillary impressions in majority of calyces	Gross dilatation and tortuosity of ureter; gross dilatation of renal pelvis and calyces; papillary impressions are no longer visible in majority of calyces

FIGURE 19.1

International classification of vesicoureteral reflux. (Modified from Rushton H. Urinary tract infections in children: epidemiology, evaluation, and management. *Pediatr Clin North Am.* 1997;44:5 and International Reflux Committee. Medical vs. surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. *Pediatrics.* 1981;67:392.)

   b. Duration: 3 to 5 days for uncomplicated cases[12]; 7 to 14 days for toxic children and those with pyelonephritis.
3. **Inadequate response to therapy:** Consider renal abscess or urinary obstruction; RBUS and repeat urine culture is indicated. Repeat cultures should also be considered in patients with recurrent UTIs to rule out persistent bacteriuria.
4. **Management of VUR:**
   a. Classification of VUR: Fig. 19.1
   b. Antibiotic prophylaxis: Evidence suggests that prophylactic trimethoprim-sulfamethoxazole reduces the risk of UTI recurrence by 50%, but with no significant difference in renal scarring. Some experts suggest that recent studies are insufficiently powered to detect a difference in the relatively rare outcomes of renal

scarring, and thus recommend shifting guideline recommendations from "no prophylaxis" to "selective prophylaxis" in certain groups of patients.[13]

c. Surgical intervention: Monitor persistence/grade of VUR annually, often in consultation with a pediatric urologist. Spontaneous resolution may occur, although less likely with higher grade. Higher-grade VUR that persists as the child grows may ultimately require surgical intervention.

5. **Asymptomatic bacteriuria:** Defined as bacteria in urine on microscopy and Gram stain in an afebrile, asymptomatic patient without pyuria. Antibiotics not necessary if voiding habits and urinary tract are normal.
6. **Referral to pediatric urology:** Consider in children with abnormal voiding patterns based on history or imaging, neurogenic bladder, abnormal anatomy, recurrent UTI, or poor response to appropriate antibiotics.

V. PROTEINURIA[14–16]

A. Definitions

1. **Orthostatic proteinuria:** Excretion of significant amounts of protein while in the upright position. A benign condition and common cause of proteinuria in children and adolescents.
2. **Fixed proteinuria:** Proteinuria found on first morning urine void over several consecutive days. Suggestive of kidney disease.
3. **Microalbuminuria:** Presence of albumin in urine below detectable range of dipsticks. In adults, defined as 30 to 300 mg/g creatinine. Most often used in screening for kidney disease secondary to diabetes.
4. **Significant proteinuria:** Urine protein to urine creatinine (UPr:UCr) ratio 0.2 to 2.0 mg/mg or 4 to 40 mg/m^2/hr in a 24-hour collection.
5. **Nephrotic-range proteinuria:** UPr:UCr ratio >2 mg/mg or >40 mg/m^2/hr in a 24-hour collection. In adults, 24-hour urine protein excretion of 3000 mg/24 hours.
6. **Nephrotic syndrome:** Nephrotic-range proteinuria, hypoalbuminemia, edema, and hyperlipidemia (cholesterol >200 mg/dL).

B. Methods of Detection

1. **Urinalysis** (see Table 19.1): Proteinuria on a urine dipstick should be verified by a urine protein/creatinine ratio in an appropriately collected first morning urine specimen. Urine samples collected immediately upon rising in the morning help distinguish the contribution of benign orthostatic proteinuria to the proteinuria detected on dipstick or randomly timed spot urine collection.
2. **First morning urine protein/creatinine ratio:**
   a. Approximates 24-hour urine collections well.
   b. Appropriate collection is essential for accurate results. A child must empty the bladder before going to bed. If the child gets up during the night, the bladder should be emptied before returning to bed. When the child wakes up in the morning, the urine sample should be provided immediately.

BOX 19.1

CAUSES OF PROTEINURIA

Transient proteinuria: Caused by fever, exercise, dehydration, cold exposure, seizure, stress

Orthostatic proteinuria

Glomerular diseases with isolated proteinuria: Idiopathic (minimal change disease) nephrotic syndrome, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, amyloidosis, diabetic nephropathy, sickle cell nephropathy

Glomerular diseases with proteinuria as a prominent feature: Acute postinfectious glomerulonephritis, immunoglobulin A nephropathy

Tubular disease: Cystinosis, Wilson disease, acute tubular necrosis, tubulointerstitial nephritis, polycystic kidney disease, renal dysplasia, toxic tubular injury (medications, heavy metals)

Adapted from Kliegman RM, Stanton BF, St. Geme JW, et al. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Saunders; 2015.

c. Normal ratios:
   (1) <2 years old: <0.5 mg/mg
   (2) >2 years old: <0.2 mg/mg
d. Abnormal ratios (mg/mg): Significant proteinuria detected on a first morning protein/creatinine ratio should prompt verification of appropriate collection. Repeat specimen should be analyzed within 1 to 2 weeks, or sooner based on clinical scenario (e.g., edema, hypertension, or symptom of concern would prompt a more expedited workup).

3. **24-hour urine protein:** May have a contribution from benign orthostatic proteinuria, which cannot be ruled out without a fractional urine collection. Protein level >4 mg/m^2/hr is considered significant.

C. Etiologies (Box 19.1)

See Section VI.E for discussion of nephrotic syndrome.

D. Evaluation[15]

Further evaluation is necessary if proteinuria is significant/symptomatic and not secondary to orthostatic proteinuria (Box 19.2).

E. Nephrotic Syndrome[16]

1. **Epidemiology:** Idiopathic nephrotic syndrome of childhood is the most common form, representing approximately 90% of cases in children between the ages of 1 and 10 years. *Minimal change disease* is the most common renal pathology found among children with idiopathic nephrotic syndrome in this age group. Nephrotic syndrome may be a manifestation of a primary kidney disease, a systemic disorder resulting in glomerular injury, or rarely medication.
2. **Clinical manifestations**: Hypoalbuminemia and decrease in oncotic pressure results in generalized edema. Initial swelling commonly occurs on the face (especially periorbital), as well as in the pretibial area. Eye swelling is often mistaken for allergic reactions or seasonal allergies (Box 19.3).

BOX 19.2

BASIC EVALUATION OF SIGNIFICANT (NEPHROTIC AND NONNEPHROTIC) PROTEINURIA

Complete metabolic panel with phosphorus
C3 and C4
ESR, CRP
Antinuclear antibody, anti–double stranded DNA antibody
Hepatitis B, C, and HIV in high-risk populations
Antineutrophil antibodies (c- and p-ANCA)
Lipid panel
Renal and bladder ultrasonography
Referral to nephrologist

BOX 19.3

FACTORS SUGGESTING DIAGNOSIS OTHER THAN IDIOPATHIC MINIMAL CHANGE NEPHROTIC SYNDROME

Age <1 year or >10 years
Family history of kidney disease
Extrarenal disease (arthritis, rash, anemia)
Chronic disease of another organ or systemic disease
Symptoms due to intravascular volume expansion (hypertension, pulmonary edema)
Kidney failure
Active urine sediment (red blood cell casts)

TABLE 19.8

ETIOLOGIES OF NEPHROTIC SYNDROME

Primary Causes (90%)	Secondary Causes (10%)
Minimal change nephrotic syndrome (MCNS): 85% of idiopathic causes in children	Infections (HIV, hepatitis B, hepatitis C)
Focal segmental glomerulosclerosis (FSGS)	Systemic lupus erythematosus
Membranous nephropathy	Diabetes mellitus
IgA nephropathy	Drugs
Genetic disorders involving the slit diaphragm	Malignancy (leukemias, lymphomas)

3. **Etiologies:** See Table 19.8.
4. **Investigations at first presentation:** UA and microscopy (microhematuria present in 30% and is not prognostic); urine P/Cr ratio; serum albumin, total protein, cholesterol, creatinine; infectious workup (consider tuberculosis, HIV, hepatitis B, hepatitis C, as indicated).
5. **Management of idiopathic nephrotic syndrome of childhood:** Empirical corticosteroid treatment without kidney biopsy is recommended for children without atypical features. Hospitalization recommended for children with overwhelming edema or infection.

a. Steroid-responsive: Approximately 95% of patients with minimal change disease (MCD) and 20% with focal segmental glomerulosclerosis (FSGS) achieve remission within 4 to 8 weeks of starting prednisone. Response to corticosteroids is the best prognostic indicator, including the likelihood of underlying MCD.
   (1) Although duration of therapy varies, one common regimen includes prednisone 60 mg/m^2 daily or 2 mg/kg/day (maximum dose 60 mg/day) for 6 weeks, followed by 40 mg/m^2 or 1.5 mg/kg on alternate days for 6 weeks.[16]
   (2) Relapses of idiopathic nephrotic syndrome are treated with a shorter duration of corticosteroids, which also vary according to the center and the consensus body. Commonly, prednisone 60 mg/m^2 or 2 mg/kg/day (maximum dose 60 mg/day) until urine protein is negative for 3 consecutive days, followed by 40 mg/m^2 or 1.5 mg/kg on alternate days for 4 weeks.
b. Frequently relapsing: Defined as 2 or more relapses within 6 months of initial response, or 4 or more relapses in any 12-month period.
c. Steroid-dependent: Defined as 2 consecutive relapses during tapering or within 14 days of cessation of steroids. Some patients can be managed with low-dose steroids, given daily or on alternate days, but many will relapse. Second-line treatments for frequently relapsing and steroid-dependent nephrotic syndrome: Cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors, levamisole, or rituximab.
d. Steroid-resistant: Lack of remission or partial remission after 8 weeks of corticosteroids. Second-line agents, including calcineurin inhibitors or MMF, are often introduced once steroid resistance is confirmed.
e. Indications for renal biopsy: Macroscopic hematuria, age <12 months or >12 years, systemic or syndromic findings, persistent creatinine elevation >1 to 2 weeks, low complement levels, and persistent proteinuria after 4 to 8 weeks of adequate steroid treatment.[17]

6. **Complications:**
   a. AKI; thromboembolic disease; potentially life-threatening infection. See Chapter 16 for vaccine recommendations.
   b. Chronic systemic steroids: Cushingoid skin changes, cataracts, accelerated atherosclerosis, osteoporosis, gastric ulcer, mood swings, insomnia, insulin resistance, immunosuppression.

VI. HEMATURIA[18]

A. Definition

1. **Microscopic hematuria:** >5 RBCs/hpf on centrifuged urine. Not visible to the naked eye.
2. **Macroscopic (gross) hematuria:** Visible blood in urine.
3. **Acute nephritic syndrome:** Classically tea or cola-colored urine, facial or body edema, hypertension, and oliguria.

B. Etiologies: See Table 19.9.

TABLE 19.9

CAUSES OF HEMATURIA IN CHILDREN

Kidney-related disease	Isolated glomerular disease	IgA nephropathy, Alport syndrome, thin glomerular basement membrane nephropathy, postinfectious/poststreptococcal glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, antiglomerular basement membrane disease
	Multisystem disease involving glomerulus	Systemic lupus erythematosus nephritis, Henoch-Schönlein purpura nephritis, granulomatosis with polyangiitis, polyarteritis nodosa, Goodpasture syndrome, hemolytic-uremic syndrome, sickle cell glomerulopathy, HIV nephropathy
	Tubulointerstitial disease	Pyelonephritis, interstitial nephritis, papillary necrosis, acute tubular necrosis
	Vascular	Arterial or venous thrombosis, malformations (aneurysms, hemangiomas), nutcracker syndrome, hemoglobinopathy (sickle cell trait/disease)
	Anatomical	Hydronephrosis, cystic kidney disease, polycystic kidney disease, multicystic dysplasia, tumor, trauma
Urinary tract disease		Inflammation (cystitis, urethritis) Urolithiasis Trauma Coagulopathy Arteriovenous malformations (AVMs) Bladder tumor Factitious

Data from Kliegman RM, Stanton BF, St. Geme JW, et al. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015.

C. Evaluation (Fig. 19.2)

Differentiate glomerular and extraglomerular hematuria: Examine urine sediment, looking for RBC casts and protein.

1. Glomerular hematuria
   a. Usually hypertensive; dysuria usually absent; edema, fever, pharyngitis, rash, and arthralgia may suggest glomerular disease.
   b. Laboratory: Dysmorphic RBCs and casts on UA, complete blood cell count (CBC) with differential and smear, serum electrolytes with calcium, BUN/creatinine, serum protein/albumin, and other testing driven by history and exam, including ANA, hepatitis B and C serologies, HIV, audiology screen, if indicated.
   c. Consider other studies to determine underlying diagnosis: C3/C4, antineutrophil antibody (c- and p-antineutrophil cytoplasmic antibodies), anti–double-stranded DNA
2. Extraglomerular hematuria
   a. Rule out infection: Urine culture, gonorrhea, chlamydia
   b. Rule out trauma: History, consider imaging of abdomen/pelvis
   c. Investigate other potential causes: Urine Ca/Cr ratio or 24-hour urine for kidney stone risk analysis, sickle cell screen, renal/bladder ultrasound. Consider serum electrolytes with calcium, coagulation studies.

D. Management (Fig. 19.3)

VII. ACUTE KIDNEY INJURY[19,20]

A. Definition

Sudden decline in kidney function; clinically represented by rising creatinine, with or without changes in urine output.

B. Etiology (Table 19.10)

Causes are generally subdivided into three categories:

1. **Prerenal:** Impaired perfusion of kidneys, the most common cause of acute kidney injury (AKI) in children. Volume depletion is a common cause of prerenal AKI.
2. **Renal:**
   a. Parenchymal disease due to vascular or glomerular lesions.
   b. Acute tubular necrosis: Diagnosis of exclusion when no evidence of renal parenchymal disease is present and prerenal and postrenal causes have been eliminated, if possible.
3. **Postrenal:** Obstruction of the urinary tract, commonly due to inherited anatomic abnormalities in children.

C. Clinical Presentation

Pallor, decreased urine output, systemic and pulmonary edema, hypertension, vomiting, and lethargy. The hallmark of early kidney failure is often oliguria.

1. **Oliguria:** Urine output <0.5 mL/kg/hr (for at least 6 hours). May reflect intrinsic or obstructive kidney disease. Always interpret urine output in the context of physical exam, clinical scenario, and fluid delivery.

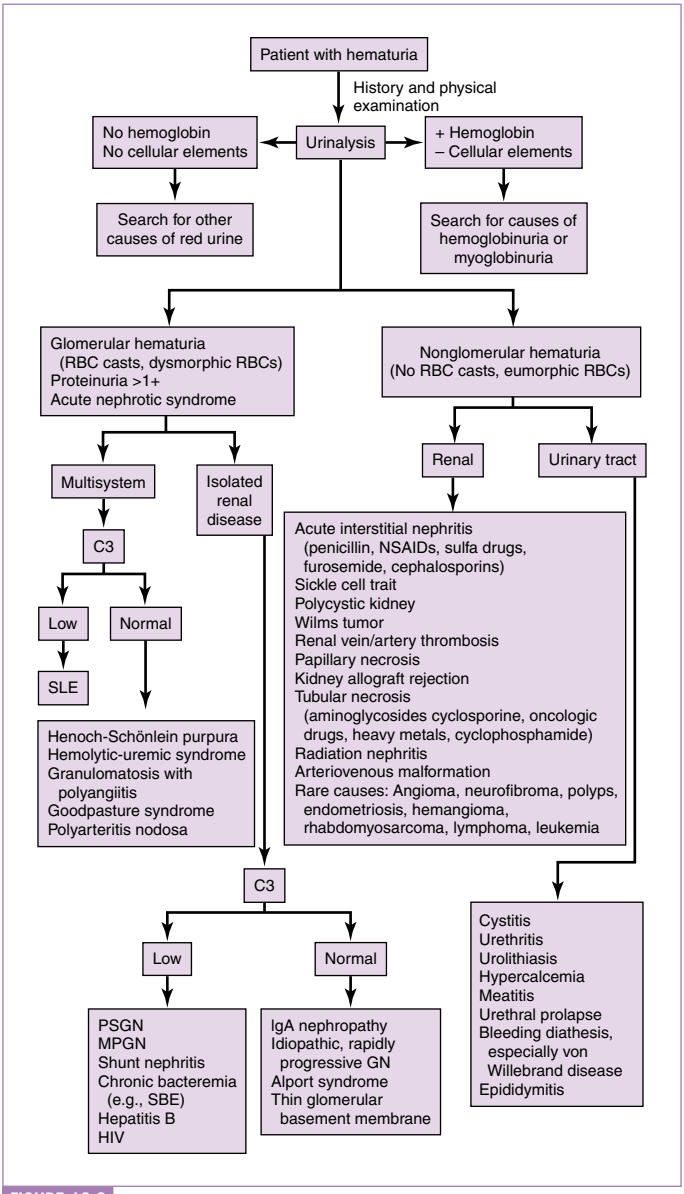


FIGURE 19.2

Diagnostic strategy for hematuria. *GN*, Glomerulonephritis; *HIV*, human immunodeficiency virus; *MPGN*, membranoproliferative glomerulonephritis; *NSAIDs*, nonsteroidal antiinflammatory drugs; *PSGN*, poststreptococcal glomerulonephritis; *RBC*, red blood cell; *SBE*, subacute bacterial endocarditis; *SLE*, systemic lupus erythematosus.

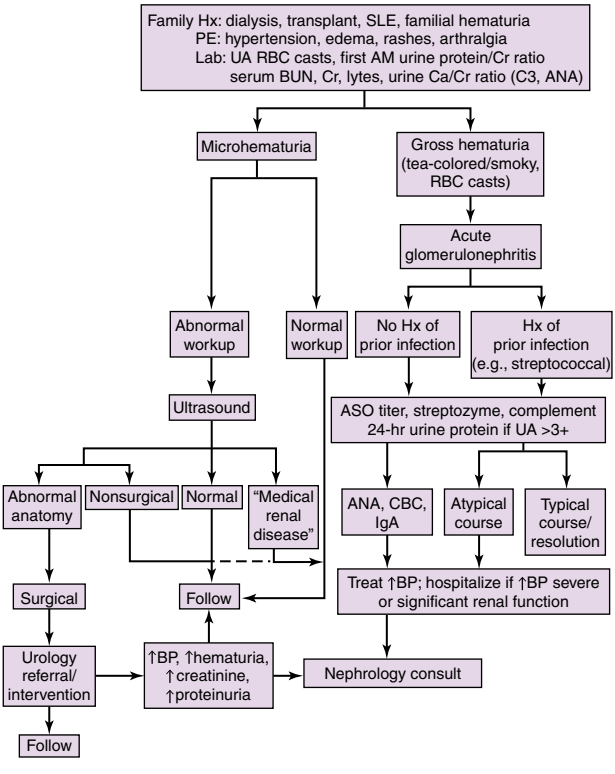


FIGURE 19.3

Management algorithm for hematuria. (Data from Hay WM, Levin MJ, Deterding RR, Azbug MJ, Sondheimer JM. *CURRENT Diagnosis & Treatment Pediatrics*. 21st ed. www.accessmedicine.com, Fig. 24.1.)

For example, low urine output may be appropriate (physiologic response to water depletion in a prerenal state) and "normal" urine output may be inappropriate in a volume-depleted patient (potentially representing kidney tubular damage or another pathologic state). Laboratory differentiation of oliguria is found in Table 19.11.

2. **Blood urea nitrogen/creatinine (BUN/Cr) ratio (both in mg/dL):** Interpret ratios with caution in small children with low serum creatinine.
   a. 10 to 20 (normal ratio): Suggests intrinsic renal disease in the setting of oliguria.

TABLE 19.10

ETIOLOGIES OF ACUTE KIDNEY INJURY

PRERENAL	**Decreased True Intravascular Volume:** Hemorrhage, volume depletion, sepsis, burns **Decreased Effective Intravascular Volume:** Congestive heart failure, hepatorenal syndrome **Altered Golmerular Hemodynamics:** NSAIDs, ACE inhibitors (when renal perfusion is already low)
INTRINSIC RENAL	**Acute Tubular Necrosis:** Hypoxic/ischemic insults Drug-induced—aminoglycosides, amphotericin B, acyclovir, chemotherapeutic agents (ifosfamide, cisplatin) Toxin-mediated—endogenous toxins (myoglobin, hemoglobin); exogenous toxins (ethylene glycol, methanol) **Interstitial Nephritis:** Drug-induced—β-lactams, NSAIDs (may be associated with high-grade proteinuria), sulfonamides, PPIs Idiopathic **Uric acid nephropathy:** Tumor lysis syndrome **Glomerulonephritis:** In most severe degree, presents as rapidly progressive glomerulonephritis (RPGN) **Vascular Lesions:** Renal artery thrombosis, renal vein thrombosis, cortical necrosis, hemolytic uremic syndrome **Hypoplasia/Dysplasia:** Idiopathic or exposure to nephrotoxic drugs in utero
POSTRENAL	Obstruction in a Solitary Kidney Bilateral Ureteral Obstruction Urethral Obstruction Bladder Dysfunction

ACE, Angiotensin-converting enzyme; *NSAIDs*, nonsteroidal antiinflammatory drugs; *PPIs*, proton pump inhibitors.
Data from Andreoli SP. Acute kidney injury in children. *Pediatr Nephrol*. 2009;24:253–263.

TABLE 19.11

LABORATORY DIFFERENTIATION OF OLIGURIA

Test	Prerenal	Renal
FENa	≤1%	>3%
BUN/Cr ratio	>20:1	<10:1
Urine specific gravity	>1.015	<1.010

BUN, Blood urea nitrogen; *Cr*, creatinine; *FENa*, fractional excretion of sodium.

b. >20: Suggests volume depletion, prerenal azotemia, or gastrointestinal bleeding.
c. <5: Suggests liver disease, starvation, or inborn error of metabolism.

D. Acute Tubular Necrosis

Clinically defined by three phases:

1. **Oliguric phase:** Period of severe oliguria that may last days. If oliguria or anuria persists for longer than 3 to 6 weeks, kidney recovery from ATN is less likely.
2. **High urine output phase:** Begins with increased urine output and progresses to passage of large volumes of isosthenuric urine containing sodium levels of 80 to 150 mEq/L.
3. **Recovery phase:** Signs and symptoms usually resolve rapidly, but polyuria may persist for days to weeks.

E. Treatment Considerations

1. Careful monitoring of volume status (daily weights, strict input/output). Consider placement of indwelling catheter to monitor urine output.
2. Prerenal and postrenal factors should be addressed or excluded.
3. Intravascular volume resuscitation and maintenance with appropriate fluids in consultation with a pediatric nephrologist.
4. Monitor metabolic/electrolyte abnormalities, discontinue unnecessary nephrotoxic medications and follow drug levels closely when available, adjust dosing of medications based on creatinine clearance (see Chapter 31), monitor blood pressure closely, and maintain appropriate nutrition (low phosphorus, low potassium).
5. See Section IX for indications for acute dialysis

F. Complications

1. Dependent on clinical severity.
2. Usually includes fluid overload (hypertension, congestive heart failure [CHF], or pulmonary edema), electrolyte disturbances (hyperkalemia), metabolic acidosis, hyperphosphatemia, and uremia.

G. Radiographic Imaging Considerations in AKI/CKD

1. To prevent radiographic contrast-induced nephropathy, select radiographic studies that do not require administration of a radiographic iodinated contrast media (RICM) if possible, particularly in high-risk populations, such as patients with AKI or CKD.[21]
2. If RICM is required, use of low or iso-osmolality contrast media is preferred.[21]
3. Hydration has been found to be effective in preventing or minimizing contrast-induced nephropathy in some studies of high-risk populations. Intravenous hydration 6 hours prior to and 6 to 12 hours after contrast administration has been studied.[21]
4. Use of N-acetylcysteine is controversial in preventing contrast-induced nephropathy.[21]
5. Gadolinium and nephrogenic systemic fibrosis: The triad of gadolinium use, a pro-inflammatory state, and renal impairment (GFR <30 mL/min per 1.73 m^2, peritoneal or hemodialysis) is associated with nephrogenic

systemic fibrosis. Gadolinium is contraindicated in patients with GFR <30 mL/min per 1.73 m^2, and caution should be used at GFR levels between 30 and 60 mL/min per 1.73 m^2.[22]

VIII. CHRONIC KIDNEY DISEASE[23]

A. Definition

Kidney damage for >3 months, as defined by structural or functional abnormalities, with or without decreased GFR. Classified as:

Stage I: Kidney injury with normal or increased GFR
Stage II: GFR 60 to 89 mL/min/1.73 m^2
Stage III: GFR 30 to 59 mL/min/1.73 m^2
Stage IV: GFR 15 to 29 mL/min/1.73 m^2
Stage V: GFR <15 mL/min/1.73 m^2 or dialysis

B. Etiology

1. Children <5 years: Most commonly due to congenital abnormalities (e.g., kidney hypoplasia/dysplasia, urologic malformations).
2. Older children: More commonly acquired glomerular diseases (e.g., glomerulonephritis, FSGS) or hereditary disorders (e.g., Alport syndrome).

C. Clinical Manifestations (Table 19.12)

D. General Management

1. **Nutrition:** Growth should be monitored closely; supplemental nutrition should be considered if not reaching caloric goals, which are higher in children with CKD. Potassium and sodium restriction may be required in advanced CKD. Growth hormone therapy may be considered in consultation with pediatric nephrology/endocrinology.
2. **Anemia:** Evaluate with CBC and iron studies. Iron deficiency is common and should be treated with oral (preferred) or IV iron. Consider erythropoietin-stimulating agents in consultation with pediatric nephrology.
3. **CKD–mineral and bone disorder:** Characterized by phosphate retention, decreased free calcium, and decreased 1,25 hydroxyvitamin D. Serum calcium, phosphate, alkaline phosphatase, vitamin D, and parathyroid hormone should be regularly monitored. Control phosphate with phosphate binders, supplement with calcium and vitamin D, as indicated.
4. **Cardiovascular:** Regularly monitor blood pressure and lipid panel. Treating hypertension slows the progression of CKD.

IX. DIALYSIS

A. Indications for Acute Dialysis

When metabolic or fluid derangements are not controlled by aggressive medical management alone. Should be initiated in consultation with a nephrologist. Generally accepted criteria include the following:

1. **Acidosis:** Intractable metabolic acidosis.

TABLE 19.12

CLINICAL MANIFESTATIONS OF CHRONIC KIDNEY DISEASE

Manifestation	Mechanisms
Edema	Accumulation of Na+ and water Decreased oncotic pressure Reduced cardiac output Mineralocorticoid excess
Uremia	Decline in GFR
Acidosis	Urinary bicarbonate wasting Decreased excretion of NH_4 and acid
Sodium wasting	Solute diuresis, tubular damage Aldosterone resistance
Sodium retention	Nephrotic syndrome CHF Reduced GFR
Urinary concentrating defect	Solute diuresis, tubular damage ADH resistance
Hyperkalemia	Decline in GFR, acidosis Aldosterone resistance
Renal osteodystrophy	Impaired production of 1,25(OH) vitamin D Decreased intestinal calcium absorption Impaired phosphorus excretion Secondary hyperparathyroidism
Growth retardation	Protein-calorie deficiency Renal osteodystrophy Acidosis Anemia Inhibitors of insulin-like growth factors
Anemia	Decreased erythropoietin production Low-grade hemolysis Bleeding, iron deficiency Decreased erythrocyte survival Inadequate folic acid intake Inhibitors of erythropoiesis
Bleeding tendency	Thrombocytopenia Defective platelet function
Infection	Defective granulocyte function Glomerular loss of immunoglobulin/opsonins
Neurologic complaints	Uremic factors
Gastrointestinal ulceration	Gastric acid hypersecretion/gastritis Reflux Decreased motility
Hypertension	Sodium and water overload Excessive renin production
Hypertriglyceridemia	Diminished plasma lipoprotein lipase activity
Pericarditis and cardiomyopathy	Unknown
Glucose intolerance	Tissue insulin resistance

ADH, Antidiuretic hormone; *CHF*, congestive heart failure; *GFR*, glomerular filtration rate; *NH_4*, ammonium.
Adapted from Brenner BM. *Brenner and Rector's The Kidney.* 10th ed. Philadelphia: Elsevier; 2015.

2. **Electrolyte abnormalities:** Hyperkalemia >6.5 mEq/L despite restriction of delivery and medical management; calcium and phosphorus imbalance (e.g., hypocalcemia with tetany, seizures in the presence of a very high serum phosphate level); derangements implicated in neurologic abnormalities.
3. **Ingestion or accumulation of dialyzable toxins or poisons:** Lithium, ammonia, alcohol, barbiturates, ethylene glycol, isopropanol, methanol, salicylates, theophylline. Consult poison control experts when available.
4. **Volume overload:** Evidence of pulmonary edema or hypertension.
5. **Uremia:** BUN >150 mg/dL (lower if rising rapidly), uremic pericardial effusion, neurologic symptoms.

B. Techniques

1. **Peritoneal dialysis (PD):** Requires catheter to access peritoneal cavity, as well as adequate peritoneal perfusion. May be used acutely or chronically. Contraindications: Abdominal wall defects (omphalocele, gastroschisis, bladder exstrophy, diaphragmatic hernia), severe inflammatory bowel disease, or infectious source in the abdomen.[24]
2. **Intermittent hemodialysis (HD):** Requires placement of special vascular access catheters. May be method of choice for certain toxins (e.g., ammonia, uric acid, poisons) or when there are contraindications to peritoneal dialysis.
3. **Continuous arteriovenous hemofiltration/hemodialysis (CAVH/D) and continuous venovenous hemofiltration/hemodialysis (CVVH/D):** Requires special vascular access catheter. Lower efficiency of solute removal compared with intermittent hemodialysis, but higher efficiency is not necessary because of the continuous nature of this form of dialysis. Sustained nature of dialysis allows for more gradual removal of volume/solutes, which is ideal for patients with hemodynamic or respiratory instability.

C. Complications

1. **PD catheter leaks:** Confirm leakage of PD fluid with glucose dipstick. Discontinue PD for 7 to 10 days or lower dialysate volume.
2. **PD associated peritonitis (PDAP):** Acute clouding of dialysate, abdominal pain/distention, vomiting. Culture peritoneal fluid and start empiric intraperitoneal antibiotics in consultation with nephrology. Refer to published Consensus Guidelines for treatment recommendations.[25]
3. **Intradialytic hypotension in HD:** Causes include rapid fluid removal, pre-dialysis antihypertensive medication, bradykinin release, hypotonic dialysate. Reduce or pause ultrafiltration.

X. TUBULAR DISORDERS

A. Renal Tubular Acidosis (Table 19.13)[26]

1. A group of transport defects resulting in abnormal urine acidification; due to defects in reabsorption of bicarbonate (HCO_3^-), excretion of hydrogen ions (H^+), or both.

TABLE 19.13

RENAL TUBULAR ACIDOSIS BIOCHEMICAL AND CLINICAL CHARACTERISTICS

	Type 1 (Distal)	Type 2 (Proximal)	Type 4 (Hypoaldosteronism)
Mechanism	Impaired distal acidification	Impaired bicarbonate absorption	Decreased aldosterone secretion or aldosterone effect
Etiology	Hereditary Sickle cell disease Toxins/drugs Cirrhosis Obstructive uropathy Connective tissue disorder	Hereditary Metabolic disease Fanconi syndrome Prematurity Toxins/heavy metals Amyloidosis PNH	Absolute mineralocorticoid deficiency Adrenal failure CAH DM Pseudohypoaldosteronism Interstitial nephritis
Minimal urine pH	>5.5	<5.5 (urine pH can be >5.5 with a bicarbonate load)	<5.5
Fractional excretion of bicarbonate ($FeHCO_3$)	↓ (<5%)	↑ (>15%)	↓ (<5%)
Plasma K^+ concentration	Normal or ↓	Usually ↓	↑
Urine anion gap	Positive	Positive or negative	Positive
Nephrocalcinosis/ nephrolithiasis	Common	Rare	Rare
Treatment	1–3 mEq/kg/day of HCO_3 (5–10 mEq/kg/day if bicarb wasting)	5–20 mEq/kg/day of HCO_3	1–5 mEq/kg/day of HCO_3 May add fludrocortisone and potassium binders

CAH, Congenital adrenal hyperplasia; *DM*, diabetes mellitus; *PNH*, paroxysmal nocturnal hemoglobinuria.
Adapted from Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein LS. *Pediatric Nephrology*. Baltimore: Springer-Verlag Berlin Heidelberg; 2016.

2. Results in a persistent normal anion gap hyperchloremic metabolic acidosis.
3. RTA syndromes have a normal GFR and often do not progress to kidney failure.
4. Clinical presentation may be characterized by failure to thrive, polyuria, constipation, vomiting, and dehydration.
5. **Fractional excretion of bicarbonate ($FeHCO_3$) should be checked after a HCO_3 load.** Can help differentiate the types of RTA. See Section II.B for equation.
6. **Urine anion gap (UAG) is also useful**; however, it should not be used when a patient is volume depleted or has an anion-gap metabolic acidosis. See Section II.B for equation.

B. Fanconi Syndrome

1. Generalized dysfunction of the proximal tubule resulting not only in bicarbonate loss but also in variable wasting of phosphate, glucose, and amino acids.
2. May be hereditary, as in cystinosis and galactosemia, or acquired through toxin injury and other immunologic factors.
3. Clinically characterized by rickets and impaired growth.

C. Nephrogenic Diabetes Insipidus

1. **Water conservation is dependent on antidiuretic hormone (ADH) and its effects on the distal renal tubules.** Polyuria (urine output >5 mL/kg/hr or >2 L/day), a hallmark of nephrogenic diabetes insipidus (NDI), is due to diminished or lack of response of the ADH receptor in the distal renal tubules. Hereditary defects of ADH receptor or acquired insults (e.g., interstitial nephritis, sickle cell disease, lithium toxicity, CKD) may underlie NDI.
2. **Must be differentiated from other causes of polyuria:** Central diabetes insipidus (ADH deficiency that may be idiopathic or acquired through infection or pituitary trauma; see Chapter 10), diabetes mellitus, psychogenic polydipsia, cerebral salt wasting.

XI. NEPHROLITHIASIS[27-30]

A. Risk Factors

Male sex; history of UTI (especially those <5 years); congenital and structural urologic abnormalities (urinary stasis), neurogenic bladder, hypercalciuria, hyperoxaluria/oxalosis, hypocitraturia, other metabolic abnormalities; family history of stones, renal failure, consanguinity.

B. Presentation

1. Microscopic hematuria (90%), flank/abdominal pain (50% to 75%), gross hematuria (30% to 55%), and concomitant UTI in up to 20%.
2. Have higher likelihood than adults of having asymptomatic stones, especially younger children.

C. Diagnostic Imaging

1. Ultrasonography is an effective and preferred modality, particularly at centers with expertise, given benefit of avoiding radiation exposure (75% sensitive for renal stones).[29]
2. Noncontrast CT may be preferred to improve diagnostic sensitivity (e.g., with radiolucent stones such as uric acid stones, ureteral stones, lack of ultrasonographic expertise).

D. Management

1. **Pain control, urine culture, hydration.** Some centers initiate α-blockers to facilitate stone passage, although evidence of benefit in children is equivocal.[30-32]

2. **Antibiotics:** Should be considered in treatment of all stones, especially if fever and/or pyuria present, because of the high association with UTI.
3. **Urologic intervention** (e.g., extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy): Consider with unremitting pain, urinary obstruction, increasing stone size, size ≥7 mm, or cystine/struvite stone, especially in the setting of AKI or at-risk patients (e.g., solitary kidney, anatomic anomalies).[32]
4. **Strain urine to collect stone; analyze stone composition to aid in prevention of future stones.**

E. Workup

1. Up to 75% of children with a kidney stone will have a metabolic abnormality (e.g., hypercalciuria, hyperoxaluria, hyperuricosuria, cystinuria).
2. Workup should include analysis of the stone (if possible); UA; basic metabolic panel; and serum calcium, phosphate, magnesium, and uric acid levels. If evidence of elevated calcium or phosphate, obtain parathyroid hormone (PTH) level and consider checking 25- and 1,25(OH) vitamin D levels.
3. After symptoms have resolved, a 24-hour urine collection should be obtained. Risk factors for stone formation should be analyzed: urine volume, osmolarity, sodium, calcium, urate, oxalate, citrate, and cystine. This test is also referred to as a "stone risk analysis."

F. Prevention

1. **All children with history of stones should increase fluid intake** (e.g., at least 2 L/day in those aged >10 years old).
2. **Targeted interventions of any identified metabolic abnormalities** (e.g., low-sodium diet in those with hypercalciuria). Pharmacologic interventions are also available in certain scenarios (e.g., citrate supplementation).
3. **Dietary Modifications:** Long–term adherence (5 years) to normal calcium, low–sodium diet may decrease recurrence of stones in people with idiopathic hypercalciuria with recurrent nephrolithiasis.[33]

XII. WEB RESOURCES

A. International Pediatric Nephrology Association: www.ipna-online.org

B. National Kidney Disease Education Program: https://www.niddk.nih.gov/health-information/communication-programs/nkdep

C. National Kidney Foundation: www.kidney.org

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 20

Neurology

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See additional content on Expert Consult

I. NEUROLOGIC EXAMINATION

A. Mental Status

Alertness, orientation (person, place, time, situation), language, cognition

1. **Infants:** Observe "cuteness" and ability to dynamically engage caretakers.
2. **Toddlers:** Bring toys. Observe and engage in play.
3. **School age:** Ask children to draw or describe school or friends.

B. Cranial Nerves (Table EC 20.A)

1. For a quick assessment of cranial nerves for all patients, observe:
   a. (II) Visual response to objects in each visual quadrant.
   b. (III, IV, VI) Conjugate gaze at full lateral and vertical positions, nystagmus.
   c. (VII) Symmetry and expressiveness of face at rest and with emotive activation.
   d. (VIII) Finger rub, or response to and localization of sound for infants.
   e. (IX, X, XII) Quality of phonation and articulation; ask about feeding, chewing, swallowing.

C. Motor

1. **Muscle bulk:** Atrophy is a red flag.
2. **Tone:** Spasticity, rigidity, hypotonia.
   a. Infants: Observe infant undressed to assess resting posture (varies with age). Active tone: traction response, axillary stability (slip-through), posture in horizontal suspension. Passive tone (resistance of movements of the joints): flap hands/feet, scarf sign.
   b. Red flags: Scissoring, toe-walking, inability to supinate hand, clasped thumb or grasp.
3. **Strength:**
   a. Observe ease of normal functions: rising from floor, standing broad jump, running, climbing onto chair or exam table. Note presence of accommodations child is making in order to execute movements (e.g., shoulder shrug or trunk tilt to raise arm).
   b. For conventional rating scale, see Box 20.1.
4. **Involuntary movements:** Fasciculations, tics, dystonia, chorea, athetosis, tremor.

D. Sensory

1. Primarily important if any concern for spinal cord defect or peripheral nerve injury.

TABLE EC 20.A

CRANIAL NERVES

Function	Cranial Nerve and Test
Smell	**I. Olfactory.**
Vision	**II. Optic.** Visual acuity and fundus (*Infants:* Fix and follow, red reflex; *Older children:* Snellen chart, fundoscopic exam).
Pupillary reflex	**II. Optic.** Detection of light and/or visual stimulus. **III. Oculomotor.** Control of pupil size in response to light, accommodation.
Eye movements and eyelids	**III. Oculomotor.** Eyelid elevation, adduction, elevation. Palsy—"down and out," ptosis. **IV. Trochlear.** Eye depression and intorsion. Palsy—head tilt. **VI. Abducens.** Lateral gaze. Note: Nystagmus can be physiologic or pathologic (intoxication, lesions in vestibular system, brainstem, or cerebellum).
Sensation	**V. Trigeminal.** Facial sensation, corneal reflex.
Mastication	**V. Trigeminal.** Clench teeth.
Facial movement	**VII. Facial.** Observation of emotional expressions and facial symmetry, eyebrow elevation, eye closure, smile, puffing out cheeks.
Hearing	**VIII. Vestibulocochlear.** Localize sound, finger rub, audiologic testing.
Vestibular.	**VIII. Vestibulocochlear.** Sense of balance, horizontal nystagmus, reading with passive head movement, Romberg, tandem gait.
Oropharynx	**IX. Glossopharyngeal.** Palate elevation, gag reflex. **X. Vagus.** Soft palate elevation, muscles of pharynx and larynx. Unilateral palsy—soft, hoarse voice; bilateral—respiratory distress.
Head control	**XI. Accessory.** Lateral head turn, shoulder shrug.
Tongue	**XII. Hypoglossal.** Tongue protrusion, push tongue against inner cheek.

BOX 20.1

STRENGTH RATING SCALE

0/5: No movement (i.e., no palpable tension at tendon)
1/5: Flicker of movement
2/5: Movement in a gravity-neutral plane
3/5: Movement against gravity but not resistance
4/5: Subnormal strength against resistance (requires accommodation to execute movement)
5/5: Normal strength against resistance (motion is smooth, comfortably executed, without any accommodations)

2. Focus initial investigation along three axes for meaningful lesion localization:
   a. Distal deficit with preserved (or less impaired) proximal sensation suggests polyneuropathy.
      (1) Pain/temperature deficit: small fiber polyneuropathy/anterior spinal cord.
      (2) Position/vibration deficit: large fiber polyneuropathy/posterior spinal cord.
   b. Lower body more affected than upper body suggests spinal cord injuries.
      (1) See Fig. 20.1 for dermatomes.
      (2) Ask about continence.
   c. If difference between left and right, concern for unilateral brain or spinal cord lesion.

E. Reflexes

1. **Tendon Reflexes:** Gradation (Box 20.2) and localization (Table EC 20.B). Helpful in localizing abnormalities including upper versus lower motor neuron pathology, especially in presence of weakness or asymmetry (Table EC 20.C). Compare right to left, upper to lower extremities, and distal to proximal reflexes. Generalized high or low reflexes of little significance in setting of normal strength and coordination.
2. **Primitive reflexes:** Expected during specific time windows (Table 20.1).

F. Coordination and Gait

1. **Evaluate coordination while watching age-appropriate activities.**
2. **Tests for cerebellar function:** Rapid alternating movements, finger-to-nose, heel-to-shin, walking, running.

II. HEADACHES[1–11]

A. Classification of Headaches

1. **Primary headaches:** Migraines, tension-type, cluster, trigeminal autonomic cephalgias (TACs), other primary headache disorders.
2. **Secondary headaches:** Trauma, infection, substance use or withdrawal, vascular disorder, neurologic disorder, increased intracranial pressure (ICP).
3. **Differential diagnosis:** Acute (Box 20.3) and chronic (Box 20.4)

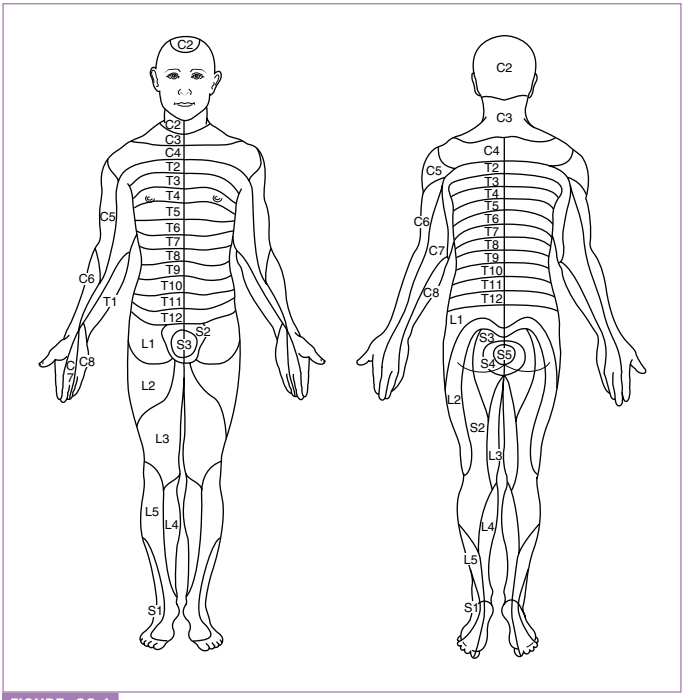

FIGURE. 20.1

Dermatomes. (From Athreya BH, Silverman BK. *Pediatric Physical Diagnosis*. Norwalk, CT: Appleton-Century-Crofts; 1985:238–239.)

BOX 20.2

REFLEX RATING SCALE

0: None
1+: Diminished (require use of clasped hands/gritting teeth to engage reflex)
2+: Normal
3+: Increased (reflexes cross neighboring joint or cross to other side)
4+: Hyperactive with clonus

B. Evaluation of Headaches

Obtain history (Box 20.5) and physical exam (Table EC 20.D); evaluate for red flags (Box 20.6). If red flags present, obtain appropriate imaging (computed tomography [CT] for hemorrhage, magnetic resonance imaging/angiography (MRI/MRA) for vascular abnormalities). Perform lumbar puncture (LP) if concern for subarachnoid hemorrhage (not detected on CT), infection, or increased ICP (Box 20.7). *If no red flags present and normal neurologic exam, imaging and LP not recommended.*

TABLE EC 20.B

MUSCLE STRETCH REFLEXES

Reflex	Site
Biceps	C5, C6
Brachioradialis	C5, C6
Triceps	C7, C8
Knee	L(2,3)4
Ankle	L5–S2

C, Cervical spinal root; *L*, lumbar spinal root.

TABLE EC 20.C

UPPER AND LOWER MOTOR NEURON FINDINGS

On Examination	Upper	Lower
Power	Decreased	Decreased
Tendon reflexes	Increased	Decreased
Tone	Increased (*Infants:* decreased)	Normal or decreased
Plantar response	Upgoing	Downgoing
Fasciculations	Absent	Present
Muscle wasting	Absent	Present

TABLE 20.1

PRIMITIVE REFLEXES[49]

Reflex	Appears	Extinguishes
Palmar grasp	28 WGA	2–3 months
Rooting	32 WGA	1 month
Moro	28 WGA	5–6 months
Tonic neck	35 WGA	6–7 months
Parachute	7–8 months	Remains for life

WGA, Weeks gestational age.

BOX 20.3

DIFFERENTIAL DIAGNOSIS OF ACUTE HEADACHE

Evaluation of the first acute headache should exclude pathologic causes listed here before more common etiologies are considered.

1. Increased ICP: Trauma, hemorrhage, tumor, hydrocephalus, idiopathic intracranial hypertension, abscess, arachnoid cyst, cerebral edema
2. Decreased ICP: Ventriculoperitoneal shunt placement, lumbar puncture, cerebrospinal fluid leak
3. Meningeal inflammation: Meningitis, leukemia/lymphoma, subarachnoid or subdural hemorrhage
4. Vascular: Vasculitis, arteriovenous malformation, hypertension, cerebrovascular accident
5. Bone, soft tissue: Referred pain from scalp, eyes, ears, sinuses, nose, teeth, pharynx, cervical spine, temporomandibular joint
6. Infection: Systemic, encephalitis, sinusitis
7. Medication/intoxicant exposure (e.g., stimulants, steroids, drugs of abuse)
8. First primary headache

ICP, Intracranial pressure.

BOX 20.4

DIFFERENTIAL DIAGNOSIS OF RECURRENT OR CHRONIC HEADACHES

1. Migraine (with or without aura)
2. Tension
3. Analgesic rebound
4. Caffeine withdrawal
5. Sleep deprivation or chronic hypoxia (e.g., sleep apnea)
6. Tumor
7. Psychogenic: Conversion disorder, malingering, depression, acute stress, mood disorder
8. Cluster headache
9. New daily persistent headache

BOX 20.5

IMPORTANT HISTORICAL INFORMATION IN EVALUATING HEADACHE

1. When did the headaches begin?
2. How did the headache begin? Associated trauma, social stressors (school, home)?
3. What is the frequency and duration of the headaches?
   a. Headache pattern (intermittent, progressive, chronic, etc.)
   b. Time of day
4. Where is the pain, what is it like, and does it radiate? Focal occipital pain is concerning for secondary headaches.
5. Associated symptoms? What do you do during the headache?
   a. Aura or prodrome
   b. Constitutional symptoms (weight changes), vision changes, or any other neurologic symptoms (weakness, tingling, photophobia, phonophobia)
   c. Triggers and alleviating/exacerbating factor
6. Other history (e.g., health problems, medications, family history of migraine)
7. How do the headaches affect your ability to function? Ask about school absences.

C. Migraine Headache

1. Migraines can be throbbing, pulsatile, or pressure-like in children. Usually bifrontal in children and unilateral in adolescents and adults. There are many potential triggers (e.g., stress, caffeine, menses, sleep disruption). See Box 20.8 for diagnostic criteria.
2. **Classification**[1]: With versus without aura. An aura is any neurologic symptom that occurs prior to onset of a migraine (e.g., visual aberrations, paresthesias, numbness, dysphasia).
3. **Precursors to migraines and close associations:** Cyclic vomiting, abdominal migraines, paroxysmal vertigo of childhood, paroxysmal torticollis of infancy, and motion sickness.
4. **Treatment**: Combination of acute and prophylactic treatment.
   a. **Acute symptomatic**: Avoid medication overuse (no more than 2 to 3 days/week); can lead to rebound headaches. Optimal acute therapy can prevent progression to chronic migraines.
   b. Outpatient setting:
      (1) Dark, quiet room and sleep.
      (2) Acetaminophen and/or nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., naproxen, ibuprofen, ketorolac).
      (3) Caffeine (e.g., coffee, tea, soda).
      (4) Triptans: Not typically used in emergency room or inpatient setting (only effective at migraine onset). Limit use to twice per week.

TABLE EC 20.D

PHYSICAL AND NEUROLOGIC EXAMINATION OF THE CHILD WHO HAS HEADACHES

Feature	Significance
Growth parameters	Chronic illness may affect linear growth Hypothalamic-pituitary dysfunction may disturb growth
Head circumference	Increased ICP before fusion of the sutures may accelerate head growth
Skin	Evidence of trauma or a neurocutaneous disorder
Blood pressure	Hypertension
Neurologic exam	Signs of increased ICP Focal abnormality on neurological exam. Key areas: Fundoscopic exam (for optic nerve edema), extraocular movements, asymmetric reflexes, asymmetric strength/weakness/motor exam, coordination (cerebellar signs), abnormal gait.
Cranial bruits	May reflect an intracranial arteriovenous malformation
Fundoscopy exam	Papilledema may reflect elevated ICP or pseudotumor cerebri

ICP, Intracranial pressure.

BOX 20.6

RED FLAGS IN HEADACHE EVALUATION

1. Progressively worsening headaches
2. "Thunderclap" headache (<5 min from onset to maximal intensity)
3. Altered mental status
4. New onset focal neurological symptoms
5. Optic nerve edema
6. Nuchal rigidity
7. Seizures
8. Visual symptoms not typical of migraines (e.g., colorful, hallucinatory, short duration), diplopia, decreased visual acuity, visual field deficits
9. Concurrent fever (especially if accompanied by other red flags)
10. Headache worse with supine position or Valsalva (cough, straining)
11. Association with persistent emesis
12. Immunocompromised or on anticoagulation
13. Signs of endocrine pathology (e.g., short stature, obesity, polyuria, sluggishness, constipation, virilization)

BOX 20.7

LUMBAR PUNCTURE[7,47]

1. See Chapter 4 for indications, contraindications, and procedure.
2. Standard tests: Cell counts + differential, Gram stain, CSF culture, protein, glucose. Consider viral studies (e.g., herpes simplex virus, enterovirus, etc.).
3. Manometer for OP if concern for increased intracranial pressure. Performed in a lateral decubitus position. OP of <28 cm H_2O generally considered normal; however, interpret results in concert with other clinical and examination findings.
4. There is inconsistent evidence regarding correction factors for CSF white blood cell counts in the setting of blood-contaminated CSF from a traumatic lumbar puncture.
5. Xanthochromia: Yellow or pink discoloration of CSF due to breakdown of hemoglobin. Suspect subarachnoid hemorrhage.

CSF, Cerebrospinal fluid; *OP*, opening pressure.

(5) Antidopaminergics have antiemetic properties, though effective even if nausea is not a predominant factor. Prochlorperazine shown to be superior to metoclopramide.[48] Sometimes more effective than NSAIDs in emergency department setting.

c. Emergency department (ED)/inpatient setting:
   (1) Often helpful to combine medications and administer intravenous (IV) "migraine cocktail" (see Fig. 20.2 for example ED algorithm).
   (2) Steroids (e.g., methylprednisolone) may be useful in intractable cases, although evidence is lacking.
   (3) Dihydroergotamine.

BOX 20.8

DIAGNOSTIC CRITERIA FOR PEDIATRIC MIGRAINE WITHOUT AURA[1-3]

At least five attacks fulfilling the following criteria:

1. Headache 2–72 hr in children younger than 18 years (untreated or unsuccessfully treated)
2. At least two of the following characteristics:
   a. Unilateral or bilateral
   b. Pulsating quality
   c. Moderate to severe in intensity
   d. Aggravated by or causing avoidance of routine physical activities
3. At least one of the following occur during the headache:
   a. Nausea and/or vomiting
   b. Photophobia and phonophobia (which may be inferred from behavior)
4. Not better accounted for by another diagnosis

d. **Preventative treatment:**
   (1) Lifestyle modification is mainstay. Adequate sleep,[9] meals, hydration, regular exercise. Avoid triggers, stress, caffeine withdrawal.
   (2) **Alternative/complementary therapies:**
      (a) Cognitive-behavioral therapy
      (b) Biofeedback
      (c) Physical therapy
      (d) Acupuncture
   (3) Consider prophylactic medications (Table EC 20.E) if migraines occurring more than once per week, affecting quality of life, frequent ED visits, complicated migraines, or migraines not responsive to abortive medications. Conflicting evidence regarding efficacy. Recent randomized controlled trial demonstrated that preventative medication was no more effective than placebo. New biologic (calcitonin gene-related peptide or CGRP)[10,11] approved in adults in 2018; there are no published studies yet in pediatric population.

III. SEIZURES[12–25]

A. Differential Diagnosis of Recurrent Events That Mimic Epilepsy in Childhood (Table 20.2)

B. Seizures: First and Recurrent

1. **Definition:** Paroxysmal, transient, synchronized discharge of cortical neurons resulting in alteration of function (motor, sensory, cognitive).
2. **Causes of seizures**
   a. Diffuse brain dysfunction: Fever, metabolic compromise, toxins or drugs, hypertension.
   b. Focal brain dysfunction: Stroke, neoplasm, focal cortical dysgenesis, trauma.

TABLE EC 20.E

PREVENTIVE THERAPIES FOR MIGRAINE[A]

Medications	Adverse Effects	Consider in Patients With the Following Comorbidities
VITAMINS		
Riboflavin, magnesium, CoQ10	Low side effect profile, limited data of efficacy in children	Poor nutritional intake
ANTIHISTAMINES		
Cyproheptadine (Periactin)	Sedation, increased appetite, hepatitis	Seasonal allergies, poor appetite, insomnia
β-BLOCKERS		
Propranolol (Inderal)	Hypotension, bronchospasm, masks hypoglycemia, bradyarrhythmia	Hypertension
ANTIDEPRESSANTS		
Amitriptyline (Elavil)	Black box: suicidal thoughts. Other: sedation, constipation, weight gain	Depression, insomnia, underweight
Nortriptyline (Pamelor)	Black box: suicidal thoughts. Other: constipation	Depression
ANTISEIZURE MEDICATIONS		
Topiramate (Topamax)	Cognitive changes, weight loss, sensory changes, paresthesia, kidney stones	Obesity, epilepsy
Divalproex sodium (Depakote)	Black box: hepatotoxicity. Other: dizziness, drowsiness, weight gain, gastrointestinal upset, teratogenicity	Bipolar disorder, epilepsy, underweight

[a]See Formulary for specific dosing.
CoQ10, Coenzyme Q10.

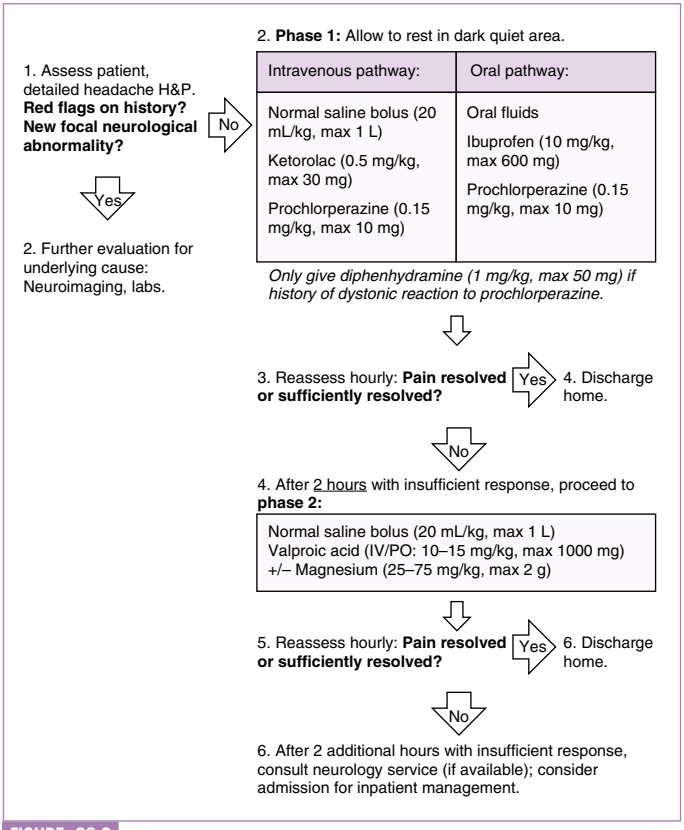

FIGURE. 20.2

ED management pathway of migraine headaches[8] at Johns Hopkins Children's Center.

3. **Febrile seizures**[12,13]
   a. Simple febrile seizure: Primary generalized seizure associated with fever in a child 6 to 60 months of age that is nonfocal, lasts for <15 minutes, and does not recur in a 24-hour period.
      (1) Management: Identify the source of fever. No further workup (neuroimaging or electroencephalogram [EEG]) or antiseizure drugs are necessary for a simple febrile seizure in a well-appearing fully immunized child with a normal neurologic examination and no meningeal signs.
      (2) Indications for LP: Meningeal signs, incomplete or unknown *Haemophilus influenzae* or *Streptococcus pneumoniae* immunization status, or if pretreated with antibiotics (which can mask signs and symptoms of meningitis).

TABLE 20.2

DIFFERENTIAL DIAGNOSIS OF RECURRENT EVENTS THAT MIMIC EPILEPSY IN CHILDHOOD[20,50]

Event	Differentiation from Epilepsy
SYNCOPE AND ANOXIC EVENTS	
Breath-holding spells (18 months–3 years)	Loss of consciousness and generalized convulsions, always provoked by an event that makes child upset.
Vasovagal syncope	Triggers: Postural change, heat, emotion. Preceded by dizziness and vision loss. Slow collapse to floor, may have brief confusion after event.
Cardiogenic syncope	Triggers: Exercise, strong emotion. Abnormal ECG/Holter monitor finding. No consistent convulsive movements.
Cough syncope	Prolonged cough spasm during sleep in asthmatic, leading to loss of consciousness, often with urinary incontinence.
BEHAVIORAL, PSYCHOLOGICAL, AND PSYCHIATRIC DISORDERS	
Psychogenic nonepileptic seizure (PNES)	Also known as pseudoseizures. No EEG changes except movement artifact during event. Thrashing, proximal truncal movements. Eye closure with resistance to opening. Guards face with hand drop. Brief/absent postictal period. Often exacerbated by psychological stressor.
SLEEP-RELATED CONDITIONS	
Narcolepsy	Excessive daytime sleepiness, cataplexy (sudden atonia triggered by emotion), sleep paralysis, sudden onset REM on EEG.
PAROXYSMAL MOVEMENT DISORDERS	
Tics	Involuntary, nonrhythmic, repetitive movements not associated with impaired consciousness. Strong urge to perform movement but suppressible.
Stereotypies (mannerisms)	Repetitive movements or vocalizations (e.g., rocking, head banging).
Paroxysmal dyskinesias	Dystonia, choreoathetosis in response to specific triggers (e.g., startle). Often familial.
MIGRAINE-ASSOCIATED DISORDERS	
Migraine	Headache or visual changes that may precede attack. Autonomic or sensory changes can mimic focal seizure. Family history of migraines. EEG with regional area of slowing during attack.
Paroxysmal vertigo (toddler)	Episode of vertigo, vomiting, staggering, and falling in a child. May become anxious, no loss of awareness.
MISCELLANEOUS EVENTS	
Sandifer syndrome	GER in infancy. Paroxysmal dystonic posturing (back arching) associated with meals.
Myoclonus	Involuntary muscle jerking or twitch

ECG, Electrocardiography; *EEG,* electroencephalography; *GER,* gastroesophageal reflux; *REM,* rapid eye movement.

b. Complex febrile seizure: Seizure associated with a fever that is focal, lasts for >15 minutes, or recurs within a 24-hour period. Management: Identify the source of fever. Consider EEG, neuroimaging. Consider prescribing rectal diazepam for home emergency use. Slightly increased risk of developing epilepsy at later age.

4. **Evaluation of unprovoked seizures**
   a. Rule out provocative factors: Obtain vitals. Consider checking glucose, electrolytes, blood urea nitrogen, creatinine, complete blood cell count, toxicology screen.
   b. EEG is recommended in all children with first unprovoked seizure to evaluate for an epilepsy syndrome, however it does not need to be emergently obtained.[14] Interictal EEGs may be normal, particularly in children with focal seizures. Repeat EEGs, prolonged EEG monitoring with video as clinically indicated.
   c. Imaging: High resolution MRI can assist with identification of underlying brain malformation, although is not routinely indicated when evaluating a first-time seizure. CT scan is not recommended.
5. **Epilepsy:** Recurrent, unprovoked seizures *or* diagnosis of genetic syndrome characterized by recurrent seizures. Assess seizure type, epilepsy classification (Table EC 20.F),[15–17] and severity of disorder. See Table 20.3 for selected epilepsy syndromes of childhood.
6. **Breakthrough seizures:** Assess for missed medications or significant weight gain, lack of sleep, stress, drugs/alcohol, physical exertion, illness, dehydration, flickering lights, menses, and drug interactions that can lower seizure threshold (tricyclic antidepressants, certain antibiotics, over-the-counter cold preparations, diphenhydramine, herbal supplements). Obtain drug levels (see Table 20.4 for therapeutic drug levels).
7. **Status epilepticus**[22]: Traditionally defined as continuous seizure activity lasting approximately > 5 minutes or two discrete seizures without return of consciousness between them. See Chapter 1 for management.
8. **Treatment**[19,20,23–25]
   a. First seizure, nonfocal, and with return to baseline: No antiseizure drug indicated. Overall recurrence approximately 50% in 2 to 5 years. Epileptiform abnormalities on EEG indicate a higher chance of recurrence.
   b. Educate parents and patient regarding seizure safety.[20] Review seizure first aid, including supervision during bathing or swimming. Be aware of driver's license laws in the state. Advocate teacher and school awareness.
   c. Pharmacotherapy (see Table 20.4): Initiate if known etiology of seizure (diagnosis of epilepsy syndrome), recurrent unprovoked seizure (risk of recurrent seizure >80% after second unprovoked seizure). Choose therapy according to seizure type. Consider rectal diazepam if seizures are prolonged or hemodynamic instability.
   d. Ketogenic diet[25]:
      (1) High-fat, low-carbohydrate therapy typically used for intractable seizures.
      (2) Should be managed by trained providers.
      (3) Urine/serum ketones can be monitored to assess compliance.
      (4) Side effects include transient GI upset and hyperlipidemia, chronic metabolic acidosis, kidney stones, fractures.

TABLE EC 20.F

INTERNATIONAL CLASSIFICATION OF SEIZURES AND EPILEPSY SYNDROMES[11,13,14]

Seizure type nomenclature	Classification of epilepsies
I. FOCAL ONSET 1. Aware (previously termed simple partial) a. With motor onset b. With nonmotor onset 2. Impaired awareness (previously termed complex partial) a. With motor onset b. With nonmotor onset **II. GENERALIZED ONSET** 1. Motor a. Tonic-clonic b. Other motor 2. Nonmotor (Absence) **III. UNKNOWN ONSET** 1. Motor a. Tonic-clonic b. Other motor 2. Nonmotor 3. Unclassified	1. Seizure types (see left column) a. Focal, generalized, or unknown b. Takes into account etiologies 2. Epilepsy type (predisposition to seizures) a. Focal, generalized, combined generalized and focal, unknown b. Takes into account seizure types, co-morbidities, and etiologies 3. Epilepsy syndrome (e.g., genetic syndrome known to cause epilepsy); takes into account seizure types, epilepsy types, and etiologies

TABLE 20.3

SELECTED EPILEPSY SYNDROMES[16,18–20]

Syndrome	Etiology	Evaluation	Treatment	Comments
Neonatal seizures (broad category encompassing a spectrum from benign to morbid syndromes)	Brain malformation, hypoxic-ischemic encephalopathy, intracranial hemorrhage, inborn errors of metabolism, CNS infection, cerebral infarction, hypoglycemia, hypocalcemia, hypomagnesemia. Consider benign neonatal seizures ("fifth day fits").	Screen for electrolyte and metabolic abnormalities, pyridoxine deficiency, and sepsis. Obtain LP, head ultrasound, CT or MRI, EEG.	Treat underlying abnormality, consider pyridoxine ± EEG, phenobarbital (± additional agents). No treatment needed for benign neonatal seizures.	Occur within first 28 days of life; may be myoclonic, tonic, clonic, or subtle. Presents as blinking, chewing, bicycling, or apnea. Distinguished from jitteriness by vital sign changes and inability to provoke or suppress movements.
Early infantile epileptic encephalopathy (Ohtahara syndrome) and early myoclonic encephalopathy	Structural malformations, metabolic disorders (glycine encephalopathy, pyridoxine dependent epilepsy, mitochondrial mutations), genetic mutations.	EEG with burst suppression pattern.	Trial of pyridoxine. Antiseizure medications, ketogenic diet. Seizures are difficult to control. If due to metabolic disorder, treat appropriately.	Tonic and myoclonic seizures with onset in neonatal period. Can progress to infantile spasms and/or Lennox Gastaut. Poor neurodevelopmental outcome.
Infantile spasms	Often early insult (HIE, postnatal hemorrhage), structural, genetic (tuberous sclerosis, Down syndrome), or metabolic abnormalities.	EEG with interictal hypsarrhythmia, MRI.	High dose steroids (oral prednisone) or ACTH; vigabatrin (particularly for tuberous sclerosis). Ketogenic diet.	Onset after age 2 months, peak onset 4–6 months. Highly variable appearance (flexor, extensor, mixed) often upon awakening and in clusters. Overall poor long-term outcomes, especially if known etiology. Early recognition and treatment can improve this.
Lennox-Gastaut syndrome	Multifactorial etiology. Often progression from other epileptic encephalopathy.	EEG with slow spike-wave discharges and intermittent runs of multiple spikes or fast activity.	Clobazam, felbamate, lamotrigine, rufinamide, topiramate, valproic acid. Ketogenic diet. Cannabidiol approved.	Multiple seizure types, cognitive impairment, and characteristic EEG findings. Significant secondary morbidity associated with atonic seizures.

Childhood absence seizures	Suspected to be genetic.	EEG with sudden generalized 3–4 Hz spike-and-wave discharges. Hyperventilation precipitates seizure.	Ethosuximide, lamotrigine, valproic acid.	Onset 4–10 years. Staring spells with diminished awareness, +/– automatisms (eye blinking, mouth movements). Often resolves by adolescence, with good neurologic outcome.
Childhood epilepsy with centro-temporal spikes (BECTS, benign rolandic epilepsy)	Suspected to be genetic.	EEG with spike wave discharges in centro-temporal region, increased with sleep.	Treatment is not always necessary. If frequent or distressing, may use levetiracetam or oxcarbazepine.	Onset 4–11 years. Seizures often nocturnal and upon awakening, with paresthesia of mouth or tongue, motor phenomena of ipsilateral face occasionally with generalization. Seizure remission by 14–16 years of age.
Dravet syndrome	Most cases caused by SCN1A mutation.	Genetic testing, EEG with polyspike-wave bursts.	Clobazam, levetiracetam, stiripentol, valproate. Cannabidiol approved.	Seizures starting in infancy or early childhood, often associated with heat. Developmental regression, prolonged (often myoclonic) seizures.
Juvenile myoclonic epilepsy	Suspected to be genetic.	Clinical history, sleep-deprived EEG (reveals generalized spike-and-wave discharges with normal background activity).	Lamotrigine, levetiracetam, valproate, zonisamide.	Adolescent onset often with absence seizures. Develop myoclonus upon awakening and GTCs. Triggers: sleep deprivation, excessive alcohol intake, photic stimulation. Full remission rare, majority require lifelong antiseizure medications.
Panayiotopoulos syndrome (early onset childhood occipital epilepsy)	Unknown	EEG with shifting multifocal spikes (often occipital spikes).	Often not treated. Occasionally intermittent benzodiazepines, levetiracetam, oxcarbazepine.	Onset 3–6 years. Characteristic autonomic component (e.g., vomiting, pallor, hypersalivation, thermoregulatory or cardiorespiratory irregularities). Resolves 2–3 years after onset.

BECTS, Benign epilepsy with centrotemporal spikes; *CNS,* central nervous system; *CT,* computed tomography; *EEG,* electroencephalography; *GTC,* generalized tonic–clonic; *HIE,* hypoxic-ischemic encephalopathy; *LP,* lumbar puncture; *MRI,* magnetic resonance imaging.

TABLE 20.4

COMMONLY USED ANTISEIZURE MEDICATIONS[21,24]

Antiseizure drug (Trade Name)	Standard Therapeutic Levels[a]	IV Preparation Available?	Side Effects
Brivaracetam (Briviact)	–	–	Somnolence/sedation, dizziness, fatigue, nausea/vomiting.
Cannabidiol (Epidiolex)	–	–	Hepatotoxicity, somnolence, decreased appetite, diarrhea, fatigue, insomnia, infections. Can interact with other antiseizure drugs (clobazam).
Carbamazepine (Tegretol/ Carbatrol)	4–12 mg/L	–	Black box: TEN/SJS in patients with HLA-B*1502 allele, aplastic anemia, agranulocytosis. Other: sedation, ataxia, diplopia, hyponatremia, hepatotoxicity, may worsen generalized seizures.
Clobazam (Onfi)	30–300 mCg/L	–	Sedation, dizziness.
Clonazepam (Klonopin)	20–70 mCg/L	–	Sedation, drooling, dependence.
Diazepam (Diastat, Valium)	–	Yes, 1:1 conversion	Sedation, dry mouth, respiratory depression.
Eslicarbazepine acetate (Aptiom)	10–35 mg/L	–	Hyponatremia, dizziness, somnolence, vomiting, headache, diplopia, vertigo, ataxia, tremor.
Ethosuximide (Zarontin)	40–100 mg/L	–	GI upset.
Felbamate (Felbatol)	30–60 mg/L	–	Black box: aplastic anemia (rare), liver failure. Other: sleep disturbances, weight loss.
Gabapentin (Neurontin)	2–20 mg/L	–	Weight gain, leg edema, dizziness.
Lacosamide (Vimpat)	5–10 mg/L	Yes, 1:1 conversion	Sedation, reduced benefit with sodium channel drugs, increased PR interval.
Lamotrigine (Lamictal)	2.5–15 mg/L	–	Black box: SJS/TEN (risk greater in pediatric patients, increased risk in combination with valproate). OCPs significantly decrease level. Other: fatigue, ataxia, diarrhea.
Levetiracetam (Keppra)	12–46 mg/L	Yes, 1:1 conversion	Abnormal behavior, irritability, rare psychosis.
Oxcarbazepine (Trileptal)	3–35 mg/L (10–hydroxy-carbazepine level)	–	Hyponatremia, weight gain, dizziness.
Perampanel (Fycompa)	–	–	Black box: psychiatric/behavioral reactions (hostility). Other: dizziness, headache.
Phenobarbital (Luminal)	10–40 mg/L	Yes, 1:1 conversion	Somnolence, syncope, erythroderma.

Phenytoin (Dilantin)	10–20 mg/L	Yes, 1:1 conversion	Ataxia, hirsutism, gingival hyperplasia, teratogenicity, morbilliform rash, purple-glove syndrome with infusion.
Pregabalin (Lyrica)	2–5 mg/L	–	Peripheral edema, weight gain, constipation, dizziness, ataxia, sedation.
Rufinamide (Banzel)	5–30 mg/L	–	Shortened QT interval, nausea, dizziness, sedation, headache. Interacts with other antiseizure drugs.
Tiagabine (Gabitril)	20–200 mCg/L	–	Can worsen generalized seizures.
Topiramate (Topamax)	5–20 mg/L	–	Cognitive side effects, weight loss, renal stones, metabolic acidosis, glaucoma.
Valproic acid (Depakote, Depakene)	50–100 mg/L	Yes, 1:1 conversion (Use total PO daily dose divided q6h, see Formulary)	Black box: hepatotoxicity. Other: weight gain, alopecia, pancreatitis, PCOS, teratogenicity.
Vigabatrin (Sabril)	0.8–36 mg/L	–	Black box: permanent visual field defects. Other: rash, weight gain, irritability, dizziness, sedation.
Zonisamide (Zonegran)	10–40 mg/L	–	Renal stones, weight loss. Rare: SJS, aplastic anemia.

[a]Draw level immediately before an oral dose for ideal sampling time.

GI, Gastrointestinal; *HLA*, human leukocyte antigen; *IV*, intravenous; *MHD*, 10-monohydroxy metabolite; *OCP*, oral contraceptive pill; *PCOS*, polycystic ovarian syndrome; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

(5) Factor in carbohydrate content of formulations when prescribing medications to child on ketogenic diet.
(6) Avoid dextrose-containing IV fluids.

e. Surgical therapies considered for children with identified seizure focus located in noneloquent cortex and/or failed antiseizure drug therapies.
(1) Device implantation: Vagus nerve stimulation, deep brain stimulation, responsive neurostimulation (NeuroPace).
(2) Resections: Hemispherectomy, focal resection (e.g., temporal lobectomy), corpus callosotomy.

IV. HYDROCEPHALUS[26–28]

A. Etiology

Communicating (due to abnormal cerebrospinal fluid [CSF] reabsorption) versus noncommunicating (due to obstruction of CSF flow) and congenital versus acquired (postinfectious, posthemorrhagic, due to mass lesions).

B. Diagnosis

1. **Clinical signs:** apneas, bradycardias, macrocephaly, increasing head circumference (HC), bulging/tense fontanelle, splayed sutures, headaches, blurry/spotty vision, decreased level of consciousness, "setting-sun" eye sign due to upward gaze paresis, vomiting, Cushing triad (hypertension, bradycardia, irregular respirations), papilledema, CN palsies (III, IV, VI).
2. **In infants, obtain serial measurements of HC.** Obtain neuroimaging if significant increase in HC percentile or if patient is symptomatic.
3. **Imaging:** Ultrafast MRI preferred to CT where available (see Chapter 26).

C. Treatment

1. **Medical:**
   a. Emergently manage acute increase of ICP (see Chapter 1).
   b. Slowly progressive hydrocephalus: Acetazolamide and furosemide may provide temporary relief by decreasing the rate of CSF production.
2. **Surgical:** CSF shunting versus endoscopic third ventriculostomy (ETV).
   a. Ventriculoperitoneal shunts used most commonly.
   b. Patients with shunt dysfunction often present with signs of increased ICP. Causes include infection, obstruction (clogging or kinking), disconnection, migration of proximal or distal tips, valve programming.
   c. Evaluation of shunt integrity: See Chapter 26 for discussion of imaging. Consult pediatric neurosurgery (if available).

V. ATAXIA[29,30]

A. Impaired Coordination of Movement and Balance; Broad-Based Gait

B. Differential Diagnosis of Acute Ataxia (**Box 20.9**)

C. Evaluation (**Box 20.10**)

BOX 20.9

DIFFERENTIAL DIAGNOSIS OF ACUTE ATAXIA

1. Ingestion (e.g., antiseizure drugs, antipsychotics, sedatives, hypnotics) or intoxication (e.g., alcohol, hydrocarbon fumes, heavy metals)
2. Postinfectious: cerebellitis (e.g., viral causes), acute disseminated encephalomyelitis
3. Head trauma: cerebellar contusion or hemorrhage, posterior fossa hematoma, vertebrobasilar dissection, postconcussion syndrome
4. Basilar migraine
5. Benign paroxysmal vertigo
6. Intracranial mass lesion: tumor, vascular malformation
7. Opsoclonus–myoclonus ataxia syndrome: Chaotic eye movements combined with ataxia and myoclonus. Postinfectious or paraneoplastic (neuroblastoma/neural crest tumors) etiology.
8. Hydrocephalus
9. Infection: labyrinthitis, abscess
10. Seizure: ictal or postictal
11. Vascular events: cerebellar hemorrhage or stroke
12. Guillain-Barré syndrome or Miller-Fisher variant (ataxia, ophthalmoplegia, and areflexia). Warning: If bulbar signs present, patient may lose ability to protect airway.
13. Rare inherited paroxysmal ataxias
14. Inborn errors of metabolism
15. Multiple sclerosis
16. Somatic symptom disorder

BOX 20.10

CONSIDERATIONS FOR INITIAL EVALUATION OF ACUTE ATAXIA

1. Complete blood cell count, electrolytes, and urine and serum toxicology
2. Imaging (CT or MRI)
3. Lumbar puncture
4. EEG
5. If neuroblastoma is suspected (opsoclonus–myoclonus ataxia syndrome), obtain urine vanillylmandelic acid and homovanillic acid, and CT of chest and abdomen.

CT, Computed tomography; *EEG,* electroencephalogram; *MRI,* magnetic resonance imaging.

VI. STROKE[31–33]

A. Pediatric Stroke

50% ischemic, 50% hemorrhagic. Presents similarly to stroke mimics, but less common and frequently missed (Box 20.11). Neonatal stroke frequently presents with nonfocal symptoms: seizures, altered level of consciousness, feeding difficulties. Important to consider stroke on differential of acute neurologic changes.

BOX 20.11

STROKE MIMICS PRESENTING WITH ACUTE-ONSET FOCAL NEUROLOGIC DEFICIT

1. Migraine
2. Seizure +/– postictal (Todd) paralysis
3. Functional disorders
4. Mass lesion
5. Infection
6. Drug toxicity (e.g., methotrexate)
7. PRES
8. Metabolic abnormality

PRES, Posterior reversible encephalopathy syndrome.

B. Etiologies Vary by Age (Table EC 20.G)[31]

Patients with increased risk of recurrent stroke: history of cardiac disease and cardiac surgery, cerebral arteriopathy, sickle cell disease, thrombophilias.

C. Management

1. **Stroke team activation** (where available) or **urgent neurology consultation,** along with transfer to a tertiary care center with expertise in childhood stroke.
2. **Supportive care and neurologic monitoring.** Maintain normoglycemia, maintain normothermia (avoid fevers). Monitor for signs of increased ICP.
3. **Optimize cerebral perfusion pressure:** Ensure adequate fluid volume and maintenance of median blood pressure (BP) for age, allow permissive hypertension.
4. **Reperfusion therapies:** Not routinely recommended in children due to lack of evidence, but an active area of research. Thrombolytic therapy with IV tissue plasminogen activator (tPA) or mechanical thrombectomy may be considered under appropriate circumstances in centers with extensive pediatric stroke experience (American Heart Association guidelines).
5. **Children with sickle cell disease:** Consult a hematologist. Hydration and emergent exchange transfusion to reduce sickle hemoglobin to <30% (see Chapter 14).

VII. ENCEPHALOPATHY/ALTERED MENTAL STATUS[34–37]

A. Definitions

1. **Encephalopathy:** Diffuse neuronal dysfunction manifesting as acute or chronic altered mental status.

TABLE EC 20.G

RISK FACTORS AND INITIAL INVESTIGATIONS FOR CHILDHOOD STROKE[31]

	Perinatal Stroke (Occurring from 20 Weeks Gestational Age to 28 Days Old)	Childhood Arterial Ischemic Stroke	Cerebral Venous Thrombosis
Risk factors	Not fully understood. Combination of maternal and fetal factors, both ante- and peripartum.	Cardiac (congenital or acquired heart diseases, surgeries) Cerebral arteriopathy (Moya Moya, arterial dissection, VZV-associated vasculopathy, CNS vasculitis, arterial dissection) Hypercoagulable state (genetic anticoagulant deficiencies, rheumatologic conditions, malignancies) Hematologic disorders (sickle cell disease, iron deficiency anemia, thrombocytosis, malignancies) Infections (meningitis, varicella) Drugs (asparaginase, estrogen, cocaine, methamphetamines) Inflammatory/autoimmune (SLE, RA, systemic vasculitis)	Inherited thrombophilia (genetic anticoagulant deficiencies) Drugs (asparaginase, estrogen) Infections (sinusitis, otitis media, mastoiditis, oropharyngeal infections, varicella) Inflammatory/autoimmune (SLE, IBD) Dehydration Nephrotic syndrome Malignancies Sickle cell disease Trauma
Initial workup	Diagnosis by neuroimaging: MRI more sensitive than CT, obtain DWI, FLAIR, SWI, GRE, and MRA sequences Thrombophilia work-up may not change management. Consider echocardiogram. Manage symptomatology.	Diagnosis by neuroimaging: MRI more sensitive than CT, obtain DWI, FLAIR, SWI, GRE, and MRA sequences Consider echocardiogram, ECG Laboratory studies based on suspected etiology (start with CBC, PT/INR, PTT, ESR, CRP, electrolytes, antithrombin III activity, lupus anticoagulant, toxicology screen) Consider CSF studies (may include VZV DNA PCR)	Diagnosis by neuroimaging: MRI more sensitive than CT, obtain MRV Laboratory studies (CBC, electrolytes, BUN, creatinine, glucose, PT, PTT, ESR, antithrombin III activity, pregnancy test)

CBC, Complete blood count; *CNS,* central nervous system; *CRP,* c-reactive protein; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *DWI,* diffusion-weighted imaging; *FLAIR,* fluid-attenuated inversion recovery; *GRE,* gradient echo; *IBD,* inflammatory bowel disease; *MRA/MRV,* magnetic resonance angiography/venography; *MRI,* magnetic resonance imaging; *PT/INR,* prothrombin time/international normalized ration; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus; *SWI,* susceptibility-weighted imaging; *VZV,* varicella zoster virus.

BOX 20.12

DIFFERENTIAL DIAGNOSIS OF ENCEPHALOPATHY

1. Infectious and parainfectious: meningitis, encephalitis, ADEM
2. Autoimmune: NMDAR, VGKC-complex, Hashimoto thyroiditis–associated
3. Trauma
4. Seizure-related: status epilepticus, postictal, epileptic encephalopathy
5. Toxins: medications, drugs, heavy metals, carbon monoxide
6. Metabolic: uremia, hyperammonemia, hyper- or hypoglycemia, lactic acidosis
7. Hypertension, PRES
8. Hypoxic-ischemic: neonatal, drowning, cardiorespiratory arrest, vascular
9. Intracranial hemorrhage
10. Malignancy
11. Genetic: leukoencephalopathy, mitochondrial, ADANE

ADANE, Autosomal-dominant acute necrotizing encephalitis; *ADEM,* acute disseminated encephalomyelitis; *NMDAR,* N-methyl-D-aspartate receptor; *PRES,* posterior reversible encephalopathy syndrome; *VGKC,* voltage-gated potassium channel.

2. **Encephalitis:** Inflammation of brain parenchyma due to infection or inflammatory response.

B. Selected Causes of Encephalopathy (Box 20.12)

C. Diagnosis

Targeted based on clinical scenario and associated symptoms. See Chapter 1 for emergency management of acute altered level of consciousness. Further workup based on suspected etiology. May require serum and/or cerebrospinal fluid (CSF) studies for infectious/inflammatory/metabolic markers, EEG, neuroimaging (e.g., MRI or PET).

D. Treatment

Dependent on etiology. See Chapter 1 for emergency management of acute altered level of consciousness. See Chapter 17 for treatment of meningitis.

VIII. NEUROMUSCULAR DISORDERS[38–45]

A. Spinal Muscular Atrophy[38,39]

1. **Etiology:** Motor neuron degeneration caused by autosomal recessive mutations in *SMN1* gene with resulting insufficient levels of SMN protein. Severity correlates inversely with copy number of *SMN2.*
2. **Clinical features:** Varying degrees of symmetric and progressive, proximal more than distal, muscle weakness with preserved cognition. Patients with severe forms do not survive past early childhood without treatment due to respiratory failure.
3. **Treatment:** Evaluation of weak/hypotonic infant for possible spinal muscular atrophy (SMA) is urgent, as effective treatment (nusinersen [Spinraza]) is possible, but magnitude of benefit decreases with time.

B. Duchenne or Becker Muscular Dystrophy[40]

1. **Etiology:** X-linked mutation in Duchenne muscular dystrophy *(DMD)* gene, encoding dystrophin, causes disruption of muscular cytoskeleton. Mostly affects males. Duchenne form is more severe and caused by complete disruption of dystrophin; partial disruption causes milder Becker muscular dystrophy (BMD).
2. **Clinical features:** Delayed motor milestones. Progressive proximal symmetric muscle weakness starting in early childhood leading to wheelchair use for mobility by age 13. Elevated serum CK levels.
3. **Treatment**: Corticosteroids (prednisone or deflazacort [Emflaza]) are mainstays.[41] Requires multidisciplinary management: At high risk for cardiomyopathy and respiratory and orthopedic complications. Novel disease-modifying agent, eteplirsen (Exondys 51), limited to patients with specific *DMD* mutations.

C. Myasthenia Gravis[42]

1. **Etiology**: Autoantibodies binding the acetylcholine receptor impair neuromuscular junction function. Subtypes include transient neonatal myasthenia (due to transplacental transfer of maternal antibodies from mother with myasthenia), congenital myasthenic syndrome (genetic defects of neuromuscular junction proteins), and juvenile (classic autoimmune in children).
2. **Clinical features:** A key feature is fatigable, variable weakness. Often concentrates in orbital muscles (double vision, ptosis, ophthalmoparesis), or bulbar weakness (slurred/nasal voice, difficulty chewing, swallowing, talking). Can also manifest with generalized weakness of limbs and trunk. Triggers include illness, fever, heat, and some medications. Bulbar weakness can worsen with illness and compromised airway. A good bedside test of bulbar muscle fatigue is the "slurp test."[43] Ask patient to imbibe four ounces of water through a straw quickly—if consumption slows after 1 or 2 ounces, at risk of bulbar decompensation; if marked slowing or times especially prolonged, at risk for respiratory failure.
3. **Treatment**: Refer to/consult specialist for management.
   a. Myasthenic crisis/rapid onset of symptoms: plasmapheresis, IVIG, and IV neostigmine. Evaluate the need to secure definitive airway.
   b. Chronic management:
      (1) Oral pyridostigmine
      (2) Prednisone (caution about paradoxical worsening with any large initial dose)
      (3) Immunosuppressive medications (e.g., mycophenolate, rituximab)
      (4) Thymectomy may be helpful

D. Acute Guillain-Barré Syndrome[44,45]

1. **Etiology:** Presumed immune attack against peripheral nerve myelin. In some cases, triggered by illness, notably *Campylobacter jejuni* infection.

2. **Clinical features and diagnosis:** Rapid decline with nadir less than two weeks after onset; respiratory status can be compromised. Back pain often prominent in children. Often with autonomic instability. Elevated spinal fluid protein without cellular infiltrate ("albumocytologic dissociation"). Nerve conduction studies can be helpful.
3. **Treatment:** Patients should be hospitalized at presentation to monitor for respiratory stability. Acute phase treatment with IVIG, plasmapheresis helpful if initiated early. Supportive care.
4. **Variants of Guillain-Barré syndrome (GBS)**
   a. Acute: Miller Fisher syndrome (ataxia, ophthalmoplegia, and areflexia), acute motor axonal neuropathy (AMAN)
   b. Chronic: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a similar but slower progressive autoimmune disorder that often requires chronic immunosuppressive therapy.

E. Infantile Botulism[46]

1. **Etiology:** Affects infants <1 year of age, most commonly <6 months, due to colonization of colon by *Clostridium botulinum* bacteria (infants are susceptible due to immaturity of gut flora). Botulinum toxin released into bloodstream, irreversibly cleaves protein complex necessary for acetylcholine vesicle release into neuromuscular junction.
2. **Clinical features and diagnosis:** Subacute onset weakness of skeletal muscles diffusely, concentrating in eye, face, and bulbar muscles early. Weak pupil constriction responses common and specific when present. Presenting symptom often constipation for days to weeks before onset of weakness, poor feeding, and weak cry. At high risk for respiratory failure due to respiratory and bulbar muscle weakness. Tachycardia is common. Confirmation of diagnosis by toxin assay of stool (not culture) performed by state lab or CDC; may use minimal amount of sterile, nonbacteriostatic water colonic enema for specimen collection. Electromyography and nerve conduction studies can help confirm diagnosis.
3. **Treatment:** Assess and stabilize airway: approximately 50% of infants require intubation/advanced airway. Treat with one-time dose of human botulism immune globulin (BabyBIG or BIG-IV), available through Infant Botulism Treatment and Prevention Program (http://www.infantbotulism.org/). Prompt treatment is key; do not wait for confirmatory testing. With appropriate treatment, prognosis for full recovery is excellent. See Chapter 16 for recommended interval before measles or varicella vaccination after botulism immune globulin administration.

IX. WEB RESOURCES

- American Academy of Neurology Practice Guidelines: www.aan.com/Guidelines
- American Migraine Foundation: www.americanmigrainefoundation.org
- Child Neurology Foundation: www.childneurologyfoundation.org
- Child Neurology Society: www.childneurologysociety.org

- Epilepsy Diagnosis (with videos): www.epilepsydiagnosis.org
- Epilepsy Foundation: www.epilepsy.com
- Headache resource (from Children's Mercy Kansas): www.headachereliefguide.com
- International League Against Epilepsy: www.ilae.org
- Muscular Dystrophy Association: www.mda.org

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A complete list of references can be found online at www.expertconsult.com.

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Chapter 21

Nutrition and Growth

Jaime La Charite, MD, MPH

I. ASSESSMENT OF GROWTH

A. Types of Growth Charts

1. Child <24 months: World Health Organization (WHO) international growth charts[1]
2. Child ≥2 years: Centers for Disease Control and Prevention (CDC) growth charts[2]
3. Growth charts for premature infants
   a. Corrected age = infant's chronologic age – number of weeks of prematurity (using 40 weeks as full-term gestation) and should be used up to 3 years.[3,4]
   b. Chronologic age should be used if child's growth "catches up" before 3 years.[5]
   c. Oslen, Bertino, and Fenton growth charts can be used to assess growth in premature infants up to 41 weeks (Oslen) to 50 weeks (Fenton).[6] After 4 to 8 weeks post-term, the WHO growth chart can be used.[7]
   d. The choice of growth chart has some variability across practice sites and preferences.[8]
4. Special populations[9,10]
   a. WHO or CDC growth charts are recommended in all cases due to limited reference data for condition-specific growth charts.
   b. Condition-specific growth charts can show families how a specific condition can alter growth potential.
   c. Growth charts have been created for Down syndrome, Prader-Willi syndrome, Williams syndrome, Cornelia de Lange syndrome, Turner syndrome, and Marfan syndrome.

B. Interpretation of Growth Charts[11,12]

1. Stunting/short stature: Length or height <5th percentile
2. Underweight:
   a. Children <2 years: Weight for length/height <5th percentile
   b. Children ≥2 years: Body mass index (BMI) for age <5th percentile or BMI <18.5 kg/m^2
3. Healthy weight: BMI for age 5th percentile to <85th percentile or BMI 18.5 to 24.9 kg/m^2
4. Overweight:
   a. Children <2 years: Weight for length/height >95th percentile

   b. Children ≥2 years: BMI for age ≥ 85th to <95th percentile or BMI 25 to 29.9 kg/m^2
5. Obese:
   a. Children <2 years: No consensus definition exists
   b. Children ≥2 years: BMI for age ≥95th percentile or BMI ≥30 kg/m^2

C. General Guidelines Regarding Appropriate Growth[13,14]

1. Term infants usually lose approximately 5% to 10% of their birth weight, but regain the weight within 2 weeks.
2. Infants should gain 20 to 30 g/day from birth to 3 months, 15 to 22 g/day from 3 to 9 months, and 6 to 11 g/day from 9 to 12 months.
3. Term infants double their birth weight in 4 to 5 months and triple it by 1 year of age.
4. Height doubles from birth to age 3 to 4 years of age.
5. The average size of a 4-year-old is 40 in. and 35 lb.
6. From age 3 to 10 years of age, children grow an average of 2.5 inches per year.

II. MANAGEMENT OF OVERWEIGHT AND OBESE CHILDREN

A. AAP Recommendations for the Prevention of Obesity[15-17]

1. Exclusive breastfeeding until 6 months of age and then breastfeeding maintenance until at least 12 months.
2. Daily breakfast and family meal times.
3. Limit sugary beverages, fast food, energy-dense foods, and encourage fruits and vegetables.
4. Develop a family media plan with limits and technology-free zones. For infants less than 18 months, no media other than video chatting. If media used with toddlers 18-24 months, parents should watch and engage with children during use. For children 2 to 5 years, a max of one hour of high-quality programming a day with co-viewing when possible.
5. Recommend 60 minutes of moderate-to-vigorous exercise per day.

B. Prevention and Management of Obesity in the Primary Care Setting (Table 21.1)

C. Conditions Associated with Obesity[15]

1. Endocrine:
   a. Polycystic ovarian syndrome
   b. Precocious puberty
   c. Pre-diabetes/Type 2 diabetes
2. Gastrointestinal:
   a. Cholelithiasis
   b. Gastroesophageal reflux
   c. Nonalcoholic fatty liver disease
3. Neurologic: Pseudotumor cerebri
4. Orthopedic:
   a. Blount disease
   b. Slipped capital femoral epiphysis (SCFE)

5. Behavioral health:
   a. Anxiety
   b. Binge eating disorder
   c. Depression

TABLE 21.1

MANAGEMENT AND MONITORING STRATEGIES FOR CHILDREN BASED ON BODY MASS INDEX[50-52]

BMI	Initial Management	Monitoring—Follow up
Normal BMI	• Praise child and family • Screen for genetic dyslipidemia with nonfasting lipid profile between ages 9–11 and 18–21 • Maintain weight velocity	Next well child visit
Normal BMI that is increasing percentiles (crossing two percentile lines is a risk factor for obesity)	• Screen for genetic dyslipidemia as above • Patient education	Next well child visit
Overweight BMI	• Patient education • If health risk factors, obtain fasting glucose, hemoglobin A1c or oral glucose tolerance test, lipid profile, ALT, and AST	2–4 weeks
Obese BMI	• Patient education • Obtain fasting glucose, hemoglobin A1c or oral glucose tolerance test, lipid profile, ALT, and AST • Some specialist clinics screen for vitamin D deficiency and insulin resistance (i.e., measure fasting insulin), but their clinical utility and cost effectiveness is unclear • No guidelines on which age to start laboratory screening, but some experts start at 2 years of age • Consider other labs (e.g., thyroid studies, cortisol) based on clinical picture	2–4 weeks

Further follow-up and management for those who are overweight or obese:

(a) At each follow-up, record weight, measure blood pressure, and use an empathetic and empowering counseling style (e.g., motivational interviewing).

(b) Establish goals: Positive behavior change, weight maintenance, or decrease in BMI velocity. Children aged 2 to 5 years who have obesity should not lose more than 1 pound/month; older children and adolescents with obesity should not lose more than an average of 2 pounds/week.

(c) If no improvement after 3 to 6 months, refer to structured weight management program. If no improvement after 3 to 6 months, the next step is a comprehensive, multidisciplinary approach. If no improvement, refer for evaluation at a tertiary care center for medication management and weight reduction surgery.

ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index.

III. MALNUTRITION IN INFANTS AND CHILDREN

A. Defining Malnutrition[16]

NOTE: Also called growth failure or under-nutrition; previously called failure to thrive.

1. Condition of under-nutrition generally identified in the first 3 years of life
2. Can be described by the following growth scenarios:
   a. Primary indicators when single data point available
      (1) Weight for length/height z-score
      (2) BMI for age z-score
      (3) Length/height for age z-score
      (4) Wasting or mid-upper arm circumference (MUAC)
      (5) Presence of nutritional edema
   b. Primary indicators when two or more data points available
      (1) Weight gain velocity (<2 years old)
      (2) Degree of weight loss (2 to 20 years of age)
      (3) Deceleration in weight for length/height z-score
      (4) Inadequate nutrient intake

B. Classifying the Degree to Which a Patient Is Malnourished (Table 21.2)[17]

1. Acute (duration <3 months)
2. Chronic or stunting (duration >3 months); suggested by height/length for age

C. Resources for Determining Z-scores[18]

1. PediTools (peditools.org)
2. Standardized height and weight calculator (https://www.quesgen.com/BMIPedsCalc.php).

TABLE 21.2

DEFINITIONS FOR CATEGORY OF MALNUTRITION[40]

	Mild	Moderate	Severe
Weight for height and BMI	−1 to −1.9 z-score	−2 to −2.9 z-score	−3 or greater z-score
Mid-upper arm circumference z-score[a]	≥ −1 to −1.9	≥ to −2.9	≥ −3
Weight gain velocity (<2 years)	Less than 75% of the norm for expected weight gain	Less than 50% of the norm for expected weight gain	Less than 25% of the norm for expected weight gain
Weight loss (2–20 years)	5% usual body weight	7.5% usual body weight	10% usual body weight
Deceleration in weight for length/height z-score	Decline of 1 z-score	Decline of 2 z-scores	Decline of 3 z-scores
Inadequate nutritional intake	51%–75% estimated energy/protein need	26%–50% estimated energy/protein need	<26% estimated energy/protein need

[a]See Section IIIC for how to calculate z-score.

BMI, Body mass index.

Adapted from Becker P, Carney LN, Corkins MR, et al. Primary indicators when 2 or more data points available. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition. *Nutr Clin Pract.* 2015;30(10):147–161. Tables 3 and 4.

3. CDC website (cdc.gov/growthcharts/zscore.htm)
4. WHO website (who.int/childgrowth/standards/chart_catalogue)

D. Differential Diagnosis of Malnutrition[19]

1. Secondary to disease/injury
2. Decreased intake (e.g., fluid restriction, cardiac failure, anorexia nervosa, food insecurity)
3. Increased requirement/hyper-metabolism (e.g., burns)
4. Excessive loss (e.g., chronic diarrhea, burn, proteinuria)
5. Malabsorption (e.g., Crohn's disease, cystic fibrosis)

E. Physical Exam Findings Consistent with Malnutrition[23-25]

1. Fat loss (e.g., orbital, buccal, triceps, ribs)
2. Muscle wasting (e.g., temporalis, pectoralis, deltoid, latissimus dorsi, quadriceps)
3. Edema
4. Functional limitations (e.g., hand grip strength)
5. Macronutrient deficiencies
   a. Iron
      (1) Exam findings: Koilonychias, pale conjunctiva and nail beds
      (2) Risk factors: Low birth weight, feeding problems, poor growth, exclusive breast feeding >6 months
   b. Vitamin C
      (1) Exam findings: Perifollicular hemorrhage, scorbutic tongue, bleeding gum, bruising
      (2) Risk factors: Limited diet, infant on cow's milk, dialysis, malabsorption
   c. Vitamin A
      (1) Exam findings: Bitot spot, follicular hyperkeratosis
      (2) Risk factors: Limited diet, fat malabsorption, alcoholism, cystic fibrosis, short bowel
   d. Vitamin B6
      (1) Exam findings: Seborrheic dermatitis, angular palpebritis, hypertrophied papillae
      (2) Risk factors: Dialysis, sickle cell disease, malabsorption; diuretic, anticonvulsant, contraceptive, and isoniazid use
   e. Zinc
      (1) Exam findings: Dermatitis, vesico-bullous lesions, diaper rash
      (2) Risk factors: Prematurity, parenteral nutrition (PN), cholestasis, diarrhea, high phytate intake, celiac or Crohn's disease, AIDS, liver or renal disease, alcoholism, trauma, burn, sleeve gastrectomy, diuretic and valproate use

F. Diagnostic Evaluation of Malnutrition[26-29]

1. There is no consensus on work-up algorithm.
2. Routine labs and imaging are often low yield and generally not recommended; work-up should be guided by clinical suspicion.
3. If warranted, reasonable initial testing could include complete blood count, complete metabolic panel, urinalysis, and erythrocyte sedimentation rate.

4. If the child's length has decelerated and is below 50%, can screen for hypothyroidism and growth hormone deficiency.
5. If recurrent or severe upper respiratory or opportunistic infections, consider testing for human immunodeficiency and tuberculosis and measuring immunoglobulin and complement levels.
6. Based on clinical suspicion, can consider celiac screening, sweat chloride testing, echocardiogram, hepatitis serology, stool studies.
7. Consider hospitalization for observed feeding if the child fails outpatient management, suspicion for abuse/neglect or traumatic injury, severe psychological caregiver impairment, serious malnutrition, or at risk for re-feeding.

G. Red Flags That Suggest a Medical Cause of Malnutrition[20]

1. Developmental delay or dysmorphic features
2. Cardiac findings (e.g., murmur, edema, jugular venous distension)
3. Failure to gain weight despite adequate calories
4. Organomegaly or lymphadenopathy
5. Recurrent or severe respiratory, mucocutaneous, or urinary infections
6. Recurrent vomiting, diarrhea, or dehydration

H. Approach to the Management of Malnourished Patients[21,22] (Box 21.1)

1. Address the etiology of malnutrition.
2. Approximately 20% to 30% more energy may be required to achieve catch-up growth in children. This should continue until the previous growth percentiles are regained.
3. Catch-up linear growth may lag several months behind weight.
4. See Box 21.1 for instructions on the calculation of catch-up growth requirements.

BOX 21.1

DETERMINING CATCH-UP GROWTH REQUIREMENTS

1. Plot the child's height and weight on the appropriate growth charts.
2. Determine recommended calories required for age [recommended dietary allowances (RDA)].
3. Determine the ideal weight (50th percentile) for child's height.
4. Multiply the RDA calories by ideal body weight for height (kg).
5. Divide this value by the child's actual weight (kg). For example, for a 12-month-old boy whose weight is 7 kg and length is 72 cm, RDA for age would be 98 kcal/kg/day, and ideal body weight for height is 9 kg (50th percentile weight for height); thus his catch-up growth requirement would be as follows:

$$98 \text{ kcal/kg/day} \times (9 \text{ kg}/7 \text{ kg}) = 126 \text{ kcal/kg/day}$$

Adapted from Nestle Health Science. Calorie and protein requirements. Pediatric nutrition helpful hints: Specialized nutrition for your most vulnerable patients. Available at https://www.nestlehealthscience.us/asset-library/documents/resources/pediatric%20helpful%20hints.pdf; and Corrales KM, Utter SL. Failure to thrive. In: Samour PQ, Helm KK, Lang CE, eds. *Handbook of Pediatric Nutrition*. 2nd ed. Aspen Publishers; 1999:406.

5. Screen for food insecurity and offer social work and community resources.
6. Pharmacotherapy (e.g., cyproheptadine, megestrol) may be helpful for patients with significant underlying diseases (e.g., cancer, cystic fibrosis).

IV. RE-FEEDING SYNDROME

A. Patients at Risk of Developing Re-Feeding Syndrome[23]

1. Chronic malnutrition (e.g., prolonged fasting ≥5 days, malignancy)
2. Renal/endocrine (e.g., chronic diuretic use, diabetic hyperglycemic hyperosmolar syndrome)
3. Gastrointestinal loss (e.g., inflammatory bowel disease, chronic pancreatitis, short bowel)
4. Infectious (e.g., AIDS, tuberculosis)
5. Cardiac (e.g., congenital heart disease)
6. Pulmonary (e.g., cystic fibrosis)
7. Psychiatric (e.g., anorexia nervosa, chronic alcohol use)
8. Social (e.g., child abuse/neglect, homelessness, food insecurity)

B. Management of Re-Feeding Syndrome[24]

1. Maintain continuous cardiorespiratory monitoring or check vital signs every 4 hours, depending on level of concern.
2. Ensure strict intake and output monitoring with calorie count and daily weights.
3. Obtain at least daily basic metabolic panel with phosphorous and magnesium. Obtain more frequently if electrolyte replacement needed, or if there are concerning trends.
4. Measure pre-albumin, albumin, zinc.
5. Consider giving thiamine 100 to 300 mg PO daily (or 50 to 100 mg IV) × 3 days before feeding. There is some debate whether this is required.
6. Give a multivitamin daily.
7. Feeding should not proceed without appropriate supplementation.
8. Recommendations vary, but start at 1/4 to 1/2 of estimated caloric needs depending on degree of risk.
9. Dietary advancement over 3 to 7 days with caloric increases of 10% to 25% per day until recommended caloric goals achieved.
10. Enteral feeding is preferred over parenteral feeding.

V. NUTRITIONAL NEEDS OF HEALTHY CHILDREN

A. Dietary Allowances for Carbohydrates and Protein (Table 21.3)

B. Fat Requirements (Table 21.4)

C. Vitamin Requirements (Tables 21.5 and 21.6)

1. Vitamin D[25,26]
   a. Breast-fed and partially breast-fed infants should be supplemented with 400 international units (IU) per day beginning in the first few days of life until 12 months.

TABLE 21.3

RECOMMENDED DIETARY ALLOWANCES, CALORIE, AND PROTEIN REQUIREMENTS[a]

Category	Age (years)	kcal/kg	Protein g/kg
Infants	0–0.5	108	2.2
	0.5–1	98	1.6
Children	1–3	102	1.2
	4–6	90	1.1
	7–10	70	1.0
Males	11–14	55	1.0
	15–18	45	0.9
	19–24	40	0.8
Females	11–14	47	1.0
	15–18	40	0.8
	19–24	38	0.8

[a]This RDA was determined and by definition meets the needs of 97% of healthy children. This is a quick reference to estimate calorie and protein needs, but further estimation may be required, using various other energy and protein need equations and factors, typically used by a registered dietitian

Data from Nestle Health Science. Calorie and protein requirements. Pediatric nutrition helpful hints. Specialized nutrition for your most vulnerable patients. Available at https://www.nestlehealthscience.us/asset-library/documents/resources/pediatric%20helpful%20hints.pdf; and Recommended Dietary Allowances. 10th ed. National Academy of Sciences, National Academy Press; 1989:33–36.

TABLE 21.4

FAT REQUIREMENTS: ADEQUATE INTAKE[a]

Age	Total Fat (g/day)	Linoleic Acid (g/day)	α-Linolenic Acid (g/day)
0–6 months	31	4.4 (n-6 PUFA)	0.5 (n-3 PUFA)
7–12 months	30	4.6 (n-6 PUFA)	0.5 (n-3 PUFA)
1–3 years	[b]	7	0.7
4–8 years	[b]	10	0.9
9–13 years, boys	[b]	12	1.2
9–13 years, girls	[b]	10	1.0
14–18 years, boys	[b]	16	1.6
14–18 years, girls	[b]	11	1.1
Pregnancy	[b]	13	1.4
Lactation	[b]	13	1.3

[a]If sufficient scientific evidence is not available to establish a recommended dietary allowance (RDA), an adequate intake (AI) is usually developed. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the group, but a lack of data or uncertainty in the data prevents from being able to specify with confidence the percentage of individuals covered by this intake.

[b]No AI, estimated average requirement (EAR), or RDA established.

PUFA, Polyunsaturated fatty acid.

From Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, DC: National Academies Press; 2006.

b. Formula-fed infants should be supplemented until the infant is taking 34 oz of formula per day.
c. For preterm infants tolerating full enteral feeds and weighing >1500-2000 g, supplement with 400 IU/day. Supplement with 200-400 IU/day for infants <1500g.
d. Supplement children and adolescents with 600 IU/day if the child is ingesting <1000 mL (34 oz) per day of vitamin D fortified milk or not taking that amount through fortified foods.

TABLE 21.5

DIETARY REFERENCE INTAKES: RECOMMENDED INTAKES FOR INDIVIDUALS—VITAMINS

Life Stage	Vit. A[a] (IU)	Vit. C (mg/day)	Vit. D[b,c] (IU)	Vit. E[d] (IU)	Vit. K (mCg/day)	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin[e] (mg/day)	Vit. B_6 (mg/day)	Folate[f] (mCg/day)	Vit. B_{12} (mCg/day)	Pantothenic Acid (mg/day)	Biotin (mCg/day)	Choline[g] (mg/day)
INFANTS														
0–6 months	**1333**	40*	400*	4*	2.0*	0.2*	0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*
7–12 months	**1666**	50*	400*	5*	2.5*	0.3*	0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*
CHILDREN														
1–3 years	**1000**	**15**	600*	**6**	**30***	**0.5**	**0.5**	**6**	**0.5**	**150**	**0.9**	2*	8*	200*
4–8 years	**1333**	**25**	600*	**7**	**55***	**0.6**	**0.6**	**8**	**0.6**	**200**	**1.2**	3*	12*	25*
MALES														
9–13 years	**2000**	**45**	600*	**11**	**60***	**0.9**	**0.9**	**12**	**1.0**	**300**	**1.8**	**4***	20*	375*
14–18 years	**3000**	**75**	600*	**15**	**75***	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	**5***	25*	550*
19–30 years	**3000**	**90**	600*	**15**	**120***	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	**5***	30*	550*
FEMALES														
9–13 years	**2000**	**45**	600*	**11**	**60***	**0.9**	**0.9**	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
14–18 years	**2333**	**65**	600*	**15**	**75***	**1.0**	**1.0**	**14**	**1.2**	**400**	**2.4**	5*	25*	400*
19–30 years	**2333**	**75**	600*	**15**	**90***	**1.1**	**1.1**	**14**	**1.3**	**400**	**2.4**	5*	30*	425*

Continued

TABLE 21.5

DIETARY REFERENCE INTAKES: RECOMMENDED INTAKES FOR INDIVIDUALS—VITAMINS—Cont'd

Life Stage	Vit. A[a] (IU)	Vit. C (mg/day)	Vit. D[b,c] (IU)	Vit. E[d] (IU)	Vit. K (mCg/day)	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin[e] (mg/day)	Vit. B_6 (mg/day)	Folate[f] (mCg/day)	Vit. B_{12} (mCg/day)	Pantothenic Acid (mg/day)	Biotin (mCg/day)	Choline[g] (mg/day)
PREGNANCY														
<18 years	**2500**	**80**	600*	**15**	75*	**1.4**	**1.4**	**18**	**1.9**	**600**	**2.6**	6*	30*	450*
19–30 years	**2567**	**85**	600*	**15**	90*	**1.4**	**1.4**	**18**	**1.9**	**600**	**2.6**	6*	30*	450*
LACTATION														
<18 years	**4000**	**115**	600*	**19**	75*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
19–30 years	**4333**	**120**	600*	**19**	90*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*

[a]One international unit (IU) = 0.3 mCg retinol equivalent.

[b]One mCg cholecalciferol = 40 IU vitamin D.

[c]In the absence of adequate exposure to sunlight.

[d]One IU = 1 mg vitamin E.

[e]As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0 to 6 months = preformed niacin (not NE).

[f]As dietary folate equivalents (DFE). 1 DFE = 1 mCg food folate = 0.6 mCg of folic acid from fortified food or as a supplement consumed with food = 0.5 mCg of a supplement taken on an empty stomach.

[g]Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is required at all life stages, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

NOTE: This table presents recommended dietary allowances (RDAs) in **bold type** and adequate intakes (AIs) in regular type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97% to 98%) individuals in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent from being able to specify with confidence the percentage of individuals covered by this intake.

Modified from Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006; www.nap.edu.

TABLE 21.6

VITAMIN D LABATORY INTERPRETATION

25-Hydroxy Vitamin D	Value (ng/mL)
Severe deficiency	<10
Deficiency	<10–20
Insufficiency	>20–<30
Optimal level	≥ 30[a]

[a]Cut-off values are not yet well-defined. Controversy exists regarding the optimal 25-hydroxy vitamin D level. Some experts recommend a level of 20 to 30 ng/mL as being sufficient. These are the Johns Hopkins Hospital Pediatrics guidelines used for dosing.

NOTE: 1,25-dihydroxy vitamin D is the physiologically active form, but 25-hydroxy vitamin D is the value to monitor for vitamin D deficiency as it approximates body stores of vitamin D.

e. At risk children (e.g., cystic fibrosis) and those with laboratory confirmed vitamin D insufficiency/deficiency should also be supplemented.
f. See Table 21.6 for interpreting vitamin D levels.

2. Folate[27,28]
   a. All women capable of becoming pregnant should consume 400 mCg from supplements or diet.
   b. This should continue as women enter prenatal care.
   c. If a woman had a prior pregnancy with a neutral tube defect and is planning another pregnancy, she should consume 4 mg of folic acid daily (requires a prescription) at least 4 weeks before becoming pregnant and continue through the first 12 weeks of pregnancy.

D. Mineral Requirements (Table 21.7)

1. Iron[29]
   a. Breast-fed term infants should receive 1 mg/kg/day of an oral iron supplement beginning at 4 months of age, preferably from iron-fortified cereal or, alternatively, elemental iron.
   b. Breast-fed preterm infants should receive 2 mg/kg/day by 1 month of age, which should continue until the infant is weaned to iron-fortified formula or begins eating complementary foods.
   c. Formula-fed term infants receive adequate iron from fortified formula.
   d. Formula-fed preterm infants need 2 mg/kg/day, which is the amount supplied by iron-fortified formulas.
2. Fluoride[30]
   a. Consider fluoride supplementation for those patients who use bottled water or home filtration systems. Some home water treatment systems can reduce fluoride levels.
   b. For infants and children at high risk for the development of caries, fluoride supplementation ranging from 0.25-1 mg/day is recommended according to the American Dental Association's schedule.
   c. Fluoridated toothpaste is recommended for all children starting at tooth eruption, using a smear (grain-of-rice-sized) until age 3 and then a pea-sized amount after that time.

TABLE 21.7

DIETARY REFERENCE INTAKES: RECOMMENDED INTAKES—ELEMENTS

Life Stage	Calcium (mg/day)	Chromium (mCg/day)	Copper (mCg/day)	Fluoride (mg/day)	Iodine (mCg/day)	Iron (mg/day)	Magnesium (mg/day)	Manganese (mg/day)	Molybdenum (mCg/day)	Phosphorus (mg/day)	Selenium (mCg/day)	Zinc (mg/day)
INFANTS												
0–6 months	200*	0.2*	200*	0.01*	110*	0.27*	30*	0.003*	2*	100*	15*	2*
7–12 months	260*	5.5*	220*	0.5*	130*	**11**	75*	0.6*	3*	275*	20*	**3**
CHILDREN												
1–3 years	**700**	11*	**340**	0.7*	**90**	**7**	**80**	1.2*	**17**	**460**	**20**	**3**
4–8 years	**1000**	15*	**440**	1.0*	**90**	**10**	**130**	1.5*	**22**	**500**	**30**	**5**
MALES												
9–13 years	**1300**	25*	**700**	2*	**120**	**8**	**240**	1.9*	**34**	**1250**	**40**	**8**
14–18 years	**1300**	35*	**890**	3*	**150**	**11**	**410**	2.2*	**43**	**1250**	**55**	**11**
19–30 years	**1000**	35*	**900**	4*	**150**	**8**	**400**	2.3*	**45**	**700**	**55**	**11**
FEMALES												
9–13 years	**1300**	21*	**700**	2*	**120**	**8**	**240**	1.6*	**34**	**1250**	**40**	**8**
14–18 years	**1300**	24*	**890**	3*	**150**	**15**	**360**	1.6*	**43**	**1250**	**55**	**9**
19–30 years	**1000**	25*	**900**	3*	**150**	**18**	**310**	1.8*	**45**	**700**	**55**	**8**
PREGNANCY												
<18 years	**1300**	29*	**1000**	3*	**220**	**27**	**400**	2.0*	**50**	**1250**	**60**	**13**
19–30 years	**1000**	30*	**1000**	3*	**220**	**27**	**350**	2.0*	**50**	**700**	**60**	**11**
LACTATION												
<18 years	**1300**	44*	**1300**	3*	**290**	**10**	**360**	2.6*	**50**	**1250**	**70**	**14**
19–30 years	**1000**	45*	**1300**	3*	**290**	**9**	**310**	2.6*	**50**	**700**	**70**	**12**

NOTE: This table presents recommended dietary allowances (RDAs) in **bold type** and adequate intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97% to 98%) individuals in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover needs of all individuals in the group, but lack of data or uncertainty in the data prevent from being able to specify with confidence the percentage of individuals covered by this intake.

Modified from Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006. Includes updates from Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.

TABLE 21.8

FIBER REQUIREMENTS: ADEQUATE INTAKE[a]

Age	Total Fiber (g/day)
0–12 months	Not determined
1–3 years	19
4–8 years	25
9–13 years, boys	31
9–13 years, girls	26
14–18 years, boys	38
14–18 years, girls	26
Pregnancy	28
Lactation	29

[a]Adequate intake (AI). If sufficient scientific evidence unavailable to establish recommended dietary allowance (RDA), an AI is usually developed. For healthy breast-fed infants, the AI is the mean intake. AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the group, but a lack of data or uncertainty in the data prevents from being able to specify with confidence the percentage of individuals covered by this intake.
g, Grams.
Modified from Otten JJ, Hellwig JP, Meyers LD, eds. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press; 2006.

E. Fiber Requirements (Table 21.8)

VI. BREASTFEEDING AND THE USE OF HUMAN MILK

A. Benefits of Breast Milk[31]

1. Decreased risk of infections (e.g., otitis media, respiratory), necrotizing enterocolitis, inflammatory bowel, sudden infant death syndrome (SIDS).
2. Decreased incidence of atopic conditions, obesity, and diabetes.

B. Contraindications to Breastfeeding[32,33] (Box 21.2)

1. Tobacco smoking is not contraindicated but is strongly discouraged because of an association with increased risks of SIDS, respiratory disease, and infections in exposed infants.
2. Alcohol should be limited to the occasional intake of 2 oz of liquor, 8 oz of wine, or two beers for the average 60 kg woman >2 hours prior to the onset of nursing.
3. Methadone and buprenorphine are not contraindications, if the mother is in a stable maintenance program and not using street drugs.

C. Use of Milk Bank Donor Human Milk[34]

1. Most commonly used in low birth weight infants (<1.5 kg).
2. Can be considered in infants with intestinal disease with documented intolerance to specialized infant formulas.

D. Safe Handling of Breast Milk[35]

1. Freshly expressed or pumped milk can be stored at room temperature for up to 4 hours, in the refrigerator for up to 4 days, in the freezer for approximately 6 months (up to 12 months), and in an insulated cooler bag with frozen packs up to 24 hours while traveling.
2. Once breast milk is thawed to room temperature or warmed, it should be used within 2 hours.

BOX 21.2
CONTRAINDICATIONS TO BREASTFEEDING[39]

Infant galactosemia
Maternal human T-cell lymphotropic virus I/II infection
Maternal untreated brucellosis
Maternal HIV (developed countries)
Maternal active, untreated tuberculosis (may give expressed BM)
Maternal active HSV lesions on breast (may give expressed BM)
Maternal varicella infection 5 days before through 2 days after delivery (may give expressed BM)
Maternal use of diagnostic or therapeutic radioactive isotopes, antimetabolites, or chemotherapeutic agents
Illicit street drugs such as cannabis, cocaine, phencyclidine, etc.

BM, Breast milk; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus.
Modified from American Academy of Pediatrics, Section on Breastfeeding. Policy Statement—Breastfeeding and the Use of Human Milk. *Pediatrics*. 2012;129:e827–e841.

3. If the baby did not finish the bottle, the leftover breast milk should only be used within 2 hours of the baby finishing the feed.

E. Breastfeeding Challenges

See Section IX.C.

VII. ENTERAL NUTRITION

A. Feeding the Healthy Infant

1. Recommended formula amount by age[36]
   a. 1st days of life: 1 to 2 ounces every 2 to 3 hours
   b. 1st month: 2 to 4 ounces every 3 to 4 hours
   c. 2nd month: 5 to 6 ounces every 4 to 5 hours
   d. 3rd to 5th month: 6 to 7 ounces every 4 to 5 hours
   e. 6th to 8th month: 24 to 32 ounces in 24 hours
   f. 8th to 10th month: 16 to 32 ounces in 24 hours
   g. 10th to 12th month: 12 to 24 ounces in 24 hours
2. Properties of formula options for healthy infants and toddlers (Table 21.9)
3. Appropriate preparation and fortification of formulas (Table 21.10)
4. Methods to further increase calories, protein, carbohydrate, fat, or a combination (Table 21.11)

B. Available Formulas for Patients with Specific Clinical Conditions or for Those Requiring Special Diets (Tables 21.12 and 21.13)

C. Use of Enteral Tube Feeds[37]

1. Insufficient oral intake (e.g., anorexia nervosa, food aversion, malabsorption, increased needs)
2. As a primary therapy (e.g., metabolic or inflammatory bowel disease, fasting intolerance)
3. Oral motor dysfunction (e.g., prematurity, neuromuscular and neurologic disease)

TABLE 21.9

PROPERTIES OF FEEDING OPTIONS FOR HEALTHY INFANTS AND CHILDREN[54-58]

	Examples	Calories (kcal/oz)	Carbohydrate Source	Protein Source	Unique Properties	Indications
Human Milk		20	Lactose	Human milk	See Section VI.A	Preferred for most infants
Cow's Milk–based Formulas	Enfamil Infant, Similac Advance, Similac Sensitive, Gerber Good Start Gentle	20	Lactose	Cow's milk		Typical term infant
Toddler/Child	Boost Kids Essential, Carnation Instant Breakfast Essential, Compleat Pediatric, Nutren Junior, Pediasure Enteral, Pediasure	20–45	Lactose	Cow's milk	Milk-based Contain added iron, vitamin C, E, and zinc, DHA/AA, calcium	Age 1 year to 10–13 years

AA, Amino acids; *DHA*, docosahexaenoic acid; *kcal*, kilocalorie; *oz*, ounce.

Data from O'Connor, N. Infant formula. *Am Fam Phys*. 2009; 79(7):565–570, Table 21.9; and Comparison of breast milk and available infant formulas, available at https://www.aafp.org/afp/2009/0401/p565.html), Table 1. Additional sources listed in references.

TABLE 21.10

PREPARATION OF INFANT FORMULAS FOR MOST FULL-TERM STANDARD AND SOY FORMULAS[a]

Formula Type	Desired Caloric Concentration (kcal/oz)	Amount of Formula 13 oz = 1 can	Water (oz)	Approximate Final Volume (oz)
Liquid concentrates (40 kcal/oz)	20	13 oz	13 oz	26 oz
	22	13 oz	11 oz	24 oz
	24	13 oz	9 oz	22 oz
	26	13 oz	7 oz	20 oz
	27	13 oz	6 oz (3/4 cup)	19 oz
	30	13 oz	4.3 oz	17.3 oz
Powder (approx 44 kcal/scoop)[b]	20	1 scoop	2 oz	2 oz
	22	3 scoop	5.5 oz	6 oz
	24	3 scoops	5 oz	5.5 oz
	26	6 scoops	9 oz	10 oz
	27	6 scoops	8.5 oz	10 oz
	30	6 scoops	7.5 oz	9 oz

[a]Does not apply to Enfacare, Neocate Infant, Alfamino Infant, or NeoSure. Of note, Enfamil A.R. and Similac for Spit-Up is not recommended to be concentrated greater than 24 kcal/oz. Use a packed measure for Nutramigen and Pregestimil; all others unpacked powder.

[b]Slight variations in brands, range 40 to 45 kcal/scoop.

kcal, kilocalorie; *oz*, ounce.

Modified from University of Michigan Hospitals & Health Centers: Powdered and liquid concentrate recipe chart, available at https://www.med.umich.edu/1libr/pa/FormulaAdjustmentstandard.pdf

TABLE 21.11

COMMON CALORIC MODULARS[a]

Component	Calories
PROTEIN	
Beneprotein (powder)	25 kcal/scoop (6 g protein)
ProSource protein powder	30 kcal/scoop (6 g protein)
Complete Amino Acid Mix (powder)	3.28 kcal/g (0.82 g protein) 2.9 g/teaspoon (9.5 kcal, 2.38 g protein)
Abbott Liquid Protein Fortifier	0.67 kcal/mL (0.167 g protein/mL)
CARBOHYDRATE	
SolCarb	3.75 kcal/g; 23 kcal/tbsp
Polycal	3.84 kcal/g; 28 kcal/tbsp; 20 kcal/scoop
FAT	
MCT oil[b]	7.7 kcal/mL
Vegetable oil	8.3 kcal/mL
Microlipid (emulsified LCT)	4.5 kcal/mL
Liquigen (emulsified MCT)[b]	4.5 kcal/mL
FAT AND CARBOHYDRATE	
Duocal (powder)	42 kcal/tbsp; 25 kcal/scoop (59% carb, 41% fat, 35% fat as MCT)

[a]Use these caloric supplements when you want to increase protein, carbohydrate or fat; or when you have reached the maximum concentration tolerated and wish to further increase caloric density.

[b]Medium-chain triglyceride (MCT) oil is unnecessary unless there is fat malabsorption.

Carb, Carbohydrate; *g*, grams; *kcal*, kilocalorie; *LCT*, long chain–triglyceride; *MCT*, medium chain–triglyceride; *mL*, milliliter; *tbsp*, tablespoon.

TABLE 21.12

FORMULA PROPERTIES AND INDICATIONS FOR SPECIFIC CONDITIONS[59-67]

	Examples	Calories (kcal/oz)	Carbohydrate Source	Protein Source	Unique Properties	Indications
Human Milk Fortifiers					Contain protein, carbohydrates, fat, vitamins, and minerals	Preterm infants, especially <1500 g who are receiving human milk
Preterm Formulas	Enfamil Premature, Similac Special Care Advance	24	Lactose	Cow's milk	Higher protein, calcium, magnesium, phosphorous, and vitamin A and D Contain taurine	Generally use until infant weighs 1800–2000 g or until 34 weeks corrected gestational age
Enriched or Transitional Formula	Enfamil Enfacare, Similac Neosure	22	Lactose	Cow's milk	Higher protein, calcium, magnesium, and phosphorous	Transition from pre-term to enriched as described above until age 6–12 months
Cow's Milk-based Formulas	Enfamil Infant, Similac Advance, Similac Sensitive	20	Lactose	Cow's milk		Typical term infant
Soy	America's Store Brand Soy, Enfamil ProSobee, Gerber Good Start Soy, Similac Soy Isomil, Similac for Diarrhea	20	Corn-based	Soy	Contain higher protein concentration and supplemental amino acids	Galactosemia, congenital lactase deficiency, strict vegan families Should NOT be used for preterm infants (increased risk of poor growth, osteopenia of prematurity). Avoided in infants with milk protein intolerance given association with soy allergy.

Continued

TABLE 21.12

FORMULA PROPERTIES AND INDICATIONS FOR SPECIFIC CONDITIONS—Cont'd

	Examples	Calories (kcal/oz)	Carbohydrate Source	Protein Source	Unique Properties	Indications
Hydrolyzed Casein	Alimentum, Nutramigen, Pregestimil	20	Corn or sucrose	Casein	Easier to digest Hypoallergenic	IgE-mediated milk protein allergy Fat malabsorption
Partially Hydrolyzed Whey	Gerber Good Start Gentle, Gerber Good Start Soothe, Similac Pro-Total Comfort	20	Corn or sucrose	Hydrolyzed whey + casein or 100% whey	Reduced lactose content	May reduce risk of developing allergic diseases (especially eczema), improve gastric emptying, decrease colic, but data limited and may differ between products
Amino Acid	Neocate Infant and Junior, Elecare Infant and Junior, Alfamino Infant and Junior, PurAmino Infant and Junior	20	Corn or sucrose	Amino acids	Easier to digest, nonallergenic	Milk protein allergy Severe malabsorption

g, Grams; *kcal*, kilocalorie; *oz*, ounce.

Data from O'Connor, N. Infant formula. *Am Fam Phys*. 2009; 79(7):565–570; Comparison of breast milk and available infant formulas, available at https://www.aafp.org/afp/2009/0401/p565.html). Additional sources listed in references.

TABLE 21.13

ADDITIONAL FORMULAS FOR SPECIAL CLINICAL CIRCUMSTANCES

A. INFANTS	
Severe carbohydrate intolerance	MJ3232A Ross Carbohydrate Free (RCF)
Requiring lower calcium and phosphorus	Similac PM 60/40
B. TODDLERS AND YOUNG CHILDREN AGED 1–10 YEARS	
Vegetarian, lactose intolerance, or milk protein intolerance	Bright Beginnings Soy Pediatric Drink
Protein allergy/intolerance and/or fat malabsorption	PediaSure Peptide (and Peptide 1.5) Pepdite Junior Peptamen Junior (with and without Prebio) Vivonex Pediatric EleCare Junior Neocate Junior Neocate Splash Alfamino Junior PurAmino Junior
Fat malabsorption, intestinal lymphatic obstruction, chylothorax	Monogen Enfaport
Increased caloric needs	Boost Kids Essentials Carnation Instant Breakfast Essentials Nutren Junior (also with fiber) PediaSure (also with fiber)
Requiring clear liquid diet	Resource Breeze Ensure Clear
Intractable epilepsy	KetoCal (3:1 and 4:1)
Blended formulas (using real foods)[a]	Pediasure Harvest Compleat Pediatric Compleat Organic Blends Compleat Pediatric Organic Blends Nourish Liquid Hope Kate Farms (Standard 1.0, Pediatric Standard 1.2, Peptide 1.5 and Pediatric Peptide 1.5)
C. OLDER CHILDREN AND ADULTS ENTERAL NUTRITION (TUBE FEEDING)	
For malabsorption of protein and/or fat	Peptamen, Peptamen w/Prebio, Peptamen 1.0 and 1.5 Pediasure Peptide 1.0 and 1.5 Vital Peptide 1.5 Perative Tolerex Vital High Protein Vital 1.0 Cal and AF 1.2 Cal, 1.5 Cal Vivonex Plus and Vivonex T.E.N.
For critically ill and/or malabsorption	Pulmocare Pivot 1.5 Cal Perative

Continued

TABLE 21.13

ADDITIONAL FORMULAS FOR SPECIAL CLINICAL CIRCUMSTANCES—Cont'd

For impaired glucose tolerance	Glucerna Glytrol Store-brand diabetic nutritional drink
For dialysis patients	Magnacal Renal Nepro NutriRenal
For patients with acute renal failure not on dialysis	Renalcal Suplena
INCREASED CALORIC NEEDS (ORAL)	
With a normal gastrointestinal (GI) tract	Boost, Boost with fiber Boost Plus, Boost High Protein Carnation Instant Breakfast Essentials with whole milk Ensure Original NUTRA Shake
For clear liquid diet	Resource Breeze Ensure Clear
For patients with cystic fibrosis (CF)	Scandishake with whole milk

[a]Some blended formulas can also be used for older children and adults. Tube bore size (French) and gravity versus bolus feeding recommendations vary and should review each formula company's recommendations. Calories and nutrient information vary among formulas. If changing from a nonblended formula, gradual transition may be beneficial for optimal tolerance.

4. Abnormal gastrointestinal tract (e.g., congenital malformations, esophageal stenosis, intestinal pseudo-obstruction)
5. Injury/critical illness (e.g., burn, trauma, surgery, sepsis)

D. Features of the Most Common Oral Rehydration Solutions (Table 21.14)

VIII. PARENTERAL NUTRITION

A. Indications for the Use of Parenteral Nutrition[38]

1. Inability to feed enterally or when alimentation via gastrointestinal tract is restricted >3 to 5 days (or earlier for premature infants and neonates)
2. Chronic gastrointestinal dysfunction and/or malabsorption
3. Increased gastrointestinal losses or requirements

B. Starting and Advancing Parenteral Nutrition (Table 21.15)

C. Frequency of Monitoring Growth Parameters and Laboratory Studies in Patients on Parenteral Nutrition (Table 21.16)

D. Recommended Formulations of PN (Table 21.17)

IX. WEB RESOURCES

A. Professional and Government Organizations

1. Growth Charts and Nutrition Information: http://www.cdc.gov

TABLE 21.14

ORAL REHYDRATION SOLUTIONS

Solution	Kcal/mL (kcal/oz)	Carbohydrate (g/L)	Na (mEq/L)	K (mEq/L)	Osmolality (mOsm/kg H_2O)
CeraLyte-50	0.16 (4.9)	Rice digest (40)	50	20	N/A
CeraLyte-70	0.16 (4.9)	Rice digest (40)	70	20	N/A
CeraLyte-90	0.16 (4.9)	Rice digest (40)	90	20	N/A
Enfalyte	0.12 (3.7)	Rice syrup solids (30)	50	25	160
Oral Rehydration Salts (WHO)	0.06 (2)	Dextrose (20)	90	20	330
Pedialyte (unflavored)	0.1 (3)	Dextrose (25)	45	20	250

g, Gram; *kcal*, kilocalorie; *kg*, kilogram; *L*, liter; *mL*, milliliter; *mOsm*, milliosmole; *oz*, ounce.

TABLE 21.15

INITIATION AND ADVANCEMENT OF PARENTERAL NUTRITION FOR INFANTS THROUGH ADOLESCENTS[a,b]

Nutrient	Initial Dose	Advancement	Goals
Glucose	3.5%–10%	1%–5%/day	5–12 (max 14–18) mg/kg/min rate of infusion
Protein	0.8–3 g/kg/day	1 g/kg/day	0.8–4 g/kg/day 10%–16% of calories
Fat[c]	1–2 g/kg/day	0.5–1 g/kg/day	1–3.5 g/kg/day[d] 0.17 g/kg/hr (maximum rate of infusion)

[a]Acceptable osmolarity of parenteral nutrition through a peripheral line varies between 900 and 1050 osm/L by institution. An estimate of the osmolarity of parenteral nutrition can be obtained with the following formula: Estimated osmolarity = (dextrose concentration × 50) + (amino acid concentration × 100) + (mEq of electrolytes × 2). Consult individual pharmacy for hospital limitations.

[b]In general, infants require the higher concentration and/or rate of glucose, protein, and fat compared to older children and adolescents

[c]Essential fatty acid deficiency may occur in fat-free parenteral nutrition within 2 to 4 weeks in infants and children and as early as 2 to 14 days in neonates. A minimum of 2% to 4% of total caloric intake as linoleic acid and 0.25% to 0.5% as linolenic acid is necessary to meet essential fatty acid requirements.

[d]If parenteral nutrition–associated cholestasis occurs, lipid minimization and/or use of fish oil or composite lipids should be considered.[41]

Modified from Corkins M, Balint J, Plogested S, eds. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum*. Maryland: American Society for Parenteral and Enteral Nutrition; 2010; Table 34.4.

g, Gram; *hr*, hour; *kg*, kilogram; *L*, liter; *mg*, milligram; *min*, minute; *osm*, osmole.

2. American Academy of Pediatrics (AAP) Children's Health Topics: http://www.healthychildren.org
3. Academy of Nutrition and Dietetics: http://www.eatright.org
4. American Society for Parenteral and Enteral Nutrition: http://www.nutritioncare.org

TABLE 21.16

MONITORING SCHEDULE FOR PATIENTS RECEIVING PARENTERAL NUTRITION[a]

Variable	Initial Period[b]	Later Period[c]
GROWTH		
Weight	Daily	2 times/week
Height	Weekly (infants) Monthly (children)	Monthly
Head circumference (infants)	Weekly	Monthly[d]
LABORATORY STUDIES		
Electrolytes and glucose	Daily ×3 or until stable	1–2× weekly
BUN/creatinine	Daily ×3 or until stable	1–2× weekly
Albumin or prealbumin	Weekly	Weekly
Ca^{2+}, Mg^{2+}, P	Daily ×3 or until stable	Weekly
ALT, AST, ALP	Weekly	Weekly
Total and direct bilirubin	Weekly	Weekly
CBC with differential	Daily x3 or until stable	1–2× weekly
Triglycerides	Daily until stable	Weekly
Vitamins	—	As indicated
Trace minerals	—	As indicated

[a]For patients on long-term parenteral nutrition, monitoring every 24 weeks is adequate in most cases.

[b]The period before nutritional goals are reached or during any period of instability.

[c]When stability is reached, no changes in nutrient composition.

[d]Weekly in preterm infants.

Modified from Worthington P, Balint J, Bechtold M, et al. When is parental nutrition appropriate? *J Parent Enter Nutr.* 2017;41(3), Table 13.2.

ALP, Alkaline phosphatase; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *BUN*, blood urea nitrogen; *CBC*, complete blood cell count; *Ca*, calcium; *Mg*, magnesium; *P*, phosphorous.

TABLE 21.17

PARENTERAL NUTRITION FORMULATION RECOMMENDATIONS

Electrolyte	Preterm	Term Infants/Children	Adolescents and Children >50 mg
Sodium (mEq/kg)	2–5	2–5	1–2
Potassium (mEq/kg)	2–4	2–4	1–2
Calcium	2–4 mEq/kg	0.5–4 mEq/kg	10–20 mEq/day
Phosphorus	1–2 mmol/kg	0.5–2 mmol/kg	10–40 mmol/day
Magnesium	0.3–0.5 mEq/kg	0.3–0.5 mEq/kg	10–30 mEq/day
Acetate and Chloride	As needed for acid base balance		

Trace Element	Preterm Neonate <3 kg (mCg/kg/day)	Term Neonate 3–10 kg (mCg/kg/day)	Children 10–40 kg (mCg/kg/day)	Adolescent > 40 kg (per day)
Zinc	400	50–250	50–125	2–5 mg
Copper[a]	20	20	5–20	200–500 mg
Manganese[a]	1	1	1	40–100 mCg
Chromium	0.05–0.2	0.2	0.14–0.2	5–15 mCg
Selenium	1.5–2	2	1–2	40–60 mCg

[a]Copper and manganese needs may be lowered in cholestasis.

From Mirtallo J, Canada T, Johnson D et al. Safe practices for parenteral nutrition. *J Parenter Enteral Nutr.* 2004;28(6):S29–S70; and Corkins M, Balint J, Plogested S, eds. *The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum.* Maryland: American Society for Parenteral and Enteral Nutrition; 2010, Tables 34.5 and 34.7.

5. U.S. Department of Agriculture Healthy Eating Guidelines: http://www.choosemyplate.gov
6. Bright Futures: Nutrition and Pocket Guide: https://brightfutures.aap.org
7. AAP Committee on Nutrition: https://www.aap.org/

B. Infant and Pediatric Formula Company Websites

1. Enfamil, Enfacare, Nutramigen, and Pregestimil: http://www.meadjohnson.com
2. Carnation, Good Start, Nutren, Peptamen, Vivonex, Boost, Alfamino, and Resource: https://www.nestlehealthscience.us/ and http://medical.gerber.com/
3. Alimentum, EleCare, Ensure, NeoSure, PediaSure, Pedialyte, and Similac: http://www.abbottnutrition.com
4. Bright Beginnings: http://www.brightbeginnings.com
5. America's Store Brand: http://www.storebrandformula.com
6. KetoCal, Neocate, and Pepdite: http://www.nutricia-na.com
7. Liquid Hope and Nourish: https://www.functionalformularies.com/
8. Kate Farms: https://www.katefarms.com/

C. Breastfeeding Resources

1. LactMed is an online resource from the National Library of Medicine/National Institutes of Health (N/IH) that provides information on the safety of maternal medications and breastfeeding: http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
2. Video instruction on breastfeeding techniques from Stanford Newborn Nursery: http://newborns.stanford.edu/Breastfeeding/FifteenMinuteHelper.html
3. Academy of Breastfeeding Medicine Protocols for the Care of Breastfeeding Mothers and Infants. Management of common breastfeeding-related challenges discussed: https://www.bfmed.org/protocols
4. National Institute of Child Health and Human Development—Breastfeeding: https://www.nichd.nih.gov/health/topics/breastfeeding/Pages/default.aspx

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Chapter 22

Oncology

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See additional content on Expert Consult

I. OVERVIEW OF PEDIATRIC MALIGNANCIES[1-4]

A. Epidemiology

1. **Incidence**
   a. Annual rate of 18.8 cases per 100,000 person-years for children under 20 years of age.
   b. Incidence rate has increased by 0.6% per year since 1975.
2. **Survival**
   a. Five-year survival has improved from 61% to 83.6% over the past 40 years.
   b. Malignant neoplasms remain the leading cause of disease-related mortality in children.

B. Presenting Signs and Symptoms

1. **General:** Fever of unknown origin, fatigue, malaise, irritability, weight loss, failure to thrive
2. **Neurologic:** See Section IV.B.
3. **Cardiorespiratory:** Cough, dyspnea, stridor, hypertension
4. **Gastrointestinal (GI):** Anorexia, emesis, hepatosplenomegaly, abdominal mass
5. **Musculoskeletal:** Localized bone/joint pain, limp, soft tissue mass
6. **Dermatologic:** Bruising, bleeding, petechiae, pallor
7. **Hematologic:** Epistaxis, gingival bleeding, hematuria
8. **Lymphatic:** Features of a pathologic lymph node include:
   a. Size: <2 cm usually insignificant unless >1 cm in supraclavicular fossa or increase in size over time >2 to 4 weeks
   b. Consistency: Rubbery (classically lymphoma), hard (malignant, granulomatous infection)
   c. Sensation: Nontender more concerning for malignancy

II. PEDIATRIC HEMATOLOGIC MALIGNANCIES[1-2] (TABLE 22.1)

III. PEDIATRIC SOLID TUMOR MALIGNANCIES[1-2] (TABLE 22.2)

IV. PEDIATRIC CENTRAL NERVOUS SYSTEM (CNS) TUMORS[1-2,5-8] (TABLE 22.3)

A. Epidemiology

1. Most common solid tumors in children.

TABLE 22.1

COMMON PEDIATRIC HEMATOLOGIC MALIGNANCIES[1-2]

Malignancy	Clinical Presentation	Initial Workup	Epidemiology, Prognosis
ALL, AML	Fever, pallor, petechiae/ecchymoses, lethargy, malaise, anorexia, bone/joint pain **Exam:** Lymphadenopathy, hepatosplenomegaly, abnormal neurologic exam, testicular enlargement; AML may include subcutaneous nodules, gingival hyperplasia, chloromas (solid collection of leukemic cells) **T-cell ALL:** can present with anterior mediastinal mass	CBC with differential, peripheral smear; CMP with phosphate, uric acid, LDH important to assess for tumor lysis CXR to assess for mediastinal mass Blood and urine cultures if febrile Definitive diagnosis requires lumbar puncture (evaluate for CNS involvement), bone marrow biopsy, flow cytometry	**ALL:** Most common pediatric cancer (approximately 25% in <15 years). Peaks at age 2–5 years. Overall five-year survival rate exceeds 90%. **AML:** Peaks in first year of life, risk increases again after adolescence. Survival rate ~60%–70%; acute promyelocytic leukemia best prognosis.
Lymphoma HD, NHL	Painless, firm lymphadenopathy (often supraclavicular or cervical nodes) Cough, shortness of breath "B symptoms" (fevers, night sweats, weight loss)	CBC with differential, peripheral smear, electrolytes; include CRP, UA, LDH CXR to assess for mediastinal mass Diagnosis requires tissue and fluid sampling, lymph node biopsy	15% of childhood malignancies HD peak incidence occurs in bimodal distribution (15–34 years old and >55 years) NHL incidence increases with age, more common in second decade of life Prognosis: HD highly curable (95% survival with stage I disease and 75% for stage IV); NHL prognosis varies with histology and stage
Histiocytic Disease	Scaly rash, long bone pain, fever, weight loss, diarrhea, dyspnea, painless lymphadenopathy, polydipsia, polyuria	Triglycerides, fibrinogen, ferritin, urine osmolality Imaging to detect lytic lesions: Skeletal survey, followed by CT/MRI, bone scan/PET	**Langerhans Cell Histiocytosis:** Median age at presentation 30 months

Note: Laboratory testing and imaging suggestions are meant as a guide for evaluation of a potential malignancy. Patients warranting definitive testing should be referred to an oncologist.

ALL, Acute lymphocytic leukemia; *AML*, acute myeloid leukemia; *CBC*, complete blood count; *CMP*, complete metabolic panel; *CNS*, central nervous system; *CRP*, c-reactive protein; *CT*, computed tomography; *CXR*, chest x-ray; *HD*, Hodgkin disease; *IV*, intravenous; *LDH*, lactate dehydrogenase; *MRI*, magnetic resonance imaging; *NHL*, non-Hodgkin lymphoma; *PET*, positron emission tomography; *UA*, urinalysis.

TABLE 22.2

COMMON PEDIATRIC SOLID TUMOR MALIGNANCIES[1-2]

Malignancy	Clinical Presentation	Initial Workup	Epidemiology, Prognosis
Neuroblastoma: Malignant tumor of neural crest cell origin	Abdominal pain or mass (hard, nontender) Periorbital ecchymoses, spinal cord compression, Horner syndrome Paraneoplastic syndromes (secretory diarrhea, diaphoresis, opsoclonus-myoclonus)	Abdominal ultrasound Definitive diagnosis requires CT chest/abdomen/pelvis, urine catecholamines (HVA, VMA), MIBG scan, biopsy	Most common malignancy in infancy; median age of diagnosis 17 months 8% childhood malignancies, 15% of deaths caused by childhood malignancy **Prognosis**: Favorable prognosis if age of diagnosis <1 year, Stage I, II, IV-S, absence of N-myc amplification
Wilms Tumor: Nephroblastoma	Abdominal mass with or without abdominal pain May see hypertension, hematuria, anemia (bleeding within the tumor)	Liver and renal function tests, urinalysis Abdominal ultrasound, chest/abdominal CT or MRI Diagnosis requires biopsy	Peaks at age 3–4 years Survival rate 90% (poor prognosis with diffuse anaplasia)
Bone Sarcoma: Osteosarcoma, Ewing sarcoma	**Osteosarcoma**: Bone pain or mass (typically in epiphysis/metaphysis of long bones) not relieved with conservative treatment **Ewing Sarcoma**: Bone pain and swelling, most commonly in femur or pelvis	X-ray of primary site, followed by MRI Metastatic evaluation: CT of chest, PET scan	**Osteosarcoma**: Peaks in adolescence during maximum growth velocity **Ewing**: Peaks between 10 and 20 years **Prognosis**: Cure rate for localized disease: 60%–70%; poor prognosis with metastatic disease, primary tumor of axial skeleton, necrosis at time of resection (osteosarcoma)

Continued

TABLE 22.2—cont'd

COMMON PEDIATRIC SOLID TUMOR MALIGNANCIES[1-2]

Malignancy	Clinical Presentation	Initial Workup	Epidemiology, Prognosis
Rhabdomyosarcoma: Soft tissue malignant tumor of skeletal muscle origin	Rapidly growing mass, may be painful Symptoms based on location HEENT: Periorbital swelling, proptosis, chronic otitis media, dysphagia, neck mass GU tract: Paratesticular swelling, hematuria, urinary frequency/retention	CT or MRI of primary site Diagnosis requires tissue biopsy, immunohistochemical staining	Peaks at 2–6 years and in adolescence **Prognosis**: Based on stage, extent of surgical resection, and histopathology (alveolar histopathology poorer prognosis than embryonal); favorable prognostic factors include localized disease, >90% tumor necrosis at resection, age between 1 and 10 years at presentation
Retinoblastoma (Rb)	Leukocoria (retrolental mass), strabismus, hyphema, irregular pupil(s)	Ophthalmology referral MRI brain to evaluate pineal gland if bilateral	Peaks at age 2 years Survival at 5 years >90% 66%–75% tumors are unilateral *Rb1* mutations carries risk for second malignancies (osteosarcoma, soft tissue sarcoma, malignant melanoma)
Hepatic Tumors: Hepatoblastoma, Hepatocellular carcinoma (HCC)	Painless abdominal mass, anorexia, emesis, abdominal pain, fever Hepatoblastoma may be associated with anemia, thrombocytosis	CBC, LFTs, AFP, hepatitis B and C titers Abdominal ultrasound	Hepatoblastoma peaks at age <3 years HCC peaks after 10 years of age (associated with hepatitis B and C) **Prognosis**: Hepatoblastoma favorable prognosis pending tumor resection at diagnosis; HCC carries poor prognosis
Gonadal/Germ Cell Tumor	**Testicular tumors**: Nontender scrotal mass, hydrocele **Ovarian tumors**: typically asymptomatic until quite large **Hormone-producing tumors**: Amenorrhea, precocious puberty, hirsutism	AFP, β-hCG CXR, abdominal ultrasound, followed by CT or MRI	Peaks <4 years, then again in adolescence Overall cure rate >80% Favorable prognostic factors include <12 years of age, lack of thoracic involvement

Note: Laboratory testing and imaging suggestions are meant as a guide for evaluation of a potential malignancy. Patients warranting definitive testing should be referred to an oncologist.

AFP, α-Fetoprotein; *β-hCG*, beta human chorionic gonadotropin; *CBC*, complete blood cell count; *CT*, computed tomography; *CXR*, chest x-ray; *GU*, genitourinary; *HEENT*, head eyes ears nose throat; *HVA/VMA*, homovanillic acid/vanillylmandelic acid (urine catecholamines); *LFTs*, liver function tests; *MIBG*, metaiodobenzylguandidine; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography.

TABLE 22.3

PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS BY INCIDENCE[1-2,5-7]

Tumor	Epidemiology	Location	Prognosis
Glioma (40%)	**Low-grade**: Average age of diagnosis: 6.5–9 years; male predominance **High-grade**: 9–10 years; 1:1 male-female ratio	Occur throughout the CNS Low-grade astrocytomas commonly occur in cerebellum, hypothalamic, third ventricular region, optic nerve	Low-grade: 50%–100% depending on ability to resect
Embryonal Tumor: Most commonly medulloblastoma (20%)	Most common group of malignant CNS tumors Bimodal distribution, peaking at 3–4 years, then again between 8 and 10 years	Commonly located in midline cerebellar vermis Older patients can present in cerebellar hemisphere	5-year survival 50%–80% Poor outcome if presents under 4 years of age
Ependymal Tumor: Derived from ependymal lining of ventricular system (10%)	Median age 6 years	~70% occur in the posterior fossa Can occur in supratentorial region, spinal cord Usually noninvasive, can extend into ventricular lumen	Long-term survival ~40% after undergoing gross total resection
Craniopharyngioma: Arise from embryonic remnant of Rathke pouch (5%–10%)	In childhood, peaks between 8 and 10 years of age Rarely occurs in infancy	Occur in suprasellar region adjacent to optic chiasm Minimally invasive	5-year survival 70%–90% Associated with significant morbidity (panhypopituitarism, growth failure, visual loss)
Germ Cell Tumor (3%–5%)	Peak incidence 10–12 years of age	Commonly arise in midline locations (pineal and suprasellar region)	5-year survival 40%–70%

CNS, Central nervous system.

2. Leading cause of childhood cancer deaths.
3. Highest incidence in infants and children under 5 years old.

B. Clinical Presentation

1. Early/generalized symptoms: Headache, lethargy/fatigue, nausea/emesis, gait abnormalities; increased head circumference in infants
2. Later symptoms related to tumor location: Seizures, altered language, encephalopathy, hemiplegia/hemi-sensory deficit, facial weakness, neuroendocrine effects (precocious/delayed puberty, diabetes insipidus), visual changes, abnormal movements, back pain, sphincter disturbance

C. Initial Workup

1. Thorough neurologic exam, including fundoscopic exam.
2. Neurosurgery/Neuro-oncology consultation.
3. Labs: Presurgical tests (complete blood count [CBC], electrolytes, blood type, coagulation factors, cross-matching); endocrine tests for suprasellar tumors; α fetoprotein (AFP) and β human chorionic gonadotropin (β hCG) if germinoma suspected.
4. Imaging: Magnetic resonance imaging (MRI) of brain (sometimes spine) with and without intravenous (IV) contrast.

D. Management Principles

1. High-dose dexamethasone: Often administered to reduce tumor-associated edema.
2. Consider seizure prophylaxis for those at high risk of seizures or seizure history.

V. ONCOLOGIC EMERGENCIES[2,9-16]

A. Fever and Neutropenia (Fig 22.1)

1. **Etiology:** Fever with temperature ≥38.3°C (some centers and medical associations also use 38.0°C sustained over an hour to define fever) in the setting of neutropenia (absolute neutrophil count [ANC] <500 cells/μL or <1000 cells/μL but expected to drop to <500 cells/μL in the next 48 hours). Presumed serious infection in a neutropenic host. While fevers may be caused by other etiologies including medications, presume infection until proven otherwise.
2. **Presentation:** May appear ill with fatigue, lethargy, or localized pain. Can also appear well, yet have subtle signs of compensated shock, including chills, rigors, tachypnea, or tachycardia. May deteriorate after initial doses of antibiotics.
3. **Management:** Broad-spectrum antibiotics with antipseudomonal coverage should be administered within 60 minutes of presentation to medical facility. Note: Antibiotic administration may lead to clinical sepsis secondary to release of endotoxin from gram-negative bacteria.

B. Hyperleukocytosis/Leukostasis

1. **Etiology:** Elevated white blood cell (WBC) count (usually >100,000/μL) in leukemia patients leads to leukostasis in the microcirculation and diminished tissue perfusion (notably in CNS and lungs). Leukostasis occurs more commonly and at lower WBC counts in acute myeloid leukemia (AML) than in acute lymphocytic leukemia (ALL).
2. **Presentation:** Hypoxia, tachypnea, dyspnea, and pulmonary hemorrhage from pulmonary leukostasis. Mental status changes, headaches, seizures, and papilledema from cerebral leukostasis. May also see GI bleeding, abdominal pain, renal insufficiency, priapism, and/or intracranial hemorrhage. Hyperleukocytosis may be asymptomatic.

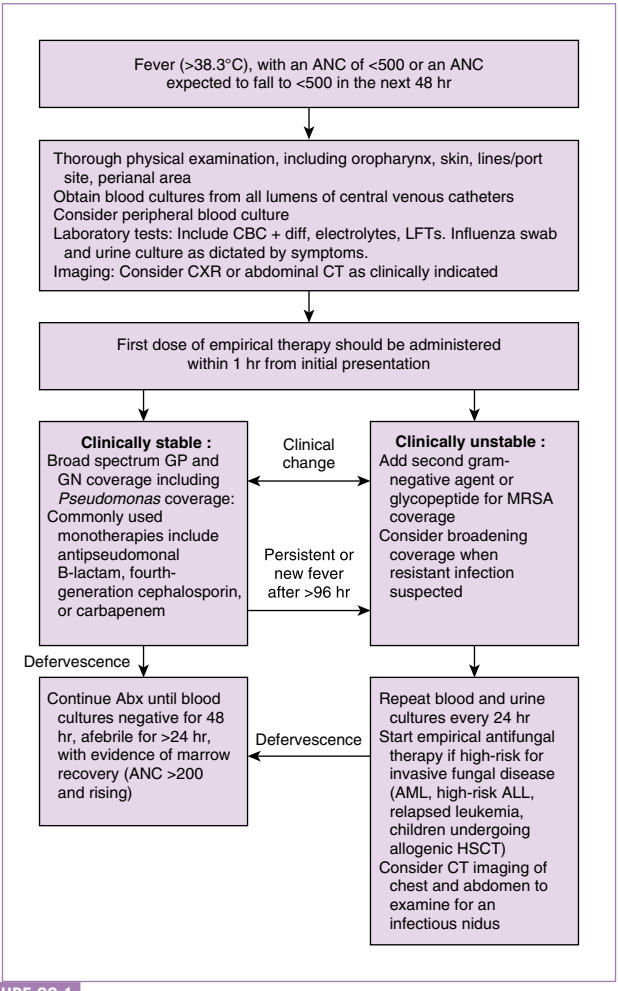

FIGURE 22.1

Algorithm for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation. Note: some centers and medical associations also use 38.0°C sustained over an hour to define fever. *Abx*, Antibiotics; *ALL*, acute lymphocytic leukemia; *AML*, acute myeloid leukemia; *ANC*, absolute neutrophil count; *CBC*, complete blood cell count; *CT*, computed tomography; *CXR*, chest x-ray; *diff*, differential; *GN*, gram-negative; *GP*, gram-positive; *HSCT*, hematopoietic stem cell transplantation; *LFTs*, liver function tests; *MRSA*, methicillin-resistant *Staphylococcus aureus*. (Data from Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. *J Clin Oncol.* 2017;35:2082–2094).

3. **Management**
   a. Prompt initiation of chemotherapy is the most effective approach.
   b. Consider leukapheresis or exchange transfusion if evidence of symptomatic leukostasis.
   c. Transfuse platelets to keep count above 20,000/μL to prevent hemorrhage.[1]
   d. Avoid red blood cell (RBC) transfusions, which raise viscosity. If required, consider partial exchange transfusion.
   e. Hydration and allopurinol should be initiated, as hyperleukocytosis increases the risk of tumor lysis syndrome.
   f. Treat coagulopathy.

C. Tumor Lysis Syndrome

1. **Etiology:** Rapid lysis of tumor cells releases intracellular contents into the blood stream spontaneously before treatment or during early stages of chemotherapy (especially Burkitt lymphoma, T-cell leukemia/lymphoma, acute leukemias with hyperleukocytosis).
2. **Presentation:** Hyperuricemia, hyperkalemia, hyperphosphatemia (with secondary hypocalcemia). Can lead to acute kidney injury. Symptoms include nausea, anorexia, arrhythmias, seizures, and altered mental status.
3. **Diagnosis:** CBC, basic metabolic panel (BMP), phosphorus, uric acid, lactate dehydrogenase (LDH), electrocardiogram (ECG).
4. **Prevention and Management**
   a. Hydration: Dextrose-containing IV fluids (without potassium, calcium, phosphate) at twice maintenance rate. Keep urine-specific gravity <1.010 and urine output >100 mL/m^2/hr. Alkalinization is no longer recommended, given increased risk of calcium phosphate precipitation.
   b. Hyperuricemia: Allopurinol inhibits formation of uric acid and should only be given PO (see Formulary for dosing). Rasburicase converts uric acid to the more soluble allantoin. Use in high-risk patients, especially those with uric acid >7.5 mg/dL. Do not use rasburicase with patients with known G6PD deficiency, as it may result in methemoglobinemia.
   c. Monitor potassium, calcium, phosphorous, uric acid, and urinalysis closely (up to Q2 hours for high-risk patients). There is an increased risk of calcium phosphate precipitation when Ca × Phos > 60. Consider early use of sevelamer.
   d. See Chapter 11 for management of abnormal electrolytes and Chapter 19 for dialysis indications.

D. Spinal Cord Compression

1. **Etiology:** Intrinsic or extrinsic compression of spinal cord. Occurs most commonly with metastases from brain tumors, spinal tumors, soft tissue sarcomas, neuroblastoma, lymphoma.
2. **Presentation:** Back pain (localized or radicular), weakness, sensory loss, bowel or bladder dysfunction, gait abnormalities. Prognosis for recovery based on duration and level of disability at presentation.

3. **Diagnosis:** MRI (preferred) or computed tomography (CT) scan of spine. Spine radiography is less sensitive.
4. **Management**
   a. In the presence of neurologic abnormalities, strong history, and rapid progression of symptoms, consider immediate dexamethasone. Note: Steroids may prevent accurate diagnosis of leukemia/lymphoma; plan diagnostic procedure as soon as possible.
   b. If tumor type is known and chemosensitive, emergent chemotherapy is indicated.
   c. If tumor type is unknown or debulking may remove most/all of tumor, emergent neurosurgery consultation is indicated to decompress the spine.

E. Increased Intracranial Pressure (ICP)

1. **Etiology:** Ventricular obstruction or impaired cerebral spinal fluid (CSF) flow. Most commonly seen with brain tumors, but also with intracranial hemorrhage, thrombosis, meningeal involvement by tumor or infection.
2. **Presentation:** Headaches, altered mental status, irritability, lethargy, nuchal rigidity, emesis, abnormal vision; Cushing triad and pupillary changes are late and ominous findings.
3. **Diagnosis**
   a. Evaluate for vital sign changes [i.e., Cushing triad (↓ heart rate, ↑ systolic blood pressure, irregular respirations)].
   b. Funduscopic evaluation for papilledema.
   c. Obtain CT or MRI of the head (MRI more sensitive for diagnosis of posterior fossa tumors).
4. **Management**
   a. See Chapter 1 for management principles.
   b. Obtain emergent neurosurgical consultation.
   c. If tumor is the cause, start IV dexamethasone (see Formulary for dosing).

F. Other Neurologic Emergencies: Cerebrovascular Accident (CVA), Seizures

1. **CVA Etiology:** Hyperleukocytosis, coagulopathy, thrombocytopenia, radiation (fibrosis) or chemotherapy-related (e.g., L-asparaginase–induced hemorrhage or thrombosis, methotrexate). Most common in patients with AML or any form of leukemia with hyperleukocytosis.
2. **Seizure Etiology**: Most common in primary CNS tumors, tumors metastatic to CNS, meningeal leukemia, chemotherapy-related (intrathecal [IT] cytarabine, IT/IV methotrexate).
3. See Chapters 1 and 20 for diagnosis and management.

G. Superior Vena Cava Syndrome/Superior Mediastinal Syndrome

1. **Etiology:** Compression of venous drainage and trachea, most commonly caused by mediastinal mass. Usually seen with T-lymphoblastic lymphoma, Hodgkin lymphoma, mature B-cell lymphoma, and germ cell tumors.
2. **Presentation:** Dyspnea, cough, wheeze, stridor, orthopnea, headaches, facial swelling, dizziness, plethora.

3. **Diagnosis:** Two-view chest radiograph. If mediastinal mass present, obtain neck radiograph to further assess. Avoid sedation if unstable, high risk for airway obstruction.
4. **Management**
   a. Control airway, place in upright position, and administer supplemental oxygen.
   b. Biopsy (e.g., bone marrow, pleurocentesis, lymph node biopsy) before therapy if patient can tolerate sedation.
   c. Empiric therapy: Radiotherapy, steroids, chemotherapy. **Note:** can confound diagnosis.

H. Typhlitis (Neutropenic Enterocolitis)

1. **Etiology:** Inflammation of bowel wall, typically localized to cecum. Associated with bacterial or fungal invasion. Associated with prolonged neutropenia, often secondary to induction therapy in leukemia.
2. **Presentation:** Right lower quadrant abdominal pain, nausea/emesis, diarrhea, fever (may be absent early in course). Risk for perforation.
3. **Diagnosis**
   a. Careful serial abdominal examinations.
   b. Abdominal ultrasound may be considered (may show pneumatosis intestinalis, bowel wall edema). CT abdomen with IV and PO contrast is most sensitive form of imaging.
4. **Management**
   a. Bowel rest: NPO on IV fluids; consider nasogastric decompression.
   b. Broad anerobic and gram-negative antibiotic coverage.
   c. Surgical consultation.

I. Cytokine Release Syndrome

1. **Etiology**: Newer immunologic agents (e.g., chimeric antigen receptor T [CAR-T] therapy and specific antibodies) can provoke release of cytokines associated with systemic inflammation and hemodynamic instability.
2. **Presentation**: Early symptoms include fever, diaphoresis, or mild evidence of hemodynamic instability (tachycardia) that can progress quickly to cardiovascular collapse and multi-organ dysfunction.
3. **Diagnosis:** Based on clinical features. Consider obtaining CRP and ferritin, although nondiagnostic.
4. **Management**
   a. Tocilizumab: recombinant humanized monoclonal antibody targeting the IL-6 receptor.
   b. Treat hypotension with IV fluids. If refractory, may require vasopressors, intensive care unit (ICU)-level care.
   c. Closely monitor neurologic status because these agents are associated with neurotoxicity. Patient should be on seizure prophylaxis.

VI. COMMONLY USED CHEMOTHERAPEUTIC DRUGS AND ASSOCIATED ACUTE TOXICITIES (TABLE 22.4)

TABLE 22.4

COMMONLY USED CHEMOTHERAPEUTIC AGENTS[a]

Drug Name (By Class)	Toxicity	Monitoring and Care
ALKYLATORS	**Significant myelosuppression, severe nausea, impaired fertility**	**Myelosuppression supportive care, aggressive antiemetics, pretreatment fertility consult**
Busulfan	Seizures, SOS, acute/chronic lung injury	Monitor weight, abdominal girth, bilirubin; seizure prophylaxis
Carmustine	Hypotension, chronic lung injury	Slow infusion, PFTs
Cyclophosphamide	Myocardial necrosis, hemorrhagic cystitis, SIADH	Hyperhydration and **mesna** to prevent hemorrhagic cystitis; ECG
Ifosfamide	Mental status changes, encephalopathy (rarely progressing to death), renal tubular damage, hemorrhagic cystitis, Fanconi syndrome	Monitor creatinine, magnesium, phosphate, potassium; hyperhydration and **mesna** to prevent hemorrhagic cystitis; methylene blue for neurotoxicity
Lomustine	Disorientation, fatigue	
Melphalan	Severe mucositis, pulmonary fibrosis	Aggressive oral hygiene, ophthalmologic examination
Procarbazine	Encephalopathy; adverse effects with tyramine-rich foods, ethanol, MAOIs, meperidine, and many other drugs	Avoid serotonergic agents/modulators, diet low in tyramine (avoid aged cheese/meats, beer, pickled food, soy sauce)
Temozolomide	Headache, seizures, thrombocytopenia	
Thiotepa	Encephalopathy, rash, burns, desquamation of skin, lower extremity weakness	Frequent bathing
NUCLEOTIDE ANALOGS	**Myelosuppression, mucositis, transaminitis**	**Supportive care, monitor LFTs**
Clofarabine	Capillary leak syndrome, SOS, nephrotoxicity, hyperbilirubinemia	Monitor creatinine; monitor weight, abdominal girth, bilirubin
Cytarabine (Ara-C)	Ara-C syndrome (maculopapular rash, fever), conjunctivitis, severe mucositis, ataxia, respiratory distress rapidly progressing to pulmonary edema	Corticosteroid eye drops; coverage for viridans streptococci with fever, systemic steroids for Ara-C syndrome
Fludarabine	Transaminitis, neurotoxicity, immunosuppression (nonmyelosuppressive)	Monitor creatinine (decreased clearance results in increased risk of neurotoxicity)
Mercaptopurine (6-MP)	Hepatotoxicity (increased risk in TPMT deficiency), pancreatitis	LFTs
Thioguanine	Hepatotoxicity (increased risk in TPMT deficiency), SOS	LFTs
DNA MODIFYING AGENTS		
Bleomycin *(DNA strand breaker)*	Anaphylaxis, pneumonitis, pulmonary fibrosis	PFTs

Continued

TABLE 22.4—cont'd

COMMONLY USED CHEMOTHERAPEUTIC AGENTS[a]

Drug Name (By Class)	Toxicity	Monitoring and Care
Carboplatin *(DNA cross-linker)*	Nephrotoxicity, ototoxicity, peripheral neuropathy	Monitor creatinine, adjust dose based on creatinine clearance, audiology evaluation
Cisplatin *(DNA cross-linker)*	Nephrotoxicity (related to cumulative dose), severe emesis, hypomagnesemia, hypophosphatemia, ototoxicity	Monitor creatinine, magnesium, phosphorous; audiology evaluation; aggressive antiemetic regimen
Etoposide *(Topoisomerase inhibitor)*	Anaphylaxis (rare), hypotension, hyperbilirubinemia, transaminitis, secondary malignancy (AML)	Slow infusion if hypotension; change formulation to etoposide phosphate if anaphylaxis; monitor bilirubin and LFTs
OTHER CHEMOTHERAPEUTIC AGENTS		
Asparaginase *(Enzyme)*	Pancreatitis, hypersensitivity reactions (acute and delayed), coagulopathy (thrombosis and bleeding), hyperammonemia	Monitor serum asparaginase activity levels, high index of suspicion for clots/bleeds, consider amylase/lipase with abdominal pain
Dactinomycin *(Antibiotic)*	Rash, hypocalcemia, radiation recall (rash), SOS	Monitor calcium; monitor weights, abdominal girth, bilirubin
Daunorubicin and Doxorubicin, Mitoxantrone (adriamycin) *(Anthracyclines)*	Arrhythmia, cardiomyopathy/heart failure (related to cumulative dose), severe mucositis, severe emesis, red urine and bodily fluids (dauno/doxo), blue–green urine (mitoxantrone), radiation recall	Limit cumulative dose; echocardiogram; consider **dexrazoxane** for cardioprotection
Methotrexate (MTX) *(Folate antagonist)*	Mucositis, diarrhea, renal dysfunction, encephalopathy, chemical arachnoiditis (intrathecal), photosensitivity, leukoencephalopathy, osteoporosis	**Leucovorin** to reduce mucositis with high-dose therapy; oral hygiene; monitor neurologic exam and developmental milestones
Vinblastine, Vincristine, and Vinorelbine *(Microtubule inhibitors)*	Constipation, bone and jaw pain, peripheral and autonomic sensory and motor neuropathy, foot drop, SIADH (rare), hyperbilirubinemia, transaminitis	Bowel regimen; monitor for neuropathy; fatal if given intrathecally, bilirubin and LFTs
MOLECULARLY TARGETED AGENTS		
Alemtuzumab (Campath) *(Monoclonal Ab binds CD52 on mature lymphocytes)*	Severe infusion reactions (hypotension, bronchospasm, ARDS, anaphylaxis), infections	Antimicrobial prophylaxis
Blinatumomab *(Bi-specific T-cell engager)*	CRS, neurotoxicity	Dexamethasone
Brentuximab *(Chimeric monoclonal Ab binds CD30)*	Peripheral neuropathy, diarrhea	

TABLE 22.4—cont'd

COMMONLY USED CHEMOTHERAPEUTIC AGENTS[a]

Drug Name (By Class)	Toxicity	Monitoring and Care
CAR T-Cells *(Immune cells genetically modified to bind tumor-specific antigens)*	CRS, neurotoxicity (headache, confusion, encephalopathy, seizure)	**Tocilizumab** (anti-IL-6R), steroids if severe/refractory
Dinutuximab *(Monoclonal Ab binds GD-2; for use in neuroblastoma)*	Rash/hives, rigors, severe pain, neuropathy, hyponatremia, hepatotoxicity, hypocalcemia, capillary leak syndrome, ocular neurologic disorders	Monitor sodium, calcium, LFTs; aggressive pain management
Imatinib (Gleevec), Dasatinib, Nilotinib *(Tyrosine kinase inhibitors)*	Congestive heart failure, edema, pleural effusions, rash, night sweats	ECG, serial echocardiograms
Nivolumab *(PD-1 checkpoint inhibitor)* and Pembrolizumab *(CTLA-4 checkpoint inhibitor)*	Autoimmune manifestations (colitis, dermatitis, hepatitis, nephritis, pneumonitis, etc.)	
Rituximab (Rituxan) *(Chimeric monoclonal Ab binds CD20 on B cells)*	Infusion reaction, urticaria	Hep B testing before use, slow infusion for first dose, immune reconstitution may be very delayed post therapy

[a]All chemotherapeutic medications may cause nausea, vomiting, fever, immunosuppression, mucositis, gastrointestinal upset. *AML*, Acute myeloid leukemia; *ARDS*, acute respiratory distress syndrome; *CAR T-cells*, chimeric antigen receptor T-cell therapy; *CRS*, cytokine release syndrome; *ECG*, electrocardiogram; *LFTs*, liver function tests; *PFTs*, pulmonary function tests; *SIADH*, syndrome of inappropriate antidiuretic hormone; *SOS*, sinusoidal obstruction syndrome; *TPMT*, thiopurine S-methyltransferase. Data from *Physician's Desk Reference*. 64th ed. Montvale, NJ: Medical Economics; 2010; and Taketomo CK, Hodding JH, Kraus DM. *American Pharmaceutical Association Pediatric Dosage Handbook*. 16th ed. Hudson, OH: Lexi-Comp, *Pediatric & Neonatal Dosage Handbook*, 25th edition; and Micromedex 2.0 (2018).

VII. COMMON CHEMOTHERAPY COMPLICATIONS AND SUPPORTIVE CARE[1,11]

Note: Transfuse only irradiated and leukoreduced packed red blood cells (pRBCs) and single-donor platelets; cytomegalovirus (CMV)-negative or leukofiltered pRBCs/platelets for CMV-negative patients. Use leukofiltered pRBCs/platelets for those who may undergo transplant in the future to prevent alloimmunization or for those who have had nonhemolytic febrile transfusion reactions. Many oncology patients have nonhemolytic reactions (fever, rash, hypotension, respiratory distress) to pRBCs and/or platelet transfusion and should subsequently be premedicated with diphenhydramine and/or acetaminophen.

A. Cytopenias: Anemia, Thrombocytopenia, Neutropenia

1. **Etiology:** Chemotherapy, medication, radiation, marrow infiltration, blood loss, hemolysis, consumptive coagulopathy.
2. **Management**
   a. See Chapter 14 for details on transfusion.

b. Anemia: Hemoglobin thresholds for pRBC transfusions in cancer patients are based on clinical status and symptoms (often ≤8 g/dL).
c. Thrombocytopenia: In general, maintain platelet count above 10,000/μL. Patients with active bleeding, fever, or before selected procedures (e.g., lumbar puncture, intramuscular injection) may require higher thresholds. Consider maintaining at higher levels for patients who have brain tumors, recent brain surgery, or history of stroke.
d. Neutropenia:
(1) Broad-spectrum antibiotics with concomitant fever (see Fig. 22.1).
(2) GCSF to assist in recovery of neutrophils.

B. Mucositis

1. **Etiology:** Damage to endothelial cells of the GI tract from chemotherapy, leading to breakdown of the mucosa. Typically peaks in the first 1 to 2 weeks after chemotherapy.
2. **Presentation:** Oropharyngeal pain, abdominal pain, nausea, vomiting, diarrhea, intolerance of PO intake.
3. **Prevention and Management:** Supportive care aimed at pain control and nutrition. Local pain control with lidocaine-containing mouthwashes and bicarbonate rinses. Systemic pain control often requires patient-controlled analgesia (PCA) infusion. Total parenteral nutrition (TPN) is commonly required.

C. Nausea and Emesis

1. **Etiology**: Chemotherapy side effect. Also suspect opiate therapy, GI and CNS radiotherapy, obstructive abdominal process, elevated ICP, certain antibiotics, or hypercalcemia.
2. **Presentation:** Can be acute (within 24 hours of chemotherapy initiation), delayed (beyond 24 hours), or anticipatory in subsequent cycles.
3. **Therapy:** Hydration plus one or more antiemetic medications (Table 22.5; see Formulary for dosing).

VIII. ANTIMICROBIAL PROPHYLAXIS IN ONCOLOGY PATIENTS (TABLE 22.6)[17-19]

Note: Treatment length and dosage may vary per protocol.

IX. HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)[1,2,20]

A. Goal

Administer healthy functioning hematopoietic stem cells from the bone marrow, peripheral blood, or umbilical cord blood to a patient whose bone marrow is diseased (e.g., hematologic malignancy) or depleted (after treatment with intense myeloablative chemotherapy). HSCT is also used for some congenital and acquired hematologic, immunologic, and metabolic disorders.

B. Preparative Regimens

1. **Myeloablative**: Elimination of recipient's diseased marrow with high-dose chemotherapy or chemotherapy plus total body irradiation (TBI) prior

TABLE 22.5

ANTIEMETIC THERAPIES[1]

Antiemetic Classes	Common Agents	Common Adverse Effects
Serotonin (5-HT_3) antagonists	Ondansetron, granisetron	QT prolongation, QRS widening, constipation
Histamine-1 antagonist	Diphenhydramine, scopolamine	Sedation, urinary retention, blurred vision
Benzodiazepines	Lorazepam	Sedation
Dopamine antagonists	Metoclopramide, prochlorperazine, promethazine	Sedation, extrapyramidal effects, QT prolongation; rarely, seizures or neuroleptic malignant syndrome. Consider diphenhydramine to reduce risk of extrapyramidal symptoms.
Substance P receptor antagonists	Aprepitant fosaprepitant	Exercise caution with agents metabolized by CYP3A4
Steroids (helpful in patients with brain tumors and prophylaxis for delayed nausea/vomiting)	Dexamethasone	Hypertension, hyperglycemia, bradycardia, osteoporosis/ osteonecrosis
Cannabinoids (also an appetite stimulant)	Dronabinol	Hallucinations, dizziness
Antipsychotics (useful in patients with refractory vomiting, can help comorbid depression)	Olanzapine	Weight gain, sedation, insulin resistance, QT prolongation; extrapyramidal side effects (rare)

TABLE 22.6

ANTIMICROBIAL PROPHYLAXIS IN ONCOLOGY PATIENTS[1,17-19]

Organism	Medication	Indication
Pneumocystis jirovecii	TMP-SMX: 2–3 consecutive days per week Alternatives: atovaquone, dapsone, or pentamidine	Chemotherapy and HSCT per protocol (usually at least 3–6 months after therapy completion)
HSV, CMV, VZV	Acyclovir or valacyclovir (dosing is different for zoster, varicella, and mucocutaneous HSV)	At risk for prolonged neutropenia (HSCT, AML, induction chemotherapy for high-risk leukemia, or reinduction therapy for relapsed leukemia)
Candida albicans	Fluconazole Alternatives: voriconazole or micafungin	Patients with leukemia or after HSCT (usually at least 28 days)
Gram-positive and gram-negative organisms	Levofloxacin	HSCT or leukemias with prolonged severe neutropenia until counts normalize

AML, Acute myeloid leukemia; *CMV*, cytomegalovirus; *HSCT*, hematopoietic stem cell transplantation; *HSV*, herpes simplex virus; *TMP-SMX*, trimethoprim–sulfamethoxazole; *VZV*, varicella zoster virus.

to stem cell infusion. Generally, provides greater anticancer activity but carries a higher risk of treatment-related organ injury.

2. **Nonmyeloablative**: Reduced-intensity conditioning regimen where marrow is not fully ablated, allowing recovery of autologous hematopoiesis if patient fails to engraft. Associated with decreased treatment-related mortality but higher risk of relapse or transplant rejection.

C. Types of HSCT

1. **Allogeneic**
   a. Recipient is transfused with donor stem cells from genetically similar but nonidentical donor, following a preparative regimen that includes chemotherapy and often radiation. Donors are screened for human leukocyte antigen (HLA) subtype matching to recipient. Possible donors include HLA-matched siblings, fully or partially HLA-matched unrelated donors, umbilical cord blood units, and HLA-haploidentical (half-matched) related donors.
   b. Increased level of mismatch between donor and recipient increases the risk for graft-versus-host disease (GVHD) but may offer greater graft-versus-leukemia (GVL) immunologic treatment effect.
   c. Used commonly for leukemias, myelodysplastic syndrome, hemophagocytic lymphohistiocytosis, and a number of nonmalignant hematologic, immunologic, and metabolic disorders.
2. **Autologous**
   a. Donor is recipient. After several cycles of conventional chemotherapy, stem cells from patient are harvested from the patient, stored, and given back after the patient has received intense myeloablative doses of chemotherapy.
   b. Generally, lacks GVHD or GVL effect.
   c. Used for high-risk neuroblastoma, lymphoma, and various high-risk solid tumors, which have demonstrated improved disease control after higher intensity chemotherapy that would otherwise be limited by excessive marrow suppression.

D. Engraftment

1. Recipient's bone marrow is repopulated with donor stem cells that proliferate and mature.
2. Usually starts within 2 to 4 weeks of transplant and may present with an inflammatory response, but can be significantly delayed with certain conditions, drug toxicity, or infection.
3. Defined as an ANC more than 500/μl for 3 consecutive days.

X. COMPLICATIONS OF HSCT[1,2,20-22]

A. Graft-Versus-Host Disease

1. **Etiology:** Donor T-cell-mediated reaction to unique host antigens. Risk factors include HLA disparity, source of stem cells (peripheral blood > bone marrow > umbilical cord blood), magnitude of conditioning-related tissue injury, and posttransplant infections.

2. **Presentation:** *Acute* GVHD most commonly occurs within 6 weeks of transplantation, typically within 100 days of transplantation; rarely, it may occur or persist beyond this time. *Chronic* GVHD traditionally presents >100 days after transplant but may occur earlier and persist.
   a. Maculopapular skin rash. Can progress to bullous lesions resembling toxic epidermal necrolysis.
   b. GI symptoms: Anorexia, dyspepsia, nausea, vomiting, abdominal cramping, secretory diarrhea.
   c. Laboratory findings: Direct hyperbilirubinemia.
   d. Chronic GVHD can involve nearly any organ. Commonly includes sclerodermatous skin changes, cholestasis/hepatitis, lung involvement (restrictive or obstructive), and/or dry eyes and mouth.
3. **Diagnosis:** Triad of rash, abdominal cramping with diarrhea, hyperbilirubinemia. Tissue biopsy of skin or mucosa can provide histologic confirmation, demonstrating lymphocytic infiltration and apoptosis. See Section XIII for clinical staging.
4. **Prevention and Management**
   a. Prophylaxis: Immunosuppression with posttransplant cyclophosphamide, cyclosporine, mycophenolate mofetil, tacrolimus, and/or sirolimus; adjuvants include methotrexate and prednisone.
   b. First-line treatment: Grade 1 and 2 GVHD may be treated locally with topical steroids (skin) or nonabsorbable enteral steroids (gut). First-line systemic treatment is corticosteroids, often with an additional immunosuppressant.
   c. Note: Patients with cGVHD are functionally asplenic and significantly immunosuppressed, requiring antimicrobial prophylaxis.

B. Sinusoidal Obstructive Syndrome (SOS); Veno-Occlusive Disease (VOD)

1. **Etiology:** Injury to endothelial cells leads to activation of the clotting cascade in liver sinusoids, causing erythrocyte congestion and occlusive fibrosis of terminal intrahepatic venules and sinusoids. Occurs as a consequence of hematopoietic cell transplantation, hepatotoxic chemotherapy, and/or high-dose liver radiation. Typically occurs within 3 weeks of the insult, most common at the end of the first week after transplant.
2. **Presentation:** Tender hepatomegaly, hyperbilirubinemia, edema, ascites, unexplained weight gain, thrombocytopenia refractory to transfusions.
3. **Diagnosis**: There are two established clinical diagnostic criteria, the Modified Seattle and Baltimore. Updated criteria based on growing understanding of the pathophysiology have recently been proposed.[26,30] As each has limitations, consideration of all factors enables earlier diagnosis, treatment, and improved outcomes.
   a. Modified Seattle Criteria: Two of the following events within 20 days of HSCT: Bilirubin >2 mg/dL; tender hepatomegaly; weight gain >2%.
   b. Baltimore Criteria: Bilirubin >2 mg/dL within 21 days of HSCT plus two of the following: Hepatomegaly; ascites; weight gain >5%.

c. Proposed updated criteria, unpublished as of this writing, have an expanded time frame with no time restriction to symptom development and broaden the definition by including transfusion refractory thrombocytopenia and imaging/biopsy results as eligible criteria.
d. Severe SOS is defined by the above, plus pulmonary and/or renal organ failure.
e. Imaging: Doppler US showing reversal of flow in the portal venous system is often found with severe SOS (although its absence does not rule out SOS).

4. **Prevention and Treatment**
   a. Prevention: Ursodeoxycholic acid from conditioning through 90 days post transplant.
   b. Treatment: Mild/moderate SOS can be managed with supportive care, including fluid and sodium restriction and diuretics. Defibrotide is the only approved pharmacologic treatment modality, with improved outcomes with earlier initiation and a 50% response rate. Maintain coagulation factors, platelets, and RBCs in stable range secondary to consumption.
   c. See Section XIII, for discussion of additional complications, including engraftment syndrome, thrombotic microangiopathy, hemorrhagic cystitis, and idiopathic pneumonia syndrome.

XI. CANCER SURVIVORSHIP[3,23-25]

A. Understand the Diagnosis

Obtain comprehensive treatment summary from oncologist summarizing diagnosis, chemotherapeutic agents, radiation, surgeries, history of HSCT, and adverse drug reactions.

B. Monitoring

1. Determine any potential problems by organ system, and devise plan for routine evaluation.
2. See Table 22.7 and www.survivorshipguidelines.org for common late effects of therapy.

C. Vaccinations in Oncology and HSCT Patients: see **Chapter 16**

XII. WEB RESOURCES

- National Cancer Institute (NCI): http://www.cancer.gov/cancertopics/pdq/pediatrictreatment
- NCI Clinical Trial Database: http://www.cancer.gov/clinicaltrials
- Surveillance, Epidemiology, and End Results (SEER) from NCI: http://seer.cancer.gov/
- Children's Oncology Group: http://www.childrensoncologygroup.org
- Long-term follow-up guidelines for survivors of pediatric cancer: http://www.survivorshipguidelines.org/
- Children's Oncology Camping Association, International: http://www.cocai.org/

TABLE 22.7

LATE EFFECTS OF CANCER TREATMENT BY ORGAN SYSTEM/SITE[1,23-25]

Organ System/Site	Specific Treatment Modality	Associated Late Effects	Suggested Monitoring (Frequency)
CNS	Cranial irradiation, intrathecal high-dose methotrexate	Cognitive dysfunction, peripheral neuropathy	Neuropsychological testing
Psychiatric	Any cancer experience	Mental health disorders, risky behaviors, psychosocial disability from pain, fatigue	Psychosocial assessment (yearly)
Vision		Cataracts, optic neuropathy	Routine ophthalmology follow-up (yearly for radiation >30 Gy; Every 3 years if <30 Gy)
Hearing	Platinum agents	Ototoxicity, sensorineural hearing loss	Regular audiology follow-up and evaluation (every 5 years if received radiation)
Thyroid		Malignancy, hyperthyroid, hypothyroid	Thyroid function testing (yearly)
Endocrine		Precocious puberty, growth hormone deficiency	Neuroendocrine monitoring, Tanner staging, BMI (twice a year until growth completed, then yearly)
Cardiac	Anthracyclines	Cardiomyopathies, pericarditis, ASCD/MI, arrhythmias	ECG, echocardiogram (every 1–5 years as indicated), HgA1C, lipid profile (every 2 years if received radiation)
Pulmonary	Bleomycin, various alkylating agents	Pulmonary fibrosis, restrictive lung disease	Pulmonary function tests with D_{LCO}
Hepatic	6-TG, methotrexate, 6-MP	Hepatic fibrosis, portal hypertension, VOD	LFTs, liver ultrasound with Doppler
Renal	Platinum agents, high-dose methotrexate, ifosfamide	Renal insufficiency/failure	UA and blood pressure (yearly), electrolytes, creatinine clearance, GFR
Urologic	Cyclophosphamide, ifosfamide	Cancer, fibrosis, hemorrhagic cystitis	UA (yearly), cystoscopy, bladder ultrasound, urine culture
Gonadal/ reproductive	Alkylating agents	Delayed puberty, ovarian failure, infertility, testosterone deficiency	Tanner staging, LH, FSH, estradiol, gynecologic evaluation Semen analysis, testosterone
Musculoskeletal	Methotrexate, corticosteroids	Osteoporosis/osteopenia, osteonecrosis, short stature, scoliosis, avascular necrosis	Serial heights and spine exam (yearly); DEXA scan; calcium and vitamin D supplementation may be recommended for high-risk patients

Continued

TABLE 22.7—cont'd

LATE EFFECTS OF CANCER TREATMENT BY ORGAN SYSTEM/SITE[1,23-25]

Organ System/Site	Specific Treatment Modality	Associated Late Effects	Suggested Monitoring (Frequency)
Secondary malignancies	Radiation therapy, alkylating agents, anthracyclines, topoisomerase II inhibitors, platinum agents, cyclophosphamide	For radiation, location is site-dependent; asssociated secondary malignancies include CNS, breast, thyroid, melanoma, solid tumors, and sarcomas Leukemia (alkylating agents) Bladder cancer (cyclophosphamide)	Yearly comprehensive history and physical, routine blood work, recommended follow-up for specific treatment modalities

ASCD, Atherosclerotic cardiac disease, *BMI*, body mass index, *CNS*, central nervous system; *DEXA*, dual-energy x-ray absorptiometry; D_{LCO}, diffusing capacity of lung for carbon monoxide; *ECG*, electrocardiogram; *FSH*, follicle-stimulating hormone; *GFR*, glomerular filtration rate; *Gy*, Gray; *HgA1C*, hemoglobin A1C; *LFT*, liver function test; *LH*, luteinizing hormone; *MI*, myocardial infarction; *UA*, urinalysis; *VOD*, veno-occlusive disease.

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A complete list of references can be found online at www.expertconsult.com.

XIII. ONLINE CONTENT

A. Complications of HSCT[1,2,19-21,25-29]

1. **Graft-Versus-Host Disease (GVHD)**

See Table EC 22.A for grading of acute GVHD. Acute GVHD should be graded weekly through day +100. If systemic treatment is started, it should be graded twice weekly while on treatment.

2. **Engraftment Syndrome**
   a. **Etiology:** Occurs several days prior to donor cell engraftment and in days following white blood cell recovery owing to endothelial injury and activated granulocytes in the setting of proinflammatory cytokines. Occurs in approximately 20% of HSCT patients.
   b. **Presentation:** Fever and rash; can have pulmonary infiltrates, diarrhea, or signs of shock.
   c. **Diagnosis:** Similar presentation to GVHD and infection. Imperative to rule out infection while treating empirically with antibiotics. Often mild and self-limited. However, if symptoms continue for ≥ 48 hours or are severe, consider initiation of corticosteroids. If insufficient steroid response after 72 hours, can biopsy for alternative diagnoses.
   d. **Treatment:** Treatment with supportive care and corticosteroids; optimization of GVHD prophylaxis. If biopsy confirms immune-mediated pathology, can treat with additional immunosuppressive agents.
3. **Transplant-Associated Thrombotic Microangiopathy (TA-TMA)**
   a. **Etiology:** Associated with immunosuppressants (e.g., cyclosporine, tacrolimus) and infection.
   b. **Presentation:** Microangiopathic hemolytic anemia and consumptive thrombocytopenia. Often associated with renal insufficiency/failure; may be associated with neurologic symptoms.
   c. **Diagnosis:** Anemia and thrombocytopenia on CBC, schistocytes on peripheral blood smear, hematuria, proteinuria, casts on urinalysis, elevated LDH, decreased haptoglobin, impaired renal function, elevated D-dimer on coagulation panel.
   d. **Treatment**: Supportive care with blood products, fluid management, and dialysis. Address underlying etiology—consider alternative immunosuppressant and treat any underlying infection. For progressive or severe TA-TMA, consider neutralization of compliment with eculizumab.[31]
4. **Hemorrhagic Cystitis**
   a. **Etiology:** Pretransplant conditioning regimens (specifically those that include cyclophosphamide, pelvic or total body irradiation [TBI]) or viral reactivation (adenovirus, BK virus).
   b. **Presentation:** Hematuria, dysuria, difficulty voiding due to clots.
   c. **Diagnosis:** Urine polymerase chain reaction (PCR) assay for adenovirus and BK virus, bacterial cultures, bladder ultrasound, CBC, coagulation studies.
   d. **Treatment**: Hydration, analgesics, platelet transfusion, treatment of any underlying infections. For obstruction, Foley catheter with bladder irrigation.

5. **Idiopathic Pneumonia Syndrome**
   a. **Etiology:** Widespread alveolar injury in the absence of infection or other known etiology. Thought to occur from a variety of insults, including toxic effects of the conditioning regimen, immunologic cell–mediated injury, and inflammation secondary to cytokine release following engraftment. Most commonly occurs within the first 120 days after transplant.
   b. **Presentation:** Rapidly progressive dry cough, dyspnea, hypoxemia, diffuse radiographic opacities; may progress to ARDS.
   c. **Diagnosis:** Imaging; bronchoalveolar lavage with transbronchial biopsy, if tolerated.
   d. **Prevention and Management:** Supportive care together with broad-spectrum antibiotics while infectious studies pending. IV corticosteroids and tumor necrosis factor-α inhibitor etanercept if no infection identified.[32]

TABLE EC 22.A

CLINICAL STAGING AND GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE

CLINICAL STAGING			
Stage	Skin (Rash)	Liver (Bilirubin)	GI System (diarrhea) [a]
1	<25% of BSA	2.1–3 mg/dL	500–1000 mL/day (10–19.9 mL/kg/day); OR severe nausea/vomiting
2	25%–50% of BSA	3.1–6 mg/dL	1001–1500 mL/day (20–30 mL/kg/day)
3	>50% of BSA	6.1–15 mg/dL	>1500 mL/day (or >30 mL/kg/day)
4	Erythroderma with bullous formation	>15 mg/dL	Severe abdominal pain and/or ileus
CLINICAL GRADE (BASED ON HIGHEST INDIVIDUAL TARGET ORGAN STAGING)			
I	Skin only (stage 1–2)		
II	Stage 3 skin OR stage 1 liver OR stage 1 GI		
III	Stage 2–3 liver OR stage 2–4 GI		
IV	Stage 4 skin OR stage 4 liver		

[a]Measured in mL/day if ≥50 kg or mL/kg/day if <50 kg.
BSA, Body surface area; *GI*, gastrointestinal.

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Chapter 23

Palliative Care

Joshua Natbony, MD

I. INTRODUCTION TO HOSPICE AND PALLIATIVE MEDICINE

A. Definition of Palliative Care[1,2]

1. Palliative care is the active total care of the child's body, mind, and spirit with the intent to prevent and relieve suffering, with a special focus on symptom control.
2. Palliative medicine supports the best quality of life for the child and family. It can be provided along with disease-directed treatment from the time of diagnosis of serious illness.
3. See Fig. 23.1 for the current accepted model of palliative care.

B. Definition of Hospice

1. Hospice care is an insurance benefit that may be initiated for patients who have a terminal illness with a life expectancy estimated to be 6 months or less.
2. It specializes in care at the end of life to promote a child's comfort and to support loved ones in their bereavement.

C. Team Composition

1. Hospice and palliative care teams are often robust and interdisciplinary.
2. They generally include physicians, nurses, nurse practitioners, physician assistants, social workers, child life specialists, pastoral care, patient care coordinators, and bereavement coordinators.

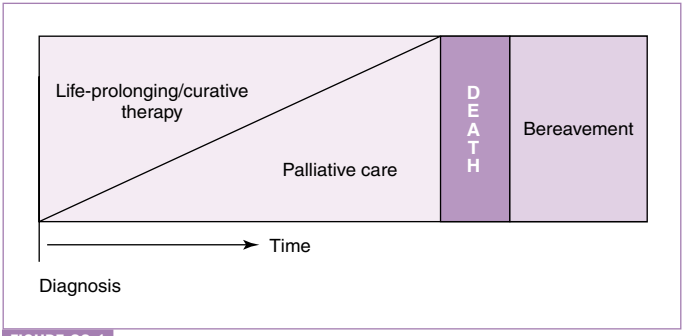

FIGURE 23.1
Current accepted model for palliative care.

II. COMMUNICATION AND DECISION MAKING

A. Decision-Making Tools[3]

1. Provide framework for discussion with families regarding medical issues, quality of life, family goals, preferences, and other contextual preferences, such as spirituality and culture.
2. Advance directives:
   a. Adolescents aged 18 years and older, if they are unable to speak for themselves, can name another adult to make healthcare decisions.
   b. Children and adolescents younger than 18 years of age can actively participate in decision making by using helpful tools such as "Five Wishes" and "Voicing My Choices" (see in Section IV).

B. Structuring Family Meetings[4]

1. Make sure that all necessary individuals are present and understand the purpose of the meeting.
2. Make sure that all clinicians are in agreement about the patient's condition and the recommendations.
3. Identify the individual who will facilitate the meeting.
4. Choose a private location with minimal distraction.
5. Always have water and tissues available.
6. Begin by introducing all participants and the purpose of the meeting.
7. Assess what the family knows and expects with respect to the patient's condition.
8. Describe the clinical situation, providing the big picture and then asking family members if they would like or are ready for more details.
9. Encourage each member of the family to express concerns and questions.
10. Explore the patient's and family's values and how they influence decision making.
11. Propose goals for the patient's care that reflect the stated values.
12. Provide a concrete follow-up plan.

C. Breaking Bad News[5]

1. Prepare yourself: Know the medical information, know what you will say, ask the patient/family if they want someone in particular present with them for the discussion.
2. Prepare the family/patient: Give a brief, calm statement that leads into the news.
3. State the news: Do this clearly and concisely, and be as definitive as possible.
4. Wait for the patient/family's reaction: Resist the urge to say more; allow others to speak first.
5. Reflect the response back: "This news is clearly very upsetting to you."
6. Legitimize the reaction: "It is understandable that you would be upset."
7. Explore: "What upsets you the most about this news?"
8. Provide realistic hope.

9. Discuss next steps (if appropriate at this time): "May I address your concerns now and talk about the next steps for treatment, or would you like more time?"

D. Other Tools for Difficult Conversations

1. Assess spirituality according to the "FICA" tool[6]:
   a. **F**aith and belief: "Do you consider yourself spiritual or religious?"
   b. **I**mportance in life: "What importance does your faith or belief system have in your life?"
   c. **C**ommunity: "Are you a part of a spiritual or religious community?"
   d. **A**ddress in care: "How would you like me, your healthcare provider, to address these issues in your healthcare?"
2. "Ask-tell-ask"[7]
   a. **Ask** the patient or family to describe their understanding of the situation or issue.
   b. **Tell** them what you need to communicate in a straightforward manner.
   c. **Ask** them questions to assess their understanding.
3. "Hope together" with the patient and family while also preparing for all possible outcomes.

III. CARE OF THE DYING CHILD

A. Limiting Interventions

The following options should be considered.

1. Do not attempt resuscitation (DNAR)—foregoing cardiopulmonary resuscitation (CPR) and other resuscitative interventions as part of an overall care plan that emphasizes comfort and quality of living.
2. Do not intubate (DNI)—although, if clinically appropriate, intubation may still allow the initiation of continuous positive-pressure ventilation or may help in managing symptoms.
3. Do not escalate treatment—the choice to forego changes in treatment, even as a patient's condition worsens, because death is expected. Examples of such requests include the following:
   a. Do not increase the dose of current medications (e.g., vasopressors).
   b. Do not add new medications (e.g., antibiotics).
   c. Do not initiate new interventions (e.g., dialysis, mechanical ventilation).
   d. However, one may still initiate and increase interventions to treat pain and reduce suffering.
4. Discontinuing current interventions—the option of discontinuing interventions that prolong the dying process must also be discussed.
5. Medical orders for life-sustaining treatment and physician orders for life-sustaining treatment (POLST) forms:
   a. These are portable and enduring medical order forms completed by patients or their authorized decision makers and are signed by a physician.

b. They contain orders regarding CPR and other life-sustaining treatments.
c. If a state offers one of these forms, the orders are valid for emergency medical service providers as well as healthcare providers and facilities within that state.
d. A copy must be provided to the patient or authorized decision maker within 48 hours of completion or sooner if the patient is to be transferred.
e. Refer to your state's laws prior to completing any documentation.
f. Additional information for US providers can be found at **www.polst.org.**

B. Involving the Child in Conversations About Death[8-11]

1. See Table 23.1 for the development of death concepts in children.[12]
2. A minor child has the capacity to meaningfully participate in medical decision making if he or she demonstrates the ability to do all of the following:
   a. Communicate understanding of the medical information.
   b. State his or her preference.
   c. Communicate understanding of the consequences of decisions.
3. Helpful documents are available for purchase from the nonprofit Aging with Dignity (see Section IV.B).
   a. Five Wishes: This is a legal advance directive with versions tailored for adolescents.
   b. Voicing My Choices: A workbook for adolescents intended to complement Five Wishes.
   c. My Wishes: A simple booklet for younger children to help them share their preferences.

TABLE 23.1

CONCEPTUALIZATION OF DEATH IN CHILDREN

Age Range	Characteristics	Concepts of Death	Interventions
0–2 years	Achieve object permanence May sense something is wrong	None	Provide maximal comfort with familiar persons and favorite toys
2–6 years	Magical thoughts	Believe death is temporary Do not personalize death Believe death can be caused by thoughts	Minimize separation from parents, correct perceptions that the illness is punishment
6–12 years	Concrete thoughts	Understand death can be personal Interested in details of death	Be truthful, evaluate fears, provide concrete details if requested, allow participation in decision making
12–18 years	Reality becomes objective Capable of self-reflection	Search for meaning, hope, purpose, and value of life	Be truthful, allow expression of strong feelings, allow participation in decision making

TABLE 23.2

SYMPTOMATIC MANAGEMENT OF THE DYING PATIENT

System	Changes as Death Approaches	Interventions
Neurologic	Pain	Morphine as needed
	Overactive senses (hearing last to diminish)	Dim lights and reduce noise, provide soft background music
	Increased need for sleep with occasional surge of energy to play or socialize	
Cardiovascular	Heart rate increases, blood pressure decreases, pulse weakens, and skin becomes cooler	Inform family that death is near
Respiratory	Increased secretions	Turn every few hours, elevate head of bed, frequent mouth care (avoid deep suctioning)
		Hyoscyamine
	Air hunger	Positive pressure through handheld fan
		Supplemental room air or oxygen as needed
		Morphine
Gastrointestinal	Nausea and vomiting	Ondansetron or prochlorperazine
	Decreased appetite, preference for liquids	Ice chips, moist mouth swabs
	Natural dehydration, fevers	Antipyretics per rectum
Dermatologic	Pruritus	Diphenhydramine
Psychiatric	Decreased interactions with outside world as thoughts and emotions are increasingly directed inward	Provide reassurance to family
		Frequently orient child to surroundings, surround with family and speak calmly
	Agitation or delirium	Lorazepam and haloperidol if needed

C. Supporting Patients Throughout the Dying Process

1. See Table 23.2 for normal changes that occur as death approaches and their recommended management.[12,13]
2. See Table 23.3 for appropriate dosing of recommended medications (NOTE: doses may be different for other indications).[12]

D. Pronouncing Death[14]

1. Preparation
   a. Know the child's name and gender.
   b. Be prepared to answer simple, pertinent questions from family and friends.
   c. Consult with nursing staff for relevant information, such as recent events and family dynamics.
   d. Determine the need and call for interdisciplinary support, such as social work, child life, pastoral care, and/or a bereavement coordinator.
2. Entering the room
   a. Enter quietly and respectfully along with the primary nurse.
   b. Introduce yourself and identify your role.

TABLE 23.3

DOSING FOR MEDICATIONS USED IN PALLIATIVE CARE[12,16-20]

Indication	Medication	Initial Regimen
Pain	Morphine	0.2–0.4 mg/kg/dose PO, SC, SL, PR Q2–4 hr[a] 0.1–0.2 mg/kg/dose IV Q2–4 hr[a] **NOTE:** Morphine should be titrated to symptomatic relief.
	Hydromorphone[b]	0.03–0.08 mg/kg/dose PO Q2–4 hr 0.015–0.02 mg/kg/dose IV, SC Q2–4 hr
	Oxycodone	0.05–0.2 mg/kg/dose PO 4hr (adult dose 5-10 mg)
Neuropathic pain	Gabapentin[b]	3–5 mg/kg/dose QHS day 1, BID day 2, then TID day 3 (titrate to effect, max dose per day 3600 mg)
Dyspnea	Morphine	0.1–0.25 mg/kg/dose PO, SC, SL, PR Q2–4 hr 0.05–0.1 mg/kg/dose IV Q2–4 hr
Agitation	Lorazepam	0.02–0.05 mg/kg/dose PO, IV, SL, PR Q4–8 hr
	Haloperidol	0.01–0.02 mg/kg/dose PO, IM, SC, IV Q8–12 hr
Pruritus	Diphenhydramine	0.5–1 mg/kg/dose PO, IV Q6–8 hr
Nausea/Vomiting	Prochlorperazine	0.1–0.15 mg/kg/dose PO, PR Q6–8 hr
	Ondansetron	0.15 mg/kg/dose PO, IV Q6–8 hr (max dose 8 mg)
	Granisetron	0.01 mg/kg IV/PO Q12hr (max 1 mg/dose)
	Olanzapine	0.1 mg/kg PO once daily (max 10 mg, titrate down in cases of oversedation)
Seizures	Diazepam	0.3–0.5 mg/kg/dose PR Q2–4 hr
	Lorazepam	0.05–0.1 mg/kg/dose SC, SL, IV Q2–4 hr
Secretions	Glycopyrrolate	0.04–0.1 mg/kg PO (max 8 mg/day) 0.004–0.01 mg/kg (4–10 mCg/kg) IV, SC

[a]Infants <6 months should receive one-third to one-half the dose. For adolescents, consider starting adult dosing of 10 to 30 mg/dose PO, 2 to 15 mg/dose IV.

[b]Medication has not been studied in neonates.

BID, twice daily; *IV*, intravenous; *PO*, oral; *PR*, rectal; *SC*, subcutaneous; *SL*, sublingual; *TID*, three times daily; *QHS*, nightly. Adapted from Himelstein BP, Hilden JM, Boldt AM, et al. Pediatric palliative care. *N Engl J Med.* 2004;350:1752–1762.
Note: For adult-sized patients, see Formulary for adult dosing recommendations.

   c. Determine the relationship of those in the room.
   d. Inform the family of the purpose of your visit ("I am here to examine your child") and invite them to remain in the room.
3. Procedure for pronouncement
   a. Check ID bracelet and pulse.
   b. Respectfully check response to tactile stimuli.
   c. Check for spontaneous respirations for a minimum of 1 minute.
   d. Check for heart sounds for a minimum of 1 minute.
   e. Record the time of death.
   f. Inform the family of death ("[Child's name] has died").
   g. Remember to convey sympathy ("I'm so sorry for your loss").
   h. Offer to contact other family members.
4. Documentation of death in the chart
   a. Write date, time of death, and the provider pronouncing the death.
   b. Document absence of pulse, respirations, and heart sounds.
   c. Identify family members who were present and informed of death.
   d. Document notification of the attending physician.

E. Explaining Autopsies[15]

1. Definitions
   a. An **autopsy** is a definitive examination of a deceased patient to determine the cause of death.
   b. A **forensic autopsy** is a legally mandated examination to determine cause of death in a criminal investigation.
   c. A **rapid autopsy** involves the urgent removal of tissues for research uses.
2. Frequently asked questions
   a. A voluntary autopsy can look at all parts of a patient's body or only some.
   b. An autopsy will not affect the patient's body cosmetically and should not affect funeral or viewing arrangements.
   c. An autopsy takes 2 to 4 hours to perform and should not delay funeral/burial arrangements.
3. Benefits of autopsy
   a. For families:
      (1) Provides closure regarding diagnosis.
      (2) Identifies possible genetic etiologies for unexplained death.
   b. For providers: clarifies potential diagnostic errors and uncertainties.

F. Organ Donation

   a. Most hospitals have a special third-party team that coordinates organ donations.
   b. Inform family members, if they are interested, that this team may be visiting soon to explain the process.

G. Completing Death Certificates[14]

1. Locate a copy of a sample death certificate for reference.
2. Cardiopulmonary arrest or respiratory arrest is NOT an acceptable primary cause of death.
3. For specific instructions for your state and/or institution, contact the Office of Decedent Affairs at your institution.
4. If you are completing a handwritten death certificate:
   a. Use BLACK INK ONLY and complete *Physician sections*.
   b. DO NOT use abbreviations (e.g., spell out the month: January 31, not 1/31).
   c. DO NOT cross out or use correction fluid; you must begin again if mistakes are made.

H. Interacting with Loved Ones After a Child's Death

1. It is appropriate to send condolence cards, contact families, or attend funerals after a child has died. These are all appropriate physician activities that are deeply valued by bereaved families. Families want to know that their children are not forgotten.
2. Numerous services are available for families, including: pastoral care, social work, bereavement coordinators, community support groups, counseling services, and bereavement follow-up programs.

IV. WEB RESOURCES

A. Center to Advance Palliative Care—capc.org

B. Aging with Dignity—https://agingwithdignity.org/

C. The American Academy of Hospice and Palliative Medicine—www.aahpm.org

D. The National Hospice and Palliative Care Organization—www.nhpco.org

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Chapter 24

Psychiatry

Christopher Morrow, MD

I. OVERVIEW

A. Epidemiology and General Approach

1. **Prevalence:** 15% to 20% of children in primary care practices require psychiatric care.[1]
2. **Surveillance and Screening:**
   a. Surveillance for mental health issues should occur at all routine well-child visits from early childhood through adolescence.
   b. The Pediatric Symptom Checklist (PSC) is a general mental health checklist that screens for a broad array of disorders (Table 24.1).
3. See the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), for full list of psychiatric diagnoses.[2]
4. Pharmacotherapy for many disorders may be managed or monitored by the pediatrician. See Riddle et al., "Pediatric Psychopharmacology for Primary Care."[3]

B. Mental Status Exam

1. General appearance: dress, self-care, demeanor, attitude, behavior
2. Motor activity: activity level (restless, fidgety, stereotyped or ritualized movements)
3. Speech and language: fluency, comprehension, rate, rhythm, volume, expressive and receptive skills
4. Mood and affect: stated and observed
5. Thought form/content
   a. What patient is thinking about
   b. Goal-directed nature of thoughts, coherence, organization, delusional content
6. Abnormal perceptual phenomena: illusions, hallucinations
7. Insight, judgment, cognition

II. POSTPARTUM DEPRESSION

A. Epidemiology[4]:

Prevalence in most studies is between 10% and 15%

B. Screening:

1. Universal screening is recommended for all postpartum women.
2. A history of depression doubles the risk of postpartum depression and should prompt careful assessment for postpartum symptoms.[5]

TABLE 24.1

MENTAL HEALTH SCREENING TESTS BY DIAGNOSIS

Symptoms or Diagnosis Evaluated	Screening Test	Age	Administration Time	Completed by	Comments	Weblink
General psychosocial screening	Pediatric Symptom Checklist (PSC)	4–16 years	<5 min	Parent or child/ adolescent	Assesses attention, externalizing, and internalizing symptoms	https://www.massgeneral.org/psychiatry/treatments-and-services/pediatric-symptom-checklist
Attention-deficit/hyperactivity disorder (ADHD)	Vanderbilt Diagnostic Rating Scales	6–12 years	10 min	Parent or teacher	Separate scales for functioning in different domains (home, school)	http://www.nichq.org/childrens-health/adhd/resources/vanderbilt-assessment-scales
Anxiety	Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED)	8+ years	5 min	Parent or patient	Separate scales for parent and patient Does not assess for OCD, PTSD	http://www.midss.org/content/screen-child-anxiety-related-disorders-scared
	Spence Children's Anxiety Scale	2.5–12 years	5–10 min	Parent or patient if 8–12 years of age	Multiple subscales of anxiety	http://www.scaswebsite.com/
Depression	Patient Health Questionnaire-2 (PHQ-2) and Patient Health Questionnaire-9 (PHQ-9)	13+ years	1 min	Patient	Brief screening tool for adolescents or parents (e.g., postpartum depression)	http://www.cqaimh.org/pdf/tool_phq2.pdf http://www.cqaimh.org/pdf/tool_phq9.pdf
	Center for Epidemiological Studies Depression Scale for Children (CES-DC)	6–17 years	5–10 min	Child/adolescent	Originally used in adult populations	http://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces_dc.pdf

OCD, obsessive-compulsive disorder; *PTSD*, posttraumatic stress disorder.

Modified from the American Academy of Pediatrics. Mental health screening and assessment tools for primary care. From Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit. 2010

C. Diagnosis:

1. Depression occurring in the 12-month period after birth.
2. Maternal depression is important to identify and treat, given the substantial impact on the health of the developing infant. Impaired maternal attachment may compromise the social, cognitive, and behavioral development of the infant.[4]
3. The Edinburgh Postnatal Depression Scale is a 10-item questionnaire which can be completed in 5 minutes or less.[6]

D. Treatment:

1. Referral to mother's primary care physician or mental health expert is preferred.
2. Integrating maternal mental health into pediatrics practice is ideal.[6]

III. COMMON PSYCHIATRIC CONDITIONS IN CHILDREN (2 TO 12 YEARS)

A. Attention-Deficit/Hyperactivity Disorder

1. **Epidemiology:**
   a. Persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.
   b. Prevalence continues to rise. This disorder affected 11.0% (6.4 million) of children in the United States in 2011, marking an increase from 9.5% (5.4 million) of children in 2007.[7,8]
   c. Most affected children continue to meet the diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) through adolescence.
2. **Screening:** Evaluate all children aged 4 to 18 years who have academic and/or behavioral concerns for ADHD and common comorbid conditions (depression, anxiety, oppositional defiant disorder, conduct disorder).[9]
3. **Diagnosis[2]:**
   a. DSM-5 diagnostic criteria: inattention, impulsivity/hyperactivity that are more frequent and severe than typically observed in children of the same developmental age.
   b. Symptoms must persist for 6 months or more, occur before the age of 12 years, and should be evident in two or more settings (e.g., home and school). [2,10]
   c. Subtypes: Combined, predominantly inattentive, or predominantly hyperactive/impulsive.
   d. Diagnosis is made using history, observation, and behavioral checklists such as the Vanderbilt Assessment Scale (see Table 24.1).
   e. If the medical history is unremarkable, no further laboratory or neurologic testing is required. Psychological and neuropsychological testing is not required for diagnosis but is recommended if other academic or developmental concerns are present.[10]

4. **Treatment:**
   a. Pharmacologic treatment works best with behavioral therapy as an adjunct.[9]
   b. Behavioral therapy may be tried alone in preschool-age children (4 to 5 years old), but for older children or in preschool-age children where behavioral therapy is ineffective, combination therapy with pharmacologic and behavioral interventions is most effective.[11]
   c. Before starting a stimulant medication, a history should be taken to exclude cardiac symptoms, Wolff-Parkinson-White syndrome, a family history of sudden death, hypertrophic cardiomyopathy, and long-QT syndrome. Screening electrocardiography is not required if there is no personal or family history of cardiac disease.[12]
   d. See Table 24.2 for recommended pharmacologic treatments. The ADHD Medication Guide provides visual information (see Section VI).
      (1) For preschool-age children (4 to 5 years old), start with behavioral therapy and, if necessary, a methylphenidate stimulant.[3,11]
      (2) For elementary-age children (6 or more years old), start with behavioral and stimulant therapy (methylphenidate or amphetamine).[3,11]
   e. Titrate medications to maximal symptom control with minimal side effects.
   f. Common side effects of stimulants to monitor include appetite suppression, abdominal pain, headaches, palpitations, and sleep disturbance.[9]
   g. If the first stimulant is ineffective, consider an alternative class of stimulant. Second-line options as alternative therapy or as an augmenting agent to stimulant therapy include guanfacine, clonidine, and atomoxetine.[3,11]
   h. If multiple medication trials prove ineffective, consultation with a pediatric psychiatrist is suggested.

B. Anxiety Disorders

1. **Epidemiology:**
   a. A group of disorders characterized by excessive fear, anxiety, and related behavioral disturbances.
   b. An estimated 4.7% of all children 3 to 17 years of age are affected, with onset most often before the age of 25 and increased prevalence (15% to 20%) among adolescents 13 to 17 years of age.[13-15]
2. **Clinical Presentation:**
   a. May present with fear or worry and without recognizing that their fear or anxiety is unreasonable.
   b. Commonly have somatic complaints of headache and abdominal pain. Patients with many primary care visits for such complaints may benefit from formal anxiety screening.
   c. Fear/anxiety may affect school performance or manifest as school avoidance.
   d. Crying, irritability, angry outbursts, and disruptive behavior are expressions of fear and an effort to avoid anxiety-provoking stimuli.

TABLE 24.2

COMMONLY USED PSYCHOTROPIC MEDICATIONS

Drug Name	Age of FDA Approval
ANTIDEPRESSANTS/ANXIOLYTICS	
Fluoxetine (Prozac)	7+ years (OCD) 8+ years (MDD)
Sertraline (Zoloft)	6+ years (OCD)
Escitalopram (Lexapro)	12+ years (MDD)
Duloxetine (Cymbalta)	7+ years (GAD)
ADHD MEDICATIONS	
METHYLPHENIDATE PREPARATIONS	
Methylphenidate (Concerta, Ritalin)	6+ years (Ritalin)
Dexmethylphenidate (Focalin)	6+ years
AMPHETAMINE PREPARATIONS	
Lisdexamfetamine (Vyvanse)	6+ years
Dextroamphetamine + amphetamine (Adderall)	3+ years (immediate release) 6+ years (extended release)
NONSTIMULANT OPTIONS	
Clonidine (Kapvay)	6+ years
Guanfacine (Tenex, Intuniv)	6+ years (Intuniv) 12+ years (Tenex)
Atomoxetine (Strattera)	6+ years
ANTIPSYCHOTICS	
Haloperidol (Haldol)	Not established
Aripiprazole (Abilify)	6+ years (irritability with ASD) 10+ years (BPD) 13+ years (schizophrenia)
Risperidone (Risperdal)	5+ years (irritability with ASD) 10+ years (BPD) 13+ years (schizophrenia)
Quetiapine (Seroquel)	10+ years (BPD) 13+ years (schizophrenia)

See Formulary for more detailed drug information, indications, and dosing.

ASD, Autism spectrum disorder; *BPD*, bipolar disorder; *GAD*, generalized anxiety disorder; *MDD*, major depressive disorder; *OCD*, obsessive-compulsive disorder.

Adapted from the Centers for Medicare and Medicaid Services factsheets (www.CMS.gov) and the US Food and Drug Administration.

3. **Screening:** Multiple tools, such as the Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED) (Table 24.1), are available.
4. **Diagnosis:**
   a. DSM-5 diagnostic criteria vary based on the specific disorder[2]: (1) generalized anxiety disorder, (2) separation anxiety disorder, (3) social anxiety disorder, (4) selective mutism, (5) specific phobia, (6) panic disorder, (7) agoraphobia
   b. Differential diagnosis: obsessive-compulsive disorder, posttraumatic stress disorder.
5. **Treatment:** Cognitive behavioral therapy (CBT) with or without pharmacotherapy (see Table 24.2) based on the disorder and its severity.[16]

C. Oppositional Defiant Disorder (ODD)[17]

1. **Epidemiology:**
   a. Pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness.
   b. Prevalence estimated at approximately 3%. Increased prevalence in boys as compared with girls in the preteen years but not in the teens.
   c. Age of onset approximately 6 years of age, frequently comorbid with ADHD.
2. **Screening:** Many screening tools are available, including the Vanderbilt Assessment Scale (see Table 24.1).[18]
3. **Diagnosis[2]:**
   a. DSM-5 diagnostic criteria: angry/irritable mood with argumentative/defiant behavior and vindictiveness for 6 or more months.
   b. Behavior must be present with at least one nonsibling.
4. **Treatment:**
   a. No evidence for pharmacologic intervention as first-line therapy for ODD.
   b. Combination of CBT and parent management training may be most effective as first-line intervention.[17]

IV. COMMON PSYCHIATRIC CONDITIONS IN ADOLESCENTS

A. Depressive Disorders

1. **Epidemiology:**
   a. A group of disorders characterized by mood changes as well as somatic and cognitive symptoms that disrupt functioning.
   b. Prevalence of major depressive disorder: 2% of children, 4% to 8% of adolescents.[15]
   c. Subclinical symptoms: 5% to 10% of children.
   d. Common comorbid conditions: anxiety disorders, disruptive behavior disorders, ADHD, substance use.
2. **Screening:**
   a. Routine screening is recommended for patients 11 years of age or older.
   b. Multiple screening tools are available (see Table 24.1). The Patient Health Questionnaire (PHQ-2) is a brief but effective tool for use in adolescents.[19]
   c. All patients with suspected depressive symptoms should be screened for suicidal ideation and referred for emergency evaluation if serious thoughts and/or action plans are endorsed (see Section V.A).
3. **Diagnosis:**
   a. DSM-5 Major Depressive Disorder diagnostic criteria:
      (1) Five or more of the following symptoms for 2 or more weeks: Must include either depressed mood/irritability OR anhedonia; changes in appetite/weight, sleep, or activity; fatigue or loss of energy; guilt/worthlessness; decreased concentration; suicidality.
      (2) Symptoms cause significant impairment in functioning.

(3) Symptoms not due to substance use or a medical condition.
(4) No history of manic episodes.[20]

b. Other depressive disorders are defined by their own diagnostic criteria[2]: (1) disruptive mood dysregulation disorder; (2) persistent depressive disorder (dysthymia); (3) premenstrual dysphoric disorder.
c. Differential diagnosis: bipolar disorder, adjustment disorder.

4. **Treatment:**
   a. Selective serotonin reuptake inhibitors (SSRIs) may be initiated in the primary care setting. Referral to subspecialist may be required depending on severity or in the case of treatment failure (Fig. 24.1).
   b. Antidepressant medications (see Table 24.2) and CBT combined are the most effective treatments, followed by medication alone and then CBT alone.[21]

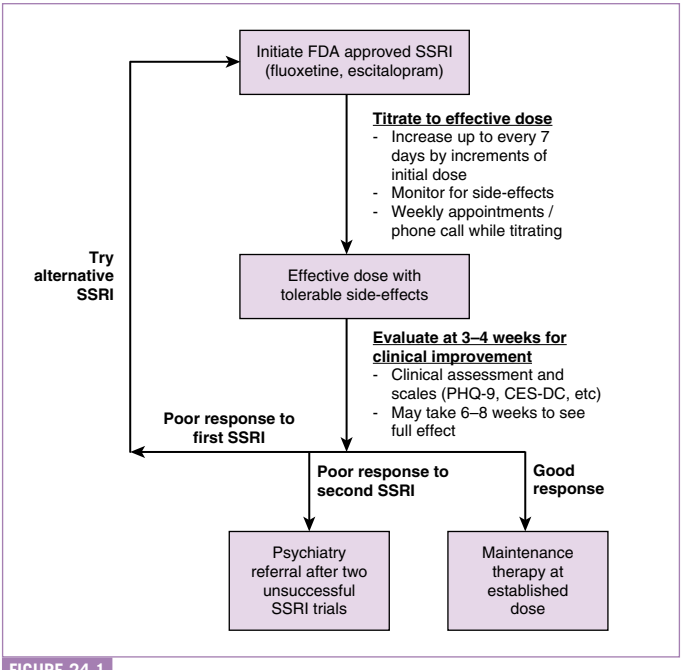

FIGURE 24.1
SSRI initiation algorithm. *CES-DC*, Center for Epidemiological Studies Depression Scale for Children; *FDA*, US Food and Drug Administration; *PHQ-9*, Patient Health Questionnaire-9; *SSRI*, selective serotonin reuptake inhibitor.

c. SSRIs have a black box warning from the US Food and Drug Administration (FDA) concerning a possible increase in suicidal thoughts or behaviors after initiation of medication.
   (1) The basis of this warning was a large meta-analysis that found no increase in completed suicides but a small increase in suicidal ideation.[22]
   (2) Multiple professional mental health groups support the continued use of SSRIs in treating depression in children and adolescents because the benefits appear to outweigh potential risks.[20,23,24]
d. Refer to the Physicians Med Guide prepared by the American Psychological Association (APA) and American Academy of Child and Adolescent Psychiatry (AACAP) for guidelines regarding medication use for depression in adolescents (see Section VI).[25]

B. Substance Use Disorders

1. **Epidemiology:**
   a. Lifetime diagnosis of alcohol abuse: 0.4% to 9%; alcohol dependence: 0.6% to 4.3%.[26]
   b. Lifetime diagnosis of drug abuse or dependence: 3.3% to 9.8%.[26]
   c. Common comorbid conditions: disruptive behavior disorders, mood disorders, anxiety disorders.
2. **Clinical Presentation:**
   a. Acute change in mood, behavior, and cognition.
      (1) Mood: low to elevated mood
      (2) Behavior: disinhibition, lethargy, hyperactivity, agitation, somnolence, hypervigilance
      (3) Cognition: impaired concentration, changes in attention span, perceptual and overt disturbances in thinking (e.g., delusions)
   b. Impairment in psychosocial and academic functioning (family conflict/dysfunction, interpersonal conflict, academic failure).
   c. Deviant or risk-taking behavior.[26]
3. **Diagnosis:**
   a. Establish standards of confidentiality.
   b. Administer CRAFFT Questionnaire (see Chapter 5).
   c. Evaluate age of onset of use; progression of use for specific substances; circumstances, frequency, and variability of use; types of agents used.
   d. Consider urine/serum toxicology evaluation if there is concern for substance use and patient consents to testing.
4. **Treatment:**
   a. Determine goals and readiness for change; promote behavioral change through motivational interviewing.[27]
   b. Families should be involved in treatment.
   c. Medications can be used to manage withdrawal symptoms and/or cravings.
   d. Treatment of comorbid conditions should occur at the same time.[26]

C. Eating Disorders

1. **Epidemiology:**
   a. Includes anorexia nervosa and bulimia nervosa as well as pica, rumination disorder (repeated regurgitation), avoidant/restrictive food intake disorder, and binge eating disorder.
   b. Twelve-month prevalence of 0.4% (anorexia nervosa) and 1% to 1.5% (bulimia nervosa); 10:1 female-to-male ratio.[5]
   c. Common comorbidities: affective and anxiety disorders.
2. **Diagnosis:**
   a. Anorexia nervosa
      (1) Restricted energy intake and low weight (body mass index [BMI] < 18.5 kg/m^2; severity stratified by BMI)
      (2) Fear of gaining weight
      (3) Disturbance in perception of body weight or shape
   b. Bulimia nervosa
      (1) Recurrent episodes of binge eating that occur at least once a week for 3 months
      (2) Recurrent inappropriate compensatory mechanisms to prevent weight gain (e.g., diuretic or laxative use, exercise) or purging (self-induced vomiting)
      (3) Self-evaluation excessively influenced by body shape or weight[5]
3. **Treatment:**
   a. Aimed at nutritional rehabilitation and therapy (family-based or as a component of day treatment programs). Hospitalization may be needed in cases of medical instability. See Chapter 21 for management of refeeding syndrome.
   b. SSRIs indicated in the treatment of bulimia nervosa (see Table 24.2). No medications have been approved for use in anorexia nervosa.[28]

V. PSYCHIATRIC EMERGENCIES

A. Suicide

1. **Epidemiology[29]:** Suicide is the **second** leading cause of death in children and adolescents.
2. **Screening:**
   a. Primary care setting: risk factor screening[30] (Fig. 24.2).
   b. Emergency department setting: the Ask Suicide-Screening Questions (ASQ) (Box 24.1) is validated for identifying pediatric patients at risk for suicide.
3. **Formal suicide assessment** (see Fig. 24.2)
   a. Any positive reply to a screening question warrants formal evaluation by a psychiatrist or other mental health professional.
   b. Goal is to determine disposition (inpatient versus outpatient) and develop a safety plan with caregivers.

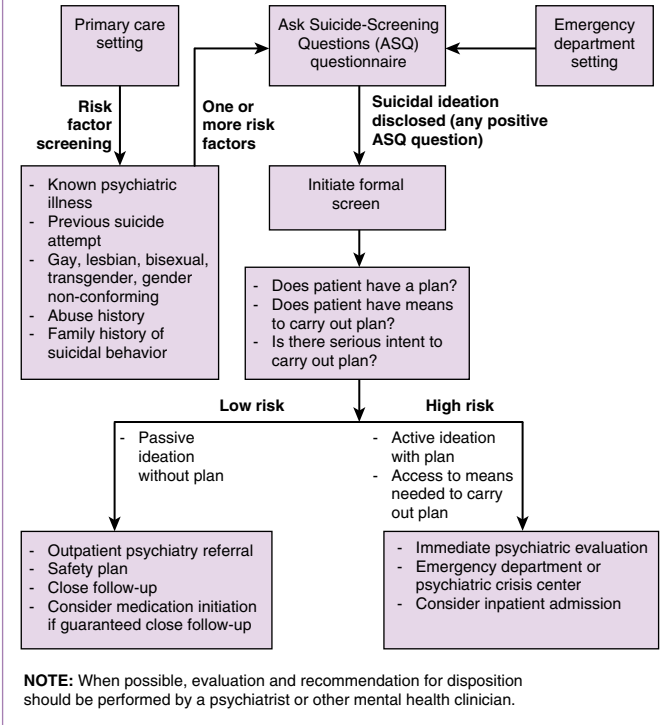

FIGURE 24.2
Suicide screening and assessment.

BOX 24.1

ASK SUICIDE-SCREENING QUESTIONS (ASQ)

Validated for identifying pediatric patients at risk for suicide.

1. In the past few weeks, have you wished you were dead?
2. In the past few weeks, have you felt that you or your family would be better off if you were dead?
3. In the past week, have you been having thoughts about killing yourself?
4. Have you ever tried to kill yourself?

Note: Any affirmative response constitutes a positive screen.

Adapted from the Ask Suicide-Screen Questions (ASQ) Toolkit. National Institute of Mental Health, National Institutes of Health. Available from: http://www.nimh.nih.gov/labs-at-nimh/asq-toolkit-materials/index.shtml

B. Agitation[31,32]

1. **Definition:**
   a. Agitation can be defined as disruptive behavior occurring during periods of emotional distress.
   b. Manifestations include
      (1) Excessive motor activity: pacing, fidgeting
      (2) Verbal aggression: yelling, shouting, rapid uninterruptable speech, threats
      (3) Physical aggression: hitting, throwing things
   c. Agitation frequently occurs as a manifestation of psychiatric illness, but it can also present in behaviorally disordered youth or as a result of organic neurologic disease.
   d. Agitation is a multifactorial symptom. Risk factors for agitation include history of aggression, history of physical abuse, past psychiatric hospitalizations, traumatic brain injury, autism spectrum disorder, delirium, and substance use.
2. **Management** (Fig. 24.3):
   Determine the etiology of agitation:
   a. Review vital signs, presenting history, past diagnoses, past episodes of agitation.
   b. Attempt to rule out underlying medical cause (e.g., ingestion, traumatic brain injury).
3. **Treatment**
   a. Nonpharmacologic
      (1) Low-stimulation environment (e.g., dim lights, move child away from busy areas, avoid unnecessary interventions).
      (2) Communicate in a calm, neutral, empathetic tone at eye level using simple language.
      (3) Utilize distraction techniques and Child Life services if available.
   b. Pharmacologic: therapy choice should target the etiology of agitation (see Fig. 24.3).
   c. Restraints and seclusion: reserved for cases where both nonpharmacologic and pharmacologic interventions fail. Regulations and requirements for use vary by state.
      (1) Close monitoring required.
      (2) Frequent reassessment of necessity of restraints.

VI. WEB RESOURCES

- ADHD Medication Guide: www.adhdmedicationguide.com
- Physicians Med Guide: parentsmedguide.org/physiciansmedguide.htm
- Substance Abuse and Mental Health Services Administration: www.samhsa.gov

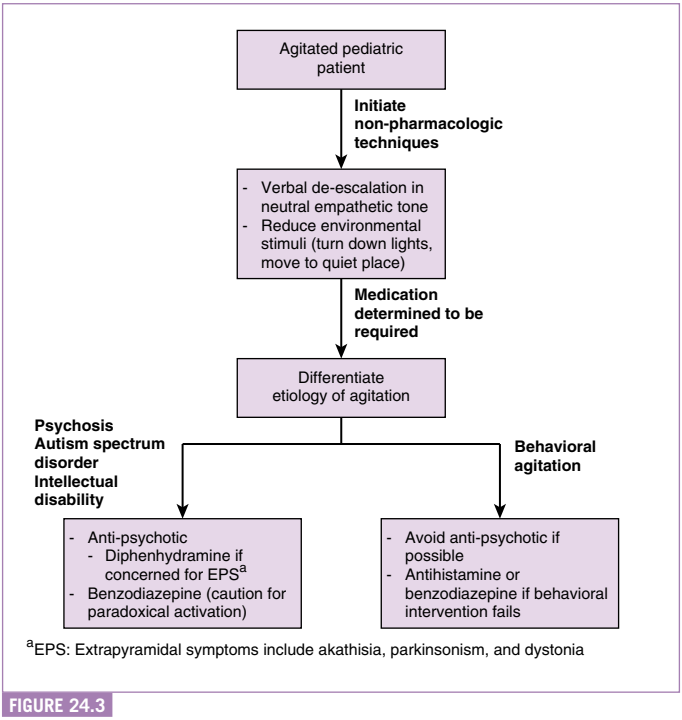

FIGURE 24.3
Agitation management algorithm.

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Chapter 25

Pulmonology and Sleep Medicine

Stephanie Tung, MD, MSc

See additional content on Expert Consult

I. EVALUATION OF PULMONARY GAS EXCHANGE

A. Pulse Oximetry[1-3]

1. Noninvasive and indirect measurement of arterial O_2 saturation (SaO_2) estimated by light absorption characteristics of oxygenated and deoxygenated hemoglobin in peripheral blood.
2. Limitations:
   a. Measures oxygen saturation, not O_2 delivery to tissues.
   b. Insensitive to hyperoxia. See Fig. EC 25.A for oxyhemoglobin dissociation curve.
   c. Artificially increased by carboxyhemoglobin levels >1% to 2%.
   d. Artificially decreased by intravenous dyes, opaque nail polish, and methemoglobin levels >1%.
   e. Unreliable when pulse signal is poor due to hypothermia, hypovolemia, shock, edema, and movement artifact.

B. Capnography[4,5]

1. Measures CO_2 concentration of expired gas by infrared or mass spectroscopy.
2. End-tidal CO_2 ($ETCO_2$) correlates with $PaCO_2$ (usually within 5 mmHg in healthy subjects).
3. Used to evaluate proper placement of an endotracheal tube, to monitor ventilation in mechanically ventilated patients, to assess effectiveness of cardiopulmonary resuscitation (CPR), and during polysomnography.

C. Blood Gases[6-8]

1. Arterial blood gas (ABG): Most accurate way to assess oxygenation (PaO_2), ventilation ($PaCO_2$), and acid-base status (pH and HCO_3^-). See Chapter 28 for normal mean values.
2. Venous blood gas (VBG): $PvCO_2$ averages 6 to 8 mmHg higher than $PaCO_2$; venous pH is slightly lower than arterial pH.
3. Capillary blood gas (CBG): Correlation with ABG is generally best for pH, moderate for PCO_2, and worst for PO_2.

D. Analysis of Acid-Base Disturbances[9-11]

The first step is to determine the primary disturbance (metabolic versus respiratory); the second step is to assess for a mixed disorder by calculating expected compensatory response. See Chapter 11 for details.

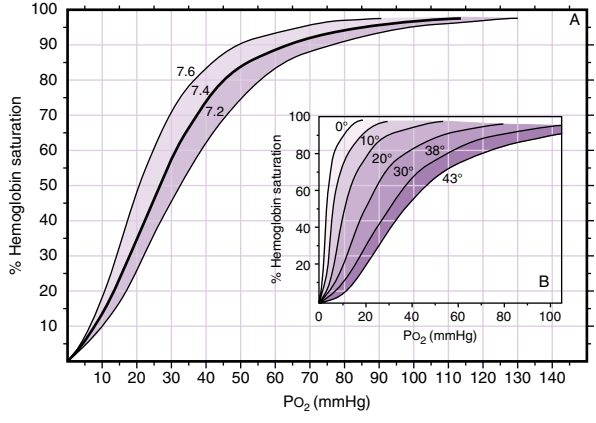


FIG. EC 25.A

Oxyhemoglobin dissociation curve. (A) Curve shifts to the left as pH increases. (B) Curve shifts to the left as temperature decreases. (Modified from Boron, WF. Transport of oxygen and carbon dioxide by the blood. Chapter 29, 647–659.e1. *Medical Physiology*. 4th edition; 2016.)

TABLE 25.1

PREDICTED AVERAGE PEAK EXPIRATORY FLOW RATES FOR NORMAL CHILDREN

Height, Inches (cm)	PEFR, L/min	Height, Inches (cm)	PEFR, L/min
43 (109)	147	56 (142)	320
44 (112)	160	57 (145)	334
45 (114)	173	58 (147)	347
46 (117)	187	59 (150)	360
47 (119)	200	60 (152)	373
48 (122)	214	61 (155)	387
49 (124)	227	62 (157)	400
50 (127)	240	63 (160)	413
51 (130)	254	64 (163)	427
52 (132)	267	65 (165)	440
53 (135)	280	66 (168)	454
54 (137)	293	67 (170)	467
55 (140)	307		

PEFR, Peak expiratory flow rate

Data from Voter KZ. Diagnostic tests of lung function. *Pediatr Rev.* 1996;17:53–63.

II. PULMONARY FUNCTION TESTS (PFT)

Provide objective and reproducible measurements of airway function and lung volumes. Used to characterize disease, assess severity, and follow response to therapy.

A. Peak Expiratory Flow Rate (PEFR)[12,13]

Maximal flow rate generated during a forced expiratory maneuver.

1. Used to follow the course of asthma and response to therapy by comparing current PEFR with the previous "personal best" and the normal predicted value.
2. Limitations: Normal values vary across racial groups, measurement is effort dependent, cannot be used reliably in many young children.
3. Normal predicted PEFR values for children are shown in Table 25.1.

B. Maximal Inspiratory and Expiratory Pressures[14,15]

Maximal pressure generated during inhalation and exhalation against a fixed obstruction. Used as a measure of respiratory muscle strength.

1. Maximal inspiratory pressure (MIP) is in the range of 80 to 120 cm H_2O at all ages. A low MIP may be an indication for ventilatory support.
2. Maximum expiratory pressure (MEP) increases with age and is greater in males. A low MEP correlates with decreased effectiveness of coughing.

C. Spirometry (for Children 6 Years of Age or Above)[16,17]

Plot of airflow versus time during rapid, forceful, complete expiration from total lung capacity (TLC) to residual volume (RV) is useful to characterize different patterns of airway obstruction (Fig. 25.1). Usually performed before and after bronchodilation to assess response to therapy or after bronchial challenge to assess airway hyperreactivity.

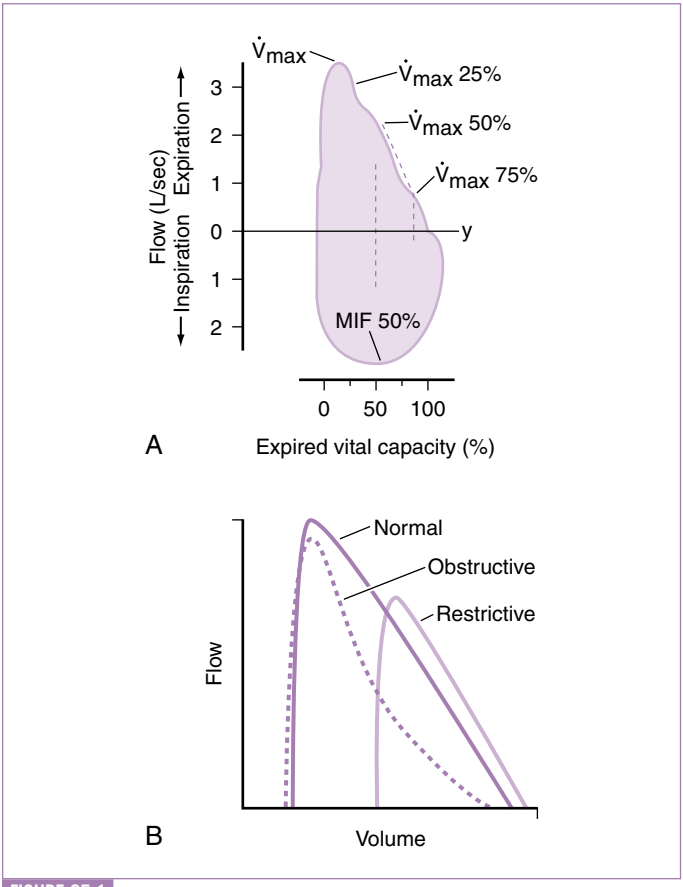


FIGURE 25.1

(A) Normal flow-volume curve. (B) Obstructive pattern seen in asthma or cystic fibrosis; restrictive pattern seen in interstitial lung disease. (B, Data from Baum GL, Wolinsky E. *Textbook of Pulmonary Diseases*. 5th ed. Boston: Little, Brown; 1994.)

1. Important definitions (Fig. 25.2)
   a. Forced vital capacity (FVC): maximal volume of air exhaled from the lungs after a maximal inspiration.
   b. Forced expiratory volume in 1 second (FEV_1): volume exhaled during the first second of the FVC maneuver.
2. Interpretation of spirometry and lung volume readings is shown in Table 25.2.

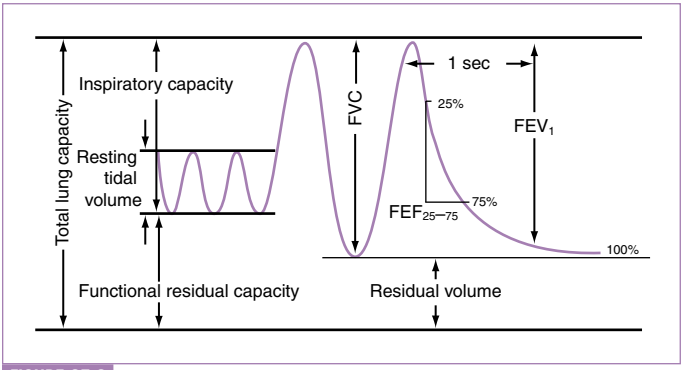


FIGURE 25.2

Lung volumes. $FEF_{25–75}$, Forced expiratory flow between 25% and 75% of FVC; FEV_1, forced expiratory volume in 1 second; *FVC*, forced vital capacity.

TABLE 25.2

INTERPRETATION OF SPIROMETRY AND LUNG VOLUME READINGS

	Obstructive Disease (Asthma, Cystic Fibrosis)	Restrictive Disease (Interstitial Fibrosis, Scoliosis, Neuromuscular Disease)
SPIROMETRY		
FVC[a]	Normal or reduced	Reduced
FEV_1[a]	Reduced	Reduced[b]
FEV_1/FVC[c]	Reduced	Normal
$FEF_{25–75}$	Reduced	Normal or reduced[b]
PEFR[a]	Normal or reduced	Normal or reduced[b]
LUNG VOLUMES		
TLC[a]	Normal or increased	Reduced
RV[a]	Increased	Reduced
RV/TLC[d]	Increased	Unchanged
FRC	Increased	Reduced

[a]Normal range: ±20% of predicted.
[b]Reduced proportional to FVC.
[c]Normal range: >85%.
[d]Normal range: 20 ± 10%.
$FEF_{25–75}$, Forced expiratory flow between 25% and 75% of FVC; FEV_1, forced expiratory volume in 1 second; *FRC*, functional residual capacity; *FVC*, forced vital capacity; *PEFR*, peak expiratory flow rate; *RV*, residual volume; *TLC*, total lung capacity.

III. ASTHMA[12,18]

A. Definition

A chronic inflammatory disorder of the airways resulting in reversible airway obstruction. It manifests as recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early

morning. The inflammation causes increased airway hyperreactivity to a variety of stimuli: viral infections, cold air, exercise, emotions, environmental allergens, and pollutants.

B. Clinical Presentation

1. Cough, increased work of breathing (tachypnea, retractions, accessory muscle use), wheezing, hypoxia, and hypoventilation. Crackles may also be present with asthma exacerbations.
2. No audible wheezing may indicate very poor air movement and severe bronchospasm.
3. Radiographic findings: peribronchial thickening, hyperinflation, patchy atelectasis.

C. Treatment

1. See Chapter 1 for acute management of status asthmaticus.
2. Initial classification and initiation of treatment for ages 0 to 4, 5 to 11, and 12 years and above (Figs. 25.3–25.5).
3. Stepwise approach to continued management for ages 0 to 4, 5 to 11, and 12 years and above (Figs. 25.6–25.8)
4. Additional management guidelines available from the Global Initiative for Asthma.[21]

D. Prevention of Exacerbations

1. Ensure up-to-date immunizations, including influenza.
2. Create an asthma action plan.
3. Identify and minimize asthma triggers and environmental exposures.
4. Assess symptom control, inhaler technique, and medication adherence with regular clinical evaluations.
5. Consider specialist referral for formal PFTs, monitoring, and allergy testing.
6. See Table EC 25.A for dosing guidelines for inhaled corticosteroids.

IV. BRONCHIOLITIS[19-23]

A. Definition

1. Lower respiratory tract infection common in infants and children aged 2 years and younger.
2. Characterized by acute inflammation, edema, and necrosis of airway epithelium, leading to increased mucus production and bronchospasm.
3. Most commonly caused by respiratory syncytial virus (RSV), but can also be seen with other viruses including parainfluenza virus, adenovirus, mycoplasma, and human metapneumovirus.

B. Clinical Presentation

1. Rhinitis and cough, which may progress to tachypnea, wheezing, rales, use of accessory muscles, and/or nasal flaring. Transient apnea may also be seen.
2. Radiographic findings: hyperinflation and atelectasis.
3. Radiographs and viral testing should NOT be routinely obtained.

CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of severity		Classification of asthma severity (0–4 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2×/month	3–4×/month	>1×/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. Exacerbations of any severity may occur in patients in any severity category.			
Recommended step for initiating therapy (See Fig. 25.6 for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

Key: EIB, exercise-induced bronchospasm

Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 25.3

Guidelines for classifying asthma severity and initiating treatment in infants and young children (aged 0 to 4 years). (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma*. August 2007.)

CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 5–11 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of severity		Classification of asthma severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2×/month	3–4×/month	>1×/week but not nightly	Often 7×/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60%–80% predicted • FEV_1/FVC = 75%–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		Consider severity and interval since last exacerbation. ← Frequency and severity may fluctuate over time → for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended step for initiating therapy (See Fig. 25.7 for treatment steps.)		Step 1	Step 2	Step 3, medium-dose ICS option	Step 3, medium-dose ICS option, or step 4
				and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 25.4

Guidelines for classifying asthma severity and initiating treatment in children 5 to 11 years of age. (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma.* August 2007.)

CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

Components of severity		Classification of asthma severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2×/month	3–4×/month	>1×/week but not nightly	Often 7×/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1 time on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		Consider severity and interval since last exacerbation. ← Frequency and severity may fluctuate over time → for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1			
Recommended step for initiating treatment (See Fig. 25.8 for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

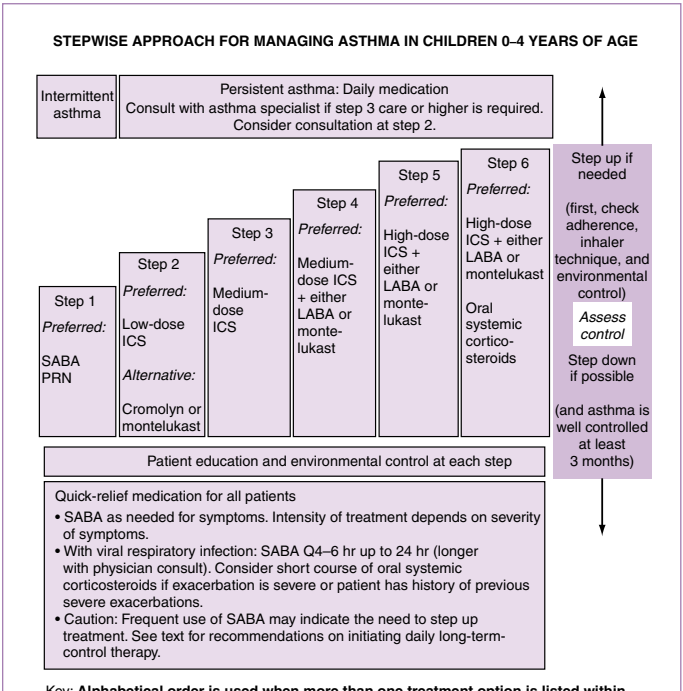
Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 25.5

Guidelines for classifying asthma severity and initiating treatment in youths 12 years of age and older. (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma*. August 2007.)



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy**. ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist; PRN, as needed; SABA, short-acting inhaled β_2-agonist

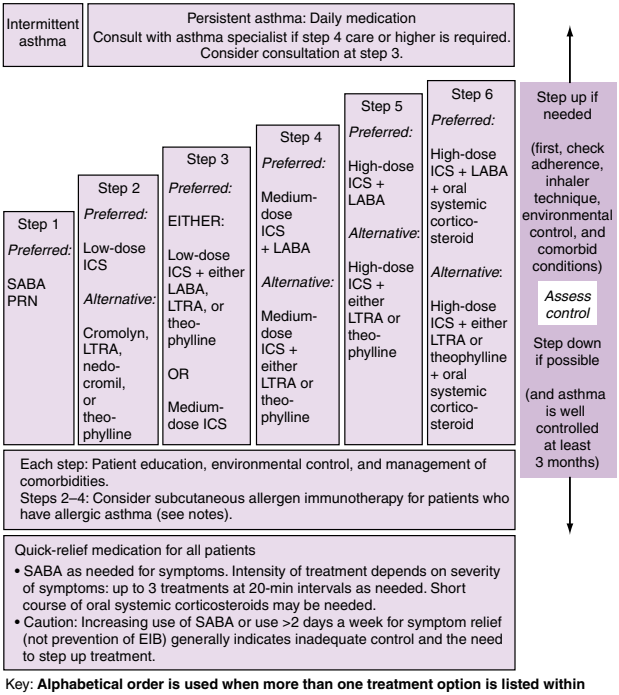
Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

FIGURE 25.6

Stepwise approach for managing asthma in infants and young children (aged 0 to 4 years). (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma*. August 2007.)

STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE



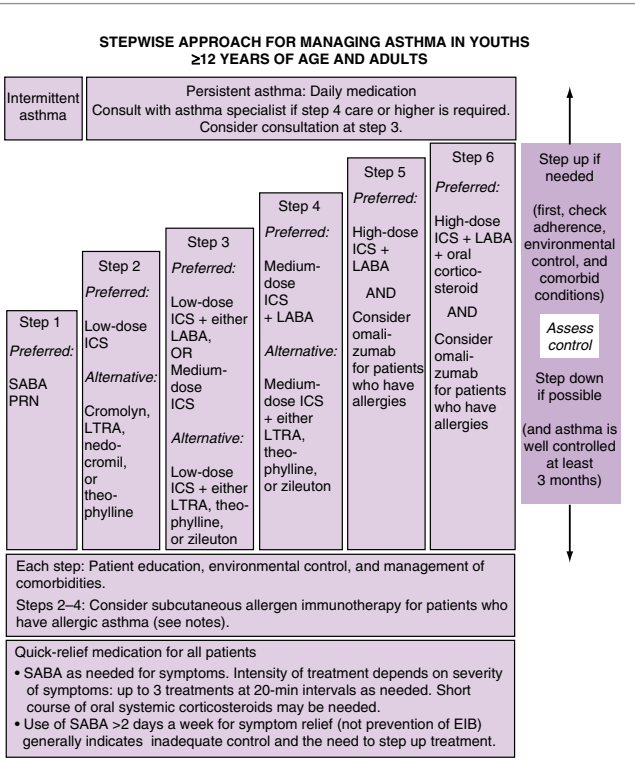
Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy**. ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist; LTRA, leukotriene receptor antagonist; PRN, as needed; SABA, short-acting inhaled β_2-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 25.7

Stepwise approach for managing asthma in children 5 to 11 years of age. (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma.* August 2007.)



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist; LTRA, leukotriene receptor antagonist; PRN, as needed; SABA, short-acting inhaled β_2-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less-desirable alternative as adjunctive therapy due to limited studies and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on Expert Panel Report 2 (1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

FIGURE 25.8

Stepwise approach for managing asthma in youths 12 years of age and older. (Adapted from National Asthma Education and Prevention Program (NAEPP)—Expert Panel Report 3. *Guidelines for the Diagnosis and Management of Asthma.* August 2007.)

TABLE EC 25.A

ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS

ICS	Strength	<12 Years Old			≥12 Years Old		
		Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
Beclomethasone/ QVar MDI	40 mCg	2–4 puffs/day	5–8 puffs/day	>8 puffs/day	2–6 puffs/day	7–12 puffs/day	>12 puffs/day
	80 mCg	1–2 puffs/day	3–4 puffs/day	>4 puffs/day	1–3 puffs/day	3–6 puffs/day	>6 puffs/day
Budesonide/ Pulmicort DPI Flexhaler	90 mCg	2–4 puffs/day	4–8 puffs/day	>8 puffs/day	2–6 puffs/day	7–12 puffs/day	>12 puffs/day
	180 mCg	1–2 puffs/day	2–4 puffs/day	>4 puffs/day	1–3 puffs/day	4–6 puffs/day	>6 puffs/day
Ciclesonide	80 mCg	*See Formulary remarks for ciclesonide*			1 puff BID	2 puffs BID	4 puffs BID
	160 mCg	*See Formulary remarks for ciclesonide*			N/A	1 puff BID	2 puffs BID
Budesonide/ Pulmicort Respule	0.25 mg neb	2 nebs/day	4 nebs/day	8 nebs/day	N/A	N/A	N/A
	0.5 mg neb	1 neb/day	2 nebs/day	4 nebs/day	N/A	N/A	N/A
Flunisolide/Aerospan MDI	80 mCg	2 puffs/day	4 puffs/day	>8 puffs/day	4 puffs/day	5–8 puffs/day	>8 puffs/day
	250 mCg	2–3 puffs/day	4–5 puffs/day	>5 puffs/day	2–4 puffs/day	5–8 puffs/day	>8 puffs/day
Fluticasone/Flovent MDI	44 mCg	2–4 puffs/day	5–8 puffs/day	>8 puffs/day	2–6 puffs/day	7–10 puffs/day	>10 puffs/day
	110 mCg	1 puff/day	2–3 puffs/day	>3 puffs/day	1–2 puffs/day	3–4 puffs/day	>4 puffs/day
	220 mCg	N/A	1 puff/day	>1 puff/day	1 puff/day	2 puffs/day	>2 puffs/day
Fluticasone/Flovent Diskus DPI	50 mCg	2–4 puffs/day	5–8 puffs/day	>8 puffs/day	2–6 puffs/day	7–10 puffs/day	>10 puffs/day
	100 mCg	1–2 puffs/day	2–4 puffs/day	>4 puffs/day	1–3 puffs/day	4–5 puffs/day	>5 puffs/day
	250 mCg	N/A	1 puff/day	>1 puff/day	1 puff/day	2 puffs/day	>2 puffs/day
Mometasone/ Asmanex Twisthaler	220 mCg	N/A	N/A	N/A	1 puff	2 puffs	>2 puffs

TABLE EC 25.A

ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS—cont'd

ICS	Strength	<12 Years Old			≥12 Years Old		
		Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
COMBINATION DRUGS: ICS + LABA[a]							
Fluticasone/ Salmeterol MDI (Advair)	45/21 mCg	2 puffs/day	2–3 puffs/day	4 puffs/day	2 puffs/day	3–4 puffs/day	
	115/21 mCg		2 puffs/day	2–4 puffs/day	2 puffs/day	2 puffs/day	3–4 puffs/day
	230/21 mCg			2–4 puffs/day			3–4 puffs/day
Fluticasone/ Salmeterol Diskus DPI (Advair)	100/50 mCg	1 puff/day	2 puffs/day	2 puffs/day		2 puffs/day	
	250/50 mCg			2 puffs/day		1 puff/day	2 puffs/day
	500/50 mCg			2 puffs/day			2 puffs/day
Budesonide/ Formoterol MDI (Symbicort)	80/4.5 mCg	1–2 puffs/day	2–4 puffs/day		1–3 puffs/day	4 puffs/day	
	160/4.5 mCg		1–2 puffs/day	2–4 puffs/day		2 puffs/day	4 puffs/day
Mometasone/ Formoterol (Dulera)	100/5 mCg	*No dosing information currently available for patients above 12 years of age*			N/A	2 puffs BID	N/A
	200/5 mCg	*No dosing information currently available for patients below 12 years of age*			N/A	N/A	2 puffs BID

[a]For ICS + LABA combination drugs, patient should not take more than two puffs per dose of the MDI, one puff per dose of the DPI, or two doses per day.

DPI, dry powder inhaler; *ICS*, inhaled corticosteroid; *LABA*, long-acting β agonist; *MDI*, metered-dose inhaler

Data from Expert Panel Report III. *Guidelines for the Diagnosis and Management of Asthma—Full Report 2007*; National Institutes of Health Pub. No. 08-4051. Bethesda, MD: National Asthma Education and Prevention Program; 2007.

C. Treatment

Mainstay is supportive care.

1. Assess risk factors for severe disease, such as age less than 12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency.
2. Clinicians should NOT administer albuterol, epinephrine, systemic corticosteroids, or chest physiotherapy to previously healthy infants and children with a diagnosis of bronchiolitis. Antibiotics should be administered only for concomitant bacterial infection.
3. Nebulized hypertonic saline may be administered to hospitalized infants and children, although evidence of effectiveness is mixed.[20-22]
4. Evidence supporting continuous pulse oximetry and supplemental O_2 when SpO_2 is greater than 90% is currently lacking.
5. Nasogastric or intravenous fluid is necessary when infant is unable to maintain oral hydration.
6. High-flow nasal cannula supports breathing in infants requiring supplemental oxygen and may decrease the rate of escalation of care.[23]
7. RSV immunoprophylaxis with palivizumab for high-risk infants (see Chapter 16).

V. BRONCHOPULMONARY DYSPLASIA (BPD)[24-27]

A. Definition

1. Also known as chronic lung disease of prematurity or chronic lung disease of infancy.
2. Chronic pulmonary condition that usually evolves after premature birth, characterized by a need for oxygen supplementation >21% for at least 28 days after birth.
3. Thought to be a result of airway inflammation, damage from hyperoxia, hypoxia, or mechanical ventilation; results in interference with normal lung alveolar, airway, and vascular development.
4. Earlier gestational age in preterm infants is associated with a higher likelihood of BPD development.

B. Clinical Presentation

Children with BPD may have persistent respiratory symptoms, airway hyperreactivity, and supplemental oxygen requirements, especially during intercurrent illness.

C. Diagnosis

Severity based on oxygen requirement at time of assessment and characterized as mild if on room air, moderate if requiring <30% oxygen or severe if requiring >30% oxygen and/or positive pressure.

1. If gestational age at birth was <32 weeks, assess infant at 36 weeks' postmenstrual age or at discharge to home, whichever comes first.
2. If gestational age at birth >32 weeks, assess infant at 28 to 56 days postnatal age or at discharge to home, whichever comes first.

D. Treatment

1. Children with BPD often require some combination of the following for their lung disease:
   a. Bronchodilators
   b. Antiinflammatory agents (corticosteroids)
   c. Supplemental oxygen therapy
   d. Diuretics
   e. Tracheostomy and prolonged mechanical ventilation for severe cases
   f. RSV prophylaxis if indicated (see Chapter 16)
2. Children with BPD need close monitoring for complications, which can affect additional organ systems and processes, including pulmonary or systemic hypertension, electrolyte abnormalities, nephrocalcinosis (from chronic diuretics), neurodevelopmental or growth delay, aspiration from dysphagia and/or gastroesophageal reflux (GER), and more severe infections with RSV or influenza.

VI. CYSTIC FIBROSIS[28-37]

A. Definition

Autosomal recessive disorder in which mutations of the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene reduce the function of a chloride channel that usually resides on the surface of epithelial cells in the airways, pancreatic ducts, biliary tree, intestine, vas deferens, and sweat glands, resulting in progressive obstructive pulmonary disease and pancreatic exocrine insufficiency.

B. Clinical Manifestations (Fig. 25.9)

C. Diagnosis

Diagnosing CF is a multistep process (Fig. 25.10); a complete evaluation involves the following:

1. Newborn screening (NBS): utilizes blood immunoreactive trypsinogen (IRT) level and/or *CFTR* gene mutation analysis.
2. Quantitative pilocarpine iontophoresis (sweat chloride) test: gold standard for diagnosis. False-positive results can be seen in untreated adrenal insufficiency, glycogen storage disease type 1, fucosidosis, hypothyroidism, nephrogenic diabetes insipidus, ectodermal dysplasia, malnutrition, mucopolysaccharidosis, and panhypopituitarism.
3. Genetic analysis: over 2000 *CFTR* mutations have been described; the most common is F508del.

D. Treatment

Patients with CF should be managed within a CF Foundation accredited care center.

1. **Pulmonary**
   a. Airway clearance therapy to mobilize airway secretions and facilitate expectoration. Often manual/mechanical percussion and postural drainage is used. Older children may use high-frequency vest therapy, mechanical chest percussors, or oscillatory positive expiratory pressure (PEP) handheld devices.

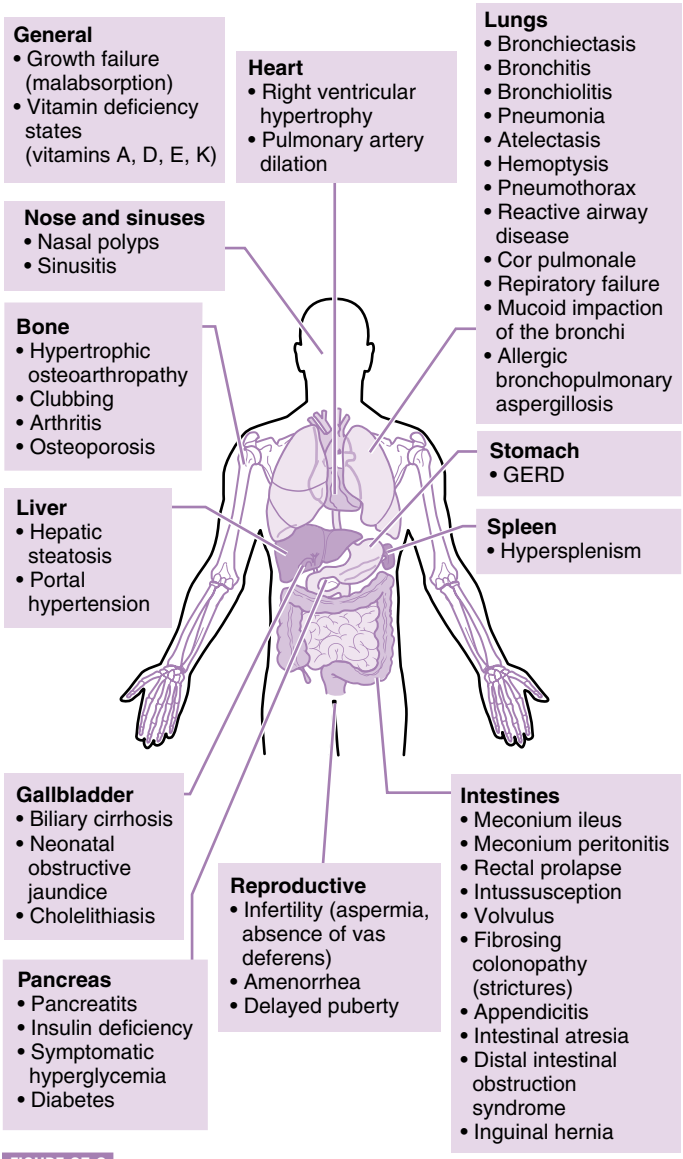


FIGURE 25.9

Clinical manifestations of cystic fibrosis. (Adapted from Kliegman R., Kliegman RM. *Nelson Essentials of Pediatrics.* St. Louis: Elsevier Saunders; 2019.)

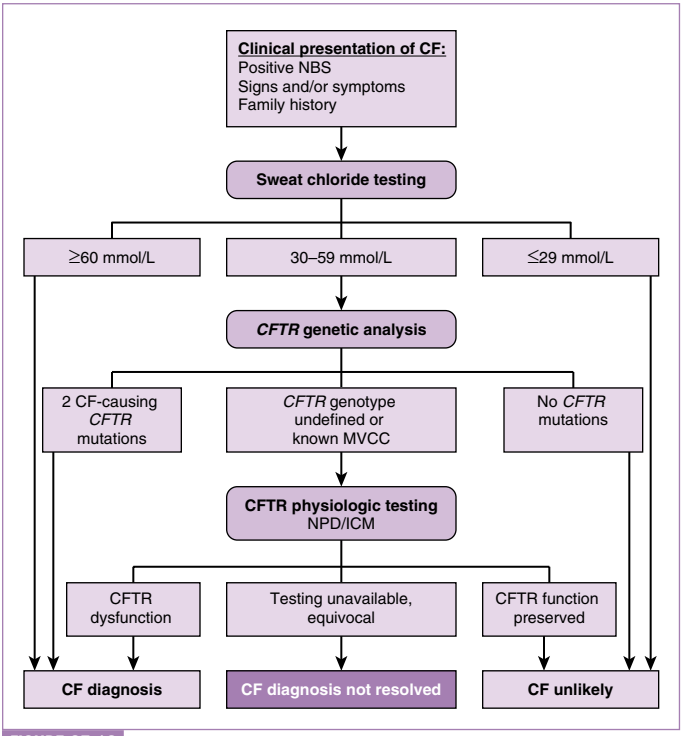


FIGURE 25.10

Diagnosis of cystic fibrosis. *CF,* Cystic fibrosis; *CFTR,* cystic fibrosis transmembrane conductance regulator; *ICM,* intestinal current measurement; *MVCC,* mutation of varying clinical consequence; *NBS,* newborn screen; *NPD,* nasal potential difference (Adapted from Farrell DW, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr.* 2017;181S:S4–S15.e1. https://doi.org/10.1016/j.jpeds.2016.09.064, Figure 1.)

b. Aerosolized medications to enhance mucociliary clearance: Recombinant human DNAase (dornase alfa) and aerosolized hypertonic saline to hydrate airway mucus and stimulate cough.
c. Chronic antibiotics. If *Pseudomonas aeruginosa* is persistently present in airway cultures, chronic aerosolized antibiotic and/or oral macrolide therapy may be considered.
d. Intermittent use of intravenous antibiotics when patient is hospitalized for exacerbations. Common bacteria that cause exacerbations include *P. aeruginosa* and *Staphylococcus aureus.* There is no current consensus regarding antibiotic choice, dosing, or duration.

e. *CFTR* modulator therapy may be effective for patients with specific mutations (G551D, F508del/F508del). Can be used in combination. See Formulary for dosing.
f. Allergic bronchopulmonary aspergillosis (ABPA) treatment may include oral corticosteroids; antifungal therapy can be a helpful adjunct therapy.
g. Lung transplantation.

2. **Extrapulmonary**
   a. Pancreatic and liver disease
      (1) Pancreatic enzyme replacement therapy prior to meals to improve digestion and intestinal absorption of dietary protein and fat.
      (2) Fat-soluble vitamin A, D, E, and K supplementation.
      (3) Nutritional supplementation to maintain body mass index (BMI) at or above the 50th percentile.
      (4) Monitoring for CF-related diabetes or liver disease.
   b. Infertility
      (1) Men have absence of the vas deferens; however, assisted fertilization is possible using aspiration of viable sperm from testes.
      (2) Women who are healthy have relatively normal fertility.
   c. Decreased life expectancy. Survival continues to improve, and median predicted survival age is more than 47 years.[37]

VII. OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS)[38-42]

A. Definition

Disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns.

B. Clinical Presentation

1. Habitual snoring sometimes accompanied by snorts, gasps, or intermittent pauses in breathing. Increased respiratory effort during sleep.
2. Disturbed or restless sleep with increased arousals and awakenings.
3. Daytime cognitive and/or behavioral problems. Young children rarely present with daytime sleepiness.
4. Long-term complications: neurocognitive impairment, behavioral problems, poor growth, cardiac dysfunction, systemic and pulmonary hypertension.
5. Risk factors: adenotonsillar hypertrophy, obesity, family history of OSAS, craniofacial or laryngeal anomalies, prematurity, nasal/pharyngeal inflammation, cerebral palsy, and neuromuscular disease.

C. Diagnosis

1. All children and adolescents should be routinely screened for snoring.
2. If a child snores on a regular basis and has any of the complaints or findings shown in Box 25.1, clinicians should obtain a polysomnogram or, if polysomnography is not available, refer the patient to a sleep specialist or otolaryngologist for more extensive evaluation.

BOX 25.1

SYMPTOMS AND SIGNS OF OBSTRUCTIVE SLEEP APNEA SYNDROME

I. History

- Frequent snoring (≥3 nights a week)
- Labored breathing during sleep
- Gasping/snorting noises or observed episodes of apnea
- Sleep enuresis (especially secondary enuresis)
- Sleeping in a seated position or with the neck hyperextended
- Cyanosis
- Headache on awakening
- Daytime sleepiness
- Attention-deficit/hyperactivity disorder
- Learning problems

II. Physical examination

- Underweight or overweight
- Tonsillar hypertrophy
- Adenoidal facies
- Micrognathia/retrognathia
- High-arched palate
- Failure to thrive
- Hypertension

Adapted from Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012;130:575–584.

3. Polysomnogrpaphy criteria for OSAS diagnosis (one of the following):
   a. One or more obstructive or mixed apnea or hypopnea events per hour (AHI ≥1).
   b. $PaCO_2$ >50 mmHg for >25% of sleep time coupled with snoring, paradoxical thoracoabdominal movement, or flattening of nasal airway pressure waveform implying flow limitation.
4. No standard severity classification. Commonly used: mild (1< AHI ≤5), moderate (5< AHI ≤10), and severe (AHI >10).

D. Treatment

1. Weight loss for patients who are overweight or obese.
2. Intranasal corticosteroids may be considered for children with mild OSAS.[38] Follow-up is needed to assess symptoms and monitor possible adverse effects of long-term intranasal steroids. Oral leukotriene inhibitor (e.g., montelukast) can also be considered.
3. Adenotonsillectomy is recommended as first-line treatment of patients with OSAS documented with an overnight polysomnogram.[42] Patients should be reevaluated postoperatively to determine whether further treatment is required.
   a. Risk factors for postoperative respiratory complications: age <3 years, severe OSAS on polysomnography (AHI ≥10, lowest oxygen

saturation <80%, and/or significant hypercapnia), cardiac complications of OSAS, failure to thrive, obesity, craniofacial anomalies, neuromuscular disorders, current respiratory infection.
   b. High-risk children warrant a more comprehensive evaluation and postoperative admission for monitoring.
4. Continuous positive airway pressure is recommended as treatment if adenotonsillectomy is not performed or if OSAS persists postoperatively.
5. Craniofacial surgery and tracheostomy are reserved for severe cases in children with syndromic craniofacial abnormalities.

VIII. INFANT AND CHILD SLEEP[43-46]

A. Sleep Duration

1. Recommended average sleep duration varies by age (Table 25.3).
2. Sleep concerns are common in childhood. Inadequate or poor-quality sleep can have negative impacts on health, behavior, and learning.
3. See Section XI for a discussion of common childhood sleep disorders.

TABLE 25.3

RECOMMENDED AVERAGE SLEEP DURATION

Age Group	Duration of Sleep (per 24 hr)
Infants (4–12 months)	12–16 hr[a]
Toddlers (1–2 years)	11–14 hr[a]
Preschool-age children (3–5 years)	10–13 hr[a]
School-age children (6–12 years)	9–12 hr
Teenagers (13–18 years)	8–10 hr

[a]Recommended sleep duration in 24-hour period includes naps. Adapted from Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2016;12(6):785–786.

B. Sleep-Related Infant Death

1. **Definition**
   a. Sleep-related infant death: sudden unexplained infant death occurring during an observed or unobserved sleep period.
   b. Sudden infant death syndrome (SIDS): cause assigned to infant death that cannot be explained after thorough case investigation.
2. **Epidemiology**
   a. Approximately 40 per 100,000 live births in 2013, more than double in African American and Native American populations.
   b. Peak incidence is at 1 to 4 months, with 90% occurring before 6 months.

3. **Safe Infant Sleep**

Evidence-based safe infant sleep recommendations to reduce the risk of sleep-related infant death from the 2016 AAP guidelines include the following[46]:

a. Back to sleep during every episode of sleep.
b. Using a firm sleep surface without soft objects or loose bedding.
c. Room sharing with the infant on a separate surface, ideally for the first year of life, but at least for the first 6 months.
d. Avoidance of overheating and head covering.
e. Avoidance of alcohol, illicit drugs, and smoke exposure during pregnancy and after birth.
f. Protective factors that should be recommended: Regular prenatal care, breastfeeding, routine immunizations.
g. Modeling of safe sleep by healthcare providers/staff, day care providers, and in advertising.

IX. BRIEF RESOLVED UNEXPLAINED EVENT (BRUE)[47,48]

A. Definition

Formerly termed an *apparent life-threatening event* (ALTE), a BRUE is defined as an event involving an infant below 1 year of age when the observer reports a sudden, brief (typically 20 to 30 seconds) and now resolved episode of at least one of the following:

1. Cyanosis or pallor
2. Absent, decreased, or irregular breathing
3. Marked change in muscle tone (hyper- or hypotonia)
4. Altered level of responsiveness

B. Differential Diagnosis

The three most common differential diagnoses are GER, seizure, and lower respiratory tract infection. If an explanation for the event is identified, then it is not a BRUE.

C. Management

An algorithm for the diagnosis, risk stratification, and management of BRUE patients is provided in Fig. 25.11.

X. WEB RESOURCES

- American Lung Association: www.lung.org
- Cystic Fibrosis Foundation: www.cff.org
- American Academy of Allergy, Asthma and Immunology: www.aaaai.org
- National Heart Lung and Blood Institute: www.nhlbi.nih.gov
- American Thoracic Society: www.thoracic.org
- American Academy of Sleep Medicine: www.aasm.org

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

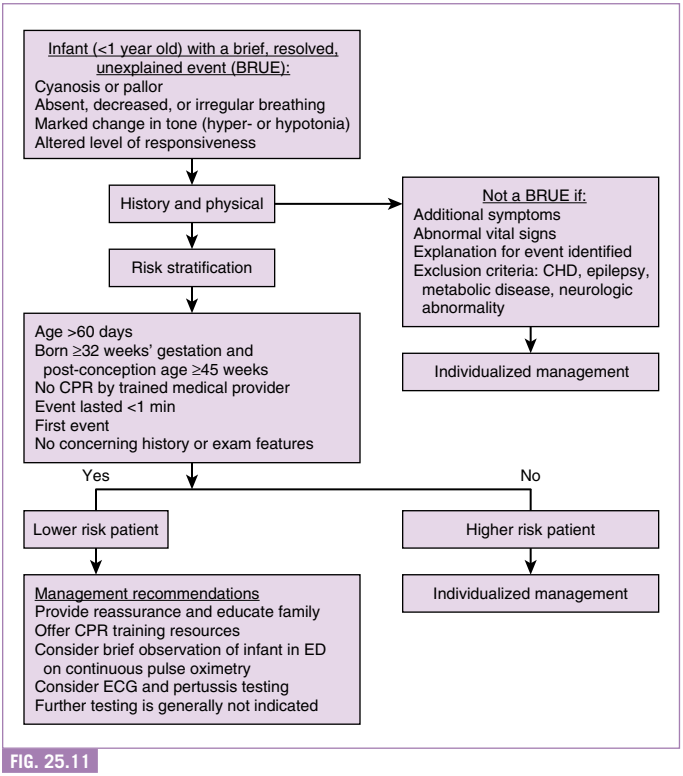


FIG. 25.11

Algorithm for diagnosis, risk stratification, and management of BRUE. *CHD,* Congenital heart disease; *CPR,* cardiopulmonary resuscitation; *ECG,* electrocardiogram; *ED,* emergency department (Adapted from *AAP Clinical Practice Guideline: Brief Resolved Unexplained Events (Formerly Apparent Life-Threatening Events) and Evaluation of Lower-Risk Infants*. May 2016.)

XI. ONLINE CONTENT

A. Evaluation of Pulmonary Gas Exchange

Oxyhemoglobin dissociation curve (see Fig. EC 25.A)

B. Asthma

Dosing of inhaled corticosteroids (see Table EC 25.A)

C. Childhood Sleep Disorders[44,45]

1. **Insomnia**
   a. Difficulty falling asleep, staying asleep, or both.
   b. In younger children, the common behavioral insomnias of childhood include limit-setting (bedtime resistance) and sleep-onset association disorder (night wakings). Treatment includes bedtime limits and appropriate sleep hygiene.
   c. In older children, psychosocial or primary insomnia is characterized by excessive worry about sleep and the consequences of inadequate sleep. Managed with behavioral interventions.
   d. Insomnia can be secondary to another sleep or medical disorder. A comprehensive evaluation is required. Referral to a sleep specialist or behavioral psychologist may be useful.
2. **Nighttime fears**
   a. Common condition that is part of normal development and stems from cognitive development.
   b. Characterized by tearful, fearful behavior at bedtime.
   c. Relieved by sleeping with member of household.
   d. Treatment involves reassurance, teaching coping skills, and use of security objects. Consider evaluation for anxiety disorder in older children/adolescents.
3. **Nightmares**
   a. Frightening dreams that result in awakening from sleep.
   b. Part of normal development.
   c. Peak at age 6 to 10 years.
   d. May be reduced by reducing stressors, avoiding exposure to frightening images, and ensuring adequate sleep.
4. **Delayed sleep phase syndrome**
   a. A circadian rhythm with a persistent, intractable shift in the sleep-wake cycle. Patients move to a late bedtime and late awakening.
   b. Seen most commonly in adolescent and young adults.
   c. Patients have daytime sleepiness and tardiness/absenteeism when unable to sleep during the day.
   d. Treatment includes behavioral therapy, bright light exposure, and melatonin. Consider evaluation by a sleep specialist.
5. **Parasomnias**
   a. Common and benign disorders of arousal.
   b. Includes sleepwalking, night terrors, and confusional arousals.
   c. Onset typically at age 4 to 6 years and usually disappear by adolescence.

d. Characterized by agitation and confusion. Child avoids comfort and does not recall event.
e. Usually occur in the first few hours of the night.
f. Treatment involves keeping child safe, ensuring adequate sleep, and avoiding triggers. Discourage parental intervention during an episode.

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Chapter 26

Radiology

Brittany Hunter, MD

See additional content on Expert Consult

I. GENERAL PEDIATRIC PRINCIPLES

A. Limit Radiation Exposure

1. Children are at increased radiation risk given their greater lifetime exposure, relatively small size, increased radiosensitivity, and longer lives during which to manifest side effects.[1]
2. Use evidence-based imaging guidelines to guide appropriate imaging choice and minimize radiation exposure.[1]
3. See Table 26.1 for relative radiation by imaging study.

B. Use Imaging Judiciously

1. Minimize use of ionizing radiation when possible.
2. Limit imaging to indicated areas to improve resolution and minimize radiation exposure.
3. Provide adequate clinical background when ordering imaging studies to assist radiologist.

II. CHOOSING THE RIGHT STUDY

1. See Table 26.2 for descriptions of imaging modalities.
2. Computed tomography (CT) versus magnetic resonance imaging (MRI): CT is often more readily available, can be performed quickly, and does not require sedation; however, CT raises safety concerns regarding radiation exposure. MRI uses nonionizing radiation and may require sedation.[1]
3. Contrast: Helps distinguish selected body areas from surrounding tissue. Oral and rectal contrast is used for bowel opacification. Intravenous is used to opacify vascular structures and solid organs.

III. HEAD

Head ultrasound (HUS) can be used for infants with open anterior fontanelles. **CT** is preferred for acute situations (e.g., trauma, hemorrhage) and for evaluating bone structure or calcifications. **MRI** offers better soft-tissue contrast and visualization of brain anatomy and is, therefore, preferred for most nontraumatic intracranial pathology. **MRI fast sequences** (such as ultrafast [UF] MRI) uses specialized sequencing to assess ventricular size and shunt position without requiring sedation. Does not allow for adequate delineation and diagnosis of other brain pathology.[1]

TABLE 26.1

COMPARATIVE RADIATION EXPOSURE

Radiation Source	mSv[17]	Equivalent Chest X-rays	Equivalent Flight Hours[18]	Equivalent Background Radiation
CXR (single view)	0.01	1	3	1 day
Abdominal XR (2 views)	0.05	5	17	5 days
Chest CT	3	300	1000	12 months
Head CT	2	200	670	8 months
Abdominal CT	5	500	1670	20 months
Upper GI series	3	300	1000	12 months
Contrast enema	4.5	450	1500	18 months

CT, Computed tomography; *CXR*, chest x-ray; *GI*, gastrointestinal.

A. Head Trauma

1. **Preferred imaging**: Noncontrast head CT. Use the Pediatric Emergency Care Applied Research Network (PECARN) rules to decide whether imaging is indicated (see Chapter 2).[2,3]

B. CSF Shunt Malfunction

1. **Preferred imaging:** Ultrafast brain MRI (UF MRI).
2. **Other imaging:** CT if UF MRI is not available or contraindicated. Shunt series (plain radiographs evaluating shunt tubing) are useful.

C. Orbital Cellulitis

1. **Preferred imaging**: Orbital contrast-enhanced CT (Fig. EC 26.A).[4]

IV. NECK AND AIRWAY

Conventional radiography (CR) anteroposterior (AP) and lateral neck views are preferred initial imaging.[5,6]

A. Normal Anatomy

1. Normal anatomy (Figs. 26.1 and 26.2).
2. Reading lateral C-spine films.
   a. Must visualize skull base, C1 to C7, top of T1.
   b. Assess alignment by evaluating four curvilinear contour lines: anterior vertebral, posterior vertebral, spinolaminar, tips of spinous process (Fig. 26.3).
   c. Evaluate vertebral bodies for fractures, displacement, subluxation, dislocations. Vertebral bodies should be same height and uniformity below C2.
   d. Evaluate predental and prevertebral spaces for widening.

B. Cervical Spine Trauma

1. **Initial imaging:** CR, lateral and AP.
2. **Other imaging:** MRI if high clinical suspicion of C-spine injury without CR findings.

TABLE 26.2

OVERVIEW OF IMAGING MODALITIES

Modality/Description	Ionizing Radiation	Advantages	Disadvantages/ Limitations	Relative Cost
Conventional radiographs (CR) Uses x-rays to create 2D images based on density	Yes	Fast, portable, readily available	2D only, poor soft-tissue contrast	+
Ultrasound (US) Uses high-frequency sound waves to produce image, can evaluate blood flow with Doppler or contrast	No	Portable, real-time imaging, multiplanar	Operator dependent, limited in obese patients, poor penetration of air-filled viscera and bone, may require preparation (e.g., fasting or full bladder), may be invasive (e.g., transvaginal)	++
Computed tomography (CT) Uses multiple x-rays to produce cross-sectional image, delineates bones, soft tissue, calcifications	Yes	Fast, cross sectional, more detailed than CR	Intermediate to high radiation dose, potential side effects from intravenous contrast if used (anaphylaxis, nephrotoxicity)	+++
Magnetic resonance imaging (MRI) Uses magnetic fields and radio waves to show detailed cross-sectional images	No	High resolution of soft tissue, multiplanar	Lengthy, slight movements can ruin image, may require sedation, contraindicated for certain implantable devices	++++
Fluoroscopy Uses x-rays and contrast to evaluate dynamic processes	Yes	Real-time imaging	Invasive, requires contrast, high radiation dose	++
Nuclear medicine (commonly PET, Meckel scan, SPECT) Uses radioactive tracer to delineate patterns of concentration or elimination of tracer, can be superimposed with MRI or CT	Yes	Functional	Intermediate to high radiation dose, may require sedation	++++

2D, two dimensional; *PET*, positron emission tomography; *SPECT*, single photon emission computed tomography

Modified from Zitelli and Davis' *Atlas of Pediatric Physical Diagnosis*. 7th ed. Philadelphia: Saunders; 2018.

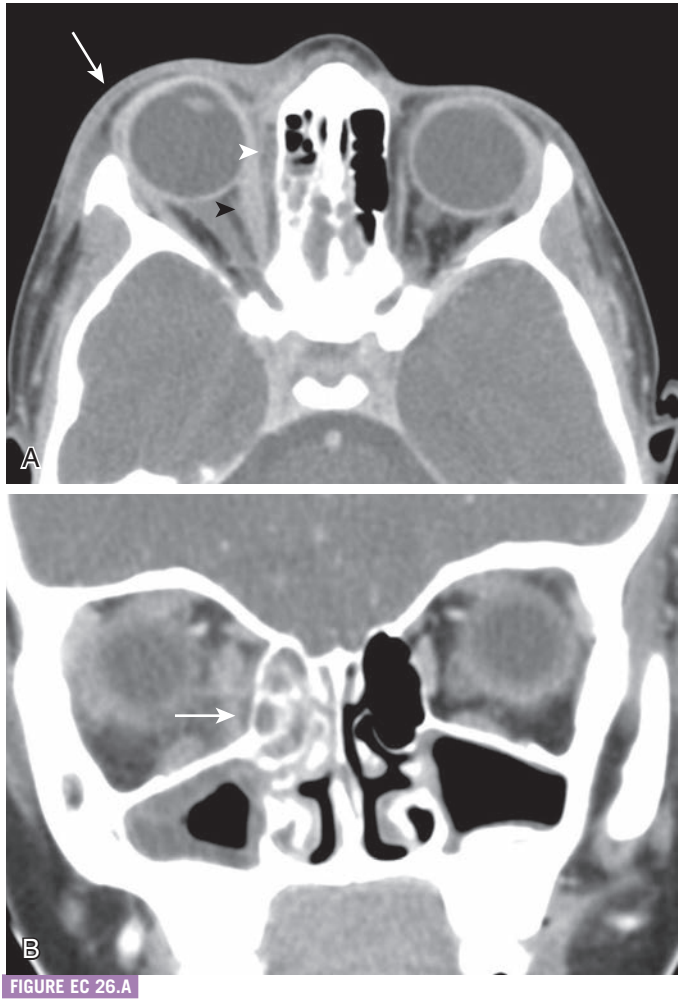


FIGURE EC 26.A

Preseptal and postseptal cellulitis. (A) Axial contrast-enhanced computed tomography (CT) of orbits shows asymmetric thickening of the right preseptal soft tissues *(arrow)*. There is also involvement of the medial extraconal postseptal soft tissues *(white arrowhead)*. The medial rectus muscle is enlarged *(black arrowhead)* due to reactive myositis. Note partial ethmoid sinus opacification. (B) Coronal contrast-enhanced CT of a different patient also showing right medial postseptal cellulitis with a small subperiosteal collection representing an early abscess *(arrow)*. Note again ethmoid sinusitis as the cause of orbital cellulitis. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 308, Fig. 8.95.)

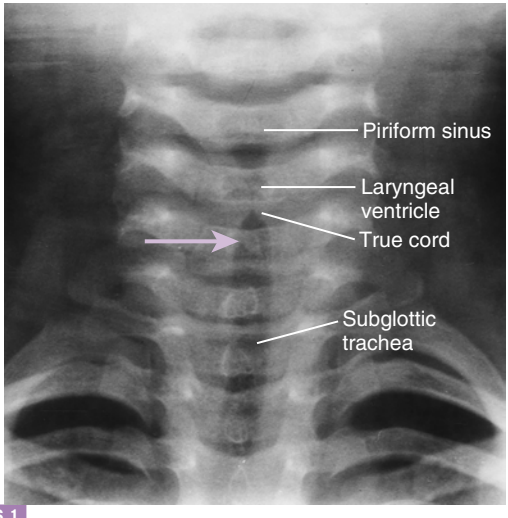


FIGURE 26.1
Anteroposterior neck film with normal anatomy. Note subglottic airway demonstrates rounded shoulders *(arrow)* that are convex outward. (Figure modified from Blickman JG, Van Die L. *Pediatric Radiology: The Requisites*. 3rd ed. Philadelphia: Elsevier; 2009, Fig. 2.17B.)

C. Classic Findings of Upper Airway Conditions on Conventional Radiographs

1. Croup: AP and lateral radiographs with subglottic narrowing (*steeple sign)* (Fig. EC 26.B).
2. Epiglottitis: Enlarged, indistinct epiglottis on lateral film (*thumbprint sign*).
3. Retropharyngeal abscess or pharyngeal mass: Soft-tissue air or enlargement of prevertebral soft tissues (Fig. EC 26.C).

D. Foreign Body

1. **Preferred imaging**: CR, AP and lateral of neck and chest. Obtain both expiratory and inspiratory films. Bilateral decubitus for younger children who cannot hold breath on command.[7]
2. **Findings**: Radiopaque foreign bodies visualized. *Indirect Signs*: hyperinflation of affected lung, atelectasis/consolidation distal to obstruction.[7]

E. Tracheoesophageal Fistula and Esophageal Atresia

1. **Initial imaging**: CR; upper GI (UGI) rarely needed.
2. **Findings**: Distended air-filled pharyngeal pouch indicates esophageal atresia (EA). Presence of distal bowel gas indicates concurrent distal TEF.[8]

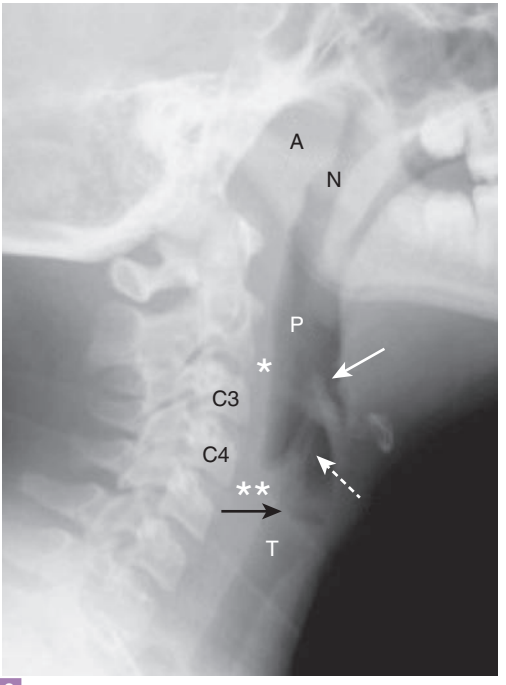


FIGURE 26.2

Normal soft tissue lateral neck radiograph. The adenoids *(A)* are seen at the base of the skull and are adjacent to the nasopharyngeal airway *(N)*. More distally is the pharynx *(P)*. The epiglottis *(solid white arrow)* is bounded superiorly by air in the vallecula. The aryepiglottic folds are thin, paired structures *(dotted white arrow)*. The normal-sized laryngeal ventricle *(black arrow)* separates the false vocal cords above from the true cords below. The trachea *(T)* starts below the true cords. The retropharyngeal soft tissue *(asterisks)* is less than one-half the width of the adjacent vertebral body above *C3/C4 (*)* and less than the width of the adjacent vertebral body below C3/C4 *(**)*. (Modified from Herring, W. *Learning Radiology: Recognizing the Basics*. 3rd ed. Philadelphia: Elsevier; 2016, Fig. 28.12.)

F. Vascular Rings and Pulmonary Slings

1. **Preferred imaging**: Contrast-enhanced CT angiography (CTA) or MR angiography (MRA).
2. **Other imaging:** Echocardiography (ECHO) in neonates and infants may be able to directly visualize vascular ring.[9] Neck and chest CR may show displacement or compression of tracheal air column. Barium swallow or UGI show extrinsic compression of esophagus.[7]

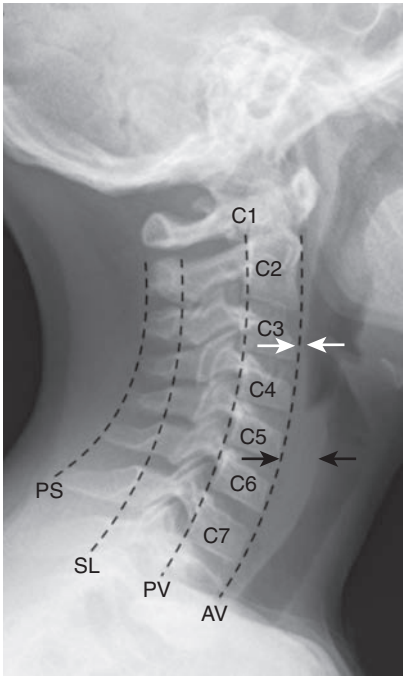


FIGURE 26.3
Normal lateral cervical spine radiograph. Four curvilinear lines can be used to help evaluate alignment: anterior vertebral line *(AV)*, posterior vertebral line *(PV)*, spinolaminar line *(SL)*, posterior spinous line *(PS)*. The retropharyngeal space should be less than one-half the width of the adjacent vertebral body above *C3/C4 (white arrows)* and the width of the adjacent vertebral body below C3/C4 *(black arrows)*.

V. CHEST

CR used for initial imaging. **CT** useful for evaluating lung parenchyma, pleura, and osseous thorax; important for identifying oncologic disease.[1,6] **US** can evaluate pleura, peripheral lung disease, and diaphragmatic motion.[6]

A. Normal Anatomy (Fig. 26.4 and Fig. EC 26.D)

B. Pulmonary Infections

1. **Preferred imaging**: CR, PA and lateral when possible.
2. **Other imaging**: CT with IV contrast for suspected complications including abscess, empyema, lung necrosis, or recurrent infection. US for parapneumonic effusions, empyema, and evaluating feasibility of percutaneous drainage.[6,9]

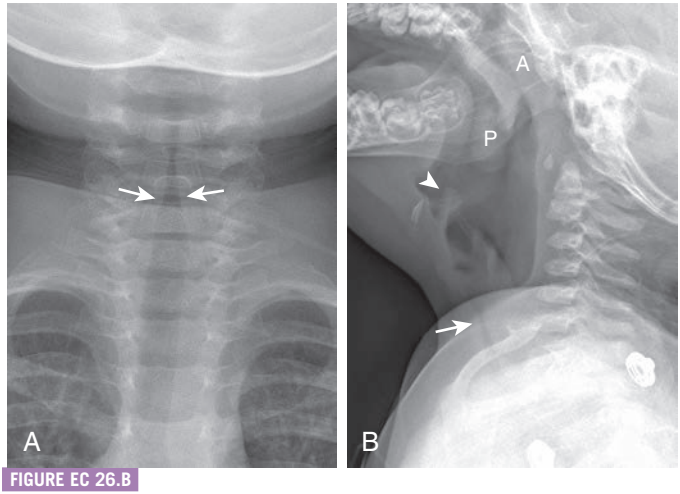


FIGURE EC 26.B

Croup. (A) Frontal radiograph showing symmetric subglottic narrowing *(arrows)* with loss of normal shouldering, "steeple sign." (B) Lateral radiograph showing subglottic narrowing *(arrow)*. Note normal-appearing epiglottis *(arrowhead)* and thin aryepiglottic folds. Also note mildly enlarged adenoid *(A)* and palatine *(P)* tonsils. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 2, Fig. 2.1.)

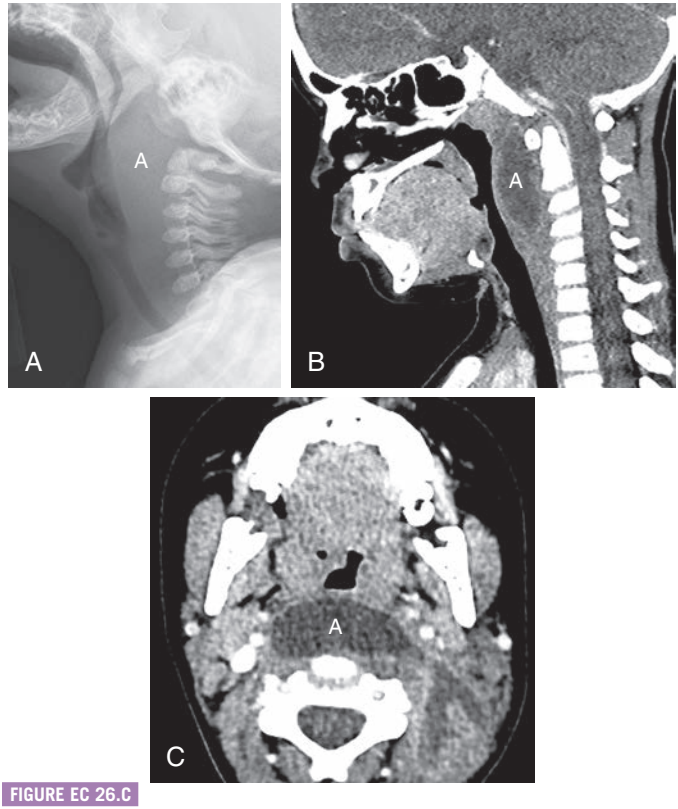


FIGURE EC 26.C

Retropharyngeal abscess. (A) Lateral radiograph showing marked thickening of the retropharyngeal soft tissues (A), which are wider than the adjacent vertebral bodies. Note the anterior convexity of soft tissues. (B and C) Contrast-enhanced computed tomography in sagittal and axial planes shows a low-attenuation region with enhancing rim (A), suggestive of a drainable abscess. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 12, Fig. 2.7.)

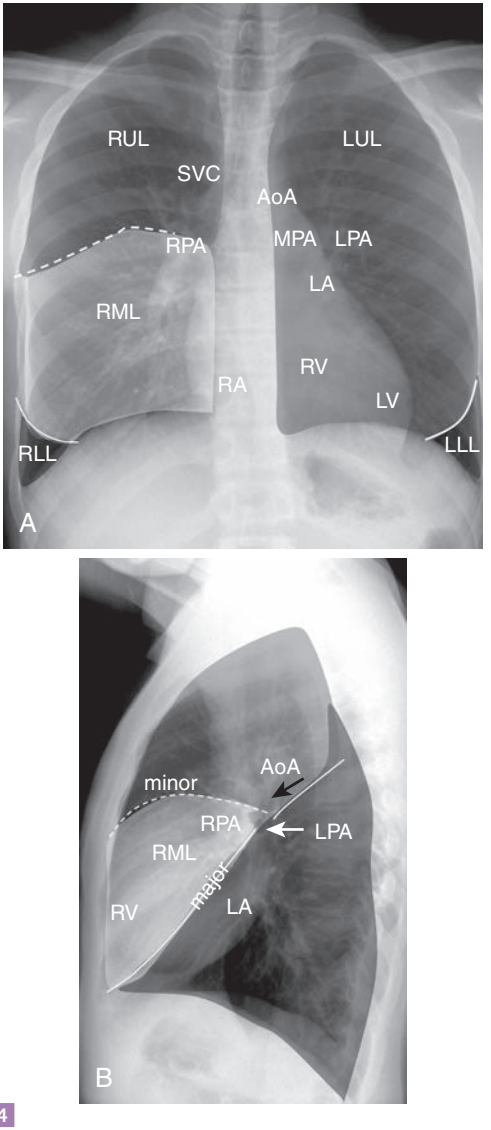


FIGURE 26.4

Normal lung and cardiac anatomy as seen on anteroposterior (A) and lateral (B) chest radiograph. *AoA*, Aortic arch; *RPA*, right pulmonary artery; *LPA*, left pulmonary artery; *RA*, right atrium; *RV*, right ventricle; *LA*, left atrium; *LV*, left ventricle; *black arrow*, posterior wall of bronchus intermedius; *white arrow*, left upper lobe airway; *RUL*, right upper lobe, *RML*, right middle lobe; *RLL*, right lower lobe; *LUL*, left upper lobe; *LLL*, left lower lobe

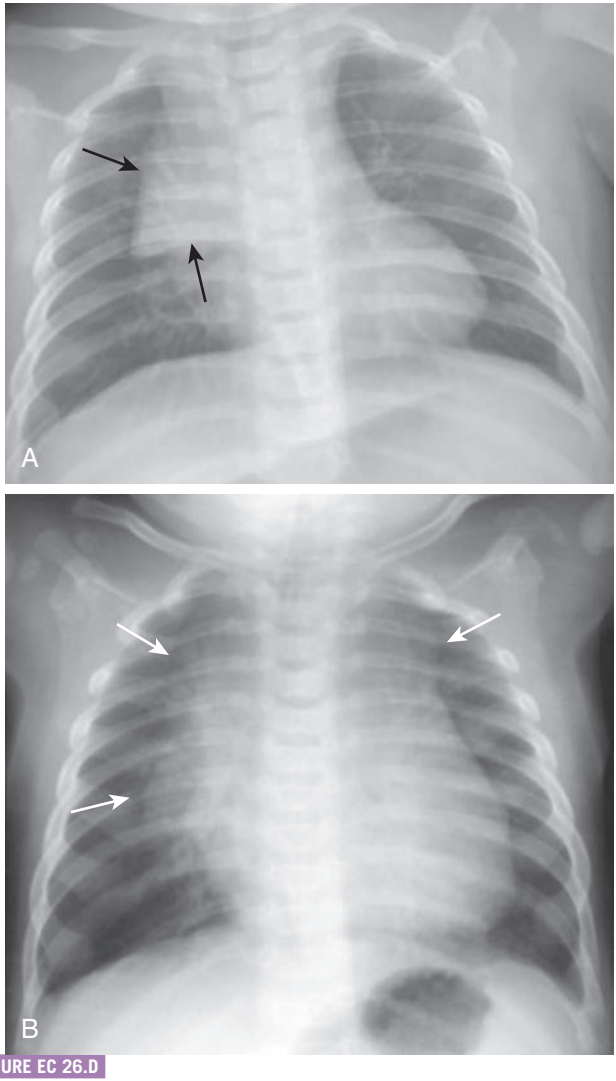


FIGURE EC 26.D

Normal thymus. (A) Radiograph shows prominent but normal thymus with rightward triangular extension, "sail sign" *(black arrows).* (B) One aid in identifying the thymus gland is that it is frequently lobulated in appearance *(white arrows).* Although the thymus gland will usually involute with age, it may still be normally visible in children as old as 3 years of age on conventional radiographs. (A from Herring, W. *Learning Radiology: Recognizing the Basics*. 3rd ed. Philadelphia: Elsevier; 2016, Fig. 28.19, B from Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 58, Fig. 3.44.)

2. Viral Infections
   a. **Nonspecific chest x-ray (CXR) findings** (often overlaps with bacterial infections): Bilateral interstitial opacities, peribronchial thickening (cuffing), hyperinflation, subsegmental atelectasis (Fig. EC 26.E).[9]
3. Bacterial Pneumonia
   a. **CXR findings**: Alveolar consolidation, air bronchograms (Fig. EC 26.F).[9,10]
   b. Localizing pneumonia on CXR:
      (1) *Silhouette sign*: Loss of normal borders between thoracic structures of same density; used to localize lung pathology (Table 26.3).[10]
      (2) *Spine sign*: Vertebral bodies of thoracic spine become less opaque (blacker) as moving inferiorly toward diaphragm. Soft tissue or fluid density involving posterior lower lobe adds density causing spine to become more opaque (whiter) above diaphragm.[1,10]
   c. Patterns of pneumonia
      Certain radiographic patterns are highly suggestive of particular microorganisms but impossible to identify with certainty (Table EC 26.A).[10]

C. Neonatal Lung Disease

1. Respiratory distress syndrome (or hyaline membrane disease): Hypoinflation, symmetrical hazy reticulogranular opacities, prominent air bronchograms, poor definition of pulmonary vessels.[6-8]
2. Transient tachypnea of the newborn (TTN): Interstitial edema, small pleural effusions, increased vascular markings, mildly enlarged cardiothymic silhouette, hyperinflation.[6,7]
3. Meconium aspiration syndrome: Bilateral, asymmetric areas of hyperinflation and atelectasis; asymmetric perihilar opacities, which can be associated with pneumothorax, pneumomediastinum, or pleural effusions.[7,8]
4. Neonatal pneumonia: Bilateral, patchy interstitial opacities, hyperinflation.[7]

D. Mediastinal Masses

1. **Preferred imaging**: CR followed by contrast-enhanced CT.
2. **Findings**: Middle mediastinal masses silhouetting the heart border and aorta.[1]

VI. HEART (SEE CHAPTER 7)

ECHO is the first-line imaging modality. **Cardiac MR (CMR)** evaluates extracardiac anatomy; gold standard for quantifying ventricular volume, mass, and ejection fraction; creates a three-dimensional reconstructions of complex congenital heart disease (CHD) without radiation. **Cardiac CT** is alternative if CMR is contraindicated (see Fig. 26.4 for normal cardiac findings on CXR).[1,8]

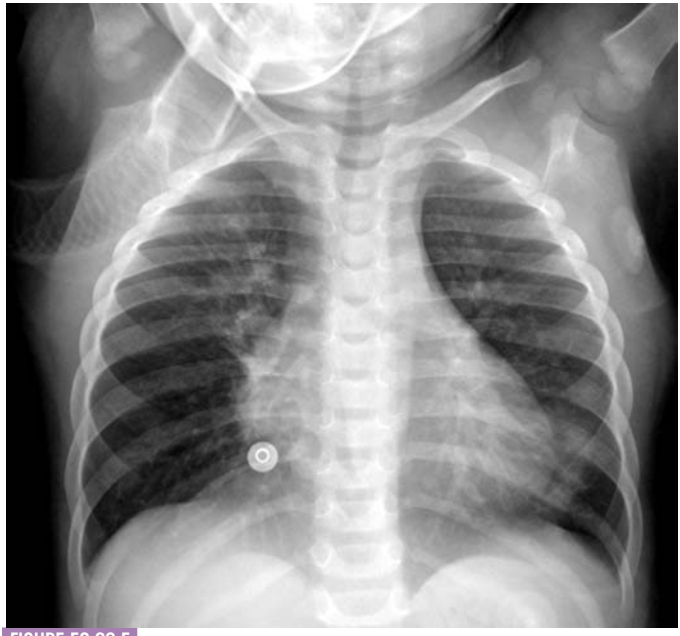


FIGURE EC 26.E

Chest radiograph of a child with viral bronchiolitis. CXR shows hyperinflated lungs with scattered areas of subsegmental atelectasis, most pronounced in the right upper and left lower lungs, as well as thickening of the peribronchial structures.

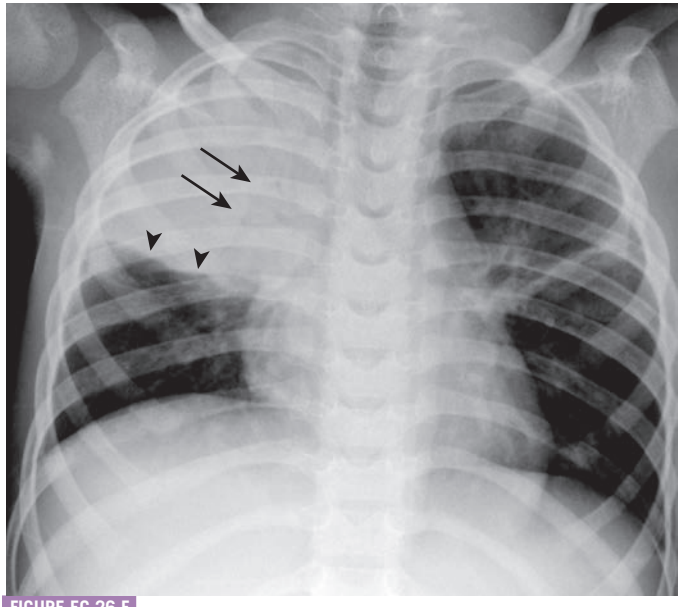


FIGURE EC 26.F

Pneumonia. Chest radiograph shows right upper lobe pneumonia with inferior bulging of the minor fissure (*arrowheads*) and air bronchograms *(arrows)*.

TABLE EC 26.A

PATTERNS OF PNEUMONIA AND ASSOCIATED ORGANISMS

Pattern	Characteristics	Typical Association
Lobar	Homogenous consolidation of a lobe. Normally contains air bronchograms.	*Streptococcus pneumoniae*
Segmental	Patchy appearance, often multifocal. Does not normally contain air bronchograms.	*Staphylococcus aureus*, *Pseudomonas aeruginosa*
Interstitial	Fine reticular pattern spread diffusely through lungs.	*Mycoplasma pneumoniae*, *Pneumocystis jirovecii* (PCP)
Round	Spherically shaped, normally located posteriorly in lower lung lobes. May be confused for a mass.	*Haemophilus influenzae*, *Streptococcus, Pneumococcus*
Cavitary	Lucent cavities (from necrosis) without air fluid levels, often seen in the upper lobe.	*Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*

Modified from Herring W. *Learning Radiology: Recognizing the Basics*. 3rd ed. Philadelphia: Elsevier; 2016, Tables 9.1 and 9.2.

TABLE 26.3

USING THE SILHOUETTE SIGN TO HELP LOCALIZE PNEUMONIA

Silhouetted Structure	Lobe
Ascending aorta	Right upper lobe
Right heart border	Right middle lobe
Right hemidiaphragm	Right lower lobe
Descending aorta	Left upper or lower lobe
Left heart border	Lingula of left upper lobe
Left hemidiaphragm	Left lower lobe

Modified from Herring W. *Learning Radiology: Recognizing the Basics.* 3rd ed. Philadelphia: Elsevier; 2016, Table 9.4.

VII. ABDOMEN

CR used for initial workup; two-view studies (supine and upright) are often preferred. Decubitus and cross-table lateral views can help localize free air, foreign bodies, and enteric tubes; may replace upright view if needed.[7] **US** is the initial modality for abdominal masses, ascites, appendicitis, abscesses, and biliary pathology.[1] **CT** is preferred for trauma and further evaluation.[1] **MRI** is becoming more frequently utilized, including magnetic resonance cholangiopancreatography (**MRCP**) for pancreatitis, biliary pathology, and trauma; and magnetic resonance enterography (**MRE**) in known or suspected inflammatory bowel disease to assess disease activity, extent of bowel involvement, and extraintestinal complications.[1] **Cross-sectional imaging** (US, CT, or MR) is preferred for suspected inflammation, infection, tumors, and lymphadenopathy. **Upper GI (UGI) series** can assess upper GI obstruction in neonates, malrotation, anatomic malformations, and motility problems.[7]

A. Normal Abdominal X-ray and Bowel Gas Pattern

1. Neonatal bowel gas pattern: Gas should be present in stomach by 15 minutes of life, in proximal small bowel by 30 to 60 minutes, in most of small intestine by 6 hours, and in colon by 12 to 24 hours (Fig. 26.5).[6,11] Bowel loop diameter and bowel wall thickness should be uniform.[5]
2. After infancy, pockets of gas should be visualized in small bowel, colon, and rectum.
3. Small bowel seen if contains gas, located centrally, has valvulae (extends across bowel), normal diameter smaller than 3 cm.
4. Large bowel contains gas and stool, located peripherally, has haustra (extends partially across bowel), normal diameter smaller than 5 cm.

B. Pneumoperitoneum (Free Intraperitoneal Air)

1. **Preferred imaging**: CR including upright imaging (cross-table or decubitus lateral if patient unable to stand or sit).
2. **Other imaging:** CT confirms diagnosis, detects small amounts of air not seen on CR.[10]
3. **Findings:** Air under diaphragm
   a. *Continuous diaphragm sign:* Air under entire diaphragm, including underneath heart silhouette

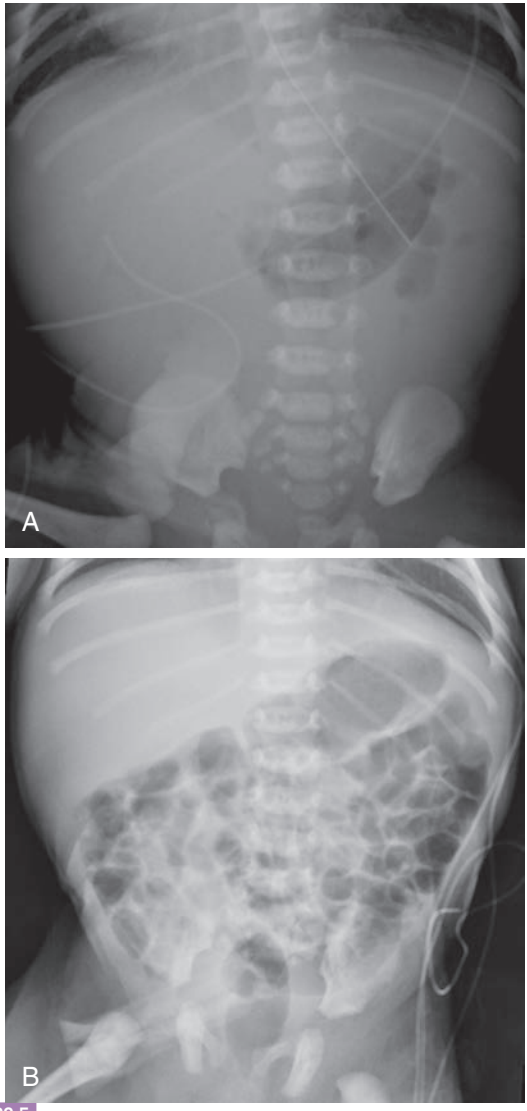


FIGURE 26.5

Normal bowel gas progression in neonates as seen on abdominal radiograph at 2 hours of life (A) and 24 hours of life (B). Note that by 12 hours of life air should have progressed through small bowel and by 24 hours of life (B) air can be visualized in the rectum.

b. *Falciform ligament sign*: Ability to visualize normally invisible falciform ligament as free air surrounds ligament (Fig. EC 26.G)
c. *Football sign*: Oval appearance of abdominal cavity outlined by gas with visualization of falciform ligament, seen in massive pneumoperitoneum (see Fig. EC 26.G)[10]

C. Neonatal Enterocolitis (see Chapter 18)

1. **Initial imaging**: CR, include cross-table lateral or left decubitus views to evaluate for free air.[7]
2. **Other imaging:** Intestinal US if high clinical suspicion for NEC and CR nonspecific or inconclusive, as can depict changes in intra-abdominal fluid, bowel wall thickness, and bowel wall perfusion before findings on CR.[12]
3. **CR findings**: *Nonspecific signs*: Diffuse gaseous distention (most common), loss of normal symmetrical distribution of gas, persistence of single dilated bowel loop (*fixed loop sign*). *Pathognomonic signs*: Pneumatosis intestinalis (intramural gas with "bubbly" appearance commonly in distal small bowel and colon), portal venous gas (branching lucencies seen projecting over liver) (Fig. 26.6).[7]

D. Neonatal Intestinal Obstruction

1. Difficult to distinguish small from large bowel in neonates.[5]
2. **Initial imaging**: CR to decipher high obstruction (stomach to proximal ileum) from low obstruction (distal ileum to colon).
3. **Further imaging:** UGI series or esophagram (obstruction proximal to ligament of Treitz), UGI series with small bowel follow-through (ligament of Treitz to ileocecal junction), contrast enema (distal to ileocecal junction).[5,7,9]
4. High intestinal obstruction
   a. CR findings: Few dilated loops of bowel.
   b. Duodenal atresia: Double bubble on CR (Fig. EC 26.H), reflecting air in dilated stomach and proximal duodenum with absence of air distally. If partial obstruction, UGI series further differentiates duodenal stenosis or web from midgut volvulus.[7]
   c. Malrotation: Malpositioned duodenojejunal junction/ligament of Treitz (normally at level of duodenal bulb and to left of spine). UGI series is the gold standard. US can be used for rapid screening.[5,7]
5. Low intestinal obstruction
   a. CR findings: Multiple dilated loops of bowel; assess further with contrast enema.
   b. Ileal atresia: Contrast enema shows opacification of diffusely small caliber large bowel (microcolon). Contrast refluxes into distal ileum, but unable to reflux further. Bowel proximal to distal ileum is air filled and dilated.
   c. Hirschsprung disease: Contrast enema shows "transition zone" between nondilated aganglionic distal colon and normal, relatively distended, proximal colon.[7]

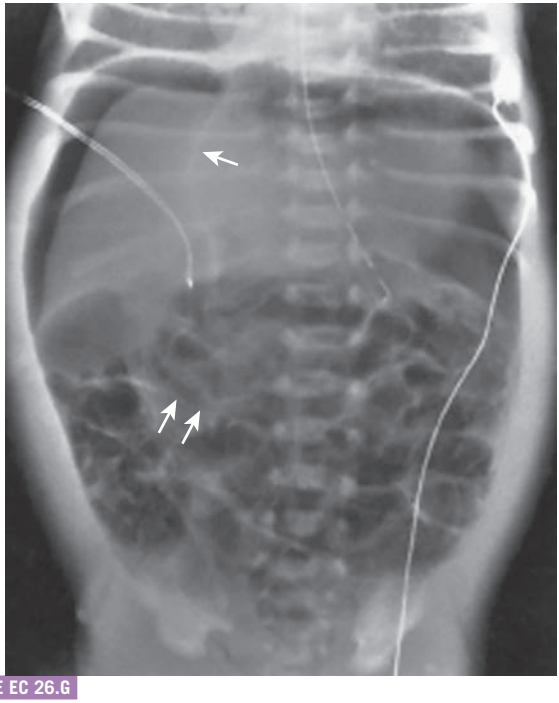


FIGURE EC 26.G

Free intraperitoneal air. An anteroposterior supine abdominal radiograph in a baby with necrotizing enterocolitis and free air demonstrates generalized lucency throughout the abdomen. Note that free air outlines the falciform ligament ("football sign") (*arrow*), and air is seen on both sides of the bowel wall ("Rigler sign") (*double arrows*). (From Walters, MM, Robertson RL. *Pediatric Radiology: The Requisites*. 4th ed. Philadelphia: Elsevier; 2017, p. 93, Fig. 4.4.)

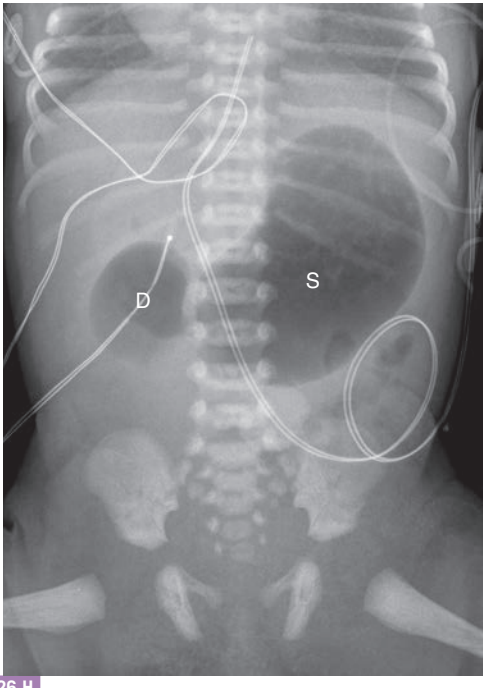


FIGURE EC 26.H

Duodenal atresia in a newborn infant. Radiograph shows air-filled, dilated stomach *(S)* and dilated duodenal bulb *(D)*, giving the appearance of a double bubble. There is no distal bowel gas. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 95, Fig. 5.8.)

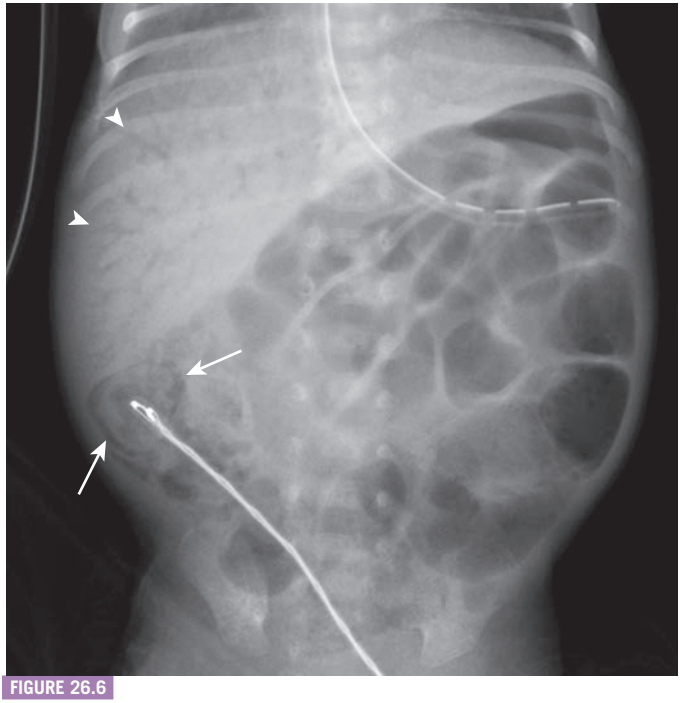


FIGURE 26.6
Necrotizing enterocolitis (NEC) in a premature infant. Radiography shows multiple dilatated bowel loops with multiple areas of linear lucency *(arrows)* along the bowel wall, consistent with pneumatosis. Note portal venous gas *(arrowheads)* as branching, tubular lucencies overlying the liver. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 92, Fig. 5.1.)

d. Meconium ileus: Contrast enema shows opacification of diffusely small caliber large bowel. Contrast refluxes into nondilated terminal ileum, which contains impacted meconium pellets. Bowel proximal to terminal ileum is dilated.[5]

E. Pyloric Stenosis

1. **Preferred imaging**: Upper abdominal US.
2. **Findings**: Abnormal thickening of pyloric muscle (≥3 mm) and elongation of pyloric channel (>15 to 17 mm).[10]

F. Intussusception

1. **Preferred imaging:** RUQ US.[1]
2. **Findings**: Donut, target, or pseudo-kidney sign.[1]
3. **Treatment**: Pneumatic enema reduction under fluoroscopic guidance.[1]

G. Ileus

1. **Preferred imaging**: CR.
2. **Findings**: Small and large bowel distention.[1,10]

H. Mechanical Bowel Obstruction

1. **Initial imaging:** CR. Supine view for identifying gas pattern. Upright/erect, cross-table lateral, or lateral decubitus for identifying free air and air-fluid levels.
2. **Other imaging**: CT with oral contrast determines obstruction site. CT with IV contrast to detect complications such as ischemia.[10] *Note: CR has low sensitivity for identifying bowel obstruction; therefore, CT should be obtained if obstruction clinically suspected.*
3. **Findings**: Dilated loops of bowel proximal to obstruction, little to no air in rectum.[1]
   a. Small bowel obstruction: Numerous air-fluid levels. Distended bowel normally more central.
   b. Large bowel obstruction: Few to no air-fluid levels. Distended bowel normally more peripheral.

I. Appendicitis

1. **Preferred imaging**: RLQ US.
2. **Other imaging:** MRI if US equivocal. CT only if MRI unavailable or patient unstable or cannot tolerate MRI.[1,7]
3. **US findings:** Fluid-filled, noncompressible, blind-ending tubular structure greater than 6 mm in diameter.[1,7]

J. Esophageal Foreign Bodies

1. **Preferred imaging**: CR, evaluate entire GI tract (AP/lateral neck, chest, abdomen).
2. **Other imaging:** Esophagram with water-soluble contrast if suspicion high but CR negative.[7]
3. **Findings**: Most commonly lodged at thoracic inlet. Only radiopaque objects can be visualized on CR. May see mass effect on adjacent structures from swelling caused by foreign body.
   a. Coins (most common): Flat object on frontal view with edge visualized on lateral.
   b. Disk batteries: Bilaminar structure, must identify as may cause serious chemical injury.[7]

K. Abdominal Trauma

1. **Preferred imaging**: CT with IV contrast.
2. **Other imaging:** If hemodynamically unstable, rapid bedside US using focused assessment with sonography for trauma (FAST) protocol to evaluate for free fluid.[7] FAST evaluates bilateral upper quadrants, bilateral pericolic gutters, pelvis, and pericardium.[1]

L. Gallbladder Disease

1. **Preferred imaging**: US. Patients should fast for 6 hours prior to allow for gallbladder filling.[1]

2. **Findings**: Posterior acoustic shadowing in cholelithiasis. Nonshadowing echogenic foci if stone disease, polyps, other masses. Gallbladder wall thickening (>3 mm), positive sonographic Murphy's sign (localized tenderness with transducer palpation over gallbladder), sludge, and pericholecystic fluid with cholelithiasis in acute cholecystitis.[1]

M. Pancreatitis

1. **Initial imaging:** US.
2. **Other imaging:** CT with IV contrast if lack of clinical improvement or equivocal US. MRCP for detecting choledocholithiasis and biliary/pancreatic duct anomalies.[13]
3. **US findings**: Pancreatic duct dilation, abnormal echogenicity, peripancreatic fluid.[1,7]

VIII. GENITOURINARY TRACT

Renal and bladder ultrasound (RBUS): first-line imaging modality; evaluates kidneys, ureters, and bladder; can assess calculi. **Fluoroscopic voiding cystourethrogram (VCUG)**, **radionuclide cystourethrography (RNC),** and **contrast-enhanced voiding urosonography (ceVUS)** assess for vesicoureteral reflux. **Nuclear renal scintigraphy (Mag-3 scan)** assesses renal perfusion, function, and excretion. **Cross-sectional imaging** (CT, MR, MR urography) assesses for genitourinary (GU) tract tumors or obstruction. Additionally, MR urography can evaluate renal function and unenhanced CT can assess collecting system calculi.[7]

A. Urinary Tract Infection

See Chapter 19.

B. Nephrolithiasis/Urolithiasis

1. **Preferred imaging:** US
2. **Other imaging:** Noncontrast CT if US equivocal.[1,7]
3. **US findings:** Echogenic, shadowing foci.[7]
4. **CT findings**: Radiodense stones, dilated ureteral or collection system, asymmetric enlargement of kidney.[1]

C. Testicular Pathology

1. **Preferred imaging:** Duplex US.[1]
2. **Testicular torsion findings:** Absence of blood flow to center of testicle.[1]
3. **Acute epididymitis findings:** Enlarged epididymis, scrotal thickening, reactive hydrocele, increased blood flow.[1]

D. Ovarian Pathology

1. **Preferred imaging:** Pelvic US.
2. **Ovarian cyst findings:** Well-circumscribed anechoic structures within pelvis measuring more than 3 cm in diameter. Hyperechoic material within cyst indicates possible hemorrhage.[9]
3. **Ovarian torsion findings:** Variable appearance, usually unilateral enlarged solid ovary with multiple peripheral follicles.[9] Absence or presence of flow on duplex not a reliable indicator of torsion.[7]

E. Congenital Hydronephrosis

1. Normally first detected on fetal US, defined as AP renal pelvis diameter greater than 4 mm in second trimester and greater than 7 mm in third trimester.
2. **Preferred imaging:** US to confirm postnatally, as can resolve spontaneously. Do not perform until at least 48 hours after delivery given risk of false negatives or underestimation of severity.[1]
3. **Findings**: Moderate-to-severe hydronephrosis (>10 mm) with clinical suspicion or family history warrants further evaluation with VCUG. Repeat US at age 4 to 6 weeks to confirm absence of hydronephrosis.[1,14]

IX. MUSCULOSKELETAL

CR is the primary imaging modality; used in trauma, infection, and suspected bone lesions.[7] **MRI** provides superior contrast resolution of soft tissue and bone marrow; preferred for patellar dislocation and avulsion fractures. Use IV contrast to delineate inflammation, ischemia, revascularization, and tumors.[1] **US** used for superficial soft-tissue masses and suspected joint effusions.

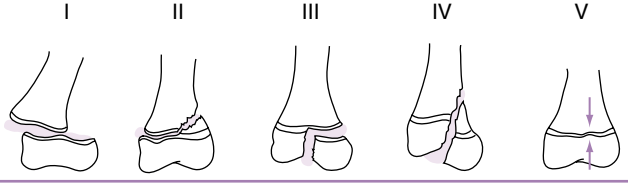
A. Fractures and Trauma

1. **Preferred imaging**: CR. For long bones, obtain at least two projections. For joints, obtain at least three projections and evaluate proximal and distal joint. Fractures may not be seen on initial XR; consider repeat XRs in 7 to 10 days as may visualize periosteal reactions around healing fracture.[1,7]
2. **Findings:** Abrupt disruption of the cortex or acute angulation of smooth contour of normal bone.[10] *Indirect signs:* soft-tissue swelling, joint effusion, periosteal reaction (if subacute or healing).
3. Describing fractures.[10]
   a. **Location:** Laterality, location on bone, relation to joint (intra-articular, extra-articular).
   b. **Type**: Complete (through whole cortex), incomplete (retains some continuity [e.g., plastic, bowing, torus, greenstick]), Salter-Harris (involves growth plate) (Table 26.4)
   c. **Number of fragments**: Simple (two fragments) or comminuted (>2).
   d. **Direction of fracture lines**: Transverse (perpendicular to long axis), oblique/diagonal (diagonal in orientation relative to long axis), spiral (corkscrew, twisting).
   e. **Relationship** (distal fracture fragment to proximal fragment): Displacement (amount distal fragment is offset in nonlongitudinal axis), angulation (angle between fragments), apposition (amount of contact between fragments), shortening (amount of overlap between fragments, change in bone length), distraction (distance fragments are separated in longitudinal axis), rotation (orientation of joint at one end of fracture relative to joint at other end).
   f. **Open versus closed:** Open or compound (communication between fracture and outside atmosphere), closed or simple.

TABLE 26.4

SALTER-HARRIS CLASSIFICATION OF GROWTH PLATE INJURY

Class I	Class II	Class III	Class IV	Class V
Fracture along growth plate	Fracture along growth plate with metaphyseal extension	Fracture along growth plate with epiphyseal extension	Fracture across growth plate, including metaphysis and epiphysis	Crush injury to growth plate without obvious fracture



4. Common pediatric fracture patterns: see Chapter 2.
5. **Elbow XRs.**
   a. **Anterior humeral line:** Line drawn tangential to anterior humeral cortex should bisect middle third of capitellum. If line more anterior, supracondylar fracture should be suspected (Figs. 26.7 and 26.8).[10]
   b. **Radiocapitellar line**: Line drawn through the center of radial neck should pass through the center of capitellum. If it does not, dislocation should be suspected (see Figs. 26.7 and 26.8).[14]
   c. **Ossification centers**: Mnemonic CRITOE commonly used to remember sequential order of appearance (Table EC 26.B and Fig. EC 26.I).[15]
   d. **Fat pad**: Normal lateral view of flexed elbow shows only anterior fat pad (lucency). Elevated anterior fat pad and visible posterior fat pad indicates intra-articular injury and possible radial head fracture (*positive fat-pad sign*) (Fig. 26.9).[12]
   e. **Hourglass sign** ('figure-of-eight'): On a true lateral view, an hourglass or figure-of-eight configuration can be visualized on the distal humerus (see Fig. 26.9).

B. Osteomyelitis

1. **Initial imaging**: CR. Findings often lag 7 to 14 days after symptom onset; however, may rule out or identify alternative diagnosis.[1]
2. **Preferred imaging**: MRI. Findings can be seen as early as 24 to 48 hours after symptom onset.[1,16]
3. **Findings:** Metaphysis of long bones most frequently affected. CR: soft-tissue swelling, bony destruction, cortical loss, periosteal reaction.[16]

C. Hip Disorders

1. Developmental dysplasia of the hip
   a. **Preferred imaging**: US, typically around 6 weeks of age.
   b. **Other imaging:** Once femoral heads ossify (within 3 to 6 months), CR more helpful.[7]

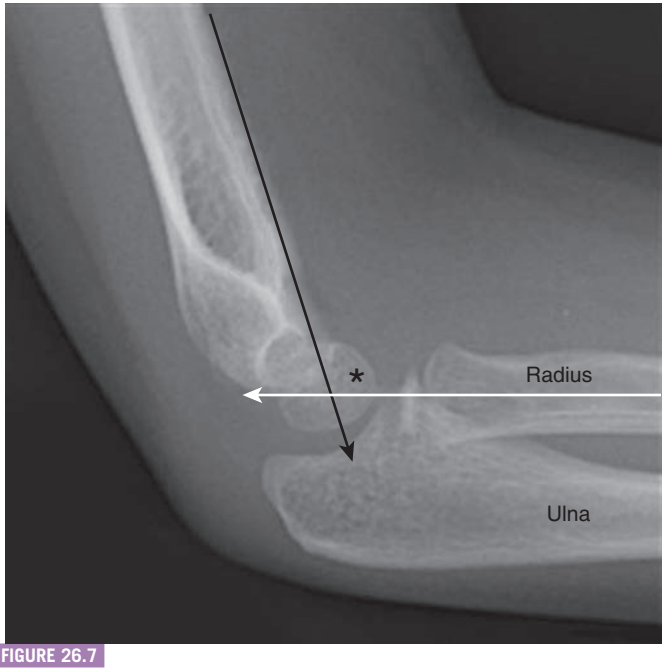


FIGURE 26.7
Normal elbow alignment on lateral radiograph. The anterior humeral line *(black arrow)* is drawn along the anterior cortex of the humerus and should intersect the middle third of the capitellum *(asterisk)*. The radiocapitellar line *(white arrow)* is drawn along the axis of the radius. (Modified from Coley, BD. *Caffey's Pediatric Diagnostic Imaging*. 13th ed. Philadelphia: Elsevier; 2019, p. 1439, Fig. 142.19.)

2. Idiopathic avascular necrosis of femoral head (Legg-Calvé-Perthes disease).
   a. **Initial imaging:** CR, AP pelvis and frog-leg lateral hip.
   b. **Other imaging:** MRI, more sensitive for early disease, useful if CR is nondiagnostic.[7]
   c. **Findings:** Small capital femoral epiphysis, sclerotic femoral head, widened joint space, curvilinear subchondral lucency from subchondral fracture (*crescent sign*).[7]
3. Slipped capital femoral epiphysis (SCFE)
   a. **Initial imaging:** CR, AP and frog-leg lateral views of pelvis.
   b. **Findings**: Asymmetric widening and/or lucency of proximal femoral physis, posterior and inferomedial displacement of femoral head relative to femoral neck (ice cream falling off cone). Can assess femoral head position by drawing line along lateral aspect of the femoral neck (Klein's line), which should intersect the capital femoral epiphysis in normal anatomy (Fig. EC 26.J).[7]

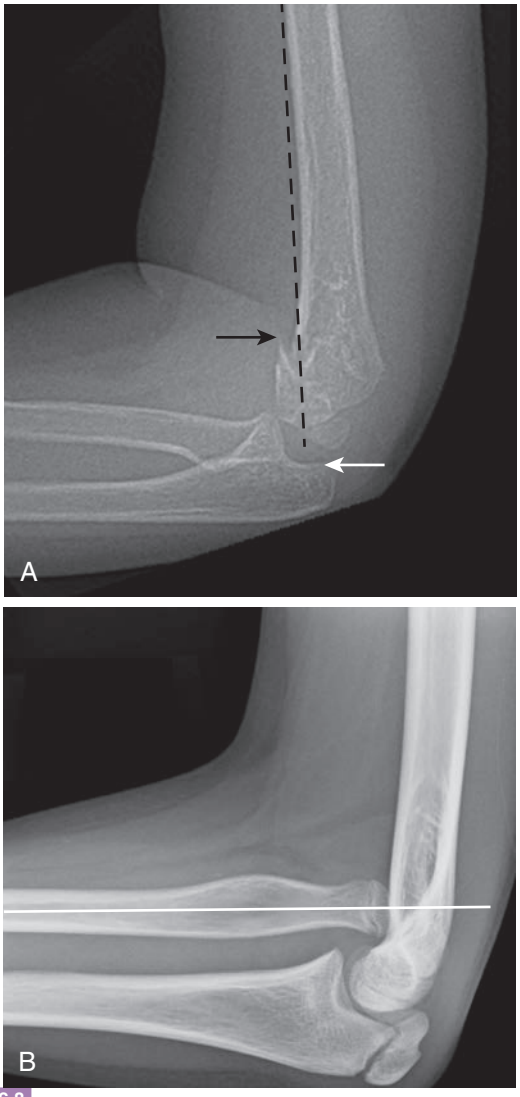


FIGURE 26.8

(A) Abnormal anterior humeral line seen in a supracondylar humeral fracture. The anterior humeral line *(dashed line)* courses anterior to the capitellum *(white arrow)* in a minimally displaced fracture of the supracondylar humerus *(black arrow)*. (B) Abnormal radiocapitellar line in a radial head dislocation. Radiocapitellar line (white line) drawn along the axis of the radius courses superior to the capitellum instead of intersecting the capitellum.

TABLE EC 26.B

ELBOW OSSIFICATION CENTERS USING MNEMONIC "CRITOE"

Ossification Center	Age at which appears (highly variable)
Capitellum	1–2
Radial head	3–4
Internal (medial) epicondyle	5–6
Trochlea	7–8
Olecranon	9–10
External (lateral) epicondyle	11–12

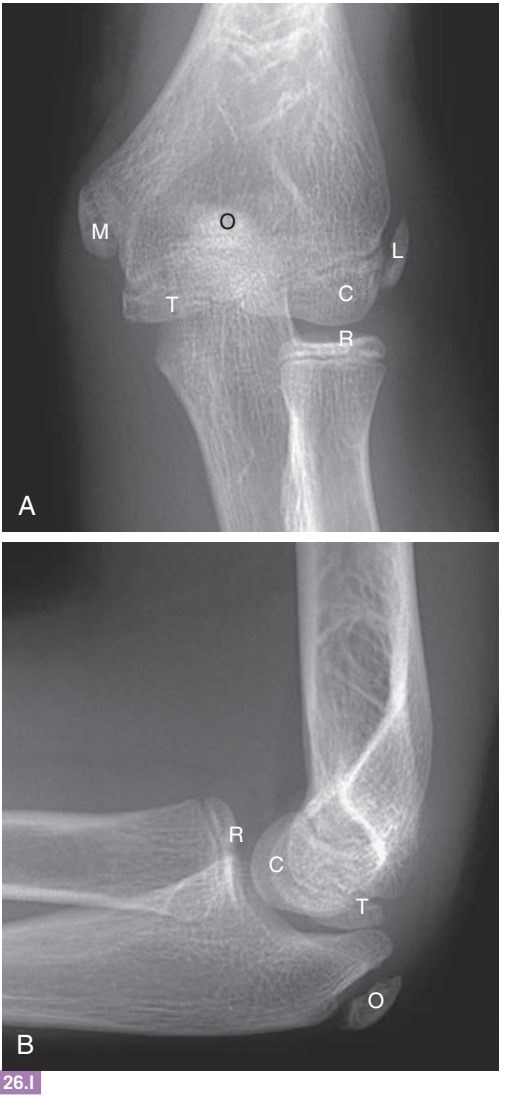


FIGURE EC 26.1

Ossification centers of normal elbow of 14-year-old boy. Anteroposterior (A) and lateral (B) radiographs. *C,* capitellum; *L*, lateral epicondyle; *M*, medial epicondyle; *O*, olecranon; *R*, radial head; *T*, trochlea (From Coley, BD. *Caffey's Pediatric Diagnostic Imaging*. 13th ed. Philadelphia: Elsevier; 2019, p. 1438, Fig. 142.17.)

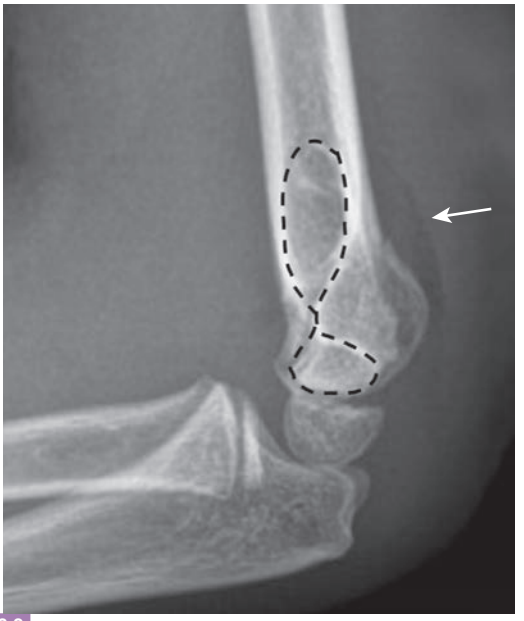


FIGURE 26.9
Lateral radiograph of elbow demonstrates visible posterior fat pad *(white arrow)*, "positive fat-pad sign." Note the "hourglass sign" *(dashed line)*.

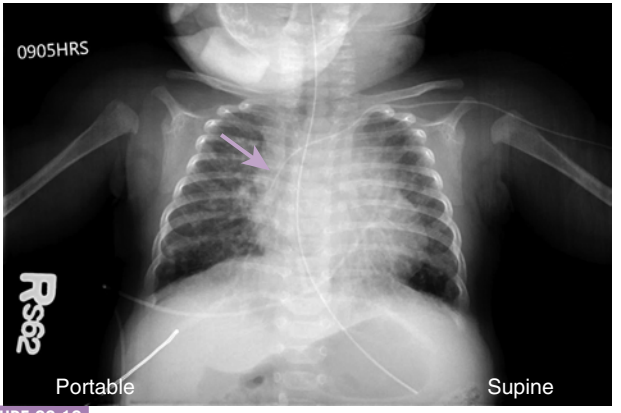


FIGURE 26.10
Central line placement on anteroposterior chest radiograph for line inserted in arm or neck. *Arrow* indicates termination of catheter at junction of superior vena cava and right atrium.

D. Scoliosis

1. **Initial imaging:** CR, upright PA view. Sitting or supine reserved for nonambulatory patients. Lateral view not necessary for initial screening; include if known scoliosis.[9]
2. **Findings**: Lateral spinal curvature greater than 10 degrees as measured by Cobb method.[9]

E. Bone Lesions

1. **Initial imaging**: CR, usually diagnostic.
2. **Other imaging:** MRI defines extent of lesion and staging of malignant lesions.[1]
3. **Findings**: *Benign lesions:* demarcated from normal bone, sclerotic margin around lesion, nonaggressive growth pattern. *Pathologic lesions:* not well demarcated from surrounding normal bone, possible accompanying soft-tissue mass, periosteal reaction, destructive bone changes. (Fig. EC 26.K to Fig. EC 26.O).[1]

F. Skeletal Survey in Suspected Nonaccidental Trauma

1. **Imaging:** CR at presentation and 2 weeks after presentation. Follow-up surveys may identify initially missed trauma by identifying healing fractures (Fig. EC 26.P).[5]
2. Evaluate for fractures inconsistent with history or developmental stage. Certain findings suspicious for nonaccidental trauma (NAT) (see Chapter 2).

X. CONFIRMING TUBE PLACEMENT AND LINE INSERTION

A. Central Venous Catheter

1. *Upper extremity*: Tip in superior vena cava (SVC) at cavoatrial junction or proximal atrium (Fig. 26.10).
2. *Lower extremity*: Tip in inferior vena cava (IVC) within 1 cm of diaphragm.

B. Umbilical Lines (Fig. 26.11)

1. Umbilical artery catheter (UAC): *High-lying (preferred)*: Tip above diaphragm between T6 and T9. *Low-lying*: Tip just above bifurcation of aorta between L3 and L5.
2. Umbilical venous catheter (UVC): Tip within 1 cm of diaphragm between T8 and T10 at junction of right atrium and inferior vena cava.
3. UACs distinguished from UVCs by initial downward course from umbilicus into internal iliac artery, whereas UVCs extend immediately superior from umbilicus.

C. Nasogastric Tube

1. Tip below diaphragm in stomach, overlying gastric bubble, at least 10 cm beyond gastroesophageal junction.

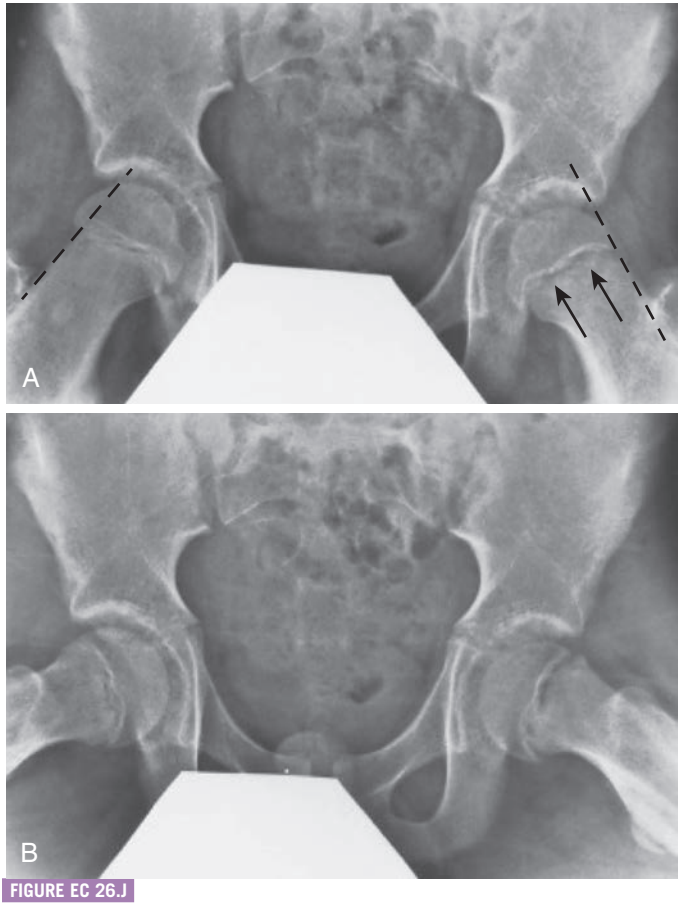


FIGURE EC 26.J

Slipped capital femoral epiphysis. (A) Anteroposterior radiograph of the pelvis shows asymmetric physeal widening on the left (*double arrows*). The Klein line (*dotted lines*) does not cross the epiphysis on the affected side. (B) Frog-leg lateral image confirms inferomedial slip of the femoral head relative to the proximal femoral metaphysis. (From Walters, MM, Robertson RL. *Pediatric Radiology: The Requisites*. 4th ed. Philadelphia: Elsevier; 2017, p. 220, Figure 7.60.)

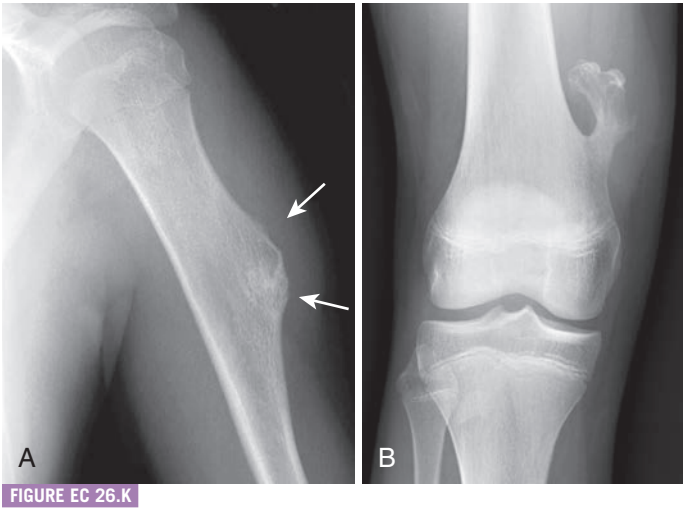


FIGURE EC 26.K

(A) Sessile osteochondroma *(arrows)* of proximal humeral diaphysis in a 16-year-old patient. (B) Pedunculated osteochondroma of the right distal femoral metaphysis in a 16-year-old patient. (From Coley, BD. *Caffey's Pediatric Diagnostic Imaging*. 13th ed. Philadelphia: Elsevier; 2019, p. 1375, Figs. 138.14–138.15.)

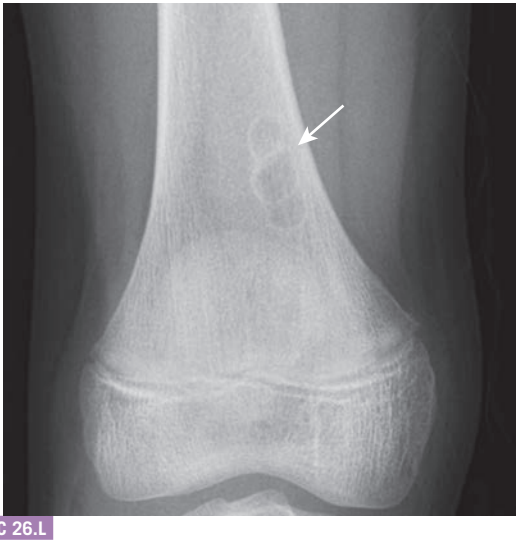


FIGURE EC 26.L

Nonossifying fibroma in a 12-year-old patient. The lesion is well defined, with a "soap bubble" appearance and sclerotic margins *(arrow)*. (From Coley, BD. *Caffey's Pediatric Diagnostic Imaging*. 13th ed. Philadelphia: Elsevier; 2019, p. 1382, Fig. 138.30.)

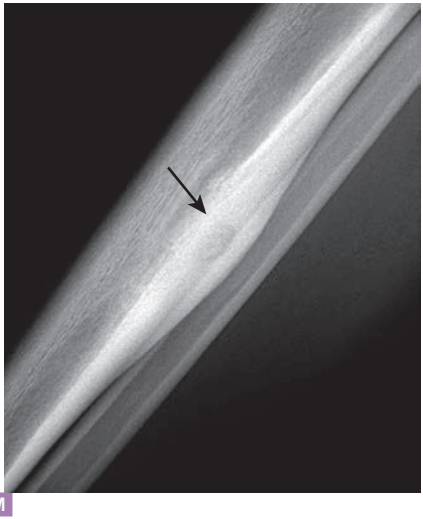


FIGURE EC 26.M

Osteoid osteoma of tibia in a 15-year-old patient. Radiograph shows cortical thickening posteriorly. Lucent nidus is faintly seen *(arrow)*. (From Coley, BD. *Caffey's Pediatric Diagnostic Imaging*. 13th ed. Philadelphia: Elsevier; 2019, p. 1387, Fig. 138.38.)

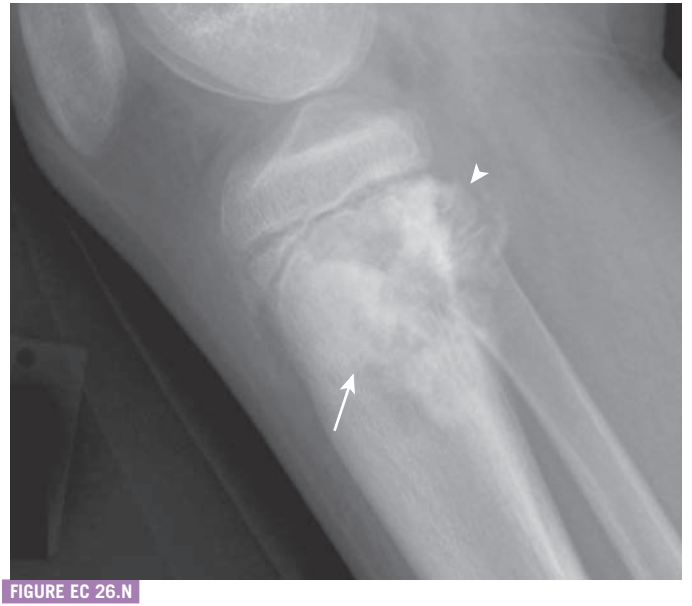


FIGURE EC 26.N

Proximal tibial osteosarcoma. Radiograph demonstrates osteoblastic osteosarcoma with osteoid matrix *(arrow)* and "sunburst" periostitis *(arrowhead)*. (Modified from Coley, BD. *Caffey's Pediatric Diagnostic Imaging*. 13th ed. Philadelphia: Elsevier; 2019, p. 1390, Fig. 138.41.)

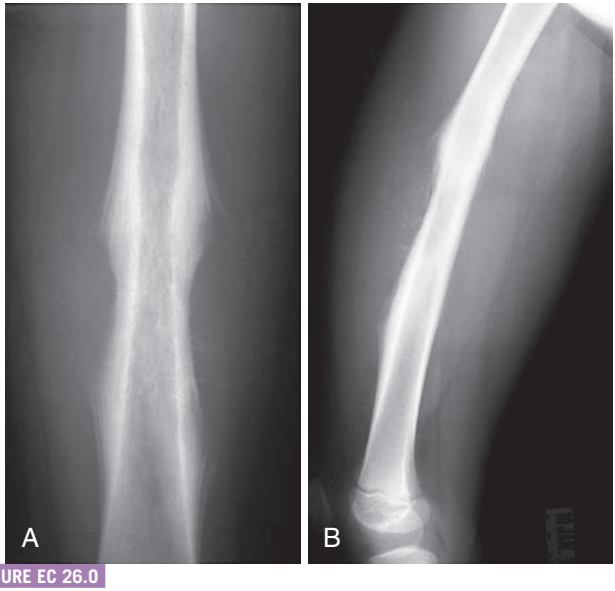


FIGURE EC 26.0

Anteroposterior (A) and lateral (B) radiographs of femur of a 6-year-old child show Ewing sarcoma arising from mid-diaphysis. Lamellar periosteal reaction and new bone formation are present, with Codman triangles at proximal and distal ends of tumor. Faint periosteal new bone extends perpendicularly into soft-tissue component of tumor. Medulla is not expanded. (From Slovis, TL. *Caffey's Pediatric Diagnostic Imaging*. 11th ed. Philadelphia: Mosby; 2008.)

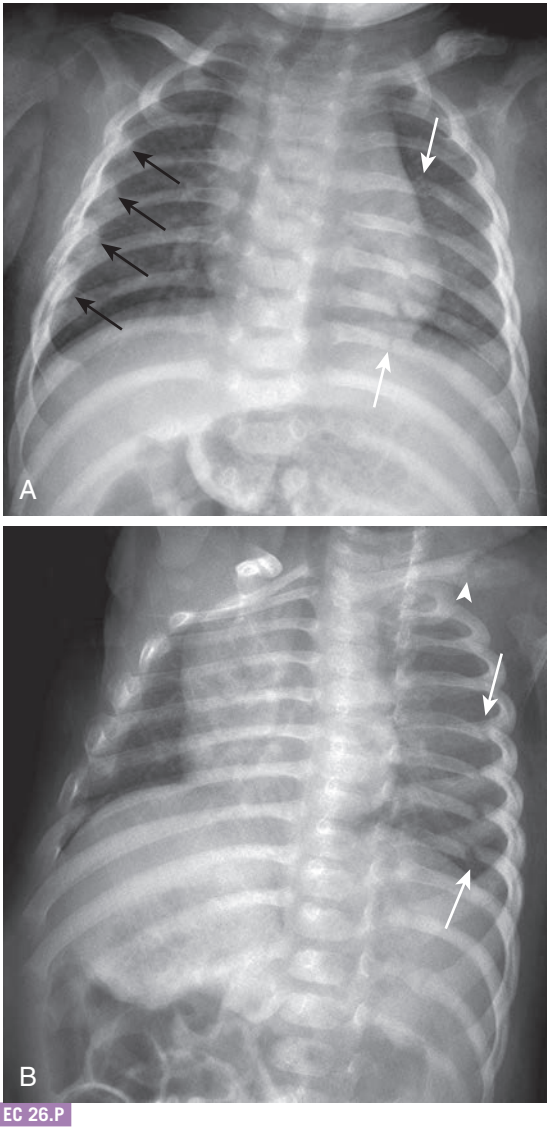


FIGURE EC 26.P

Frontal (A) and oblique (B) radiographs show healing fractures *(black arrows)* of right third, fourth, fifth, and sixth ribs. There are acute fractures *(white arrows)* of the posterior left fifth, sixth, seventh, eighth, and ninth ribs. Fractures are better appreciated on the oblique view. Note subacute healing left clavicular fracture *(arrowhead)*. (From Donnelly, LF. *Fundamentals of Pediatric Imaging*. 2nd ed. Philadelphia: Elsevier; 2017, p. 56, Fig. 3.39.)

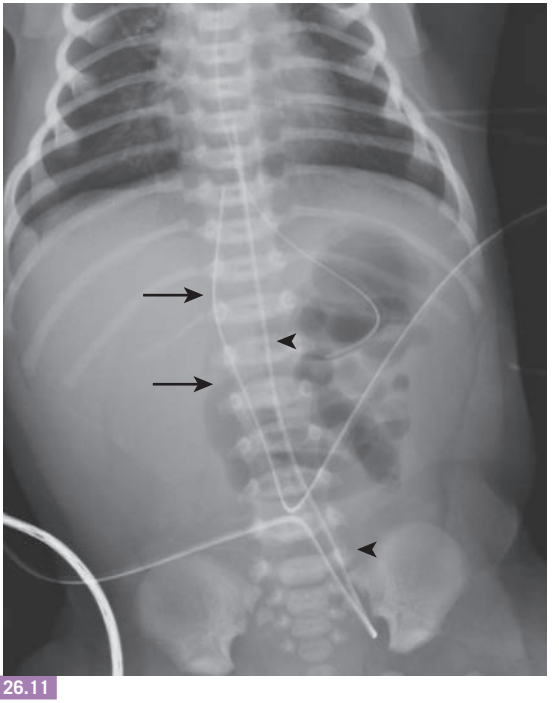


FIGURE 26.11
Umbilical catheters. Umbilical venous catheter (UVC) terminates at inferior cavoatrial junction *(arrows)*. The umbilical arterial catheter (UAC) first descends the iliac artery before it ascends the aorta and terminates in a typical "high" position, at T7 *(arrowheads)*.

D. Nasoduodenal Tube

1. Tip should pass through stomach, cross midline, and pass into duodenal bulb, tip ends approximately 10 to 12 cm into small bowel.

E. Endotracheal Tube

1. Tip about midway between thoracic inlet/interclavicular line and carina.

XII. WEB RESOURCES

- American College of Radiology Appropriateness Criteria: http://www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality/Pediatric
- Image Gently Alliance: www.imagegently.org
- Society for Pediatric Radiology: http://www.pedrad.org

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Chapter 27

Rheumatology

Shani Jones, MD

I. BRIEF OVERVIEW OF CLINICAL CHARACTERISTICS OF RHEUMATOLOGIC DISEASES

A. Juvenile Idiopathic Arthritis (JIA)[1–5]

1. JIA involves joint swelling or limitation/tenderness upon range of motion lasting at least 6 weeks, shown not to be due to another identifiable cause, and presenting in children less than 16 years of age.
2. See Table 27.1 for information organized by the divisions of the disease.

B. Reactive Arthritis[6–8]

1. Affects males more than females (3:1).
2. Sterile inflammatory arthritis as a response to preceding (1 to 4 weeks) bacterial or viral infection, particularly of the respiratory, gastrointestinal, or genitourinary tracts.
3. Involves acute asymmetrical oligoarticular arthritis of larger joints, often the lower extremities.
4. Associated with fever, weight loss, fatigue, tendinitis, bursitis, anterior uveitis, conjunctivitis, erythema nodosum, urethritis, and cervicitis.

C. Systemic Lupus Erythematosus (SLE)[1,9–11]

1. SLE typically affects women of childbearing age (occurring nine times more often in women than men).
2. People of African descent and Native Americans are affected more commonly than Caucasians.
3. See Box 27.1 for clinical criteria for diagnosis.

D. Drug-Induced Systemic Lupus Erythematosus[1,6,9]

1. Manifests as polyarthritis, myalgia, fever, and serositis, which resolve after discontinuation of the inciting drug.
2. Inciting drugs include but are not limited to hydralazine, minocycline, procainamide, quinidine, isoniazid, interferon-alfa, chlorpromazine, ethosuximide, carbamazepine, therapy against tumor necrosis factor alpha (anti-TNF α therapy).

E. Neonatal Systemic Lupus Erythematosus[1,12]

1. Neonates born to mothers with active SLE can develop a transient lupus-like syndrome due to transplacental passage of anti-Ro (anti-SS-A) and anti-La (anti-SS-B) antibodies.
2. Inflammatory features resolve within 6 months as maternal autoantibodies are cleared.

TABLE 27.1

CLASSIFICATION OF JUVENILE IDIOPATHIC ARTHRITIS (JIA)

ILAR JIA Subtype (% of Total Patients)	Demographics	Typical Joint Involvement	Occurrence of Uveitis	Other Features
Oligoarticular • Persistent • Extended (40%–50%)	F > M Early childhood	≤4 joints Large joints: knees, ankles, wrist Persistent disease: <4 joints affected Extended disease: Involves >4 joints after first 6 months of disease	Common (30%), especially if ANA-positive Usually asymptomatic	ANA positive in 60%–80%
Polyarticular (RF-negative) (20%–25%)	F > M 2 peaks: 2–4 years and 6–12 years	≥5 joints Symmetric	Common (15%)	ANA positive in 25% May also involve cervical spine and TMJ
Polyarticular (RF-positive) (5%)	F > M Late childhood/early adolescence	Symmetric small and large joints Erosive joint disease	Rare (<1%)	ANA positive in 75% Rheumatoid nodules: Nontender subcutaneous nodules found on bony prominences, extensor surfaces, or adjacent to joints
Systemic (5%–10%)	M = F Throughout childhood	Poly- or oligoarticular	Rare (<1%)	Daily (quotidian) fever for ≥2 weeks Evanescent rash, lymphadenopathy, hepatosplenomegaly, serositis
Enthesitis-related arthritis (5%–10%)	M > F Late childhood/adolescence	Weight-bearing joints, especially hip and intertarsal joints History of inflammatory back pain or sacroiliac joint tenderness	Symptomatic acute uveitis (~7%)	Enthesitis: HLA-B27 positive, axial involvement (including sacroiliitis), family history of HLA-B27-associated disease

TABLE 27.1–cont'd

CLASSIFICATION OF JUVENILE IDIOPATHIC ARTHRITIS (JIA)

ILAR JIA Subtype (% of Total Patients)	Demographics	Typical Joint Involvement	Occurrence of Uveitis	Other Features
				Juvenile ankylosing spondyloarthritis: Subgroup requiring radiologic evidence of bilateral sacroiliitis
Psoriatic arthritis (5%–10%)	F > M 2 peaks: 2–4 years and 9–11 years	Asymmetric or symmetric small or large joints	Common (10%)	Nail pits, onycholysis, dactylitis Psoriasis: May appear after arthritis Family history of psoriasis may be present
Undifferentiated (10%)				Does not fulfill criteria for any other category or fulfills criteria for >1 category

ANA, Antinuclear antibodies; *F*, female; *HLA*, human leukocyte antigen; *ILAR*, International League of Associations for Rheumatology; *M*, male; *RF*, rheumatoid factor; *TMJ*, temporomandibular joint.
Data from Gowdie, Tse, *Pediatric Clinics of North America 2012. Based on International League of Associations for Rheumatology (ILAR) Classification of JIA:* Second Revision Edmonton, 2001.

BOX 27.1

CLINICAL CRITERIA FOR THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS[10]

1. **Patient satisfies at least four of the following criteria, including at least one clinical criterion and one immunologic criterion:**
   Clinical criteria: Cutaneous findings, oral/nasopharyngeal ulcers, nonscarring alopecia, synovitis, serositis, renal manifestations, neurologic manifestations, hemolytic anemia, leukopenia/lymphopenia, hrombocytopenia
   Immunologic criteria: Antinuclear antibody (ANA), anti-dsDNA, anti-Sm, antiphospholipid antibody, low complement (C3, C4, CH50), direct Coombs test (in the absence of hemolytic anemia)
   OR
2. **The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies**

3. Clinical features include rash (annular erythema on eyelids and scalp, papular or plaque-like lesions), hepatomegaly, thrombocytopenia, hemolytic anemia, congenital atrioventricular heart block, and hydrops fetalis.

F. Vasculitis (Table 27.2)[1,6,13–23]

G. Sarcoidosis[6,14,24–26]

1. Before puberty (very rare): primarily affects Caucasians. During and after puberty: predominantly affects African Americans. Males and females affected equally.
2. Multisystem, infiltrative, noncaseating granulomatous disease of unknown etiology.
3. Lung is the organ most commonly involved; however, it can involve nearly all organ systems and have widespread manifestations including but not limited to:
   a. Pulmonary: Bilateral hilar adenopathy, restrictive and obstructive disease.
   b. CNS: Bilateral or unilateral Bell palsy, seizures, aseptic meningitis.
   c. Cutaneous: Erythema nodosum, plaques, alopecia.

H. Scleroderma[6,14,27]

1. Both juvenile localized scleroderma and juvenile systemic sclerosis typically present in mid-childhood between 6 and 11 years of age with a female predominance.
2. Localized (limited) scleroderma: More common than systemic; sclerosis limited to skin, muscle, and bone.
3. Diffuse cutaneous systemic scleroderma: Fibrous degenerative changes of skin, synovium, digital arteries, and internal organs (gastrointestinal tract, heart, lungs, kidneys, and esophagus).

I. Sjögren Syndrome[1,6,14,28]

1. Female-to-male ratio 5:1 in children.
2. Widespread lymphocytic infiltration of salivary and lacrimal glands with secondary atrophy and obliteration of secretory acini.
3. Keratoconjunctivitis sicca (dry eyes secondary to decreased tear production by lacrimal glands).
4. Xerostomia (dry mouth from decreased salivary gland production).
5. May present as parotid gland swelling in children.

II. INTERPRETATION OF LABORATORY STUDIES USED IN THE DIAGNOSIS AND MONITORING OF RHEUMATOLOGIC DISEASES

Most laboratory studies used to diagnose rheumatic diseases are nonspecific, and results must be interpreted within the context of the full clinical picture. Once a diagnosis is established, however, they can be used to follow the condition's clinical course, indicating flares or remission of the rheumatic disease.

A. Acute-Phase Reactants

Indicate presence of inflammation when elevated. Elevation is nonspecific and can result from trauma, infection, rheumatic diseases, or malignancy.[1] Markers include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), platelet count, ferritin, haptoglobin, fibrinogen, serum amyloid A, and complement.[1,6]

TABLE 27.2

CHILDHOOD VASCULITIS SYNDROMES

Vasculitis Syndrome	Involved Vessels	Epidemiology	Clinical Manifestations
Takayasu arteritis	Large arteries	Young women	Aneurysms, thrombosis, and stenosis of large arteries; hypertension is common
Giant cell (temporal) arteritis	Aorta and large branches—extracranial branches of carotid artery	Rare in children	Fever, weight loss, partial or total blindness, headache, jaw claudication, stiffness in neck and shoulders
Kawasaki disease	Medium-sized arteries	Children less than 5 years old	Mucocutaneous lymph node syndrome (see Chapter 7)
Polyarteritis nodosa	Renal, hepatic, coronary, and mesenteric arteries	Juvenile polyarteritis with a mean age of 9 years	Cutaneous lesions (livedo reticularis, tender nodules, purpura), hypertension, renal failure, abdominal pain, intestinal infarction, peripheral neuropathy, stroke
Microscopic polyangiitis (MPA)	Small arterioles and venules	Associated with streptococcal infections or URIs	Necrotizing glomerulonephritis and pulmonary capillaritis leading to alveolar hemorrhage and hemoptysis
Henoch-Schönlein purpura	Venules, capillaries, arterioles, and intrapa-renchymal distal arteries; IgA-dominant immune deposits within vessel walls	Most common pediatric vasculitis; frequently affects males 2–7 years old; preceding viral URI common	Palpable purpura involving buttocks and lower extremities, colicky abdominal pain, subcutaneous or scrotal edema, migratory arthralgias/arthritis, proteinuria, glomerulonephritis, intussusception (frequently ileoileal) Treatment: Supportive care with hydration and analgesics; consider corticosteroids if severe abdominal pain or nephritis Follow-up: serial urinalyses and blood pressure measurements up to 6 months after diagnosis
Granulomatosis with polyangi-itis (GPA)	Small and medium-sized arteries	Rare in childhood; has female predominance and presents in adolescence	Respiratory tract: Recurrent epistaxis, chronic purulent nasal discharge, lung nodules, cavi-ties, infiltrates Kidney involvement: proteinuria, hematuria, glomerulonephritis

Continued

TABLE 27.2—cont'd

CHILDHOOD VASCULITIS SYNDROMES

Vasculitis Syndrome	Involved Vessels	Epidemiology	Clinical Manifestations
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Vessels of respiratory tract	More prevalent in those of European descent	Associated with asthma, nasal polyps and allergic rhinitis
Juvenile dermatomyositis	Capillary vasculopathy affecting skin, GI tract, and striated muscle	Peak onset 5–14 years; females affected more commonly	Heliotrope or malar rash, Gottron papules, dystrophic calcifications, photosensitivity (skin findings required for diagnosis), symmetric proximal muscle pain or weakness More severe disease with dysphagia, skin ulcers, and restrictive lung disease
Behçet disease	Systemic vasculitis affecting arteries and veins	Most prevalent in Turkey; peak age in young adulthood but up to 26% of cases <16 years	Recurrent oral ulcers, genital ulcers, ocular disease, skin lesions, positive skin pathergy test (traumatic injury to skin results in development of a sterile pustule in 24–48 hr)
Raynaud phenomenon	Exaggeration of vasoconstriction due to increase in α-2 adrenergic response	More common in women age 15–30; family history common	Response to cold or emotional stress: sudden onset color change in digits with demarcated skin pallor due to constricted blood flow, followed by cyanotic skin, and finally erythema with reperfusion

GI, Gastrointestinal; URI, upper respiratory infection.

1. **ESR**
   a. Measure of the rate of fall of red blood cells in anticoagulated blood within a vertical tube; reflects level of rouleaux formation caused by acute-phase reactants.[1]
   b. Can be falsely lowered in afibrinogenemia, polycythemia, and sickle cell disease; these states interfere with rouleaux formation.[2]
   c. Can be outside normal range for age due to obesity, pregnancy, and anemia.[29]
   d. Serial measurements may help in monitoring disease severity or activity in conditions such as SLE and JIA.

2. **CRP**[1,30]
   a. Synthesized by the liver, assists in clearance of pathologic bacteria and damaged cells via activation of complement-mediated phagocytosis, and mediates acute inflammation by altering cytokine release.
   b. Increases and decreases rapidly owing to short half-life (approximately 18 hours).[14]
   c. Elevation is nonspecific, indicating only inflammation:
      (1) Most active phases of rheumatic disease result in elevation to 1 to 10 mg/dL.
      (2) Level greater than 10 mg/dL raises concern for bacterial infection or systemic vasculitis.[31]

B. Autoantibodies (Table 27.3)[14]

The positive predictive value of any autoantibody assay depends on clinical context. These studies can prove valuable in confirming clinical suspicion. Sensitivities and specificities must be considered with any clinical decision.

1. **Antinuclear antibody (ANA)**
   a. ANA is a nonspecific test for SLE and other rheumatic disease.[1]
   b. Positive in approximately 60% to 70% of children with an autoimmune disease, but can be seen in about 25% of the normal population.[32,33]
   c. If positive, consider ordering individual autoantibodies.[6]
   d. Can be positive in nonrheumatologic diseases[33]:
      (1) Malignancy (e.g., acute lymphoblastic leukemia)
      (2) Infections (transiently positive): Mononucleosis, endocarditis, hepatitis, malaria
   e. If positive in JIA, there is increased risk of chronic uveitis.[29]
2. **Rheumatoid factor (RF)**[1,29]
   a. M antibodies to the Fc portion of IgG.
   b. Positive in rheumatic and nonrheumatic diseases:
      (1) Rheumatic diseases: Rheumatoid arthritis, SLE, mixed connective tissue disease, scleroderma, and primary Sjögren syndrome.
      (2) Infections: Hepatitis B/C, subacute bacterial endocarditis, tuberculosis, toxoplasmosis, rubella, cytomegalovirus, herpes.
   c. Negative RF does not rule out rheumatic disease.
   d. Prognostic importance in polyarticular JIA: Positive RF suggests more aggressive disease.[29]
3. **Anticyclic citrullinated peptide (anti-CCP) antibodies**
   a. Known to be highly specific for rheumatoid arthritis in adults; found primarily in children with polyarticular JIA.[29]
   b. Anti-CCP positivity correlates with erosive joint disease in JIA.[34,35]

TABLE 27.3

COMMON RHEUMATOLOGIC DISEASES AND AUTOANTIBODIES

Disease	Associated Antibody	Interpetation of Results	Clinical Considerations
SLE	ANA Anti-double-stranded DNA Anti-Smith Anti-phospholipids	ANA sensitivity >95% Anti-dsDNA specificity is 97% Anti-Smith specificity 55%–100%	Most patients with positive ANA do not have SLE, but almost all patients with SLE have a positive ANA Measure anti-dsDNA when ANA positive Anti-phospholipids present in up to 50% of SLE patients; associated with thrombosis and fetal loss
Juvenile idiopathic arthritis	ANA	ANA positive in 80% of those with oligoarticular type	Typically RF and CCP negative; when positive may indicate erosive disease
Vasculitis	ANCA-cytoplasmic/PR3 (proteinase-3) ANCA-perinuclear/MPO (myeloperoxidase)	90% of patients with active GPA and MPA are ANCA positive	c-ANCA associated with GPA p-ANCA associated with MPA and Churg-Strauss
Dermatomyositis/Polymyositis	ANA Anti-Jo-1	Specificity of Anti-Jo-1 99% ANA may be normal	Anti-Jo-1 associated with polymyositis with interstitial lung disease and JDM
Mixed connective tissue disease	Anti-RNP	The presence of antibodies to RNP is required for diagnosis	Also present in SLE, systemic sclerosis
Scleroderma	ANA Anticentromere Anti-Scl-70	ANA sensitivity >85% Anticentromere specificity >98%	Anti-Scl-70 associated with diffuse systemic sclerosis, while anti-centromere with limited disease
Sjögren syndrome	Anti-Ro/SS-A Anti-La/SS-B	Anti-Ro sensitivity 75%	Associated with neonatal cutaneous lupus Incidence of congenital heart block increased for infants born to mothers with high titers of anti-Ro and anti-La
Drug-induced SLE	Anti-histone	Sensitivity >95%	Anti-histone antibodies do not distinguish drug-induced lupus from SLE

ANA, Antinuclear antibody; *ANCA*, antineutrophil cytoplasmic antibodies; *CCP*, cyclic citrullinated peptide; *GPA*, granulomatosis with polyangiitis; *JDM*, juvenile dermatomyositis; *MPA*, microscopic polyangiitis; *SLE*, systemic lupus erythematosus.

Data from Imboden, JB, Hellman DB, Stone, JH. *Current Diagnosis & Treatment in Rheumatology*. 3rd ed. McGraw-Hill Medical; 2013.

C. Complement[1,5]

The complement system is composed of a series of plasma proteins and cellular receptors that function together to mediate host defense and inflammation. Inflammatory processes may increase the synthesis of complement proteins or increase their consumption.

1. **Total hemolytic complement level (CH_{50})**
   a. Immune complex disease leads to depletion of complement components and decreased level of CH_{50}.
   b. Increased in the acute phase response of numerous inflammatory states.
   c. Useful screening test for homozygous complement deficiency states which have the strongest association with SLE.[29]
   d. Typically decreased in SLE, acute poststreptococcal glomerulonephritis, subacute bacterial endocarditis.[14]
2. **C3 and C4**
   a. Most common complement proteins assayed.
   b. May be increased or decreased in rheumatic diseases, depending on disease stage or severity.
   c. **Decreased levels of complement proteins:**
      (1) Indicator of immune complex formation.
      (2) Complete deficiency of C3 manifests as severe, recurrent infections with pyogenic organisms.[14]
      (3) Can occur in active SLE, some vasculitides, and multiple infections, including gram-negative sepsis, hepatitis, and pneumococcal infections.
      (4) Decreased levels typically signify more severe SLE, particularly with regard to renal disease.
      (5) Persistently low C3 associated with lupus nephritis.
      (6) Severe hepatic failure: Synthesis of complement proteins occurs primarily in the liver.
      (7) Congenital complement deficiency, which may predispose to development of autoimmune disease.
   d. **Increased levels of complement proteins:**
      (1) Indicates the active phase of most rheumatic diseases (e.g., JIA, dermatomyositis).
      (2) May be seen in multiple infections (e.g., hepatitis, pneumococcal pneumonia) as part of the acute-phase response.

III. PRIMARY CARE MANAGEMENT OF RHEUMATOLOGIC DISEASES[36,38,39]

A. Vaccination

1. Patients on immunosuppressive therapies cannot receive live vaccines, but can receive killed/inactivated vaccines.
2. Special considerations should be made for immunocompromised patients on biologic or immunosuppressive therapy (see Chapter 16).

TABLE 27.4

ANTIARTHRITIC DRUG TOXICITY AND RECOMMENDED SURVEILLANCE

Agent	Major Side Effects	Recommended Surveillance
DMARDS		
Methotrexate	GI upset, liver toxicity, oral ulcers, bone marrow toxicity, teratogenic	Baseline CMP, then every 2–3 months CBC with differential every 4–6 weeks
Hydroxychloroquine	Retinal toxicity, GI upset, neuropathy, myopathy, tinnitus	Ophthalmologic monitoring every 6 months
Sulfasalazine	Hematologic toxicity, hepatic toxicity, hypogammaglobulinemia	CBC with differential, liver enzymes and urinalysis every 2–3 months IgG levels every 6 months
Leflunomide	Hepatic toxicity, hematologic, mucositis, teratogenic, neuropathy	Baseline CBC and LFTs, monthly for 6 months, then every 8–12 weeks
Mycophenolate mofetil	GI upset, cytopenias, teratogenic, future malignancy, progressive multifocal leukoencephalopathy	CBC with differential every 4–6 weeks
CYTOTOXIC AGENTS		
Azathioprine	Bone marrow, liver and lung toxicity	CBC with differential weekly until stable dose established, then monthly Baseline hepatic enzymes, BUN, and serum creatinine, then monthly
Cyclophosphamide	Leukopenia, thrombocytopenia, bladder toxicity, SIADH, teratogenicity, fertility issues	Vitals when administering IV formulation (pretreatment with Mesna) Urinalysis pre- and postinfusion Urine output monitoring CBC with differential days 7, 10, 14 s/p infusion
Cyclosporine	Hypertension, immune suppression, renal toxicity, liver toxicity, hirsutism	Baseline renal function (BUN, urinalysis, creatinine), then monthly Hepatic enzymes, CBC with differential monthly
BIOLOGIC AGENTS		
Anti-TNF agents	Opportunistic infections, drug-induced lupus, malignancy, autoantibody production	Baseline TB screening Routine CBC Routine autoantibody screening

ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *BUN*, blood urea nitrogen; *CBC*, complete blood count; *CMP*, comprehensive metabolic panel; *DMARD*, disease-modifying antirheumatic drug; *GI*, gastrointestinal; *IV*, intravenous; *LFT*, liver function test; *SIADH*, syndrome of inappropriate antidiuretic hormone; *s/p*, status post; *TB*, tuberculosis; *TNF*, tumor necrosis factor.

Data from McMillan JA, Feigin RD, DeAngelis CD, et al. *Oski's Pediatrics*, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.

B. Weight Management

1. Obesity and cushingoid fat distribution often result from chronic steroid use.
2. In addition to physical health consequences, this may also cause psychologic issues.

C. Bone and Skin Health

1. Patients with arthritis or on chronic steroids are at increased risk of osteopenia. Ensure adequate calcium and vitamin D intake and weight-bearing activities.
2. Patients with SLE and dermatomyositis are particularly vulnerable to ultraviolet radiation. They should not be exposed to the sun without wearing a broad-spectrum sunscreen with a high sun-protection factor (SPF) and should not use tanning booths.

D. Reproductive Health

1. Disease-modifying antirheumatic drugs (DMARDs) and biologics, especially methotrexate, are teratogenic.
2. Teenage patients should receive counseling on the use of contraception.

E. Other Aspects of Primary Care Coordination

1. Children with JIA have an increased risk of developing uveitis, which is often insidious and asymptomatic. Routine pediatric ophthalmologic screening is required.[37]
   a. The first ophthalmologic exam should occur within 1 month of diagnosis.
   b. In active disease, exams should occur every 3 months regardless of ANA status.
   c. In inactive disease, frequency varies based on ANA status, disease duration, and age of diagnosis.
2. Patients require supportive therapies in the form of physical therapy, occupational therapy, and input from rehabilitation specialists, psychologists, and social workers.

F. Laboratory Monitoring

See Table 27.4 for information on antiarthritic drug toxicity and recommended surveillance.

IV. WEB RESOURCES

American College of Rheumatology: http://www.rheumatology.org/

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

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PART III

REFERENCE

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Chapter 28

Blood Chemistry and Body Fluids

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See additional content on Expert Consult

Determining normal reference ranges of laboratory studies in pediatric patients poses some major challenges. Available literature is often limited due to small sample sizes of patients used to derive these suggested reference ranges.

The following values have been compiled from both published literature and the Johns Hopkins Hospital Department of Pathology. Reference range values vary with the analytic method used. Consult your laboratory for its analytic method and range of reference values, and for less commonly used parameters that are beyond the scope of this text. **Additional reference laboratory values may be found in Chapters 10 (Endocrinology), Chapter 14 (Hematology), and Chapter 15 (Immunology and Allergy).**

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I. REFERENCE VALUES

(Table 28.1)

II. EVALUATION OF BODY FLUIDS

A. Evaluation of Cerebrospinal Fluid

(Table 28.2)

B. Evaluation of Urine

(Table 28.3)

C. Evaluation of Transudate / Exudate

(Table EC 28.A)

D. Evaluation of Synovial Fluid

(Table EC 28.B)

TABLE 28.1

REFERENCE VALUES

	Conventional Units	SI Units
ALANINE AMINOTRANSFERASE (ALT)[a,1]		
0 to <1 year	5–33 U/L	5–33 U/L
1 to <13 years	9–25 U/L	9–25 U/L
13–19 years (male)	9–24 U/L	9–24 U/L
13 to <19 years (female)	8–22 U/L	8–22 U/L
ALBUMIN[b,1]		
0–14 days	3.3–4.5 g/dL	33–45 g/L
15 days to <1 year	2.8–4.7 g/dL	28–47 g/L
1 to <8 years	3.8–4.7 g/dL	38–47 g/L
8 to <15 years	4.1–4.8 g/dL	41–48 g/L
15 to <19 years (male)	4.1–5.1 g/dL	41–51 g/L
15 to <19 years (female)	4.0–4.9 g/dL	40–49 g/L
ALKALINE PHOSPHATASE[1]		
0–14 days	90–273 U/L	90–273 U/L
15 days to <1 year	134–518 U/L	134–518 U/L
1 to <10 years	156–369 U/L	156–369 U/L
10 to <13 years	141–460 U/L	141–460 U/L
13 to <15 years (male)	127–517 U/L	127–517 U/L
13 to <15 years (female)	62–280 U/L	62–280 U/L
15 to <17 years (male)	89–365 U/L	89–365 U/L
15 to <17 years (female)	54–128 U/L	54–128 U/L
17 to <19 years (male)	59–164 U/L	59–164 U/L
17 to <19 years (female)	48–95 U/L	48–95 U/L
AMMONIA[5]		
0–14 days	35.8–161.8 mCg/dL	21–95 mcmol/L
15 days to 6 years	27.2–115.8 mCg/dL	16–68 mcmol/L
>6 years	30.7–122.6 mCg/dL	18–72 mcmol/L
AMYLASE[1]		
0–14 days	3–10 U/L	3–10 U/L
15 days to <13 weeks	2–22 U/L	2–22 U/L
13 weeks to <1 year	3–50 U/L	3–50 U/L
1 year to <19 years	25–101 U/L	25–101 U/L
ANTISTREPTOLYSIN O TITER[1]		
0 to <6 months	0 IU/mL	0 IU/mL
6 months to <1 year	0–30 IU/mL	0–30 IU/mL
1 to <6 years	0–104 IU/mL	0–104 IU/mL
6 to <19 years	0–331 IU/mL	0–331 IU/mL
ASPARTATE AMINOTRANSFERASE (AST)[c,1]		
0–14 days	32–162 U/L	32–162 U/L
15 days to <1 year	20–67 U/L	20–67 U/L
1 to <7 years	21–44 U/L	21–44 U/L
7 to <12 years	18–36 U/L	18–36 U/L
12 to <19 years (male)	14–35 U/L	14–35 U/L
12 to <19 years (female)	13–26 U/L	13–26 U/L
BICARBONATE[1]		
0–14 days	5–20 mEq/L	5–20 mmol/L
15 days to <1 year	10–24 mEq/L	10–24 mmol/L

TABLE 28.1—CONT'D

	Conventional Units	SI Units
1 to <5 years	14–24 mEq/L	14–24 mmol/L
5 to <15 years	17–26 mEq/L	17–26 mmol/L
Male 15 to <19 years	18–28 mEq/L	18–28 mmol/L
Female 15 to <19 years	17–26 mEq/L	17–26 mmol/L
BILIRUBIN (TOTAL)[1]		
See Chapter 18 for more complete information about neonatal hyperbilirubinemia.		
0–14 days	0.19–16.60 mg/dL	3.25–283.92 mcmol/L
15 days to <1 year	0.05–0.68 mg/dL	0.86–11.63 mcmol/L
1 to <9 years	0.05–0.40 mg/dL	0.86–6.84 mcmol/L
9 to <12 years	0.05–0.55 mg/dL	0.86–9.41 mcmol/L
12 to <15 years	0.10–0.70 mg/dL	1.71–11.97 mcmol/L
15 to <19 years	0.10–0.84 mg/dL	1.71–14.37 mcmol/L
BILIRUBIN (CONJUGATED)[1]		
0–14 days	0.33–0.71 mg/dL	5.64–12.14 mcmol/L
15 days to <1 year	0.05–0.30 mg/dL	0.86–5.13 mcmol/L
1 to <9 years	0.05–0.20 mg/dL	0.86–3.42 mcmol/L
9 to <13 years	0.05–0.29 mg/dL	0.86–4.96 mcmol/L
13 to <19 years (female)	0.10–0.39 mg/dL	1.71–6.67 mcmol/L
13 to <19 years (male)	0.11–0.42 mg/dL	1.88–7.18 mcmol/L

BLOOD GAS, ARTERIAL (BREATHING ROOM AIR)[6]

	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	HCO_3^- (mEq/L)
Cord blood	7.28 ± 0.05	18.0 ± 6.2	49.2 ± 8.4	14–22
Newborn (birth)	7.11–7.36	8–24	27–40	13–22
5–10 min	7.09–7.30	33–75	27–40	13–22
30 min	7.21–7.38	31–85	27–40	13–22
60 min	7.26–7.49	55–80	27–40	13–22
1 day	7.29–7.45	54–95	27–40	13–22
Child/adult	7.35–7.45	83–108	32–48	20–28

NOTE: Venous blood gases can be used to assess acid-base status, not oxygenation. $PvCO_2$ averages 6–8 mmHg higher than $PaCO_2$, and pH is slightly lower. Peripheral venous samples are strongly affected by the local circulatory and metabolic environment. Capillary blood gases correlate best with arterial pH and moderately well with $PaCO_2$.

C-REACTIVE PROTEIN (HIGH SENSITIVITY)[1]		
0–14 days	0.3–6.1 mg/L	0.3–6.1 mg/L
15 days to <15 years	0.1–1.0 mg/L	0.1–1.0 mg/L
15 to <19 years	0.1–1.7 mg/L	0.1–1.7 mg/L
CALCIUM (IONIZED)[7]		
0–1 month	3.9–6.0 mg/dL	1.0–1.5 mmol/L
1–6 months	3.7–5.9 mg/dL	0.95–1.5 mmol/L
1–19 years	4.9–5.5 mg/dL	1.22–1.37 mmol/L
CALCIUM (TOTAL)[1]		
0 to <1 year	8.5–11.0 mg/dL	2.1–2.7 mmol/L
1 year to <19 years	9.2–10.5 mg/dL	2.3–2.6 mmol/L
CARBON MONOXIDE (CARBOXYHEMOGLOBIN)[6]		
Nonsmoker	0–2% of total hemoglobin	
Smoker	0–9% of total hemoglobin	

Continued

TABLE 28.1—CONT'D

	Conventional Units	SI Units
CHLORIDE (SERUM)[8]		
3–5 years	100–107 mEq/L	100–107 mmol/L
6–11 year	101–107 mEq/L	101–107 mmol/L
12–29 years (male)	101–106 mEq/L	101–106 mmol/L
12–29 years (female)	100–107 mEq/L	100–107 mmol/L
CHOLESTEROL		
(See LIPIDS, further on)		
COPPER[9]		
6 months to 2 years	72–178 mCg/dL	11.3–28.0 mcmol/L
3–4 years	80–160 mCg/dL	12.6–25.2 mcmol/L
5–6 years	76–167 mCg/dL	12.0–26.3 mcmol/L
7–8 years	79–147 mCg/dL	12.4–23.1 mcmol/L
9–10 years	84–154 mCg/dL	13.2–24.2 mcmol/L
11–12 years	73–149 mCg/dL	11.5–23.4 mcmol/L
13–14 years	66–137 mCg/dL	10.4–21.6 mcmol/L
15–16 years	60–132 mCg/dL	9.4–20.8 mcmol/L
17–18 years	59–146 mCg/dL	9.3–23.0 mcmol/L
CREATINE KINASE[10]		
6 months to 2 years (male)	50–292 U/L	50–292 U/L
6 months to 2 years (female)	38–260 U/L	38–260 U/L
3–5 years (male)	59–296 U/L	59–296 U/L
3–5 years (female)	42–227 U/L	42–227 U/L
6–8 years (male)	54–275 U/L	54–275 U/L
6–8 years (female)	50–231 U/L	50–231 U/L
9–11 years (male)	55–324 U/L	55–324 U/L
9–11 years (female)	52–256 U/L	52–256 U/L
12–14 years (male)	63–407 U/L	63–407 U/L
12–14 years (female)	45–257 U/L	45–257 U/L
15–17 years (male)	68–914 U/L	68–914 U/L
15–17 years (female)	45–458 U/L	45–458 U/L
CREATININE (SERUM) (ENZYMATIC)[1]		
0–14 days	0.32–0.92 mg/dL	28.29–81.33 mcmol/L
15 days to <2 years	0.10–0.36 mg/dL	8.84–31.82 mcmol/L
2 to <5 years	0.20–0.43 mg/dL	17.68–38.01 mcmol/L
5 to <12 years	0.31–0.61 mg/dL	27.40–53.93 mcmol/L
12 to <15 years	0.45–0.81 mg/dL	39.78–71.61 mcmol/L
15 to <19 years (male)	0.62–1.08 mg/dL	54.81–95.47 mcmol/L
15 to <19 years (female)	0.49–0.84 mg/dL	43.32–74.26 mcmol/L
ERYTHROCYTE SEDIMENTATION RATE (ESR)[6]		
Child	0–10 mm/hr	
Adult male	0–15 mm/hr	
Adult female	0–20 mm/hr	
FERRITIN[1]		
4 to <15 days	100–717 ng/mL	224–1611 pmol/L
15 days to <6 months	14–647 ng/mL	31–1454 pmol/L
6 months to <1 year	8–182 ng/mL	19–409 pmol/L

TABLE 28.1—CONT'D

	Conventional Units	SI Units
1 to <5 years	5–100 ng/mL	12–224 pmol/L
5 to <14 years	14–79 ng/mL	31–177 pmol/L
14 to <19 years (female)	6–67 ng/mL	12–152 pmol/L
14 to <16 years (male)	13–83 ng/mL	28–186 pmol/L
16 to <19 years (male)	11–172 ng/mL	25–386 pmol/L
FOLATE (RBC)[5]		
Deficient	≤3.9 ng/mL	≤8.7 nmol/L
Indeterminate	4.0–5.8 ng/mL	9.1–13.1 nmol/L
Normal	≥5.9 ng/mL	≥13.4 nmol/L
FOLATE (SERUM)[5]	≥366 ng/mL	≥831 nmol/L
GAMMA-GLUTAMYL TRANSFERASE (GGT)[d,1]		
0–14 days	23–219 U/L	23–219 U/L
15 days to <1 year	8–127 U/L	8–127 U/L
1 to <11 years	6–16 U/L	6–16 U/L
11 to <19 years	7–21 U/L	7–21 U/L
GLUCOSE		
See Chapter 10.		
HAPTOGLOBIN[1]		
0–14 days	0–10 mg/dL	0–0.10 g/L
15 days to <1 year	7–221 mg/dL	0.07–2.21 g/L
1 to <12 years	7–163 mg/dL	0.07–1.63 g/L
12 to <19 years	7–179 mg/dL	0.07–1.79 g/L
HEMOGLOBIN A1C		
See Chapter 10.		
HEMOGLOBIN F, % TOTAL HEMOGLOBIN[5]		
0–1 month	45.8–91.7	
2 months	32.7–85.2	
3 months	14.5–73.7	
4 months	4.2–56.9	
5 months	1.0–38.1	
6–8 months	0.9–19.4	
9–12 months	0.6–11.6	
13–23 months	0.0–8.5	
2 years and older	0.0–2.1	
IRON[1]		
0 to <14 years	16–128 mCg/dL	2.8–22.9 mcmol/L
14–19 years (male)	31–168 mCg/dL	5.5–40.0 mcmol/L
14–19 years (female)	20–162 mCg/dL	3.5–29.0 mcmol/L
LACTATE[7]		
0–90 days	9–32 mg/dL	1.0–3.5 mmol/L
3–24 months	9–30 mg/dL	1.0–3.3 mmol/L
2–18 years	9–22 mg/dL	1.0–2.4 mmol/L
LACTATE DEHYDROGENASE[1]		
0–14 days	309–1222 U/L	309–1222 U/L
15 days to <1 year	163–452 U/L	163–452 U/L
1 to <10 years	192–321 U/L	192–321 U/L

Continued

TABLE 28.1—CONT'D

	Conventional Units	SI Units
10 to <15 years (male)	170–283 U/L	170–283 U/L
10 to <15 years (female)	157–272 U/L	157–272 U/L
15 to <19 years	130–250 U/L	130–250 U/L
LEAD		
See Chapter 3.		
LIPASE[1]		
0 to <19 years	4.0–39.0 U/L	4.0–39.0 U/L
LIPIDS[11]		

	Desirable	Borderline	High[g]
Total cholesterol	<170 mg/dL (4.4 mmol/L)	170–199 mg/dL (4.4–5.2 mmol/L)	≥200 mg/dL (5.2 mmol/L)
LDL	<110 mg/dL (2.8 mmol/L)	110–129 mg/dL (2.8–3.3 mmol/L)	≥130 mg/dL (3.4 mmol/L)
Non-HDL	<120 mg/dL (3.1 mmol/L)	120–144 mg/dL (3.1–3.7 mmol/L)	≥145 mg/dL (3.8 mmol/L)
HDL	>45 mg/dL (1.2 mmol/L)	40–45 mg/dL (1.0–1.2 mmol/L)	≤40 mg/dL (1.0 mmol/L)
Triglycerides (0–9 years)	<75 mg/dL (0.8 mmol/L)	75–99 mg/dL (0.8–1.1 mmol/L)	≥100 mg/dL (1.1 mmol/L)
Triglycerides (10–19 years)	<90 mg/dL (1.0 mmol/L)	90–129 mg/dL (1.0–1.5 mmol/L)	≥130 mg/dL (1.5 mmol/L)

	Conventional Units	SI Units
MAGNESIUM[1]		
0–14 days	1.99–3.94 mg/dL	0.82–1.62 mmol/L
15 days to <1 year	1.97–3.09 mg/dL	0.81–1.27 mmol/L
1 to <19 years	2.09–2.84 mg/dL	0.86–1.17 mmol/L
OSMOLALITY[5]		
0–16 years	271–296 mOsm/kg	271–296 mmol/kg
17 years and older	280–303 mOsm/kg	280–303 mmol/kg
PHOSPHORUS[1]		
0–14 days	5.6–10.5 mg/dL	1.8–3.4 mmol/L
15 days to <1 year	4.8–8.4 mg/dL	1.5–2.7 mmol/L
1 to <5 years	4.3–6.8 mg/dL	1.4–2.2 mmol/L
5 to <13 years	4.1–5.9 mg/dL	1.3–1.9 mmol/L
13 to <16 years (male)	3.5–6.2 mg/dL	1.1–2.0 mmol/L
13 to <16 years (female)	3.2–5.5 mg/dL	1.0–1.8 mmol/L
16 to <19 years	2.9–5.0 mg/dL	0.9–1.6 mmol/L
PORCELAIN[12]		
Male	5.28–20.15 mg/dL	6.15–20.13 mmol/L
Female	7.20–19.21 mg/dL	7.01–20.15 mmol/L
POTASSIUM[6]		
Preterm	3.0–6.0 mEq/L	3.0–6.0 mmol/L
Newborn	3.7–5.9 mEq/L	3.7–5.9 mmol/L
Infant	4.1–5.3 mEq/L	4.1–5.3 mmol/L

TABLE 28.1—CONT'D

	Conventional Units	SI Units
Child	3.4–4.7 mEq/L	3.4–4.7 mmol/L
Thereafter	3.5–5.1 mEq/L	3.5–5.1 mmol/L
PREALBUMIN[1]		
0–14 days	2–12 mg/dL	0.02–0.12 g/L
15 days to <1 year	5–24 mg/dL	0.05–0.24 g/L
1 to <5 years	12–23 mg/dL	0.12–0.23 g/L
5 to <13 years	14–26 mg/dL	0.14–0.26 g/L
13 to <16 years	18–31 mg/dL	0.18–0.31 g/L
16 to <19 years (male)	20–35 mg/dL	0.20–0.35 g/L
16 to <19 years (female)	17–33 mg/dL	0.17–0.33 g/L
RHEUMATOID FACTOR[1]		
0–14 days	9.0–17.1 IU/mL	9.0–17.1 IU/mL
15 days to <19 years	0–9.0 IU/mL	0–9.0 IU/mL
SODIUM[8]		
3–5 years	135–142 mEq/L	135–142 mmol/L
6–15 years	136–143 mEq/L	136–143 mmol/L
16–49 years (male)	137–143 mEq/L	137–143 mmol/L
16–49 years (female)	137–142 mEq/L	137–142 mmol/L
TOTAL IRON-BINDING CAPACITY (TIBC)[5]		
0–2 months	59–175 mCg/dL	11–31 mcmol/L
3 months to 17 years	250–400 mCg/dL	45–72 mcmol/L
18 years and older	240–450 mCg/dL	43–81 mcmol/L
TOTAL PROTEIN[1]		
0–14 days	5.3–8.3 g/dL	53–83 g/L
15 days to <1 year	4.4–7.1 g/dL	44–71 g/L
1 to <6 years	6.1–7.5 g/dL	61–75 g/L
6 to <9 years	6.4–7.7 g/dL	64–77 g/L
9 to <19 years	6.5–8.1 g/dL	65–81 g/L
TRANSFERRIN[1]		
0 to <9 weeks	104–224 mg/dL	1.04–2.24 g/L
9 weeks <1 year	107–324 mg/dL	1.07–3.24 g/L
1 to <19 years	220–337 mg/dL	2.2–3.37 g/L
TRIGLYCERIDES		
(See LIPIDS, earlier)		
UREA NITROGEN[1]		
0 to <14 days	2.8–23.0 mg/dL	1.0–8.2 mmol/L
15 days to <1 year	3.4–16.8 mg/dL	1.2–6.0 mmol/L
1 to <10 years	9.0–22.1 mg/dL	3.2–7.9 mmol/L
Male 10 to <19 years	7.3–21 mg/dL	2.6–7.5 mmol/L
Female 10 to <19 years	7.3–19 mg/dL	2.6–6.8 mmol/L
URIC ACID[1]		
0–14 days	2.8–12.7 mg/dL	0.2–0.8 mmol/L
15 days to <1 year	1.6–6.3 mg/dL	0.1–0.4 mmol/L
1 to <12 years	1.8–4.9 mg/dL	0.1–0.3 mmol/L

Continued

TABLE 28.1—CONT'D

	Conventional Units	SI Units
Male 12 to <19 years	2.6–7.6 mg/dL	0.2–0.5 mmol/L
Female 12 to <19 years	2.6–5.9 mg/dL	0.2–0.4 mmol/L
VITAMIN A (RETINOL)[1]		
0 to <1 year	8.0–53.6 mg/dL	0–2 mcmol/L
1 to <11 years	27.5–44.4 mg/dL	1–2 mcmol/L
11 to <16 years	24.9–55.0 mg/dL	1–2 mcmol/L
16 to <19 years	28.7–75.1 mg/dL	1–3 mcmol/L
VITAMIN B_1 (THIAMINE) RBC[6]	4.5–10.3 mCg/dL	106–242 nmol/L
VITAMIN B_2 (RIBOFLAVIN)[6]	4–24 mCg/dL	106–638 nmol/L
VITAMIN B_{12} (COBALAMIN)[1]		
5 days to <1 year	259–1576 pg/mL	191–1163 pmol/L
1 to <9 years	283–1613 pg/mL	209–1190 pmol/L
9 to <14 years	252–1125 pg/mL	186–830 pmol/L
14 to <17 years	244–888 pg/mL	180–655 pmol/L
17 to <19 years	203–811 pg/mL	150–599 pmol/L
VITAMIN C (ASCORBIC ACID)[6]	0.4–2.0 mg/dL	23–114 mcmol/L
VITAMIN D (1,25-DIHYDROXY-VITAMIN D)[13]		
0 to <1 year	32.1–196.2 pg/mL	77–471 pmol/L
1 to <3 years	47.1–151.2 pg/mL	113–363 pmol/L
3 to <19 years	45.0–102.5 pg/mL	108–246 pmol/L
VITAMIN D (25-HYDROXY-VITAMIN D)[14,15]		
Deficient	<12 ng/mL	<30 nmol/L
Insufficient	12–20 ng/mL	30–50 nmol/L
Sufficient[f]	≥20 ng/mL	≥50 nmol/L
Excess	>50–60 ng/mL	>125–150 nmol/L
VITAMIN E (α-TOCOPHEROL)[1]		
0 to <1 year	0.2–2.1 mg/dL	5.0–50.0 mcmol/L
1 to <19 years	0.6–1.4 mg/dL	14.5–33.0 mcmol/L
ZINC[9]		
6 months to 2 years	56–125 mCg/dL	8.6–19.1 mcmol/L
3–4 years	60–120 mCg/dL	9.2–18.4 mcmol/L
5–6 years	64–117 mCg/dL	9.8–17.9 mcmol/L
7–8 years	65–125 mCg/dL	9.9–19.1 mcmol/L
9–10 years	66–125 mCg/dL	10.1–19.1 mcmol/L
11–12 years	66–127 mCg/dL	10.1–19.4 mcmol/L
13–14 years	69–124 mCg/dL	10.6–19.0 mcmol/L
15–16 years	62–123 mCg/dL	9.5–18.8 mcmol/L
17–18 years	62–133 mCg/dL	9.5–20.3 mcmol/L

[a]These reference ranges are similar to data from the SAFETY study,[2] which examined 12- to 17-year-old NHANES participants and identified the 95th percentile of ALT in boys to be 25.8 U/L and in girls to be 22.1 U/L. In all age groups, similar yet slightly higher ALT cutoffs were published in Bussler et al.[3] (LIFE Child cohort) and in Zierk et al.[4]

[b]Assay with bromocresol green.

[c]In all age groups, similar, yet slightly higher AST cutoffs were published in Bussler et al.[3] (LIFE Child cohort) and in Zierk et al.[4]

[d]Similar data can also be referenced for all age groups in Bussler et al.[3] (LIFE Child cohort) and Zierk et al.[4]

[e]It is important to note that these values have not been validated to demonstrate increased risk of atherosclerosis or cardiovascular events.

[f]Controversy exists regarding optimal 25-hydroxyvitamin D level. Some experts recommend a level ≥30 ng/mL as sufficient.[16]

TABLE 28.2

EVALUATION OF CEREBROSPINAL FLUID

WBC		
Age	**Count/mcL (median)**	**95th Percentile**
0–28 days[17]	0–12[a] (4)	16
29–60 days[17]	0–8[a] (2)	11
Child[18]	0–7	
GLUCOSE		
Age	**Median**	**5th Percentile**
0–28 days[17]	45 mg/dL	35 mg/dL
29–60 days[17]	47 mg/dL	37 mg/dL
	Conventional Units	**SI Units**
Infant, child[6]	60–80 mg/dL	3.3–4.4 mmol/L
Adult[6]	40–70 mg/dL	2.2–3.9 mmol/L
PROTEIN		
Age	**Median**	**95th Percentile**
0–28 days[17]	66 mg/dL	118 mg/dL
29–60 days[17]	49 mg/dL	91 mg/dL
	Conventional Units	**SI Units**
6 months to 2 years[19]	6–25 mg/dL	60–250 mg/L
2–6 years[19]	5–25 mg/dL	50–250 mg/L
6–12 years[19]	5–28 mg/dL	50–280 mg/L
12–18 years[19]	6–34 mg/dL	60–340 mg/L
OPENING PRESSURE (LATERAL RECUMBENT POSITION[18,20])		
Newborn	8–11 cm H_2O	
1–18 years	11.5–28 cm H_2O[a]	
Respiratory variations	0.5–1 cm H_2O	

[a]Up to 90th percentile.

WBC, White blood cell

TABLE 28.3

EVALUATION OF URINE

Urine Analyte	Normal Range
ALBUMIN[18,21]	
Random	<30 mg urine albumin/g creatinine (on first morning urine)
24-hr collection	
4–16 years (male)	3.35–13.15 mg/1.73 m^2/day
4–16 years (female)	3.75–18.34 mg/1.73 m^2/day
CALCIUM[21]	
Random	
0–6 months	<0.8 mg/mg creatinine
7–12 months	<0.6 mg/mg creatinine
≥2 years	<0.21 mg/mg creatinine
24-hr collection	<4 mg/kg/day
CHLORIDE[6]	
Random	
Male	25–253 mEq/g creatinine
Female	39–348 mEq/g creatinine
24-hr collection	
Infant	2–10 mEq/day
Child <6 years	15–40 mEq/day
6–10 years (male)	36–110 mEq/day
6–10 years (female)	18–74 mEq/day
10–14 years (male)	64–176 mEq/day
10–14 years (female)	36–173 mEq/day
Adult	110–250 mEq/day
CREATININE[6]	
Random	
Male <40 years	24–392 mg/dL
Female <40 years	16–327 mg/dL
24-hr collection	
Infant	8–20 mg/kg/day
Child	8–22 mg/kg/day
Adolescent	8–30 mg/kg/day
Adult (male)	14–26 mg/kg/day
Adult (female)	11–20 mg/kg/day
POTASSIUM[6]	
Random	
Male	13–116 mEq/g creatinine
Female	8–129 mEq/g creatinine
24-hr collection	
6–10 years (male)	17–54 mEq/day
6–10 years (female)	8–37 mEq/day
10–14 years (male)	22–57 mEq/day
10–14 years (female)	18–58 mEq/day
Adult	25–125 mEq/day

TABLE 28.3—CONT'D

PROTEIN[18,21]	
Random	
6 months to 24 months	<0.5 mg protein/mg creatinine
>2 years	<0.2 mg protein/mg creatinine
24-hr collection	
At rest	50–80 mg/day
After intense exercise	<250 mg/day
SODIUM[6]	
Random	
Male	23–229 mEq/g creatinine
Female	26–297 mEq/g creatinine
24-hr collection	
Full-term, 7–14 days	~20% that of adults
6–10 years (male)	41–115 mEq/day
6–10 years (female)	20–69 mEq/day
10–14 years (male)	63–177 mEq/day
10–14 years (female)	48–168 mEq/day
Adult	40–220 mEq/day
UREA NITROGEN[6]	
Random	
Male	2,864–9,851 mg/g creatinine
Female	3,129–11,639 mg/g creatinine
24-hr collection	12–20 g/day
URINE OSMOLALITY[6]	
Random	50–1,200 mOsm/kg H_2O, depending on fluid intake
On average fluid intake	300–900 mOsm/kg H_2O
After 12 hr fluid restriction	>850 mOsm/kg H_2O
24-hr collection	~300–900 mOsm/kg H_2O

TABLE EC 28.A

EVALUATION OF TRANSUDATE VERSUS EXUDATE (PLEURAL, PERICARDIAL, OR PERITONEAL FLUID)

Measurement[a]	Transudate	Exudate[b]
Protein (g/dL)	<3.0	>3.0
Fluid/serum protein ratio	<0.5	≥0.5
LDH (IU/L)	<200	≥200
Fluid/serum LDH ratio	<0.6	≥0.6
WBCs (mm^3)[c]	<10,000 (PMN)	>10,000 (PMN)
RBCs (mm^3)	<5,000	>5,000
Glucose (mg/dL)	>40	<40
pH[d]	>7.2	<7.2

[a]Always obtain serum for glucose, LDH, protein, amylase, etc. for comparison.

[b]All of the following criteria do not have to be met for consideration as an exudate.

[c]In peritoneal fluid, WBC count >800/mcL suggests peritonitis.

[d]Collect anaerobically in a heparinized syringe.

Amylase >5000 U/mL or pleural fluid/serum ratio >1 suggests pancreatitis.

LDH, Lactate dehydrogenase; *RBCs,* red blood cells; *WBCs,* white blood cells

Data from Nichols DG, Ackerman AD, Carcillo JA, et al. *Rogers Textbook of Pediatric Intensive Care.* 4th ed. Baltimore: Williams & Wilkins; 2008.

TABLE EC 28.B

CHARACTERISTICS OF SYNOVIAL FLUID

Group	Condition	Synovial Complement	Color/Clarity	Viscosity	Mucin Clot	WBC Count	PMN (%)	Miscellaneous Findings
Noninflammatory	Normal	N	Yellow Clear	↑↑	G	<200	<25	
	Traumatic arthritis	N	Xanthochromic Turbid	↑	F–G	<2,000	<25	Debris
	Osteoarthritis	N	Yellow Clear	↑	F–G	1,000	<25	
Inflammatory	Systemic lupus erythematosus	↓	Yellow Clear	N	N	5,000	10	Lupus cells
	Rheumatic fever	N–↑	Yellow Cloudy	↓	F	5,000	10–50	
	Juvenile rheumatoid arthritis	N–↓	Yellow Cloudy	↓	Poor	15,000–20,000	75	
	Reactive arthritis	↑	Yellow Opaque	↓	Poor	20,000	80	
Pyogenic	Tuberculous arthritis	N–↑	Yellow-white Cloudy	↓	Poor	25,000	50–60	Acid-fast bacteria
	Septic arthritis	↑	Serosanguineous Turbid	↓	Poor	50,000–300,000	>75	Low glucose, bacteria

F, Fair; *G,* good; *H,* high; *N,* normal; *PMN,* polymorphonuclear leukocyte; *WBC,* white blood cell; ↓, decreased; ↑, increased

From Cassidy JT, Petty RE. *Textbook of Pediatric Rheumatology.* 5th ed. Philadelphia: WB Saunders; 2005.

III. CONVERSION FORMULAS

A. Temperature

1. **To convert degrees Celsius to degrees Fahrenheit:**

$$[(9/5) \times \text{Celsius}] + 32$$

2. **To convert degrees Fahrenheit to degrees Celsius:**

$$(\text{Fahrenheit} - 32) \times (5/9)$$

B. Length and Weight

1. **Length:** To convert inches to centimeters, multiply by 2.54
2. **Weight:** To convert pounds to kilograms, divide by 2.2

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Chapter 29

Biostatistics and Evidence-Based Medicine

Matthew Molloy, MD, MPH

I. EVIDENCE-BASED MEDICINE

Evidence-based medicine refers to the method of integrating individual clinical expertise with the best available evidence from the literature. The following is a framework on how to formulate a clinical question and appraise the evidence[1]:

A. Formulate the Clinical Question (PICO Process)

1. **P: Describe the *patient* or *problem*,** deciding whether the evidence you seek is regarding therapy, diagnosis, prognosis, etiology, or cost effectiveness.
2. **I: Describe the *intervention*** under consideration.
3. **C: *Compare* the intervention** with an alternative or current standard of care.
4. **O: Formulate a specific *outcome*** of interest.

B. Search for the Evidence to Answer the Question

1. **Define search terms** that fit the clinical question.
2. **Develop your search strategy** using primary search sources such as PubMed and secondary sources such as Cochrane.
3. **Review your results,** and apply methodological filters to target the right type of study.

C. Critically Appraise the Evidence

1. **Therapy**
   a. Were patient groups randomized for treatment?
   b. Were groups comparable and treated equally, aside from the allocated treatment?
   c. Were study subjects and investigators blinded?
   d. Were all patients entering the trial accounted for in the groups they were randomized to (intention to treat)?
   e. How large was the treatment effect?
2. **Diagnosis**
   a. Was the test compared with an independent reference standard?
   b. Was the test evaluated in an appropriate spectrum of patients?
3. **Prognosis**
   a. Were study patients defined early in their course and followed up over a sufficient time?
   b. How likely is it that the outcomes occur during a defined time period?
   c. How precise are the estimates of prognosis?

4. **Guidelines for judging *causality* between a variable and outcome**[2]
   a. Is there a temporal relationship?
   b. What is the strength of association?
   c. Is there a dose-response relationship?
   d. Were the findings replicated?
   e. Are the findings biologically plausible?
   f. What happens with cessation of exposure?
   g. Is this explanation consistent with other knowledge?
5. **Bias:** Consider these types of bias that may influence results or distort statistical findings[2]:
   a. *Selection bias:* Caused by a nonrandom or dissimilar sample (between cases/controls or exposed/unexposed) from a population. Examples include sampling bias, loss to follow-up, and exclusion bias. Mitigated by randomization and selection of participants who are representative of the target population.
   b. *Information bias*: Caused by flawed collection of information about exposures or outcomes. Examples include recall bias, observer bias, and lead-time bias. Mitigated by blinding researchers to subject status and standardizing data collection procedures.

D. Apply the Evidence to the Clinical Question

If the evidence is valid and important, integrate it with your clinical expertise and decide whether:

1. The patient will benefit from the therapy and be able to tolerate potential harms.
2. The test is available, affordable, accurate, and precise.

II. BIOSTATISTICS AND EPIDEMIOLOGY

A. Statistical Tests

The following statistical tests are used to determine whether observed differences are statistically significant (Table 29.1).[3-5]

1. *Parametric tests* are used when data follow a particular distribution (e.g., a normal distribution—a bell-shaped distribution where the median, mean, and mode are all equal). These tests are generally more powerful.
2. *Nonparametric tests* are used when a particular distribution cannot be assumed; they rank data rather than taking absolute differences into account.
3. *Unpaired tests* compare values from independent samples.
4. *Paired tests* are performed on paired data. For example, where the same parameter is measured on each patient before and after an intervention.
5. *Two-tailed tests* should be used when an intervention could potentially lead to either an increase or decrease of the outcome.
6. *One-tailed tests* should be used when an intervention can have only one plausible effect on the outcome.

TABLE 29.1

COMMONLY USED STATISTICAL TESTS

Purpose of Test	Parametric Test	Nonparametric Test	Example
Compares two independent samples	Two-sample (unpaired) *t* test	Mann-Whitney *U* test	To compare girls' heights with boys' heights
Compares two sets of observations on a single sample	One-sample (paired) *t* test	Wilcoxon matched pairs test	To compare weight of infants before and after a feeding
Compares three or more sets of observations made on a single sample	One-way analysis of variance (*F* test) using total sum of squares	Kruskal-Wallis analysis of variance by ranks	To determine whether plasma glucose level is higher 1 hr, 2 hr, or 3 hr after a meal
As above, but tests the influence (and interaction) of two different variables	Two-way analysis of variance (ANOVA)	Two-way analysis of variance by ranks	In the above example, to determine whether the results differ in male and female subjects
Tests the null hypothesis that the distribution of a categorical variable is the same in two (or more) independent samples	χ^2 (chi square) test	Fisher exact test	To assess whether acceptance into medical school is more likely if the applicant was born in Britain
Assesses the strength of the straight-line association between two continuous variables	Product moment correlation coefficient (Pearson *r*)	Spearman rank correlation coefficient (rσ)	To assess whether and to what extent plasma HbA1C concentration is related to plasma triglyceride concentration in diabetic patients
Describes the numerical relation between two quantitative variables, allowing one value to be predicted from the other	Regression by least squares method	Nonparametric regression (various tests)	To see how peak expiratory flow rate varies with height
Describes the numerical relationship between a dependent variable and several predictor variables (covariates)	Multiple regression by least squares method	Nonparametric regression (various tests)	To determine whether and to what extent a person's age, body fat, and sodium intake determine his or her blood pressure

Adapted from Greenhalgh T. How to read a paper: Statistics for the non-statistician. I: Different types of data need different statistical tests. *BMJ.* 1997;315(7104):364–366.

B. Statistical Terminology

1. **α (Alpha): Significance level of a statistical test**[3,6]
   a. **α:** Probability of making a **type I error**; the probability of rejecting the null hypothesis when the null hypothesis is true (i.e., a difference is seen by chance alone).

   b. **α** is typically set at less than 0.05 in medical research, which allows interpretation with 95% certainty that a detected association is true.
   c. The ***P* value** is the probability of obtaining the observed values if the null hypothesis is true. For example, if $P = 0.01$, there is a 1 in 100 chance of the values being from chance alone. The *P* value is judged against α, the preset level of significance. If *P* is less than the significance level α, the detected association is considered significant.
2. **β (Beta): Power of a statistical test**
   a. **β:** Probability of making a **type II error**; the probability of accepting the null hypothesis when the alternative hypothesis is true (i.e., no difference is seen even though there is one).
   b. **Power = 1 – β:** Probability of correctly rejecting the null hypothesis (i.e., finding a difference when there truly is one).
   c. **Power** is typically set at a minimum of 0.80, which allows interpretation with 80% certainty that a detected lack of association is true.
3. **Sample size:** The number of subjects required in a study to detect an effect with a predetermined power and α.
4. **95% confidence interval:** Describes the values between which there is a 95% chance that the true population value falls. When confidence intervals for groups overlap, they have no statistically significant difference.
5. **Confounder:** A variable associated with both the disease and the exposure (risk factor), leading to detection of a false relationship between the disease and exposure if the confounder is not accounted for. Can be controlled for by adjustment, matching, blinding, and randomization.
6. **Effect modifier (interaction):** A variable that modifies the observed effect of an exposure on disease. For example, if a new drug is effective in female children but not male children, then sex is an effect modifier. Can be controlled by stratification.

C. Types of Study Designs[7] (see Table 29.2)

D. Measurement of Disease Occurrence and Treatment Effects[2]:

See Table 29.3 for equations in this section.

1. **Prevalence:** Proportion of population who has a disease at a point in time. Obtained in cross-sectional studies.

$$\text{Prevalence} = \frac{\text{Number of total cases}}{\text{Population size}}$$

2. **Incidence:** Rate of people developing a disease in the population during a defined time period. Obtained in cohort studies and clinical trials.

$$\text{Incidence} = \frac{\text{Number of new cases}}{\text{Population size}} \text{ per unit of time}$$

TABLE 29.2

STUDY DESIGN COMPARISON[a]

Design Type	Cross-Sectional	Case-Control (Retrospective)	Cohort (Usually Prospective, Occasional Retrospective)	Clinical Trial (Experimental)	Meta-Analysis
Definition	In study population, concurrently measure outcome (disease) and risk factor Compare proportion of diseased group with risk factor to proportion of nondiseased group with risk factor	Define cases (with outcome of interest) and controls (without outcome) Compare proportion of cases with exposure (risk factor) to proportion of controls with exposure (risk factor)	In study population, define exposed group (with risk factor) and nonexposed group (without risk factor) Over time, compare proportion of exposed group with outcome (disease) to proportion of nonexposed group with outcome (disease)	In study population, randomly assign subjects to receive intervention or receive no intervention Compare rate of outcomes between intervention and control groups	Combines data from multiple independent studies to maximize precision and power in testing for statistical significance
Advantages	Defines prevalence Short time to complete Inexpensive	Good for rare diseases/outcomes Small sample size Shorter study times Less expensive Can study association of multiple exposures with outcome	Defines incidence Stronger evidence for causality Decreases biases (sampling, measurement, reporting) Can study association of exposure with multiple outcomes	Randomized controlled trial is gold standard Randomization reduces confounding Best evidence for causality	Higher statistical power Can control for inter-study variation
Disadvantages	Selection bias Weak evidence for causality	Highest potential for biases Weak evidence for causality Unable to determine prevalence, incidence	Expensive Long study times May not be feasible for rare diseases/outcomes Factors related to exposure and outcome may falsely alter effect of exposure on outcome (confounding)	Expensive Risks of experimental treatments in humans Longer study time Not suitable for rare diseases/outcomes	Publication bias

[a]Listed in order of strength of evidence, with cross-sectional studies generally providing the weakest evidence and meta-analyses the strongest.

Adapted from Hulley SB, Cummings SR, Browner WS, et al. Designing Clinical Research. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2013:84–207.

TABLE 29.3

GRID FOR CALCULATIONS IN CLINICAL STUDIES

Exposure or Risk Factor or Treatment	Disease or Outcome	
	Positive	**Negative**
Positive	A	B
Negative	C	D

Also known as a contingency table.

3. **Relative risk (RR):** The ratio of incidence of disease among people with an exposure to incidence of disease among people without the exposure. Obtained in cohort studies and clinical trials; cannot be obtained in case-control studies.

$$RR = \frac{\frac{A}{(A+B)}}{\frac{C}{(C+D)}}$$

   a. RR = 1: No effect of exposure or treatment on outcome
   b. RR <1: Exposure or treatment protective against outcome
   c. RR >1: Exposure or treatment increases the outcome
   d. The **relative risk reduction (RRR)**, which measures the strength of the impact of an exposure or treatment, is equal to 1 – RR.

4. **Odds ratio (OR):** The ratio of the odds of an exposed person developing a disease to the odds of a nonexposed person developing the disease. Obtained in case-control studies, cohort studies, and clinical trials.

$$OR = \frac{\frac{A}{B}}{\frac{C}{D}} = \frac{A \times D}{B \times C}$$

   a. OR approximates RR when the disease is rare (incidence <0.10)
   b. OR =1: No association between risk factor and disease
   c. OR <1: Suggests that risk factor is protective against disease
   d. OR >1: Suggests positive association between risk factor and disease

5. **Risk difference:** The difference between the risk of the outcome in control and the risk of the outcome in treatment group. If the risk of the outcome is decreased by the treatment, **absolute risk reduction (ARR)** is used. If the risk of the outcome is increased by the treatment, **absolute risk increase (ARI)** is used.

$$ARR = \frac{C}{(C+D)} - \frac{A}{(A+B)}$$
$$ARI = \frac{A}{(A+B)} - \frac{C}{(C+D)}$$

6. **Number needed to treat (NNT):** Number of patients who need to be treated to prevent one undesired outcome, expressed as the inverse of ARR.

$$NNT = \frac{1}{ARR}$$

TABLE 29.4

GRID FOR EVALUATING A CLINICAL TEST

Test Result	Disease Status	
	Has Disease	Does Not Have Disease
Positive	TP (true positive)	FP (false positive)
Negative	FN (false negative)	TN (true negative)

7. **Number needed to harm (NNH):** Number of patients who need to be treated to cause one additional patient harm, expressed as the inverse of ARI.

$$\text{NNH} = \frac{1}{\text{ARI}}$$

E. Measurements of Test Performance[2]

See Table 29.4 for equations in this section.

1. **Validity:** The ability of a test to indicate which patients have or do not have disease. Intrinsic to the test—not affected by disease prevalence.
   a. **Sensitivity:** Proportion of all patients with disease who have a positive test. Measures the ability of the test to correctly identify those who have the disease. Use a highly sensitive test to help rule out a disease. Good for screening.

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

   b. **Specificity:** Proportion of all patients without disease who have a negative test. Measures the ability of the test to correctly identify those who do not have the disease. Use a highly specific test to help confirm a disease.

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

2. **Positive predictive value (PPV):** Proportion of those with positive tests who truly have disease. PPV is increased with higher disease prevalence.

$$\text{PPV} = \frac{\text{TP}}{\text{TP} + \text{FP}}$$

3. **Negative predictive value (NPV):** Proportion of those with negative tests who truly do not have disease. NPV is increased with lower disease prevalence.

$$\text{NPV} = \frac{\text{TN}}{\text{TN} + \text{FN}}$$

4. **Likelihood ratio (LR):** Incorporates the validity of a test (sensitivity and specificity) to determine the magnitude of the effect of a test result on changing the pretest probability. Used with Bayes nomogram (Fig. 29.1)

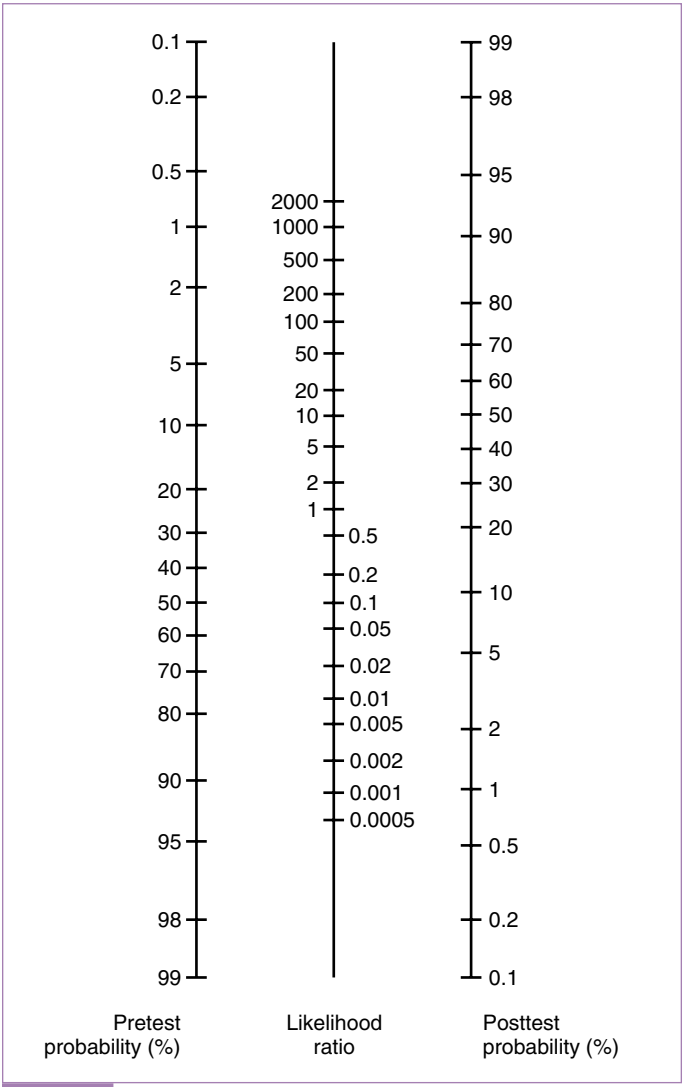

FIGURE 29.1

Bayes nomogram: Draw a line connecting the baseline probability (pretest probability) with the value for the likelihood ratio for the test used. Extend this line to the right to find the posttest probability. (Adapted from Fagan TJ. Nomogram for Bayes Theorem. *N Engl J Med*. 1975;293(5):257.)

to estimate posttest probability of a disease based on a given test result. Tests that provide the greatest impetus to changing clinical management are those with an LR ≥10 (or LR ≤0.1 for negative tests). LR is unaffected by disease prevalence.

$$\text{LR for positive test} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

$$\text{LR for negative test} = \frac{1 - \text{Sensitivity}}{\text{Specificity}}$$

III. WEB RESOURCES

A. Evidence-Based Resources

- Agency for Healthcare Research and Quality: www.ahrq.gov/research/findings/evidence-based-reports/index.html
- Centre for Evidence Based Medicine: www.cebm.net
- Cochrane Reviews: www.cochranelibrary.com
- JAMA evidence: www.jamaevidence.com
- PubMed: www.ncbi.nlm.nih.gov/pubmed
- U.S. Preventive Services Task Force: www.uspreventiveservicestaskforce.org/BrowseRec/Index

B. Biostatistics and Epidemiology Resources

- BMJ Statistics at Square One: www.bmj.com/collections/statsbk/index.dtl
- Centers for Disease Control and Prevention Epi Info: www.cdc.gov/epiinfo/

REFERENCES

A complete list of references can be found online at www.expertconsult.com.

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Chapter 30

Drug Dosages

Carlton K.K. Lee, PharmD, MPH

I. NOTE TO READER

The author has made every attempt to check dosages and medical content for accuracy. Because of the incomplete data on pediatric dosing, many drug dosages will be modified after the publication of this text. We recommend that the readers check product information and published literature for changes in dosing, especially for newer medicines. The US Food and Drug Administration (FDA) provides the following pediatric drug information data sources:

- New Pediatric Labeling Information: www.fda.gov/NewPedLabeling
- Drug Safety Report Updates: www.fda.gov/PedDrugSafety
- Pediatric Study Characteristics Database: www.fda.gov/PedStudies

Ongoing and completed clinical research study information of pediatric medicines in development is located in www.Clinicaltrials.gov.

To prevent prescribing errors, the use of abbreviations has been greatly discouraged. The following is a list of abbreviations that The Joint Commission considers prohibited for use.

THE JOINT COMMISSION

Official "Do Not Use" List[a]

Do Not Use	Potential Problem	Use Instead
U (unit)	Mistaken for "0" (zero), the number "4" (four) or "cc"	Write "unit"
IU (International Unit)	Mistaken for IV (intravenous) or the number 10 (ten)	Write "International Unit"
Q.D., QD, q.d., qd (daily)	Mistaken for each other	Write "daily"
Q.O.D., QOD, q.o.d, qod (every other day)	Period after the Q mistaken for "I" and the "O" mistaken for "I"	Write "every other day"
Trailing zero (X.0 mg)[b]	Decimal point is missed	Write X mg
Lack of leading zero (.X mg)		Write 0.X mg
MS	Can mean morphine sulfate or magnesium sulfate	Write "morphine sulfate" Write "magnesium sulfate"
MSO_4 and $MgSO_4$	Confused for one another	

[a]Applies to all orders and all medication-related documentation that is handwritten (including free-text computer entry) or on preprinted forms.

[b]Exception: A "trailing zero" may be used only where required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes. It may not be used in medication orders or other medication-related documentation.

Additional Abbreviations, Acronyms, and Symbols (For possible future inclusion in the Official "Do Not Use" List)

Do Not Use	Potential Problem	Use Instead
> (greater than)	Misinterpreted as the number "7" (seven) or the letter "L"	Write "greater than"
< (less than)	Confused for one another	Write "less than"
Abbreviations for drug names	Misinterpreted due to similar abbreviations for multiple drugs	Write drug names in full
Apothecary units	Unfamiliar to many practitioners Confused with metric units	Use metric units
@	Mistaken for the number "2" (two)	Write "at"
cc	Mistaken for U (units) when poorly written	Write "mL" or "ml" or "milliliters" ("mL" is preferred)
μg	Mistaken for mg (milligrams), resulting in one thousand-fold overdose	Write "mCg" or "micrograms"

II.SAMPLE ENTRY

Pharmacogenomics: Indicates need for assessing patient genotype or genetic polymorphism affecting dosing, drug selection, or anticipated pharmacological effects.

Liver: Indicates need for caution or need for dose adjustment in hepatic impairment.

Kidney: Indicates need for caution or need for dose adjustment in renal impairment (see also Chapter 31).

Breast: Refer to explanation of breast-feeding categories (see p. 668).

Pregnancy: Refer to explanation of pregnancy categories (see p. 668).

How Supplied

ALLOPURINOL ← Generic name

Zyloprim, Aloprim, and generics ← Trade name and other names

Uric acid–lowering agent, xanthine oxidase inhibitor ← Drug category

C	2	Yes	Yes	Yes

Tabs: 100, 300 mg
Oral suspension: 20 mg/mL
Injection (Aloprim and generics): 500 mg
Contains ~ 1.45 mEq Na/500 mg drug
For use in tumor lysis syndrome, see Chapter 22 for additional information.

Mortar and pestle: Indicates need for extemporaneous compounding by a pharmacist

Child:

Oral: 10 mg/kg/24 hr PO ÷ BID–QID; **max. dose:** 800 mg/24 hr

Injectable: 200 mg/m^2/24 hr IV ÷ Q6–12 hr; **max. dose:** 600 mg/24 hr

Adult:

Oral: 200–800 mg/24 hr PO ÷ BID–TID

Injectable: 200–400 mg/m^2/24 hr IV ÷ Q6–12 hr; **max. dose:** 600 mg/24 hr

Drug dosing

Discontinue use at the first appearance of skin rash or other signs of an allergic reaction. Avoid use in individuals with HLA-B*58:01 allele as they are at significant risk for developing severe cutaneous adverse reactions (e.g., Stevens Johnson Syndrome and TEN). Side effects include rash, neuritis, hepatotoxicity, GI disturbance, bone marrow suppression, and drowsiness. **Adjust dose in renal insufficiency (see Chapter 31).** Must maintain adequate urine output and alkaline urine.

Drug interactions: increases serum theophylline level; may increase the incidence of rash with ampicillin and amoxicillin; increased risk of toxicity with azathioprine, didanosine and mercaptopurine; and increased risk of hypersensitivity reactions with ACE inhibitors and thiazide diuretics. Use with didanosine is **contraindicated** due to increased risk for didanosine toxicity. Rhabdomyolysis has been reported with clarithromycin use. IV dosage form is very alkaline and must be **diluted to a minimum concentration** of 6 mg/mL and infused over 30 min.

Brief remarks about side effects, drug interactions, precautions, therapeutic monitoring, and other relevant information

For explanation of icons, see p. 667

III. EXPLANATION OF BREASTFEEDING CATEGORIES

See sample entry on page previous page.

1 Compatible
2 Use with caution
3 Unknown with concerns
X Contraindicated
? Safety not established

IV. EXPLANATION OF PREGNANCY CATEGORIES

A Adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.

B Animal studies have not demonstrated a risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus during the first trimester of pregnancy, and there is no evidence of risk in later trimesters.

C Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.

D There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

X Studies in animals or humans demonstrate fetal abnormalities or adverse reaction; reports indicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefit.

V. NOMOGRAM AND EQUATION FOR BODY SURFACE AREA

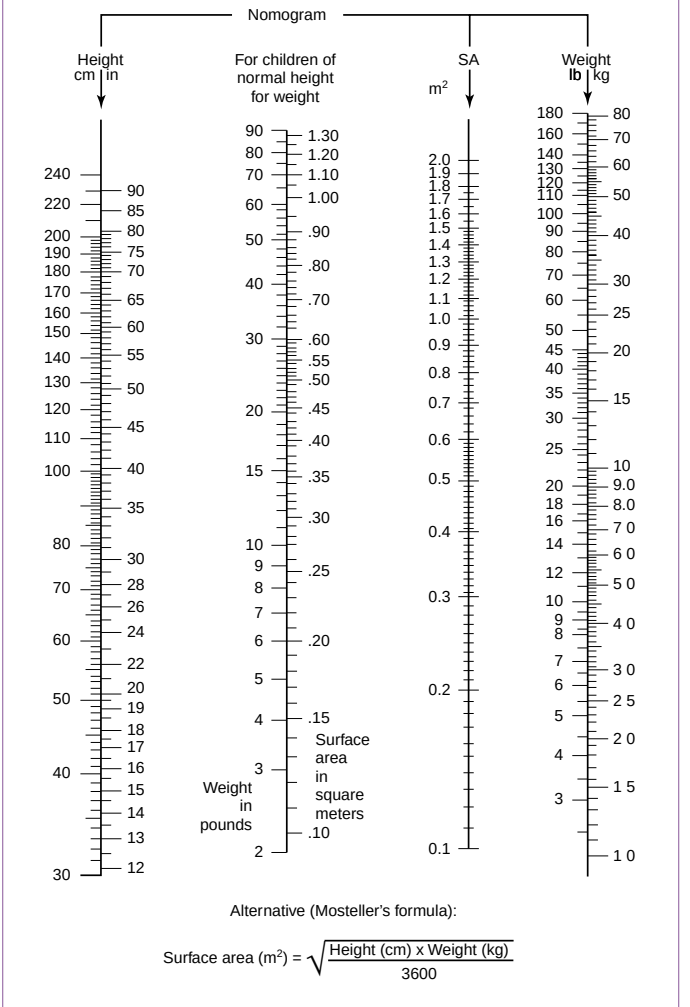

FIG. 30.1

Nomogram and equation for body surface area. (From Kliegman RM, Stanton BF, Schor NF, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia, PA: Elsevier; 2016.)

VI. DRUG INDEX

Trade Names	Generic Name
1,25-dihydroxycholecalciferol	Calcitriol
2-PAM[a]	Pralidoxime Chloride
3TC[a]	Lamivudine
5-aminosalicylic acid	Mesalamine
5-ASA	Mesalamine
5-FC[a]	Flucytosine
5-Fluorocytosine[a]	Flucytosine
8-Arginine Vasopressin[a]	Vasopressin
9-Fluorohydrocortisone[a]	Fludrocortisone Acetate
27% Elemental Ca	Calcium Chloride
A-200	Pyrethrins
Abelcet	Amphotericin B Lipid Complex
Absorica	Isotretinoin
Abstra	Fentanyl
Accolate	Zafirlukast
AccuNeb (prediluted nebulized solution)	Albuterol
Accutane	Isotretinoin
Acetadote	Acetylcysteine
Acticin	Permethrin
Actigall	Ursodiol
Actiq	Fentanyl
Activase	Alteplase
Acular, Acular LS	Ketorolac
Acuvail	Ketorolac
Aczone	Dapsone
Adalat CC	Nifedipine
Adderall, Adderall XR	Dextroamphetamine + Amphetamine
Adenocard	Adenosine
Adoxa	Doxycycline
Adrenaline	Epinephrine HCl
Advair Diskus, Advair HFA	Fluticasone Propionate and Salmeterol
Advil, Children's Advil	Ibuprofen
Aerospan	Flunisolide
Afrin	Oxymetazoline
AK-Poly-Bac Ophthalmic	Bacitracin + Polymyxin B
AK-Spore H.C. Otic	Polymyxin B Sulfate, Neomycin Sulfate, Hydrocortisone
AK-Sulf	Sulfacetamide Sodium Ophthalmic
AKTob	Tobramycin
AK-Tracin Ophthalmic	Bacitracin
Albuminar	Albumin, Human
Albutein	Albumin, Human
Aldactone	Spironolactone
Aleve [OTC]	Naproxen/Naproxen Sodium
Allegra, Allegra ODT	Fexofenadine
Allegra-D 12 Hour, Allegra-D 24 Hour	Fexofenadine + Pseudoephedrine
Allergen Ear Drops	Antipyrine and Benzocaine

Trade Names	Generic Name
Alloprim	Allopurinol
Almacone, Almacone II Double Strength	Aluminum Hydroxide with Magnesium Hydroxide
Alsuma	Sumatriptan Succinate
AlternaGEL	Aluminum Hydroxide
Alu-Cap	Aluminum Hydroxide
Alvesco	Ciclesonide
AmBisome	Amphotericin B, Liposomal
Amicar	Aminocaproic Acid
Amikin	Amikacin Sulfate
Amnesteem	Isotretinoin
Amoclan	Amoxicillin-Clavulanic Acid
Amoxil	Amoxicillin
Amphadase	Hyaluronidase
Amphocin	Amphotericin B
Amphojel	Aluminum Hydroxide
Anacin	Aspirin
Anaprox	Naproxen/Naproxen Sodium
Ancef	Cefazolin
Ancobon	Flucytosine
Anectine	Succinylcholine
Antilirium	Physostigmine Salicylate
Antipyrine and Benzocaine Otic	Antipyrine and Benzocaine
Antizol	Fomepizole
Anzemet	Dolasetron
Apresoline	Hydralazine Hydrochloride
Apriso	Mesalamine
Aquachloral Supprettes	Chloral Hydrate
Aquasol A	Vitamin A
Aquasol E	Vitamin E
Aquavit-E	Vitamin E
Aralen	Chloroquine HCl/Phosphate
Aranesp	Darbepoetin Alfa
Arbinoxa	Carbinoxamine
Arestin	Minocycline
Aridol	Mannitol
Aristospan	Triamcinolone
ASA[a]	Aspirin
Asacol, Asacol HD	Mesalamine
Asmanex Twisthaler	Mometasone Furoate
Asprin Free Anacin	Acetaminophen
Astelin	Azelastine
Astepro	Azelastine
Astragraf XL	Tacrolimus
Ativan	Lorazepam
AtroPen	Atropine Sulfate
Atrovent	Ipratropium Bromide
Augmentin, Augmentin ES-600, Augmentin XR	Amoxicillin-Clavulanic Acid
Auralgan (available in Canada)	Antipyrine and Benzocaine
Auro Ear Drops	Carbamide Peroxide
Avinza	Morphine Sulfate

Trade Names	Generic Name
Avita	Tretinoin
Ayr Saline	Sodium Chloride—Inhaled Preparations
Azactam	Aztreonam
Azasan	Azathioprine
Azasite	Azithromycin
Azo-Standard [OTC]	Phenazopyridine HCl
Azulfidine, Azulfidine EN-Tabs	Sulfasalazine
Baciguent Topical	Bacitracin
Bactrim	Sulfamethoxazole and Trimethoprim
Bactroban, Bactroban Nasal	Mupirocin
BAL[a]	Dimercaprol
Beconase AQ	Beclomethasone Dipropionate
Benadryl	Diphenhydramine
Benzac AC Wash 2½, 5, 10; Benzac 5, 10	Benzoyl Peroxide
Beta-Val	Betamethasone
Bethkis	Tobramycin
Biaxin, Biaxin XL	Clarithromycin
Bicillin C-R, Bicillin C-R 900/300	Penicillin G Preparations—Penicillin G Benzathine and Penicillin G Procaine
Bicillin L-A	Penicillin G Preparations—Benzathine
Bio-Statin	Nystatin
Bioxiverz	Neostigmine
Bleph 10	Sulfacetamide Sodium Ophthalmic
Brevibloc	Esmolol HCl
Brevoxyl Creamy Wash	Benzoyl Peroxide
Brisdelle	Paroxetine
British anti-Lewisite	Dimercaprol
Bufferin	Aspirin
Bumex	Bumetanide
Buminate	Albumin, Human
Cafcit	Caffeine Citrate
Cafergot	Ergotamine Tartrate + Caffeine
Calcidol	Ergocalciferol
Caldolor	Ibuprofen
Calan, Calan SR	Verapamil
Calciferol	Ergocalciferol
Calcijex	Calcitriol
Calcionate	Calcium Glubionate
Calciquid	Calcium Glubionate
Cal-Citrate	Calcium Citrate
Calcium disodium versenate	Edetate (EDTA) Calcium Disodium
Cal-Glu	Calcium Gluconate
Cal-Lac	Calcium Lactate
Calphron	Calcium Acetate
Camphorated opium tincture	Paregoric
Canasa	Mesalamine
Cancidas	Caspofungin
Cankaid	Carbamide Peroxide
Capoten	Captopril

Trade Names	Generic Name
Carafate	Sucralfate
Carbatrol	Carbamazepine
Cardene, Cardene SR	Nicardipine
Cardizem, Cardizem SR, Cardizem CD, Cardizem LA	Diltiazem
Carnitor	Carnitine
Catapres, Catapres TTS	Clonidine
Cathflo Activase	Alteplase
Caysten	Aztreonam
Ceclor, Ceclor CD	Cefaclor
Cecon	Ascorbic Acid
Cedax	Ceftibuten
Cefotan	Cefotetan
Ceftin	Cefuroxime Axetil
Cefzil	Cefprozil
Celestone	Betamethasone
CellCept	Mycophenolate Mofetil
Cephulac	Lactulose
Ceptaz	Ceftazidime
Cerebyx	Fosphenytoin
Chemet	Succimer
Chloromycetin	Chloramphenicol
Chlor-Trimeton	Chlorpheniramine Maleate
Cholestyramine Light	Cholestyramine
Chronulac	Lactulose
Ciloxan ophthalmic	Ciprofloxacin
Cipro, Cipro XR, Ciprodex, Cipro HC Otic	Ciprofloxacin
Citracel	Calcium Citrate
Claforan	Cefotaxime
Claravis	Isotretinoin
Claritin, Claritin Children's Allergy, Claritin RediTabs	Loratadine
Claritin-D 12 Hour, Claritin-D 24 Hour	Loratadine + Pseudoephedrine
Cleocin-T, Cleocin	Clindamycin
Cogentin	Benztropine Mesylate
Colace	Docusate
Colocort	Hydrocortisone
CoLyte	Polyethylene Glycol—Electrolyte Solution
Compazine	Prochlorperazine
Concerta	Methylphenidate HCl
Copegus	Ribavirin
Cordarone	Amiodarone HCl
Cordron-D NR, Cordron-D	Carbinoxamine + Pseudoephedrine
Coreg, Coreg CR	Carvedilol
Cortef	Hydrocortisone
Cortenema	Hydrocortisone
Cortifoam	Hydrocortisone
Cortisporin Otic	Polymyxin B Sulfate, Neomycin Sulfate, Hydrocortisone
Co-Trimoxazole	Sulfamethoxazole and Trimethoprim

Trade Names	Generic Name
Coumadin	Warfarin
Covera-HS	Verapamil
Cozaar	Losartan
Crolom	Cromolyn
Cruex	Clotrimazole
Cuprimine	Penicillamine
Curosurf	Surfactant, Pulmonary/Poractant Alfa
Cutivate	Fluticasone Propionate
Cuvposa	Glycopyrrolate
Cyanoject	Cyanocobalamin/Vitamin B_{12}
Cyclogyl	Cyclopentolate
Cyclomydril	Cyclopentolate with Phenylephrine
Cyomin	Cyanocobalamin/Vitamin B_{12}
Cytovene	Ganciclovir
D-3, D3-5, D3-50	Cholecalciferol
Dantrium	Dantrolene
Daraprim	Pyrimethamine
Daytrana	Methylphenidate HCl
DDAVP[a]	Desmopressin Acetate
DDS[a]	Dapsone
D Drops	Cholecalciferol
Debrox	Carbamide Peroxide
Decadron	Dexamethasone
Deltasone	Prednisone
Delzicol	Mesalamine
Deodorized tincture of opium	Opium Tincture
Depacon	Valproic Acid
Depakene	Valproic Acid
Depakote, Depakote ER	Divalproex Sodium
Depen	Penicillamine
Depo-Medrol	Methylprednisolone
Depo-Provera	Medroxyprogesterone
Depo-Sub Q Provera 104	Medroxyprogesterone
Desquam-E 5, Desquam-E 10	Benzoyl Peroxide
Desyrel (previously available as)	Trazodone
Dexedrine Spansules	Dextroamphetamine
DexFerrum	Iron—Injectable Preparations (iron dextran)
Dexpak Taperpak	Dexamethasone
DextroStat	Dextroamphetamine ± Amphetamine
Di-5-ASA[a]	Olsalazine
Dialume	Aluminum Hydroxide
Diaminodiphenylsulfone	Dapsone
Diamox	Acetazolamide
Diastat, Diastat AcuDial	Diazepam
Diflucan and others	Fluconazole
Digibind, DigiFab	Digoxin Immune Fab (Ovine)
Digitek	Digoxin
Dilacor XR	Diltiazem
Dilantin, Dilantin Infatab	Phenytoin
Dilaudid, Dilaudid-HP	Hydromorphone HCl

Trade Names	Generic Name
Di-mesalazine	Olsalazine
Dimetapp Children's Cold and Allergy	Brompheniramine with Phenylephrine
Diovan	Valsartan
Dipentum	Olsalazine
Diprolene, Diprolene AF	Betamethasone
Diprosone	Betamethasone
DisperMox	Amoxicillin
Ditropan, Ditropan XL	Oxybutynin Chloride
Diuril	Chlorothiazide
DMSA [dimercaptosuccinic acid][a]	Succimer
Dobutrex (previously available as)	Dobutamine
Dolophine	Methadone HCl
Dopram	Doxapram HCl
Doryx	Doxycycline
Doxidan	Bisacodyl
Dramamine, Children's Dramamine	Dimenhydrinate
Drisdol	Ergocalciferol
Dulcolax	Bisacodyl
Dulera	Mometasone Furoate + Formoterol Fumarate
Duraclon	Clonidine
Duragesic	Fentanyl
Duramist 12-Hr Nasal	Oxymetazoline
Duricef	Cefadroxil
Dycill	Dicloxacillin Sodium
Dynacin	Minocycline
Dyrenium	Triamterene
EC-Naprosyn	Naproxen
Efidac/24-Pseudoephedrine	Pseudoephedrine
Elavil	Amitriptyline
Elidel	Pimecrolimus
Elimite	Permethrin
Eliphos	Calcium Acetate
Elitek	Rasburicase
Elixophyllin	Theophylline
Elocon	Mometasone Furoate
Emfamil D-Vi-Sol	Cholecalciferol
EMLA, Eutectic mixture of lidocaine and prilocaine	Lidocaine and Prilocaine
E-Mycin	Erythromycin Preparations
Enbrel	Etanercept
Endocet	Oxycodone and Acetaminophen
Endodan	Oxycodone and Aspirin
Enemeez	Docusate
Enlon	Edrophonium Chloride
Entocort EC	Budesonide
Enuloase	Lactulose
Epaned	Enalapril Maleate
EpiPen	Epinephrine HCl
Epitol	Carbamazepine
Epivir, Epivir-HBV	Lamivudine

Trade Names	Generic Name
Epogen	Epoetin Alfa
Epsom salts	Magnesium Sulfate
Ergomar	Ergotamine Tartrate
Ery-Ped	Erythromycin
Erythrocin, Pediamycin, E-Mycin, Ery-Ped	Erythromycin
Erythropoietin	Epoetin Alfa
Eryzole	Erythromycin Ethylsuccinate and Acetylsulfisoxazole
Exalgo	Hydromorphone HCl
Extina	Ketoconazole
Famvir	Famciclovir
Fansidar	Pyrimethamine + Sulfadoxine
Felbatol	Felbamate
Fentora	Fentanyl
Feosol	Iron—Oral Preparations (Ferrous sulfate)
Fergon	Iron—Oral Preparations (Ferrous sulfate)
Fer-In-Sol	Iron—Oral Preparations (Ferrous gluconate)
Ferrlecit	Iron—Injectable Preparations (Ferric gluconate)
Feverall	Acetaminophen
Fiberall	Psyllium
First-Lansoprazole	Lansoprazole
First-Omeprazole	Omeprazole
FK506	Tacrolimus
Flagyl, Flagyl ER	Metronidazole
Flebogamma DIF	Immune Globulin
Fleet Babylax	Glycerin
Fleet Laxative, Fleet Bisacodyl	Bisacodyl
Fleet Mineral Oil	Mineral Oil
Fleet, Fleet Phospho-Soda	Sodium Phosphate
Fletcher's Castoria	Senna/Sennosides
Flonase HFA	Fluticasone Propionate
Florinef Acetate	Fludrocortisone Acetate
Flovent Diskus	Fluticasone Propionate
Floxin, Floxin Otic	Ofloxacin
Flumadine	Rimantadine
Fluohydrisone	Fludrocortisone Acetate
Fluoritab	Fluoride
Focalin, Focalin XR	Dexmethylphenidate
Folvite	Folic Acid
Foradil Aerolizer	Formoterol
Fortamet	Metformin
Fortaz	Ceftazidime
Fortical Nasal Spray	Calcitonin—Salmon
Foscavir	Foscarnet
Fulvicin U/F, Fulvicin P/G	Griseofulvin
Fungizone	Amphotericin B
Furadantin	Nitrofurantoin
Gabitril	Tiagabine
Gablofen	Baclofen

Trade Names	Generic Name
Galzin	Zinc Salts, Systemic
Gamaplex	Immune Globulin
Gamma benzene hexachloride[a]	Lindane
Gammaked	Immune Globulin
Garamycin	Gentamicin
Gastrocrom	Cromolyn
Gas-X	Simethicone
Gengraf	Cyclosporine Modified
GlucaGen, Glucagon Emergency Kit	Glucagon HCl
Glucophage, Glucophage XR	Metformin
Gly-Oxide	Carbamide Peroxide
Glycate	Glycopyrrolate
GoLYTELY	Polyethylene Glycol—Electrolyte Solution
Gralise	Gabapentin
Granisol	Granisetron
Grifulvin V	Griseofulvin
Grisactin	Griseofulvin
Gris-PEG	Griseofulvin
Gyne-Lotrimin 3, Gyne-Lotrimin	Clotrimazole
H.P. Acthar Gel	Corticotropin
Haldol, Haldol Decanoate 50, Haldol Decanoate 100	Haloperidol
Hecoria	Tacrolimus
Hexadrol	Dexamethasone
Horizant	Gabapentin
Humatin	Paromomycin Sulfate
Hydro-Tussin CBX	Carbinoxamine + Pseudoephedrine
Hylenex	Hyaluronidase
Hypersal	Sodium Chloride—Inhaled Preparations
Imitrex	Sumatriptan Succinate
Imodium, Imodium AD	Loperamide
Imuran	Azathioprine
Inapsine	Droperidol
Inderal, Inderal LA	Propranolol
Indocin, Indocin SR, Indocin IV	Indomethacin
Infasurf	Surfactant, Pulmonary/Calfactant
INFeD	Iron—Injectable Preparations (iron dextran)
INH[a]	Isoniazid
Intal (previously available as)	Cromolyn
Intropin (previously available as)	Dopamine
Intuniv	Guanfacine
Invanz	Ertapenem
Iosat	Potassium Iodide
Iquix	Levofloxacin
IsonaRif	Isoniazid
Isoptin SR	Verapamil
Isopto Carpine	Pilocarpine HCl
Isopto Hyoscine	Scopolamine Hydrobromide
Isuprel	Isoproterenol
Jantoven	Warfarin

Trade Names	Generic Name
Kadian	Morphine Sulfate
Kantrex	Kanamycin
Kaopectate	Bismuth Subsalicylate
Kao-Tin	Bismuth Subsalicylate
Kapvay	Clonidine
Kayexalate	Sodium Polystyrene Sulfonate
Keflex	Cephalexin
Kemstro	Baclofen
Kenalog	Triamcinolone
Keppra, Keppra XR	Levetiracetam
Ketalar	Ketamine
Kionex	Sodium Polystyrene Sulfonate
Klonopin	Clonazepam
Klout	Pyrethrins with Piperonyl Butoxide
Kondremul	Mineral Oil
Konsyl	Psyllium
K-PHOS Neutral	Phosphorus Supplements
Kristalose	Lactulose
Kytril	Granisetron
Lamictal, Lamictal ODT, Lamictal XR	Lamotrigine
Laniazid	Isoniazid
Lanoxin	Digoxin
Lariam	Mefloquine HCl
Lasix	Furosemide
Lax-Pills	Senna/Sennosides
Lazanda	Fentanyl
L-Carnitine	Carnitine
Levaquin, Quixin, Iquix	Levofloxacin
Levocarnitine	Carnitine
Levophed and others	Norepinephrine Bitartrate
Lialda	Mesalamine
Licide	Pyrethrins with Piperonyl Butoxide
Lidoderm	Lidocaine
Lioresal	Baclofen
Liquid Pred	Prednisone
Lithobid	Lithium
L-M-X	Lidocaine
Loniten (previously available as)	Minoxidil
Lopressor, Toprol-XL	Metoprolol
Lotrimin AF	Clotrimazole
Lotrimin AF	Miconazole
Lovenox	Enoxaparin
Luminal	Phenobarbital
Luride	Fluoride
Luvox CR	Fluvoxamine
Maalox, Maalox Maximum Strength Liquid	Aluminum Hydroxide with Magnesium Hydroxide
Macrobid	Nitrofurantoin
Macrodantin	Nitrofurantoin
Mag-200, Mag-Ox 400, Uro-Mag	Magnesium Oxide

Trade Names	Generic Name
Marinol	Dronabinol
Maxidex	Dexamethasone
Maxipime	Cefepime
Maxivate	Betamethasone
Maxolon	Metoclopramide
Medrol, Medrol Dosepack	Methylprednisolone
Mefoxin	Cefoxitin
Mephyton	Phytonadione/Vitamin K_1
Mepron	Atovaquone
Merrem	Meropenem
Mestinon	Pyridostigmine Bromide
Metadate ER	Methylphenidate HCl
Metamucil	Psyllium
Methadose	Methadone HCl
Methylin, Methylin ER	Methylphenidate HCl
Metozolv	Metoclopramide
MetroCream	Metronidazole
MetroGel, MetroGel-Vaginal	Metronidazole
MetroLotion	Metronidazole
Miacalcin, Miacalcin Nasal Spray	Calcitonin—Salmon
Micatin	Miconazole
Microzide	Hydrochlorothiazide
Milk of Magnesia	Magnesium Hydroxide
Millipred	Prednisolone
Minocin	Minocycline
Mintezol	Thiabendazole
Mintox	Aluminum Hydroxide with Magnesium Hydroxide
MiraLax	Polyethylene Glycol—Electrolyte Solution
Monistat	Miconazole
Motrin, Children's Motrin	Ibuprofen
MS Contin	Morphine Sulfate
Mucomyst	Acetylcysteine
Mucosol	Acetylcysteine
Murine Ear	Carbamide Peroxide
Myambutol	Ethambutol HCl
Mycamine	Micafungin Sodium
Mycelex, Mycelex-7	Clotrimazole
Mycobutin	Rifabutin
Mycostatin	Nystatin
Myfortic	Mycophenolate Sodium
Mylanta Gas	Simethicone
Mylanta, Mylanta Extra Strength	Aluminum Hydroxide with Magnesium Hydroxide
Mylicon	Simethicone
Myorisan	Isotretinoin
Mysoline	Primidone
Nallpen	Nafcillin
Naprelan	Naproxen/Naproxen Sodium
Naprosyn, Naprosen DR	Naproxen/Naproxen Sodium
Narcan	Naloxone
Nasacort AQ	Triamcinolone

Trade Names	Generic Name
Nasalcrom	Cromolyn
Nasarel	Flunisolide
Nascobal	Cyanocobalamin/Vitamin B_{12}
Nasonex	Mometasone Furoate
Nebcin	Tobramycin
NebuPent	Pentamidine Isethionate
Nembutal	Pentobarbital
NeoBenz Micro	Benzoyl Peroxide
Neo-fradin	Neomycin Sulfate
Neo-Polycin	Neomycin/Polymyxin B/Bacitracin
NeoProfen (IV)	Ibuprofen
Neoral	Cyclosporine
Neosporin, Neosporin Ophthalmic, Neo To Go	Neomycin/Polymyxin B/Bacitracin
Neosporin GU Irrigant	Neomycin/Polymyxin B
Neo-Synephrine	Phenylephrine HCl
Neo-Synephrine 12-Hr Nasal	Oxymetazoline
Nephron	Epinephrine, Racemic
Neupogen, G-CSF	Filgrastim
Neurontin	Gabapentin
Neut	Sodium Bicarbonate
Nexiclon XR	Clonidine
Nexium	Esomeprazole
Nexterone	Amiodarone HCl
Niacor	Niacin (Vitamin B_3)
Niaspan	Niacin (Vitamin B_3)
Nicotinic acid	Niacin (Vitamin B_3)
Nifediac CC	Nifedipine
Niferex	Iron—Oral Preparations
Nilstat	Nystatin
Nipride (previously available as)	Nitroprusside
Nitro-Bid	Nitroglycerin
Nitro-Dur	Nitroglycerin
Nitro-Mist	Nitroglycerin
Nitropress	Nitroprusside
Nitrostat	Nitroglycerin
Nitro-Time	Nitroglycerin
Nix	Permethrin
Nizoral, Nizoral A-D	Ketoconazole
Noriate	Metronidazole
Normal Serum Albumin (Human)	Albumin, Human
Normodyne	Labetalol
Noroxin	Norfloxacin
Norvasc	Amlodipine
Nostrilla	Oxymetazoline
NuCort	Hydrocortisone
NuLYTELY	Polyethylene Glycol—Electrolyte Solution
Nutr-E-Sol	Vitamin E/α-Tocopherol
NVP[a]	Nevirapine
Nydrazid	Isoniazid
OCL[a]	Polyethylene Glycol—Electrolyte Solution

Trade Names	Generic Name
Ocuflox	Ofloxacin
Ocusulf-10	Sulfacetamide Sodium Ophthalmic
Omnaris	Ciclesonide
Ofirmev	Acetaminophen
Omeprazole and Syrspend SF Alka	Omeprazole
Omnicef	Cefdinir
Omnipaque 140, Omnipaque 180, Omnipaque 240, Omnipaque 300, and Omnipaque 350	Iohexol
Omnipen	Ampicillin
Onfi	Clobazam
Onmel	Itraconazole
Opticrom	Cromolyn
Optivar	Azelastine
Oralone	Corticosteroid
Oramorph SR	Morphine Sulfate
Orapred, Orapred ODT	Prednisolone
Oraqix	Lidocaine and Prilocaine
Orasone	Prednisone
OraVerse	Phentolamine Mesylate
Orazinc	Zinc Salts, Systemic
Os-Cal	Calcium Carbonate
Osmitrol	Mannitol
OsmoPrep	Sodium Phosphate
Oxtellar	Oxcarbazepine
Oxy-5, Oxy-10	Benzoyl Peroxide
OxyContin	Oxycodone
Oxytrol	Oxybutynin Chloride
Pacerone	Amiodarone HCl
Palasbumin	Albumin, Human
Palgic	Carbinoxamine
Pamelor	Nortriptyline Hydrochloride
Pamix	Pyrantel Pamoate
Panadol	Acetaminophen
Paracetamol	Acetaminophen
Pataday	Olopatadine
Patanase	Olopatadine
Patanol	Olopatadine
Pathocil	Dicloxacillin Sodium
Paxil, Paxil CR	Paroxetine
Pediaflor	Fluoride
Pedia-Lax	Glycerin
Pediamycin	Erythromycin Preparations
Pediapred	Prednisolone
Pediazole	Erythromycin Ethylsuccinate and Acetylsulfisoxazole
PediOtic	Polymyxin B Sulfate, Neomycin Sulfate, Hydrocortisone
Pentam 300	Pentamidine Isethionate
Pentasa	Mesalamine

Trade Names	Generic Name
Pepcid, Pepcid AC [OTC], Maximum Strength Pepcid AC [OTC], Pepcid Complete [OTC], Pepcid RPD	Famotidine
Pepto-Bismol	Bismuth Subsalicylate
Percocet	Oxycodone and Acetaminophen
Percodan	Oxycodone and Aspirin
Perforomist	Formoterol
Periactin (previously available as)	Cyproheptadine
Periostat	Doxycycline
Pexeva	Paroxetine
Pfizerpen	Penicillin G Preparations—Aqueous Potassium and Sodium
PGE_1[a]	Alprostadil
Phazyme	Simethicone
Phenergan	Promethazine
Phenytek	Phenytoin
PhosLo	Calcium Acetate
Phoslyra	Calcium Acetate
Pilopine HS	Pilocarpine HCl
Pima	Potassium Iodide
Pin-Rid	Pyrantel Pamoate
Pin-X	Pyrantel Pamoate
Pipracil	Piperacillin
Pitressin	Vasopressin
Plaquenil	Hydroxychloroquine
Polymox	Amoxicillin
Polysporin Ophthalmic	Bacitracin + Polymyxin B
Polysporin Topical	Bacitracin + Polymyxin B
Polytrim Ophthalmic Solution	Polymyxin B Sulfate and Trimethoprim Sulfate
Posture-D	Calcium Phosphate, Tribasic
Potassium Phosphate	Phosphorus Supplements
Precidex	Dexmedetomidine
Prelone	Prednisolone
Prevacid, Prevacid SoluTab	Lansoprazole
Prevalite	Cholestyramine
Prilosec, Prilosec OTC	Omeprazole
Primacor	Milrinone
Primaxin IV	Imipenem and Cilastatin
Principen	Ampicillin
Prinivil	Lisinopril
Privagen	Immune Globulin
ProAir HFA	Albuterol
Procanbid	Procainamide
Procardia, Procardia XL	Nifedipine
ProCentra	Dextroamphetamine Sulfate
Procrit	Epoetin Alfa
Proglycem	Diazoxide
Prograf	Tacrolimus
Pronestyl	Procainamide
Pronto	Pyrethrins

Trade Names	Generic Name
Prostaglandin E_1	Alprostadil
Prostigmin	Neostigmine
Prostin VR Pediatric	Alprostadil
Protonix	Pantoprazole
Protopam	Pralidoxime Chloride
Protopic	Tacrolimus
Protostat	Metronidazole
Proventil, Proventil HFA (aerosol inhaler)	Albuterol
Provera	Medroxyprogesterone
Prozac, Prozac Weekly	Fluoxetine Hydrochloride
Pseudo Carb Pediatric	Carbinoxamine + Pseudoephedrine
PTU[a]	Propylthiouracil
Pulmicort Respules, Pulmicort Flexhaler	Budesonide
Pulmozyme	Dornase Alfa/DNase
Pyrazinoic acid amide	Pyrazinamide
Pyridium	Phenazopyridine HCl
Pyrinyl	Pyrethrins
Qnasl	Beclomethasone Dipropionate
Quelicin, Quelicin-1000	Succinylcholine
Questran, Questran Light	Cholestyramine
Quinidex	Quinidine
Quixin	Levofloxacin
QVAR[a]	Beclomethasone Dipropionate
Raniclor	Cefaclor
Rapamune	Sirolimus
Rayos	Prednisone
Rebetol	Ribavirin
Reese's Pinworm	Pyrantel Pamoate
Regitine	Phentolamine Mesylate
Reglan	Metoclopramide
Regonal	Pyridostigmine Bromide
Renova	Tretinoin
Resectisol	Mannitol
Restasis	Cyclosporine, Cyclosporine Microemulsion, Cyclosporine Modified
Retin-A, Retin-A Micro	Tretinoin
Retrovir, AZT	Zidovudine
Revatio	Sildenafil
Reversol	Edrophonium Chloride
Revonto	Dantrolene
R-Gene 10	Arginine Chloride
Rhinaris	Sodium Chloride—Inhaled Preparations
Rhinocort Aqua Nasal Spray	Budesonide
Ribaspheres	Ribavirin
RID	Pyrethrins
Rifadin	Rifampin
Rifamate	Isoniazid + Rifampin
Rifater	Pyrazinamide + Isoniazid + Rifampin
Rimactane	Rifampin
Riomet	Metformin

Trade Names	Generic Name
Risperdal, Risperdal M-Tab, Risperdal Consta	Risperidone
Ritalin, Ritalin SR, Ritalin LA	Methylphenidate HCl
Robinul	Glycopyrrolate
Rocaltrol	Calcitriol
Rocephin	Ceftriaxone
Rogaine, Men's Rogaine Extra Strength	Minoxidil
Romazicon	Flumazenil
Rowasa, SfRowasa	Mesalamine
Roxanol	Morphine Sulfate
Roxicet	Oxycodone and Acetaminophen
Roxicodone	Oxycodone
Roxilox	Oxycodone and Acetaminophen
RuLox Plus	Aluminum Hydroxide with Magnesium Hydroxide
S-2 Inhalant	Epinephrine, Racemic
Sabril	Vigabatrin
Salagen	Pilocarpine HCl
Salicylazosulfapyridine	Sulfasalazine
Sal-Tropine	Atropine Sulfate
Sancuso	Granisetron
Sandimmune	Cyclosporine
Sandostatin, Sandostatin LAR Depot	Octreotide Acetate
Sani-Supp	Glycerin
Sarafem	Fluoxetine Hydrochloride
SAS[a]	Sulfasalazine
Scopace	Scopolamine Hydrobromide
Selsun and others	Selenium Sulfide
Senna-Gen	Senna/Sennosides
Senokot	Senna/Sennosides
Septra	Sulfamethoxazole and Trimethoprim
Serevent Diskus	Salmeterol
Sildec	Carbinoxamine + Pseudoephedrine
Silvadene	Silver Sulfadiazine
Simply Saline	Sodium Chloride—Inhaled Preparations
Singulair	Montelukast
Slo-Niacin	Niacin (Vitamin B_3)
Slow FE	Iron—Oral Preparations
Sodium Phosphate	Phosphorus Supplements
Solodyn	Minocycline
Solu-cortef	Hydrocortisone
Solu-Medrol	Methylprednisolone
Soluspan	Betamethasone
Sporanox	Itraconazole
SPS[a]	Sodium Polystyrene Sulfonate
SSD Cream, SSD AF Cream	Silver Sulfadiazine
SSKI[a]	Potassium Iodide
Stadol	Butorphanol
Stavzor	Valproic Acid
Stimate	Desmopressin Acetate
Stomach Relief, Stomach Relief Max St, Stomach Relief Plus	Bismuth Subsalicylate

Trade Names	Generic Name
Strattera	Atomoxetine
Streptase	Streptokinase
Sublimaze	Fentanyl
Sudafed	Pseudoephedrine
Sulfatrim	Sulfamethoxazole and Trimethoprim
Sulfazine, Sulfazine EC	Sulfasalazine
Sunkist Vitamin C	Ascorbic Acid
Suprax	Cefixime
Surfak	Docusate
Surfaxin	Surfactant, Pulmonary/Lucinactant
Survanta	Surfactant, Pulmonary/Beractant
Symbicort	Budesonide and Formoterol
Symmetrel	Amantadine Hydrochloride
Synagis	Palivizumab
Synercid	Quinupristin and Dalfopristin
Synthroid	Levothyroxine T_4
Tagamet, Tagamet HB [OTC]	Cimetidine
Tambocor	Flecainide Acetate
Tamiflu	Oseltamivir Phosphate
Tapazole	Methimazole
Tazicef	Ceftazidime
Tazidime	Ceftazidime
Tegretol, Tegretol-XR	Carbamazepine
Tempra	Acetaminophen
Tenex	Guanfacine
Tenormin	Atenolol
Tensilon	Edrophonium Chloride
Tetrahydrocannabinol	Dronabinol
THC[a]	Dronabinol
Theo-24	Theophylline
Theochron	Theophylline
Thera-Ear	Carbamide Peroxide
Therazene	Silver Sulfadiazine
Thorazine	Chlorpromazine
ThyroSave	Potassium Iodide
ThyroShield	Potassium Iodide
Tiazac	Diltiazem
Tigan	Trimethobenzamide HCl
Timentin	Ticarcillin and Clavulanate
Tinactin	Tolnaftate
Tirosint	Levothyroxine
Tisit	Pyrethrins
TMP-SMX[a]	Sulfamethoxazole and Trimethoprim
TOBI, TOBI Podhaler	Tobramycin
Tobrex	Tobramycin
Tofranil, Tofranil-PM	Imipramine
Topamax	Topiramate
Topiragen	Topiramate
Toprol-XL	Metoprolol
Totacillin	Ampicillin

Trade Names	Generic Name
tPA[a]	Alteplase
Trandate	Labetalol
Transderm Scop	Scopolamine Hydrobromide
Trianex	Corticosteroid
Triaz	Benzoyl Peroxide
Triderm	Corticosteroid
Trileptal	Oxcarbazepine
Trilisate and others	Choline Magnesium Trisalicylate
TriLyte	Polyethylene Glycol—Electrolyte Solution
Trimethoprim-Sulfamethoxazole	Sulfamethoxazole and Trimethoprim
Trimox	Amoxicillin
Trokenndi XR	Topiramate
Tums	Calcium Carbonate
Tylenol	Acetaminophen
Tylenol #1, #2, #3, #4	Codeine and Acetaminophen
Tylox	Oxycodone and Acetaminophen
Uceris	Budesonide
Unasyn	Ampicillin/Sulbactam
Unithroid, Unithroid Direct	Levothyroxine
Urecholine	Bethanechol Chloride
Uro-KP-Neutral	Phosphorus Supplements
Urolene Blue	Methylene Blue
Urso 250, Urso Forte	Ursodiol
Vagistat-3	Miconazole
Valcyte	Valganciclovir
Valium	Diazepam
Valtrex	Valacyclovir
Vancocin	Vancomycin
Vantin	Cefpodoxime Proxetil
VariZig	Varicella-Zoster Immune Globulin (Human)
Vasotec	Enalapril Maleate
Vasotec IV	Enalaprilat
Veetids	Penicillin V Potassium
Venofer	Iron—Injectable Preparations (iron sucrose)
Ventolin HFA	Albuterol
Veramyst	Fluticasone Propionate
Verelan, Verelan PM	Verapamil
Veripred	Prednisolone
Vermox	Mebendazole
Versed (previously available as)	Midazolam
VFEND	Voriconazole
Viagra	Sildenafil
Vibramycin	Doxycycline
Vimpat	Lacosamide
Viramune, Viramune XR	Nevirapine
Virazole	Ribavirin
Visicol	Sodium Phosphate
Visine LR	Oxymetazoline
Vistaril	Hydroxyzine
Vistide	Cidofovir

Trade Names	Generic Name
Vitamin B_1	Thiamine
Vitamin B_2	Riboflavin
Vitamin B_{12}	Cyanocobalamin/Vitamin B_{12}
Vitamin B_3	Niacin/Vitamin B_3
Vitamin B_6	Pyridoxine
Vitamin C	Ascorbic Acid
Vitrase	Hyaluronidase
Vitrasert	Ganciclovir
VoSpire ER	Albuterol
Vyvanse	Lisdexamfetamine
VZIG	Varicella-Zoster Immune Globulin (Human)
WinRho-SDF	Rh_0 (D) Immune Globulin Intravenous (Human)
Wycillin	Penicillin G Preparations—Procaine
Wymox	Amoxicillin
Xolegel	Ketoconazole
Xopenex, Xopenex HFA	Levalbuterol
Xylocaine	Lidocaine
Zantac, Zantac 75 [OTC], Zantac 150 Maximum Strength [OTC]	Ranitidine HCl
Zarontin	Ethosuximide
Zaroxolyn	Metolazone
Zegerid	Omeprazole
Zemuron	Rocuronium
Zenatane	Isotretinoin
Zenzedi	Dextroamphetamine Sulfate
Zestril	Lisinopril
Zetonna	Ciclesonide
Zinacef	Cefuroxime
Zirgan	Ganciclovir
Zithromax, Zithromax TRI-PAK, Zithromax Z-PAK, Zmax	Azithromycin
Zoderm	Benzoyl Peroxide
Zofran	Ondansetron
Zolicef	Cefazolin
Zoloft	Sertraline HCl
Zonegran	Zonisamide
ZORprin	Aspirin
Zosyn	Piperacillin with Tazobactam
Zovirax	Acyclovir
Zyloprim	Allopurinol
Zyrtec, Children's Zyrtec	Cetirizine
Zyrtec-D 12 Hour	Cetirizine + Pseudoephedrine
Zyvox	Linezolid

[a]Common abbreviation or other name (not recommended for use when writing a prescription)

TABLE 30.1

EXAMPLES OF INDUCERS AND INHIBITORS OF CYTOCHROME P450 SYSTEM

Isoenzyme	Substrates (Drugs Metabolized by Isoenzyme)	Inhibitors[a]	Inducers
CYP1A2	Caffeine, theophylline, estradiol, propranolol	Cimetidine, quinolones, fluvoxamine, ketoconazole, lidocaine	Carbamazepine, smoking, phenobarbital, rifampin
CYP2B6	Cyclophosphamide, efavirenz, propofol	Paroxetine, sertraline	Carbamazepine, (fos)phenytoin, phenobarbital, rifampin
CYP2C9/10	Warfarin, phenytoin, tolbutamide, fluoxetine, sulfamethoxazole, fosphenytoin	Amiodarone, fluconazole, ibuprofen, indomethacin, nicardipine	Carbamazepine, (fos)phenytoin, rifampin, phenobarbital
CYP2C19	Diazepam, PPIs, phenytoin, desogestrel, ifosfamide, phenobarbital, sertraline, voriconazole	Cimetidine fluvoxamine, fluconazole, isoniazid, PPIs, sertraline	Carbamazepine, (fos)phenytoin, rifampin
CYP2D6	Captopril, codeine, haloperidol, dextromethorphan, tricyclic antidepressants, hydrocodone, oxycodone, phenothiazines, metoprolol, propranolol, paroxetine, venlafaxine, risperidone, flecainide, sertraline, aripiprazole, fluoxetine, lidocaine, fosphenytoin, ritonavir	Chlorpromazine, cinacalcet, dexmedetomidine, cocaine, cimetidine, quinidine, ritonavir, fluoxetine, sertraline, amiodarone	None known
CYP2E1	Acetaminophen, alcohol, isoniazid, theophylline, isoflurane	Disulfiram	Alcohol
CYP3A4	Amlodipine, aripiprazole, budesonide, cocaine, clonazepam, diltiazem, efavirenz, erythromycin, estradiol, fentanyl, fluticasone, nifedipine, verapamil, cyclosporine, carbamazepine, cisapride, tacrolimus, midazolam, alfentanil, diazepam, ifosfamide, imatinib, itraconazole, ketoconazole, cyclophosphamide, PPIs, haloperidol, lidocaine, medroxyprogesterone, methadone, methylprednisolone, salmeterol, theophylline, quetiapine, ritonavir, indinavir, sildenafil, ivacaftor	Erythromycin, cimetidine, clarithromycin, isoniazid, ketoconazole, itraconazole, metronidazole, sertraline, ritonavir, indinavir, imatinib, nicardipine, propofol, quinidine	Rifampin, (fos)phenytoin, phenobarbital, carbamazepine, dexamethasone, lumacaftor

Note: The cytochrome P450 enzyme system is composed of different isoenzymes. Each isoenzyme metabolizes a unique group of drugs or substrates. When an *inhibitor* of a particular isoenzyme is introduced, the serum concentration of any drug or *substrate* metabolized by that particular isoenzyme will *increase*. When an *inducer* of a particular isoenzyme is introduced, the serum concentration of drugs or *substrates* metabolized by that particular isoenzyme will *decrease*.

PPI, Proton pump inhibitor.

[a]Only strong and some moderate inhibitors are listed here. Weak inhibitors also exist.

Data from Taketomo CK, Hodding JH, Kraus DM. *American Pharmaceutical Association Pediatric Dosage Handbook*. 16th ed. Hudson, OH: Lexi-Comp; 2009; Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet*. 1999;36:425–438; Cupp MJ, Tracy TS. Cytochrome P450: new nomenclature and clinical implications. *Am Fam Physician*. 1998;57:107–116.

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For explanation of icons, see p. 667

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A

ACETAMINOPHEN

Tylenol, Tempra, Panadol, Feverall, Anacin Asprin Free, Paracetamol, Ofirmev, and many others

Analgesic, antipyretic

Tabs and Caplets [OTC]: 325, 500, 650 mg
Chewable tabs [OTC]: 80 mg; some may contain phenylalanine
Child suspension/syrup [OTC]: 160 mg/5 mL; may contain sodium benzoate
Oral liquid [OTC]: 160 mg/5 mL; may contain sodium benzoate and propylene glycol
Elixir [OTC]: 160 mg/5 mL; may contain sodium benzoate and propylene glycol
Extended-release caplets [OTC]: 650 mg
Capsules [OTC]: 325, 500 mg
Dispersible tabs (Tylenol Children's Meltaways) [OTC]: 80, 160 mg; contains sucralose
Suppositories [OTC]: 80, 120, 325, 650 mg
Injection:
Ofirmev: 10 mg/mL (100 mL); preservative free

PO/PR (maximum daily doses include all routes of acetaminophen administration):

Neonate: 10–15 mg/kg/dose PO/PR Q6–8 hr. Some advocate loading doses of 20–25 mg/kg/dose for PO dosing or 30 mg/kg/dose for PR dosing.

Pediatric: 10–15 mg/kg/dose PO/PR Q4–6 hr; **max. dose:** 90 mg/kg/24 hr or 4 g/24 hr. For rectal dosing, some may advocate a 40–45 mg/kg/dose loading dose.

Dosing by weight (preferred) or age (PO/PR Q4–6 hr):

Weight (lbs)	Weight (kg)	Age	Dosage (mg)
6–11	2.7–5	0–3 mo	40
12–17	5.1–7.7	4–11 mo	80
18–23	7.8–10.5	1–2 yr	120
24–35	10.6–15.9	2–3 yr	160
36–47	16–21.4	4–5 yr	240
48–59	21.5–26.8	6–8 yr	320
60–71	26.9–32.3	9–10 yr	400
72–95	32.4–43.2	11 yr	480

Adult: 325–650 mg/dose
Max. dose: 4 g/24 hr, 5 doses/24 hr

IV (maximum daily doses include all routes of acetaminophen administration):

Neonate and infant:

≤28 days old: 12.5 mg/kg/dose Q6 hr IV up to a **maximum** of 50 mg/kg/24 hr

≥29 days old to <2 yr: 15 mg/kg/dose Q6 hr IV up to a **maximum** of 60 mg/kg/24 hr.

Child (≥2–12 yr) and adolescent (≥13 yr)/adult <50 kg: 15 mg/kg/dose Q6 hr, ***OR*** 12.5 mg/kg/dose Q4 hr IV up to a **maximum** of 75 mg/kg/24 hr up to 3750 mg/24 hr with a **maximum** single dose of 15 mg/kg/dose up to 750 mg.

Adolescent (≥13 yr) and adult (≥50 kg): 1000 mg Q6 hr, ***OR*** 650 mg Q4 hr up to a **maximum** of 4000 mg/24 hr with a **maximum** single dose of 1000 mg/dose.

Does not possess antiinflammatory activity. **Use with caution** in patients with known G6PD deficiency.

$T_{1/2}$: 1–3 hr, 2–5 hr in neonates; metabolized in the liver; see Chapter 3 and acetylcysteine for management of drug overdose.

Some preparations contain alcohol (7%–10%) and/or phenylalanine; all suspensions should be shaken before use.

For explanation of icons, see p. 667

ACETAMINOPHEN *continued*

May be used for the treatment of patent ductus arteriosus when standard NSAID is contraindicated or has failed. Most commonly reported dosage is 15 mg/kg dose Q6 hr IV/PO for 3 days (may be given up to 7 days or with a repeated 3-day course).

May decrease the activity of lamotrigine and increase the activity/toxicity of busulfan, warfarin, and zidovudine. Barbiturates, phenytoin, rifampin, and anticholinergic agents (e.g., scopolamine) may decrease the effect of acetaminophen. Increased risk for hepatotoxicity may occur with barbiturates, carbamazepine, phenytoin, carmustine (with high acetaminophen doses), chronic alcohol use, and inducers of CYP 450 2E1 (e.g., isoniazid). **Adjust dose in renal failure (see Chapter 31).**

FOR IV USE: administer dose undiluted over 15 min. Most common side effects with IV use include nausea, vomiting, constipation, pruritus, agitation and atelectasis in children; and nausea, vomiting, headache and insomnia in adults. Rare risk of serious skin reactions (e.g., SJS, TEN) has been reported.

ACETAZOLAMIDE

Various generics; previously available as Diamox

Carbonic anhydrase inhibitor, diuretic

Tabs: 125, 250 mg
Oral suspension: 25 mg/mL
Capsules (extended release): 500 mg
Injection (sodium): 500 mg
Contains 2.05 mEq Na/500 mg drug

Diuretic (PO, IV)

Child: 5 mg/kg/dose once daily or every other day

Adult: 250–375 mg/dose once daily or every other day

Glaucoma

Child:

PO: 8–30 mg/kg/24 hr ÷ Q6–8 hr; **max. dose:** 1000 mg/24 hr

IM/IV: 20–40 mg/kg/24 hr ÷ Q6 hr; **max. dose:** 1000 mg/24 hr

Adult:

PO (Simple chronic; open angle): 1000 mg/24 hr ÷ Q6 hr

IV (Acute secondary; closed angle): For rapid decrease in intraocular pressure, administer 500 mg/dose IV

Seizures (extended-release product not recommended):

Child and adult: 8–30 mg/kg/24 hr ÷ Q6–12 hr PO; **max. dose:** 1 g/24 hr

Urine alkalization:

Adult: 5 mg/kg/dose PO repeated BID-TID over 24 hr.

Management of hydrocephalus (see remarks): Start with 20 mg/kg/24 hr ÷ Q8 hr PO/IV; may increase to 100 mg/kg/24 hr up to a **max. dose** of 2 g/24 hr

Pseudotumor cerebri (PO; see remarks):

Child: Start with 25 mg/kg/24 hr ÷ once daily-QID, increase by 25 mg/kg/24 hr until clinical response or as tolerated up to a **maximum** of 100 mg/kg/24 hr.

Adolescent: Start with 1 g/24 hr ÷ once daily-QID, increase by 250 mg/24 hr until clinical response or as tolerated up to a **maximum** of 4 g/24 hr.

Contraindicated in hepatic failure, severe renal failure (GFR <10 mL/min), and hypersensitivity to sulfonamides.

$T_{1/2}$: 2–6 hr; **do not use** sustained release capsules in seizures; **IM** injection may be painful; bicarbonate replacement therapy may be required during long-term use (see Citrate or Sodium Bicarbonate).

/kg/24 hr may be required.

ACETAZOLAMIDE *continued*

Possible side effects (more likely with long-term therapy) include GI irritation, paresthesias, sedation, hypokalemia, acidosis, reduced urate secretion, aplastic anemia, polyuria, and development of renal calculi.

May increase toxicity of carbamazepine, and cyclosporine. Aspirin may increase toxicity of acetazolamide. May decrease the effects of salicylates, lithium and phenobarbital. False-positive urinary protein may occur with several assays. **Adjust dose in renal failure (see Chapter 31).**

ACETYLCYSTEINE

Various generics, Acetadote, previously available as Mucomyst

Mucolytic, antidote for acetaminophen toxicity

Solution for inhalation or oral use: 100 mg/mL (10%) (4, 10, 30 mL) or 200 mg/mL (20%) (4, 10, 30 mL); may contain EDTA

Injectable (Acetadote and generics): 200 mg/mL (20%) (30 mL); may contain EDTA 0.5 mg/mL

Preservative-free versions of the inhalation and oral solutions and injectable forms exist.

Acetaminophen poisoning (see Chapter 3 for additional information):

PO: 140 mg/kg (**max.** 15 g/dose) × 1, followed by 70 mg/kg/dose (**max.** 7.5 g/dose) Q4 hr for a total of 17 doses. Repeat dose if vomiting occurs with 1 hr of administration.

IV: 150 mg/kg (**max.** 15 g/dose) × 1 diluted in D_5W or D_5W ½ NS administered over 60 min, followed by 50 mg/kg (**max.** 5 g/dose) diluted in D_5W administered over 4 hr, then 100 mg/kg (**max.** 10 g/dose) diluted in D_5W administered over 16 hr. Recommended weight-based drug dilution volumes:

Weight (kg)	Volume of D_5W or D_5W½NS for 150 mg/kg Loading Dose Administered Over 60 min	Volume of D_5W for 50 mg/kg Second Dose Administered Over 4 hr	Volume of D_5W for 100 mg/kg Third Dose Administered Over 16 hr
≤20	3 mL/kg	7 mL/kg	14 mL/kg
>20 to ≤40	100 mL	250 mL	500 mL
>40	200 mL	500 mL	1000 mL

Nebulizer:

Infant: 1–2 mL of 20% solution (diluted with equal volume of H_2O, or sterile saline to equal 10%), or 2–4 mL of 10% solution; administered TID-QID

Child: 3–5 mL of 20% solution (diluted with equal volume of H_2O, or sterile saline to equal 10%), or 6–10 mL of 10% solution; administer TID-QID.

Adolescent: 5–10 mL of 10% or 20% solution; administer TID-QID

Distal intestinal obstruction syndrome in cystic fibrosis:

Adolescent and adult: 10 mL of 20% solution (diluted in a sweet drink) PO QID with 100 mL of 10% solution PR as an enema once daily-QID

Use with caution in asthma. For nebulized use, give inhaled bronchodilator 10–15 min before use and follow with postural drainage and/or suctioning after acetylcysteine administration. Prior hydration is essential for distal intestinal obstruction syndrome treatment.

May induce bronchospasm, stomatitis, drowsiness, rhinorrhea, nausea, vomiting, and hemoptysis. Serious hypersensitivity reactions have been reported with IV use in children. Be aware of potential fluid overload resulting in hyponatremia with IV volume dilution; reduce diluent volume if needed.

For IV use, elimination $T_{1/2}$ is longer in newborns (11 hr) than in adults (5.6 hr). $T_{1/2}$ is increased by 80% in patients with severe liver damage (Child-Pugh score of 7–13) and biliary cirrhosis (Child-Pugh score of 5–7).

For oral administration, chilling the solution and mixing with carbonated beverages, orange juice, or

For explanation of icons, see p. 667

ACTH

See Corticotropin

ACYCLOVIR
Zovirax, Avaclyr, and generics
Antiviral

Capsules: 200 mg
Tabs: 400, 800 mg
Oral suspension: 200 mg/5 mL (473 mL); may contain parabens
Ointment: 5% (5, 15, 30 g)
Cream: 5% (5 g); may contain propylene glycol
Ophthalmic ointment (Avaclyr): 3% (3.5 g)
Injection in solution (with sodium): 50 mg/mL (10, 20 mL)
Contains 4.2 mEq Na/1 g drug

***IMMUNOCOMPETENT*:**
Neonatal (HSV and HSV encephalitis; birth–3 mo):
Initial IV therapy (duration of therapy: 14 days for cutaneous/mucous membrane infection or 21 days for CNS/disseminated infection):
<34 wk postmenstrual age: 40 mg/kg/24 hr ÷ Q12 hr IV
≥34 wk postmenstrual age: 60 mg/kg/24 hr ÷ Q8 hr IV
Oral therapy for HSV suppression and neurodevelopment following treatment with IV acyclovir for 14–21 days: 300 mg/m^2/dose Q8 hr PO × 6 mo
HSV encephalitis (duration of therapy: 14–21 days):
Birth–3 mo: use aforementioned IV dosage
3 mo–12 yr: 30–45 mg/kg/24 hr ÷ Q8 hr IV
≥12 yr: 30 mg/kg/24 hr ÷ Q8 hr IV
Mucocutaneous HSV (including genital, ≥12 yr):
Initial infection:
IV: 15 mg/kg/24 hr or 750 mg/m^2/24 hr ÷ Q8 hr × 5–7 days
PO: 1000–1200 mg/24 hr ÷ 3–5 doses per 24 hr × 7–10 days. For pediatric dosing, use 40–80 mg/kg/24 hr ÷ Q6–8 hr × 5–10 days (**max. pediatric dose:** 1000 mg/24 hr)
Recurrence (≥12 yr):
PO: 1000 mg/24 hr ÷ 5 doses per 24 hr × 5 days, or 1600 mg/24 hr ÷ Q12 hr × 5 days, or 2400 mg/24 hr ÷ Q8 hr × 2 days
Chronic suppressive therapy (≥12 yr):
PO: 800 mg/24 hr ÷ Q12 hr for up to 1 yr
Zoster:
IV (all ages): 30 mg/kg/24 hr or 1500 mg/m^2/24 hr ÷ Q8 hr × 7–10 days
PO (≥12 yr): 4000 mg/24 hr ÷ 5×/24 hr × 5–7 days
Varicella:
IV (≥2 yr): 30 mg/kg/24 hr or 1500 mg/m^2/24 hr ÷ Q8 hr × 7–10 days
PO (≥2 yr): 80 mg/kg/24 hr ÷ QID × 5 days (begin treatment at earliest signs/symptoms); **max. dose**: 3200 mg/24 hr
Max. dose of oral acyclovir in children = 80 mg/kg/24 hr.

ACYCLOVIR *continued*

IMMUNOCOMPROMISED:

HSV:

IV (all ages): 750–1500 mg/m²/24 hr ÷ Q8 hr × 7–14 days

PO (≥2 yr): 1000 mg/24 hr ÷ 3–5 times/24 hr × 7–14 days; **max. dose** for child: 80 mg/kg/24 hr

HSV prophylaxis:

IV (all ages): 750 mg/m²/24 hr ÷ Q8 hr during risk period

PO (≥2 yr): 600–1000 mg/24 hr ÷ 3–5 times/24 hr during risk period; **max. dose** for child: 80 mg/kg/24 hr

Varicella or zoster:

IV (all ages): 1500 mg/m²/24 hr ÷ Q8 hr × 7–10 days

PO (consider using valacyclovir or famciclovir for better absorption):

Infant and child: 20 mg/kg/dose (**max.** 800 mg) Q6 hr × 7–10 days

Adolescent and adult: 20 mg/kg/dose (**max.** 800 mg) 5 times daily × 7–10 days

Max. dose of oral acyclovir in children = 80 mg/kg/24 hr.

TOPICAL:

Cream (see remarks):

Herpes labialis (≥12 and adult): Apply to affected areas 5 times a day × 4 days

Ointment:

Immunocompromised genital or mucocutaneous HSV: Apply 0.5-inch ribbon of 5% ointment for 4-inch square surface area 6 times a day × 7 days.

OPHTHALMIC:

Herpes simplex keratitis (≥2 yr and adolescent): Apply 1 cm (½-inch) ribbon onto the lower eyelid of affected eye(s) 5 times a day while awake (~Q3 hr) until corneal ulcer heals then reduce dosage to TID for 7 days.

See most recent edition of the AAP Red Book for further details. Use with **caution** in patients with preexisting neurologic or **renal impairment (adjust dose; see Chapter 31)** or dehydration. Adequate hydration and slow (1 hr) IV administration are essential to prevent crystallization in renal tubules. **Do not use** topical product on the eye or for the prevention of recurrent HSV infections. Oral absorption is unpredictable (15%–30%); consider using valacyclovir or famciclovir for better absorption. Use ideal body weight for obese patients when calculating dosages. Resistant strains of HSV and VZV have been reported in immunocompromised patients (e.g., advanced HIV infection).

Inflammation or phlebitis at the injection site and transient elevations of sCr and BUN are the most frequent IV use side effects. Can cause renal impairment and has been associated with headache, vertigo, insomnia, encephalopathy, GI tract irritation, elevated liver function tests, rash, urticaria, arthralgia, fever, and adverse hematologic effects. Probenecid decreases acyclovir renal clearance. Acyclovir may increase the concentration of tenofovir, and meperidine and its metabolite (normeperidine).

Topical cream acyclovir 5% in combination with hydrocortisone 1% (Xerese) is indicated for herpes labialis (≥6 yr and adults) at a dosage of 5 applications per day for 5 days. Use a finger cot or rubber glove when applying topical cream or ointment.

Ophthalmic ointment: patient should close his or her eyes for 1–2 min after each application and wipe away any excess ointment. Most common side effects include stinging, punctuate keratitis, and follicular conjunctivitis. Blepharitis and hypersensitivity reactions have been reported.

ADAPALENE ± BENZOYL PEROXIDE

Differin and generics

In combination with benzoyl peroxide: Epiduo, Epiduo Forte

Synthetic retinoic acid derivative; topical acne product

Topical cream: 0.1% (45 g)

Topical gel: 0.1% [OTC], 0.3% (45 g); some preparations may contain methylparabens and propylene glycol

Topical lotion: 0.1% (59 mL); some preparations may contain methylparabens and propylene glycol

For explanation of icons, see p. 667

ADAPALENE ± BENZOYL PEROXIDE *continued*

Topical solution as a swab: 0.1% (1.2 g per swab; 14 or 30 unit of use swabs per box)

In combination with benzoyl peroxide as a topical gel:

Epiduo: 0.1% adapalene +2.5% benzoyl peroxide (45 g)

Epiduo Forte: 0.3% adapalene +2.5% benzoyl peroxide (15, 30, 45, 60, 70 g)

Adapalene (≥12 yr and adult): Apply a thin film of cream, gel or lotion to affected areas of cleansed and dried skin QHS

Adapalene and benzoyl peroxide: Apply a thin film to affected areas of cleansed and dried skin once daily

Epiduo: Indicated for children ≥9 yr and adults with limited data in children 7–<9 yr

Epiduo Forte: Indicated for children ≥12 yr and adults.

Avoid contact with eyes, mucous membranes, abraded skin and open wounds; excessive sun exposure; and use of other irritating topical products. A mild transitory warm or stinging sensation of the skin may occur during the first 4 wk of use. Clean and dry the skin before each use.

ADAPALENE: Onset of therapeutic benefits seen in 8–12 wk. Common side effects include dry skin, erythema, and scaly skin. When compared with tretinoin in clinical trials for acne vulgaris, adapalene was as effective and had a more rapid onset of clinical effects with less skin irritation.

ADAPALENE + BENZOYL PEROXIDE: Onset of therapeutic benefits seen in 4–8 wk. Side effects reported in placebo-controlled studies include dry skin, erythema, skin irritation, and contact dermatitis. When compared with isotretinoin in a clinical trial for nodulocystic acne, adapalene + benzoyl peroxide plus doxycycline was not inferior to isotretinoin and was less effective in reducing the number of total lesions (nodules, papules/pustules, and comedones).

ADDERALL

See Dextroamphetamine ± Amphetamine

ADENOSINE

Adenocard and generics

Antiarrhythmic

Injection: 3 mg/mL (2, 4 mL); preservative free

Supraventricular tachycardia (see remarks):

Neonate: 0.05–0.1 mg/kg by rapid IV push over 1–2 sec; may increase dose by 0.05–0.1 mg/kg increments every 2 min to a **max single dose** of 0.3 mg/kg or until termination of SVT.

Child: 0.1 mg/kg (**initial max. dose**: 6 mg) by rapid IV/IO push over 1–2 sec; may repeat in 2 min at 0.2 mg/kg IV/IO, then 0.3 mg/kg IV/IO after 2 min (**all subsequent max. single doses**: 12 mg), or until termination of SVT.

Adolescent and adult≥ 50 kg: 6 mg rapid IV push over 1–2 sec; if no response after 1–2 min, give 12 mg rapid IV push. May repeat a second 12 mg dose after 1–2 min if required. **Max. single dose:** 12 mg.

Contraindicated in 2nd and 3rd degree AV block or sick-sinus syndrome unless pacemaker placed. **Use with caution** in combination with digoxin (enhanced depressant effects on SA and AV nodes). If necessary, doses may be administered IO.

Follow each dose with NS flush. $T_{1/2}$: <10 sec.

May precipitate bronchoconstriction, especially in asthmatics. Side effects include transient asystole, facial flushing, headache, shortness of breath, dyspnea, nausea, chest pain, and lightheadedness.

Carbamazepine and dipyridamole may increase the effects/toxicity of adenosine. Methylxanthines (e.g., caffeine and theophylline) may decrease the effects of adenosine.

ALBUMIN, HUMAN

Albumin-ZLB, Albutein, Buminate, Plasbumin, and many others

Blood product derivative, plasma volume expander

Injection: 5% (50 mg/mL) (50, 100, 250, 500, mL); 25% (250 mg/mL) (20, 50, 100 mL); both concentrations contain 130–160 mEq Na/L

Hypoalbuminemia:

Child: 0.5–1 g/kg/dose IV over 30–120 min; repeat Q1–2 days PRN

Adult: 25 g/dose IV over 30–120 min; repeat Q1–2 days PRN

Max. dose: 2 g/kg/24 hr

Hypovolemia:

Child: 0.5–1 g/kg/dose IV rapid infusion; may repeat PRN; **max. dose:** 6 g/kg/24 hr

Adult: 12.5–25 g/dose IV rapid infusion; may repeat PRN; **max. dose:** 250 g/48 hr

Contraindicated in cases of CHF or severe anemia; rapid infusion may cause fluid overload; hypersensitivity reactions may occur; may cause rapid increase in serum sodium levels. Recommended maximum infusion rates:

Product Concentration	Patients with Normal Plasma Volume	Patients with Hypoproteinemia
5%	2–4 mL/min	5–10 mL/min
25%	1 mL/min	2–3 mL/min

Caution: 25% concentration is considered **contraindicated** in preterm infants due to risk of IVH. Use product specific recommended in-line filter size. Both 5% and 25% products are isotonic but differ in oncotic effects. Dilutions of the 25% product should be made with D_5W or NS; **avoid sterile water as a diluent.**

ALBUTEROL

VoSpire ER (sustained release tabs); ProAir HFA, Proventil HFA, Ventolin HFA (aerosol inhaler); ProAir RespiClick, ProAir Digihaler (breath activated aerosol powder inhaler); AccuNeb (prediluted nebulized solution); and many generics

β_2-Adrenergic agonist

Tabs: 2, 4 mg

Sustained release tabs: 4, 8 mg

Oral solution: 2 mg/5 mL (473 mL)

Aerosol inhaler (HFA): 90 mCg/actuation (60 actuations/inhaler) (8.5 g)

Breath activated aerosol powder inhaler:

ProAir RespiClick and ProAir Digihaler: 90 mCg/actuation (200 actuations/inhaler) (0.65 g); contains milk proteins and small amounts of lactose. ProAir Digihaler contains an electronic event monitor which detects, records, and stores data on inhaler use events, including peak inspiratory flow rate.

Nebulization solution (dilution required): 0.5% (5 mg/mL) (0.5, 20 mL)

Prediluted nebulized solution: 0.63 mg in 3 mL NS, 1.25 mg in 3 mL NS, and 2.5 mg in 3 mL NS (0.083%); some preparations may be preservative free

Inhalations (nonacute use; see remarks):

Aerosol (HFA): 2 puffs (90 mCg/puff) Q4–6 hr PRN

Breath activated aerosol: 2 inhalations (90 mCg/inhalation) Q4–6 hr PRN

For explanation of icons, see p. 667

ALBUTEROL *continued*

Nebulization:

<1 yr: 0.05–0.15 mg/kg/dose Q4–6 hr

1–5 yr: 1.25–2.5 mg/dose Q4–6 hr

5–12 yr: 2.5 mg/dose Q4–6 hr

>12 yr: 2.5–5 mg/dose Q4–8 hr

For use in acute exacerbations, more aggressive dosing may be used.

Exercise-induced bronchospasm (administered 15–30 min before exercise):

Aerosol (HFA): 2 puffs (90 mCg/puff)

Breath activated aerosol: 2 inhalations (90 mCg/inhalation)

Oral (highly discouraged—see remarks):

2–6 yr: 0.3 mg/kg/24 hr PO ÷ TID; **max. dose:** 12 mg/24 hr

6–12 yr: 6 mg/24 hr PO ÷ TID; **max. dose:** 24 mg/24 hr

>12 yr and adult: 2–4 mg/dose PO TID-QID; **max. dose:** 32 mg/24 hr

Inhaled doses may be given more frequently than indicated. In such cases, consider cardiac monitoring and monitoring of serum potassium (hypokalemia). Systemic effects are dose related. Please verify the concentration of the nebulization solution used.

Safety and efficacy for the treatment of symptoms or bronchospasms associated with obstructive airway disease have not been demonstrated for children <4 yr of age (either dose studied was not optimal in this age or drug is not effective in this age group).

Use of oral dosage form is discouraged due to increased side effects and decreased efficacy compared with inhaled formulations.

Possible side effects include tachycardia, palpitations, tremor, insomnia, nervousness, nausea, and headache.

The use of tube spacers or chambers may enhance efficacy of the HFA metered dose inhalers and have been proven to be just as effective and sometimes safer than nebulizers. **Do not** use a spacer device with any of the breath activated inhaler dosage forms. Breath-activated dosage forms require patients to generate a minimum inspiratory flow rate of ≥30 L/min for proper dose activation.

ALLOPURINOL

Zyloprim, Aloprim, and generics

Uric acid lowering agent, xanthine oxidase inhibitor

Tabs: 100, 300 mg

Oral suspension: 20 mg/mL

Injection (Aloprim and generics): 500 mg

Contains ~1.45 mEq Na/500 mg drug

For use in tumor lysis syndrome, see Chapter 22 for additional information.

Child:

Oral: 10 mg/kg/24 hr PO ÷ BID-QID; **max. dose**: 800 mg/24 hr

Injectable: 200 mg/m²/24 hr IV ÷ Q 6–12 hr; **max. dose**: 600 mg/24 hr

Adult:

Oral: 200–800 mg/24 hr PO ÷ BID-TID

Injectable: 200–400 mg/m²/24 hr IV ÷ Q 6–12 hr; **max. dose**: 600 mg/24 hr

ALLOPURINOL *continued*

Discontinue use at the first appearance of skin rash or other signs of an allergic reaction. **Avoid** use in individuals with HLA-B*58:01 allele as they are at significant risk for developing severe cutaneous adverse reactions (e.g., Stevens-Johnson syndrome and TEN).

Side effects include rash, neuritis, hepatotoxicity, GI disturbance, bone marrow suppression, and drowsiness.

Adjust dose in renal insufficiency (see Chapter 31). Must maintain adequate urine output and alkaline urine.

Drug interactions: increases serum theophylline level; may increase the incidence of rash with ampicillin and amoxicillin; increased risk of toxicity with azathioprine, didanosine and mercaptopurine; and increased risk of hypersensitivity reactions with ACE inhibitors and thiazide diuretics. Use with didanosine is **contraindicated** due to increased risk for didanosine toxicity. Rhabdomyolysis has been reported with clarithromycin use.

IV dosage form is very alkaline and must be **diluted to a minimum concentration** of 6 mg/mL and infused over 30 min.

ALMOTRIPTAN MALATE
Generics; previously available as Axert
Antimigraine agent, selective serotonin agonist

Tabs: 6.25, 12.5 mg

Treatment of acute migraines with or without aura:

Oral (Safety of an average of >4 headaches in a 30-day period has not been established; see remarks):

Child ≥12 and adult: Start with 6.25–12.5 mg PO × 1. If needed in 2 hr, a second dose may be administered. **Max. daily dose:** 2 doses/24 hr and 25 mg/24 hr.

Contraindicated in ischemic/vasospastic coronary artery disease, significant underlying cardiovascular disease, cerebrovascular syndromes, peripheral vascular disease, uncontrolled hypertension, or hemiplegic/basilar migraine. **Do not** administer with any ergotamine-containing medication ergot-type medication, any other 5-HT_1 agonist (e.g., triptans), methylene blue, or with/within 2 wk of discontinuing an MAO inhibitor or linezolid.

FDA-labeled indication for adolescents is acute migraine treatment in patients with a history of migraine lasting ≥4 hr when left untreated. Efficacy for the treatment of migraine associated symptoms of nausea, photophobia, and phonophobia were not established for adolescents.

Most common side effects include dizziness, somnolence, headache, paresthesia, nausea, and vomiting. Reported serious adverse effects include coronary artery spasm, ischemia (myocardial, gastrointestinal, peripheral vascular), cerebral/subarachnoid hemorrhage, cerebrovascular accident/disease, and vision loss.

Use with **caution** in renal impairment (CrCl ≤30 mL/min) or hepatic impairment; use initial dose of 6.25 mg dose with a max. daily dose of 12.5 mg/24 hr.

Almotriptan is a minor substrate for CYP 450 2D6 and 3A4. Use lower initial single dose of 6.25 mg with maximum daily dose of 12.5 mg if receiving a potent CYP 450 3A4 inhibitor (e.g., itraconazole, ritonavir). **Do not use** almotriptan in the presence of renal or hepatic impairment and receiving a potent CYP 3A4 inhibitor.

Doses may be administered with or without food.

For explanation of icons, see p. 667

ALPROSTADIL
Prostin VR Pediatric, prostaglandin E_1, PGE_1
Prostaglandin E1, vasodilator

Injection: 500 mCg/mL (1 mL); contains dehydrated alcohol

Neonate:
Initial: 0.05–0.1 mCg/kg/min. Advance to 0.2 mCg/kg/min if necessary.
Maintenance: When increase in PaO_2 is noted, decrease immediately to lowest effective dose. Usual dosage range: 0.01–0.4 mCg/kg/min; doses >0.4 mCg/kg/min not likely to produce additional benefit.
To prepare infusion: see inside front cover.

For palliation only. Continuous vital sign monitoring essential. May cause apnea (10%–12%; especially in those weighing <2 kg at birth), fever, seizures, flushing, bradycardia, hypotension, diarrhea, gastric outlet obstruction, and reversible cortical proliferation of long bones (with prolonged use). May decrease platelet aggregation.

ALTEPLASE
Activase, Cathflo Activase, tPA
Thrombolytic agent, tissue plasminogen activator

Injection:
Cathflo Activase: 2 mg
Activase: 50 mg (29 million unit), 100 mg (58 million unit)
All products contain: L-arginine and polysorbate 80

Occluded IV catheter:
Aspiration method: Use 1 mg/1 mL concentration as follows:
Central venous line (dosage per lumen, treating one lumen at a time):
<30 kg: Instill a volume equal to 110% of internal lumen volume of the catheter **NOT exceeding** 2 mg.
≥30 kg: 2 mg each lumen.
Subcutaneous port: Instill a volume equal to 110% of internal lumen and line volume of the port **NOT exceeding** 2 mg.
Instill into catheter over 1–2 min and leave in place for 2 hr before attempting blood withdrawal. After 2 hr, attempts to withdraw blood may be made every 2 hr for 3 attempts. Dose may be repeated once in 24 hr using a longer catheter dwell time of 3–4 hr. After 3–4 hr (repeat dose), attempts to withdrawal blood may be made every 2 hr for 3 attempts. **DO NOT** infuse into patient.
Systemic thrombolytic therapy (limited data, use in consultation with a hematologist; see remarks):
Low-dose initial infusion:
<90 days old: 0.06 mg/kg/hr; **max. dose:** 2 mg/hr
≥90 days old–21 yr: 0.03 mg/kg/hr; **max. dose:** 2 mg/hr
High-dose initial infusion: 0.1–0.5 mg/kg/hr; **max. dose:** 25 mg/hr
Dosage regimens ranging from lower dosages (0.01 mg/kg/hr) to higher dosages (0.1–0.6 mg/kg/hr) have been reported (Chest 2008;133:887–968S). The length of continuous infusion is variable as patients may respond to longer or shorter courses of therapy.

Current use in the pediatric population is limited. May cause bleeding, rash, angioedema, and increase prothrombin time. Rare fatal hypersensitivity reaction has been reported.
THROMBOLYTIC USE: History of stroke, transient ischemic attacks, other neurologic disease and hypertension are **contraindications for adults** but considered **relative contraindications for children**. Monitor fibrinogen, thrombin clotting time, PT and aPTT when used as a thrombolytic. For

ALTEPLASE *continued*

systemic thrombosis therapy, efficacy has been reported at 40%–97% with the risk for bleeding at 3%–27%. Poor efficacy in VTE in children has been recently reported. **Use with caution** in severe hepatic or renal dysfunction (systemic use only).

Newborns have reduced plasminogen levels (~50% of adult values) which decrease the thrombolytic effects of alteplase. Plasminogen supplementation may be necessary.

ALUMINUM HYDROXIDE

Various generics; previously available as Amphojel

Antacid, phosphate binder

Oral suspension [OTC]: 320 mg/5 mL (473 mL)

Each 5 mL suspension contains <0.13 mEq Na.

Antacid (see remarks):

Child: 320–960 mg PO 1–3 hr PC and QHS

Adult: 640 mg PO 1–3 hr PC and HS; **max. dose:** 3840 mg/24 hr

Hyperphosphatemia (administer all doses with meals and titrate to normal serum phosphorus):

Child: 50–150 mg/kg/24 hr ÷ Q4–6 hr PO

Adult: 300–600 mg TID-QID PO between meals and QHS

Max. dose (all ages): 3000 mg/24 hr

Chronic antacid use is not recommended for children with GERD. **Use with caution** in patients with renal failure and upper GI hemorrhage.

Interferes with the absorption of several orally administered medications, including digoxin, ethambutol, indomethacin, isoniazid, naproxen, mycophenolate, tetracyclines, fluoroquinolones (e.g., ciprofloxacin), and iron. In general, **do not** take oral medications within 1–2 hr of taking aluminum dose unless specified.

May cause constipation, decreased bowel motility, encephalopathy, and phosphorus depletion.

ALUMINUM HYDROXIDE WITH MAGNESIUM HYDROXIDE

Maalox, Maalox Advanced Maximum Strength Liquid, Mylanta Maximum Strength, Almacone Antacid Antigas, Almacone Double Strength, RuLox, and many other generics (see remarks)

Antacid

Chewable tabs [OTC]: (Al $[OH]_3$: Mg $[OH]_2$)

Almacone and generics: 200 mg AlOH, 200 mg MgOH, and 25 mg simethicone

Oral suspension [OTC] (see remarks):

Maalox, Almacone Antacid Antigas, RuLox and generics: each 5 mL contains 200 mg AlOH, 200 mg MgOH, and 20 mg simethicone (150, 360, 720 mL); some preparations may contain 0.2% alcohol, benzyl alcohol, or propylene glycol

Mylanta Maximum Strength, Maalox Advanced Maximum Strength liquid, Almacone Double Strength, and generics: each 5 mL contains 400 mg AlOH, 400 mg MgOH, and 40 mg simethicone (360, 480 mL); some preparations may contain benzyl alcohol

Many other combinations exist

Contains 0.03–0.06 mEq Na/5 mL

Continued

For explanation of icons, see p. 667

ALUMINUM HYDROXIDE WITH MAGNESIUM HYDROXIDE *continued*

Antacid (mL volume dosages are based on the 200 mg AlOH, 200 mg MgOH, and 20 mg simethicone per 5 mL oral suspension concentration):

Child ≤12 yr: 0.5–1 mL/kg/dose (**max. dose:** 20 mL/dose) PO 1–3 hr PC and HS

>12 yr and adult: 10–20 mL PO 1–3 hr PC and HS; **max. dose:** 80 mL/24 hr

Chronic antacid use is not recommended for children with GERD. May have laxative effect. May cause hypokalemia. **Use with caution** in patients with renal insufficiency (magnesium), gastric outlet obstruction. **Do not use** for hyperphosphatemia.

Interferes with the absorption of the benzodiazepines, chloroquine, digoxin, naproxen, mycophenolate, phenytoin, quinolones (e.g., ciprofloxacin), tetracyclines, and iron. In general, do not take oral medications within 1–2 hr of taking antacid dose unless specified.

DO NOT use Maalox Total Relief (bismuth subsalicylate), Mylanta New Tonight Soothing Liquid (calcium carbonate + magnesium hydroxide + simethicone), Maalox Regular Strength Chewable Tablets and Children's Mylanta Chewable Tablets (calcium carbonate), Maalox Maximum Strength Chewable (calcium carbonate and simethicone), and Mylanta Gas (simethicone) as these products do not contain aluminum hydroxide and magnesium hydroxide.

AMANTADINE HYDROCHLORIDE

Immediate release dosage forms: Symmetrel and generics
Extended-release dosage forms: Gocovri, Osmolex ER
Antiviral agent

Capsule: 100 mg
Tabs: 100 mg
Extended-release capsule (Gocovri; see remarks): 68.5, 137 mg
Extended-release tabs (Osmolex ER; see remarks): 129, 193, 258 mg
Oral solution or syrup: 50 mg/5 mL (480 mL); may contain parabens

Influenza A prophylaxis and treatment (for treatment, it is best to initiate therapy immediately after the onset of symptoms; within 2 days; see remarks):

1–9 yr: 5 mg/kg/24 hr PO ÷ BID; **max. dose**: 150 mg/24 hr

≥10 yr:

<40 kg: 5 mg/kg/24 hr PO ÷ BID; **max. dose** 200 mg/24 hr

≥40 kg: 200 mg/24 hr PO ÷ BID

Duration of therapy:

Prophylaxis:

Single exposure: at least 10 days

Repeated/uncontrolled exposure: up to 90 days

Use with influenza A vaccine when possible.

Symptomatic treatment:

Continue for 24–48 hr after disappearance of symptoms.

The CDC has reported resistance to influenza A and does not recommend its use for treatment and prophylaxis. Check with local microbiology laboratories and the CDC for seasonal susceptibility/resistance. Individuals immunized with live attenuated influenza vaccine should not receive amantadine prophylaxis for 14 days after the vaccine.

Do not use in the first trimester of pregnancy. **Use with caution** in patients with liver disease, seizures, renal disease, congestive heart failure, peripheral edema, orthostatic hypotension, history of recurrent eczematoid rash, and in those receiving CNS stimulants. **Adjust dose in patients with renal insufficiency (see Chapter 31)**.

AMANTADINE HYDROCHLORIDE *continued*

Extended-release capsule and tablet dosage forms are indicated for the treatment of dyskinesia in patients with Parkinson disease receiving levodopa-based therapy.

May cause dizziness, anxiety, depression, mental status change, rash (livedo reticularis), nausea, orthostatic hypotension, edema, CHF, and urinary retention. Impulse control disorder has been reported. Neuroleptic malignant syndrome has been reported with abrupt dose reduction or discontinuation (especially if patient is receiving neuroleptics).

AMIKACIN SULFATE

Various generics; previously available as Amikin

Antibiotic, aminoglycoside

Injection: 250 mg/mL (2, 4 mL); may contain sodium bisulfite

Initial empirical dosage; patient specific dosage defined by therapeutic drug monitoring (see remarks).

Neonate: See the following table.

Postconceptional Age (wk)	Postnatal Age (days)	Dose (mg/kg/dose)	Interval (hr)
≤29[a]	0–7	18	48
	8–28	15	36
	>28	15	24
30–34	0–7	18	36
	>7	15	24
≥35	ALL	15	24[b]

[a]Or significant asphyxia, PDA, indomethacin use, poor cardiac output, reduced renal function.
[b]Use Q36 hr interval for HIE patients receiving whole-body therapeutic cooling.

Infant and child: 15–22.5 mg/kg/24 hr ÷ Q8 hr IV/IM; infants and patients requiring higher doses (e.g., cystic fibrosis) may receive initial doses of 30 mg/kg/24 hr ÷ Q8 hr IV/IM

Cystic fibrosis (if available, use patient's previous therapeutic mg/kg dosage):

Conventional Q8 hr dosing: 30 mg/kg/24 hr ÷ Q8 hr IV

High-dose extended interval (once daily) dosing (limited data): 30–35 mg/kg/24 hr Q24 hr IV

Nontuberculous mycobacterium (part of a multiple drug regimen):

Infant and child: 15–30 mg/kg/dose Q24 hr IV; **max. dose:** 1500 mg/24 hr

Adolescent: 10–15 mg/kg/dose Q24 hr IV; **max. dose:** 1500 mg/24 hr

Adult: 15 mg/kg/24 hr ÷ Q8–12 hr IV/IM

Initial max. dose: 1.5 g/24 hr, then monitor levels

Use with **caution** in preexisting renal, vestibular, or auditory impairment; concomitant anesthesia or neuromuscular blockers, neurotoxic; concomitant neurotoxic, ototoxic, or nephrotoxic drugs; sulfite sensitivity; and dehydration. **Adjust dose in renal failure (see Chapter 31**). Longer dosing intervals may be necessary for neonates receiving indomethacin for PDAs and for all patients with poor cardiac output. Rapidly eliminated in patients with cystic fibrosis, burns, and in febrile neutropenic patients. CNS penetration is poor beyond early infancy.

Continued

For explanation of icons, see p. 667

AMIKACIN SULFATE *continued*

Therapeutic Drug Monitoring Goals:

Dosing Method/ Indication	Peak Level	Trough Level	Recommended Serum Sampling Time
Conventional dosing	20–30 mg/L; 25–30 mg/L for CNS, pulmonary, bone, life-threatening, Pseudomonas infections and febrile neutropenia.	5–10 mg/L	Trough within 30 min before the third consecutive dose and peak 30–60 min after the administration of the third consecutive dose (at steady state)
High-Dose Extended Interval (Q24 hr) for Cystic Fibrosis	80–120 mg/L	<10 mg/L	Trough within 30 min before the 2nd dose and peak 30–60 min after administration of 2nd dose
Extended Interval (Q24 hr) for nontuberculous mycobacterium	20–40 mg/L	<10 mg/L	Trough within 30 min before the 2nd dose and peak 30–60 min after administration of 2nd dose

For initial dosing in obese patients, use an adjusted body weight (ABW). ABW = ideal body weight + 0.4 (total body weight − ideal body weight).

May cause ototoxicity, nephrotoxicity, neuromuscular blockade, and rash. Loop diuretics may potentiate the ototoxicity of all aminoglycoside antibiotics.

AMINOCAPROIC ACID
Amicar and generics
Hemostatic agent

Tabs: 500, 1000 mg

Oral liquid/syrup: 250 mg/mL (240, 480 mL); may contain 0.2% methylparaben and 0.05% propylparaben

Injection: 250 mg/mL (20 mL); may contain 0.9% benzyl alcohol

Child (IV/PO):
Loading dose: 100–200 mg/kg
Maintenance: 100 mg/kg/dose Q4–6 hr; **max. dose:** 30 g/24 hr

Adult (IV/PO): 4–5 g during the first hour, followed by 1 g/hr × 8 hr or until bleeding is controlled. **Max. dose**: 30 g/24 hr.

Contraindications: DIC, hematuria. **Use with caution** in patients with cardiac or renal disease. Should not be given with factor IX complex concentrates or antiinhibitor coagulant concentrates because of risk for thrombosis. Dose should be reduced by 75% in oliguria or end stage renal disease. Hypercoagulation may be produced when given in conjunction with oral contraceptives.

May cause nausea, diarrhea, malaise, weakness, headache, decreased platelet function, hypotension, and false increase in urine amino acids. Elevation of serum potassium may occur, especially in patients with renal impairment. Prolonged use may increase risk for skeletal muscle weakness and rhabdomyolysis.

AMINOPHYLLINE
Various generics
Bronchodilator, methylxanthine

Injection: 25 mg/mL (79% theophylline) (10, 20 mL)
Note: Pharmacy may dilute IV dosage forms to enhance accuracy of neonatal dosing.

Neonatal apnea:
Loading dose: 5–6 mg/kg IV
Maintenance dose: 1–2 mg/kg/dose Q6–8 hr, IV

Asthma exacerbation and reactive airway disease:
IV loading: 6 mg/kg IV over 20 min (each 1.2 mg/kg dose raises the serum theophylline concentration 2 mg/L)
IV maintenance: **Continuous IV drip:**
Neonate: 0.2 mg/kg/hr
6 wk–6 mo: 0.5 mg/kg/hr
6 mo–1 yr: 0.6–0.7 mg/kg/hr
1–9 yr: 1–1.2 mg/kg/hr
9–12 yr and young adult smoker: 0.9 mg/kg/hr
>12 yr healthy nonsmoker: 0.7 mg/kg/hr
The above total daily doses may also be administered IV ÷ Q4–6 hr.

Consider milligrams of theophylline available when dosing aminophylline. For oral route of administration, use theophylline.

Monitoring serum levels is essential, especially in infants and young children. Intermittent dosing for infants and children 1–5 yr may require Q4 hr dosing regimen due to enhanced metabolism/clearance. Side effects: restlessness, GI upset, headache, tachycardia, seizures (may occur in absence of other side effects with toxic levels).

Therapeutic level (as theophylline): for asthma, 10–20 mg/L; for neonatal apnea, 6–13 mg/L.

Recommended guidelines for obtaining levels:
IV bolus: 30 min after infusion
IV continuous; 12–24 hr after initiation of infusion
PO liquid, immediate-release tab (theophylline product):
Peak: 1 hr post dose
Trough: just before dose
PO sustained-release (theophylline product):
Peak: 4 hr post dose
Trough: just before dose

Ideally, obtain levels after steady state has been achieved (after at least one day of therapy). Liver impairment, cardiac failure, and sustained high fever may increase theophylline levels. See *Theophylline* for drug interactions.

Use in breast feeding may cause irritability in infant. It is recommended to avoid breast feeding for 2 hr after IV or 4 hr after immediate-release oral intermittent dose.

For explanation of icons, see p. 667

AMIODARONE HCL
Pacerone, Nexterone, and various generics
Antiarrhythmic, Class III

Tabs: 100, 200, 400 mg
Oral suspension: 5 mg/mL
Injection: 50 mg/mL (3, 9, 18 mL) (contains 20.2 mg/mL benzyl alcohol and 100 mg/mL polysorbate 80 or Tween 80)
Premixed injection (Nexterone): 1.5 mg/mL (100 mL) (iso-osmotic solution, each 1 mL contains 15 mg sulfbutylether β-cyclodextrin [SBECD; see remarks], 0.362 mg citric acid, 0.183 mg sodium citrate and 42.1 mg dextrose), 1.8 mg/mL (200 mL) (iso-osmotic solution, each 1 mL contains 18 mg SBECD, 0.362 mg citric acid, 0.183 mg sodium citrate and 41.4 mg dextrose)
Contains 37.3% iodine by weight.

See algorithms in front cover of book for arrest dosing.
Child PO for tachyarrhythmia:
<1 yr: 600–800 mg/1.73 m^2/24 hr ÷ Q12–24 hr × 4–14 days and/or until adequate control achieved, then reduce to 200–400 mg/1.73 m^2/24 hr.
≥1 yr: 10–15 mg/kg/24 hr ÷ Q12–24 hr × 4–14 days and/or until adequate control achieved, then reduce to 5 mg/kg/24 hr ÷ Q12–24 hr if effective.
Child IV for tachyarrhythmia (limited data):
5 mg/kg (**max. dose:** 300 mg) over 30 min followed by a continuous infusion starting at 5 micrograms (mCg)/kg/min; infusion may be increased up to a **max. dose** of 15 mCg/kg/min or 20 mg/kg/24 hr or 2200 mg/24 hr.
Adult PO for ventricular arrhythmias:
Loading dose: 800–1600 mg/24 hr ÷ Q12–24 hr for 1–3 wk
Maintenance: 600–800 mg/24 hr ÷ Q12–24 hr × 1 mo, then 200 mg Q12–24 hr
Use lowest effective dose to minimize adverse reactions.
Adult IV for ventricular arrhythmias:
Loading dose: 150 mg over 10 min (15 mg/min) followed by 360 mg over 6 hr (1 mg/min); followed by a maintenance dose of 0.5 mg/min. Supplemental boluses of 150 mg over 10 min may be given for breakthrough VF or hemodynamically unstable VT, and the maintenance infusion may be increased to suppress the arrhythmia. **Max. dose**: 2.1 g/24 hr.

Used in the resuscitation algorithm for ventricular fibrillation/pulseless ventricular tachycardia (**see front cover for arrest dosing and back cover for PALS algorithm**). Overall use of this drug may be limited to its potentially life-threatening side effects and the difficulties associated with managing its use.
Contraindicated in severe sinus node dysfunction, marked sinus bradycardia, second- and third-degree AV block. **Use with caution** in hepatic impairment.
Long elimination half-life (40–55 days). Major metabolite is active. Use of premixed injection (Nexterone) is not recommended in renal insufficiency due to accumulation of cyclodextrin excipient.
Increases cyclosporine, digoxin, phenytoin, tacrolimus, warfarin, calcium channel blockers, theophylline, and quinidine levels. Amiodarone is a CYP P450 3A3/4 substrate and inhibits CYP 3A3/4, 2C9, and 2D6. Risk of rhabdomyolysis is increased when used with simvastatin at doses greater than 20 mg/24 hr and lovastatin at doses greater than 40 mg/24 hr. Serious symptomatic bradycardia has been reported when used with sofosbuvir.
Proposed therapeutic level with chronic oral use: 1–2.5 mg/L.
Asymptomatic corneal microdeposits should appear in all patients. Alters liver enzymes, thyroid function. Pulmonary fibrosis reported in adults. May cause worsening of preexisting arrhythmias with bradycardia and AV block. May also cause hypotension, anorexia, nausea, vomiting, dizziness, paresthesias, ataxia, tremor, SIADH, and hypothyroidism or hyperthyroidism. Drug rash with eosinophilia and systemic symptoms (DRESS) and acute respiratory distress syndrome have been reported.

AMIODARONE HCL *continued*

Correct hypokalemia, hypocalcemia or hypomagnesemia whenever possible before use as these conditions may exaggerate QTc prolongation.

Intravenous continuous infusion concentration for peripheral administration should not exceed 2 mg/mL and **must be** diluted with D_5W. The intravenous dosage form can leach out plasticizers such as DEHP. It is recommended to reduce the potential exposure to plasticizers in pregnant women and children at the toddler stages of development and younger by using alternative methods of IV drug administration.

Oral administration should be consistent with regards to meals because food increases the rate and extent of oral absorption.

AMITRIPTYLINE
Generics; previously available as Elavil
Antidepressant, tricyclic (TCA)

Tabs: 10, 25, 50, 75, 100, 150 mg
Oral syrup: 1 mg/mL

Antidepressant:

Child: Start with 1 mg/kg/24 hr ÷ TID PO for 3 days; then increase to 1.5 mg/kg/24 hr. Dose may be gradually increased to a **max. dose** of 5 mg/kg/24 hr if needed. Monitor ECG, BP, and heart rate (HR) for doses >3 mg/kg/24 hr.

Adolescent: 10 mg TID PO and 20 mg QHS; dose may be gradually increased up to a **max. dose** of 200 mg/24 hr if needed.

Adult: 40–100 mg/24 hr ÷ QHS-BID PO; dose may be gradually increased up to 300 mg/24 hr if needed; gradually decrease dose to lowest effective dose when symptoms are controlled.

Augment analgesia for chronic pain:

Child: Initial: 0.1 mg/kg/dose QHS PO; increase as needed and tolerated over 2–3 wk to 0.5–2 mg/kg/dose QHS

Migraine prophylaxis (limited data):

Child: Initial 0.1–0.25 mg/kg/dose QHS PO; increase as needed and tolerated every 2 wk by 0.1–0.25 mg/kg/dose up to a **max. dose** of 2 mg/kg/24 hr or 75 mg/24 hr. For doses >1 mg/kg/24 hr, divide daily dose BID and monitor ECG.

Adult: Initial 10–25 mg/dose QHS PO; reported range of 10–400 mg/24 hr.

Contraindicated in narrow-angle glaucoma, seizures, severe cardiac disorders, and patients who received MAO inhibitors within 14 days. See Chapter 3 for management of TCA toxic ingestion.

$T_{1/2}$ = 9–25 hr in adults. **Maximum** antidepressant effects may not occur for 2 wk or more after initiation of therapy. **Do not abruptly discontinue therapy in patients receiving high doses for prolonged periods.**

Therapeutic levels (sum of amitriptyline and nortriptyline): 100–250 ng/mL. Recommended serum sampling time: obtain a single level 8 hr or more after an oral dose (following 4–5 days of continuous dosing). Amitriptyline is a substrate for CYP 450 1A2, 2C9, 2C19, 2D6, and 3A3/4 and inhibitor for CYP 450 1A2, 2C19, 2C9, 2D6 and 2E1. Rifampin can decrease amitriptyline levels. Amitriptyline may increase side effects of tramadol.

Pharmacogenomic dosing considerations for CYP 2D6 and 2C19 phenotype (Clinical Pharmacology and Therapeutics. 2016;102[1]:37–44): see next page.

Continued

For explanation of icons, see p. 667

AMITRIPTYLINE *continued*

Phenotype	CYP 2D6 Ultra-Rapid Metabolizer	CYP 2D6 Normal Metabolizer	CYP 2D6 Intermediate Metabolizer	CYP 2D6 Poor Metabolizer
CYP 2C19 Ultra-rapid or Rapid Metabolizer	Avoid use, use alternative therapy	Consider alternative therapy not metabolized by CYP 2C19	Consider alternative therapy not metabolized by CYP 2C19	Avoid use; use alternative therapy
CYP 2C19 Normal Metabolizer	Avoid use but if use necessary, titrate to higher target dose	Use recommended initial dose	Consider a 25% initial dose reduction	Avoid use but if use necessary, consider 50% initial dose reduction
CYP 2C19 Intermediate Metabolizer	Avoid use; use alternative therapy	Use recommended initial dose	Consider a 25% initial dose reduction	Avoid use but if use necessary, consider 50% initial dose reduction
CYP 2C19 Poor Metabolizer	Avoid use; use alternative therapy	Avoid use but if use necessary, consider 50% initial dose reduction	Avoid use; use alternative therapy	Avoid use; use alternative therapy

Side effects include sedation, urinary retention, constipation, dry mouth, dizziness, drowsiness, liver enzyme elevation, and arrhythmia. May discolor urine (blue/green). QHS dosing during first weeks of therapy will reduce sedation. Monitor ECG, BP, CBC at start of therapy and with dose changes. Decrease dose if PR interval reaches 0.22 sec, QRS reaches 130% of baseline, HR rises greater than 140/min, or if BP is >140/90. Tricyclics may cause mania. **For antidepressant use, monitor for clinical worsening of depression and suicidal ideation/behavior following the initiation of therapy or after dose changes.**

AMLODIPINE
Norvasc and generics
Calcium channel blocker, antihypertensive

Tabs: 2.5, 5, 10 mg
Oral suspension: 1 mg/mL

Child:

Hypertension: Start with 0.1 mg/kg/dose (**max. dose:** 5 mg) PO once daily–BID; dosage may be gradually increased to a **max. dose** of 0.6 mg/kg/24 hr up to 20 mg/24 hr. An effective antihypertensive dose for 6–17-yr-olds of 2.5–5 mg once daily has been reported and doses >5 mg have not been evaluated.

Adult:

Hypertension: 5–10 mg/dose once daily PO; use 2.5 mg/dose once daily PO in patients with hepatic insufficiency. **Max. dose:** 10 mg/24 hr.

AMLODIPINE *continued*

Use with caution in combination with other antihypertensive agents. Younger children (<6 yr) may require higher mg/kg doses than older children and adults. A BID dosing regimen may provide better efficacy in children.

Reduce dose in hepatic insufficiency. Allow 5–7 days of continuous initial dose therapy before making dosage adjustments because of the drug's gradual onset of action and lengthy elimination half-life. Amlodipine is a substrate for CYP 450 3A4 and **should be used with caution** with 3A4 inhibitors such as protease inhibitors and azole antifungals (e.g., fluconazole and ketoconazole). May increase levels and toxicity of cyclosporine, tacrolimus and simvastatin.

Dose-related side effects include edema, dizziness, flushing, fatigue, and palpitations. Other side effects include headache, nausea, abdominal pain, and somnolence.

Limited data reports amlodipine present in breast milk at low levels, undetectable in infant plasma with no adverse effects to breastfed infants.

AMMONIUM CHLORIDE
Various generics
Diuretic, urinary acidifying agent

Injection: 5 mEq/mL (26.75%) (20 mL); contains EDTA
1 mEq = 53 mg

Urinary acidification:
Child: 75 mg/kg/24 hr ÷ Q6 hr IV; **max. dose:** 6 g/24 hr
Adult: 1.5 g/dose Q6 hr IV

Drug administration: Dilute to concentration ≤0.4 mEq/mL. Infusion **not to exceed** 50 mg/kg/hr or 1 mEq/kg/hr.

Contraindicated in severe hepatic or renal insufficiency and primary respiratory acidosis.
Use with caution in infants.

May produce acidosis, hyperammonemia, and GI irritation. Monitor serum chloride level, acid/base status, and serum ammonia.

AMMONUL

See Sodium Phenylacetate + Sodium Benzoate

AMOXICILLIN
Various generics; previously available as Amoxil and Trimox
Antibiotic, aminopenicillin

Oral suspension: 125, 250 mg/5 mL (80, 100, 150 mL); and 200, 400 mg/5 mL (50, 75, 100 mL)
Caps: 250, 500 mg
Tablets: 500, 875 mg
Chewable tabs: 125, 250 mg; may contain phenylalanine

Continued

For explanation of icons, see p. 667

AMOXICILLIN *continued*

Neonate – ≤3 mo: 20–30 mg/kg/24 hr ÷ Q12 hr PO
Child:
Standard dose: 25–50 mg/kg/24 hr ÷ Q8–12 hr PO
High dose (resistant Streptococcus pneumoniae; see remarks): 80–90 mg/kg/24 hr ÷ Q8–12 hr PO
Max. dose: 2–3 g/24 hr; some experts recommend a **maximum** dosage up to 4 g/24 hr
Adult:
Mild/moderate infections: 250 mg/dose Q8 hr PO OR 500 mg/dose Q12 hr PO
Severe infections: 500 mg/dose Q8 hr PO OR 875 mg/dose Q12 hr PO
Max. dose: 2–3 g/24 hr
Tonsillitis/pharyngitis (S. pyogenes): 50 mg/kg/24 hr ÷ Q12 hr PO × 10 days; **max. dose:** 1 g/24 hr.
SBE prophylaxis: administer dose 1 hr before procedure
Child: 50 mg/kg PO × 1; **max.** 2 g/dose
Adult: 2 g PO × 1
Early Lyme disease:
Child: 50 mg/kg/24 hr ÷ Q8 hr PO × 14–21 days; **max. dose:** 1.5 g/24 hr
Adult: 500 mg/dose Q8 hr PO × 14–21 days

Renal elimination. **Adjust dose in renal failure (see Chapter 31)**. Serum levels about twice those achieved with equal dose of ampicillin. Fewer GI effects, but otherwise similar to ampicillin. Side effects: rash and diarrhea. Rash may develop with concurrent EBV infection. May increase warfarin's effect by increasing INR.

High-dose regimen is recommended in respiratory infections (e.g., CAP), acute otitis media, and sinusitis, owing to increasing incidence of penicillin resistant pneumococci. **Chewable tablets may contain phenylalanine and should not be used by phenylketonurics.**

AMOXICILLIN-CLAVULANIC ACID
Augmentin, Augmentin ES-600, and generics; previously available as Augmentin XR
Antibiotic, aminopenicillin with β-lactamase inhibitor

Tabs:
For TID dosing: 250, 500 mg (with 125 mg clavulanate);
For BID dosing: 875 mg amoxicillin (with 125 mg clavulanate)
Extended-release tabs (previously available as Augmentin XR): 1 g amoxicillin (with 62.5 mg clavulanate);
Chewable tabs:
For BID dosing (7:1 amoxicillin:clavulanate): 200, 400 mg amoxicillin (28.5 and 57 mg clavulanate, respectively); contains saccharin and aspartame
Oral suspension:
For TID dosing (4:1 amoxicillin:clavulanate): 125, 250 mg amoxicillin/5 mL (31.25 and 62.5 mg clavulanate/5 mL, respectively) (75, 100, 150 mL); contains saccharin
For BID dosing:
7:1 amoxicillin:clavulanate: 200, 400 mg amoxicillin/5 mL (28.5 and 57 mg clavulanate/5 mL, respectively) (50, 75, 100 mL)
14:1 amoxicillin:clavulanate (Augmentin ES-600 and generics): 600 mg amoxicillin/5 mL; contains 42.9 mg clavulanate/5 mL) (75, 125, 200 mL); contains saccharin and/or aspartame
Contains 0.63 mEq K^+ per 125 mg clavulanate (Augmentin ES-600 contains 0.23 mEq K^+ per 42.9 mg clavulanate)

AMOXICILLIN-CLAVULANIC ACID *continued*

Dosage based on amoxicillin component (see remarks for resistant S. pneumoniae).

Infant 1–<3 mo: 30 mg/kg/24 hr ÷ Q12 hr PO (recommended dosage form is 125 mg/5 mL suspension)

Child ≥3 mo:

Non–high-dose amoxicillin regimens:

<40 kg:

TID dosing (see remarks): 20–40 mg/kg/24 hr ÷ Q8 hr PO

BID dosing (see remarks): 25–45 mg/kg/24 hr ÷ Q12 hr PO

***≥40 kg*:** use adult dosage

High-dose amoxicillin regimens:

≥3 mo and <40 kg (use 14:1 amoxicillin:clavulanate dosage form, Augmentin ES-600 or generic oral suspension): 90 mg/kg/24 hr ÷ Q8–12 hr PO; Q8 hr recommended for CAP, orbital cellulitis, and severe infections

≥40 kg: use adult dosage

Adult: 250–500 mg/dose Q8 hr PO or 875 mg/dose Q12 hr PO for more severe and respiratory infections

Extended-release tablet:

≥16 yr and adult: 2 g Q12 hr PO × 10 days for acute bacterial sinusitis or × 7–10 days for community-acquired pneumonia

See Amoxicillin for additional comments. **Adjust dose in renal failure (see Chapter 31)**. **Contraindicated** in patients with a history of cholestatic jaundice/hepatic dysfunction associated with amoxicillin-clavulanic acid. Extended-release tablet dosage form is **contraindicated** in patients with CrCl <30 mL/min.

Clavulanic acid extends the activity of amoxicillin to include β-lactamase–producing strains of *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, and some *Staphylococcus aureus* and may increase the risk for diarrhea.

The BID dosing schedule is associated with less diarrhea. For BID dosing, the 875 mg, 1 g tablets, the 200 mg, 400 mg chewable tablets or the 200 mg/5mL, 400 mg/5 mL, 600 mg/5 mL suspensions should be used. These BID dosage forms contain phenylalanine and **should not be used** by phenylketonurics. For TID dosing, the 250 mg, 500 mg tablets, the 125 mg 250 mg chewable tablets or the 125 mg/5 mL, 250 mg/5 mL suspensions should be used.

Higher doses of 80–90 mg/kg/24 hr (amoxicillin component) have been recommended for resistant strains of *S. pneumoniae* in acute otitis media and pneumonia (use BID formulations containing 7:1 or 14:1 ratio of amoxicillin to clavulanic acid or Augmentin ES-600, respectively).

The 250 or 500 mg tablets **cannot** be substituted for Augmentin XR tablets.

AMPHETAMINE
Evekeo, Adzenys ER, Adzenys XR-ODT, Dyanavel XR
CNS stimulant

Tabs, immediate release:

Evekeo and generics: 5, 10 mg; both tablets are scored

Extended-release dispersible tabs:

Adzenys XR-ODT: 3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg

Extended-release oral suspension:

Adzenys ER: 1.25 mg/mL (450 mL); contains parabens and propylene glycol

Dyanavel XR: 2.5 mg/mL (464 mL); contains parabens and polysorbate 80

Continued

For explanation of icons, see p. 667

AMPHETAMINE *continued*

DO NOT substitute extended-release formulations for other amphetamine products on a milligram per milligram basis due to differences in potency and pharmacokinetic profiles. If converting from other amphetamine products, discontinue that treatment first and titrate new dosage form as indicated in the drug dosage section.

Attention-deficit/hyperactivity disorder:

Immediate release tabs (Evekeo and generics; PO):

3–5 yr: 2.5 mg/24 hr QAM; increase by 2.5 mg/24 hr at weekly intervals until desired response. Incremental dosages may be administered BID-TID with the first dose at awakening and subsequent doses spaced at 4–6 hr intervals. Doses rarely exceed 40 mg/24 hr.

≥6 yr and adolescent: 5 mg once daily or BID; increase by 5 mg/24 hr at weekly intervals until desired response. Incremental dosages may be administered BID-TID with the first dose at awakening and subsequent doses spaced at 4–6 hr intervals. Doses rarely exceed 40 mg/24 hr.

Extended-release suspension (see how supplied section, earlier):

Product	Dosage (PO)	Maximum Daily Dosage
Adzenys ER[a]	6–17 yr: Start at 6.25 mg/24 hr QAM; increase by 3.125–6.25 mg every 7 days until desired response up to the maximum dose	6–12 yr: 18.75 mg/24 hr 13–17 yr: 12.5 mg/24 hr
Dyanavel XR	≥6 yr and adolescent: Start at 2.5 or 5 mg/24 hr QAM; increase by 2.5–10 mg/24 hr every 4–7 days until desired response up to a maximum dose	20 mg/24 hr

[a]If converting from Adderall XR, see dosage equivalent information in Adzenys ER product information.

Extended-release dispersible tabs (see how supplied section, earlier; Adzenys XR-ODT; PO):

6–17 yr: 6.3 mg/24 hr QAM; increase by 3.1 or 6.3 mg/24 hr at weekly intervals until desired response. **Maximum** dose: 6–12 yr: 18.8 mg/24 hr; 13–17 yr: 12.5 mg/24 hr.

Adult: 12.5 mg/24 hr QAM

If converting from Adderall XR, see dosage equivalent information in Adzenys XR-ODT product information.

Narcolepsy:

Immediate release tabs (Evekeo and generics; PO):

6–12 yr: 5 mg QAM; increase by 5 mg/24 hr at weekly intervals until desired response. Incremental doses may be administered with the first dose at awakening and subsequent doses (5 or 10 mg) spaced at 4–6 hr intervals. Usual daily dosage range: 5–60 mg/24 hr in divided doses.

≥13 yr and adult: 10 mg QAM; increase by 10 mg/24 hr at weekly intervals until desired response. Incremental doses may be administered with the first dose at awakening and subsequent doses (5 or 10 mg) spaced at 4–6 hr intervals. Usual daily dosage range: 5–60 mg/24 hr in divided doses.

Use with caution in presence of hypertension or cardiovascular disease. **Avoid use** in known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may increase risk of sympathomimetic effects of amphetamines (sudden death, stroke, and MI have been reported). **Contraindicated** with MAO inhibitors, including linezolid and IV methylene blue, as a hypertensive crisis may occur if used within 14 days of discontinuance of MAO inhibitor. Serotonin syndrome may occur with used in combination with MAO inhibitors, SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, TCAs, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort.

Amphetamine is a minor substrate of CYP 450 2D6. Alkalinizing agents should be **avoided** as they can increase the effects/toxicity of amphetamines by decreasing its secretion. **Avoid use** of GI acid blockers (e.g., PPIs) with Adzenys ER as amphetamine dose dumping may occur.

AMPHETAMINE *continued*

Not recommended for patients <3 yr of age. Medication should generally not be used in children <5 yr, because diagnosis of ADHD in this age group is extremely difficult (use in consultation with a specialist). Interrupt administration occasionally to determine need for continued therapy.

Common side effects include headache, insomnia, anorexia (monitor growth), abdominal pain, anxiety, mood swings, and agitation. Psychotic disorder, peripheral vascular disease (including Raynaud phenomenon), and cerebrovascular accident have been reported.

Evekeo has an additional labeled indication for the treatment of exogenous obesity in ≥12 yr and adults. Doses may be administered with or without food. **Do not** crush or chew the extended-release dispersible tabs (Adzenys XR-ODT). Shake oral suspension bottle (Adzenys ER and Dyanavel XR) well before dispensing and administering each dose.

AMPHOTERICIN B (CONVENTIONAL)
Various generics; previously available as Fungizone
Antifungal, polyene

Injection: 50 mg vials

IV: mix with D_5W to concentration 0.1 mg/mL (peripheral administration) or 0.25 mg/mL (central line only). pH >4.2. Infuse over 2–6 hr.

Optional test dose: 0.1 mg/kg/dose IV up to **max. dose** of 1 mg (followed by remaining initial dose).

Initial dose: 0.5–1 mg/kg/24 hr; if test dose NOT used infuse first dose over 6 hr and monitor frequently during the first several hours.

Increment: Increase as tolerated by 0.25–0.5 mg/kg/24 hr once daily or every other day. Use larger dosage increment (0.5 mg once daily) for critically ill patients.

Usual maintenance:

Once daily dosing: 0.5–1 mg/kg/24 hr once daily

Every other day dosing: 1.5 mg/kg/dose every other day

Max. dose: 1.5 mg/kg/24 hr

Intrathecal (limited data): 25–100 mCg Q48–72 hr. Increase to 500 mCg as tolerated. Dosages as high as 1500 mCg have been recommended by the 2018 AAP Red Book.

Bladder irrigation for urinary tract mycosis (limited data): 5–15 mg in 100 mL sterile water for irrigation at 100–300 mL/24 hr. Instill solution into bladder, clamp catheter for 1–2 hr then drain; repeat TID–QID for 2–5 days.

Monitor renal, hepatic, electrolyte, and hematologic status closely. Hypercalciuria, hypokalemia, hypomagnesemia, RTA, renal failure, acute hepatic failure, hypotension, and phlebitis may occur. **For dosing information in renal failure, see Chapter 31**.

Common infusion-related reactions include fever, chills, headache, hypotension, nausea, and vomiting; may premedicate with acetaminophen and diphenhydramine 30 min before and 4 hr after infusion. Meperidine useful for chills. Hydrocortisone, 1 mg/mg ampho (**max**.: 25 mg) added to bottle may help to prevent immediate adverse reactions. Use total body weight for obese patients when calculating dosages.

Salt loading with 10–15 mL/kg of NS infused prior to each dose may minimize the risk of nephrotoxicity. Maintaining sodium intake of >4 mEq/kg/24 hr in premature neonates may also reduce risk for nephrotoxicity. Nephrotoxic drugs such as aminoglycosides, chemotherapeutic agents, and cyclosporine may result in synergistic toxicity. Hypokalemia may increase the toxicity of neuromuscular blocking agents and cardiac glycosides.

Although there is no breast-feeding data for amphotericin, many experts believe it is compatible since the drug is highly protein bound, has a large molecular weight and is not absorbed orally.

For explanation of icons, see p. 667

AMPHOTERICIN B LIPID COMPLEX
Abelcet, ABLC
Antifungal, polyene

Injection: 5 mg/mL (20 mL)
(formulated as a 1:1 molar ratio of amphotericin B to lipid complex comprised of dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol)

IV: 3–5 mg/kg/24 hr once daily
For visceral leishmaniasis that failed to respond to or relapsed after treatment with antimony compound, a dosage of 1–3 mg/kg/24 hr once daily × 5 days has been used.
Mix with D_5W to concentration 1 or 2 mg/mL for fluid restricted patients.
Infusion rate: 2.5 mg/kg/hr; shake the infusion bag every 2 hr if total infusion time exceeds 2 hr. **Do not** use an in-line filter.

Monitor renal, hepatic, electrolyte, and hematologic status closely. Thrombocytopenia, anemia, leukopenia, hypokalemia, hypomagnesemia, diarrhea, respiratory failure, skin rash, nephrotoxicity, and increases in liver enzymes and bilirubin may occur. See conventional amphotericin for drug interactions.
Highest concentrations achieved in spleen, lung, and liver from human autopsy data from one heart transplant patient. CNS/CSF levels are lower than amphotericin b, liposomal (AmBisome). In animal models, concentrations are higher in the liver, spleen, and lungs but the same in the kidneys when compared with conventional amphotericin B. Pharmacokinetics in renal and hepatic impairment have not been studied.
Common infusion-related reactions include fever, chills, rigors, nausea, vomiting, hypotension, and headache; may premedicate with acetaminophen, diphenhydramine and meperidine (see Conventional *Amphotericin B* remarks).

AMPHOTERICIN B, LIPOSOMAL
AmBisome
Antifungal, polyene

Injection: 50 mg (vials); contains soy, 900 mg sucrose
(formulated in liposomes composed of hydrogenated soy phosphatidylcholine, cholesterol, distearoylphosphatidylglycerol, and α-tocopherol)

Systemic fungal infections: 3–5 mg/kg/24 hr IV once daily; an upper dosage limit of 10 mg/kg/24 hr has been suggested based on pharmacokinetic endpoints and risk for hypokalemia. However, dosages as high as 15 mg/kg/24 hr have been used. Dosages as high as 10 mg/kg/24 hr have been used in patients with Aspergillus.
Empiric therapy for febrile neutropenia: 3 mg/kg/24 hr IV once daily
Cryptococcal meningitis in HIV: 6 mg/kg/24 hr IV once daily
Leishmaniasis (a repeat course may be necessary if infection does not clear):
Immunocompetent: 3 mg/kg/24 hr IV on days 1 to 5, 14, and 21
Immunocompromised: 4 mg/kg/24 hr IV on days 1 to 5, 10, 17, 24, 31, and 38.
Mix with D_5W to concentration 1–2 mg/mL (0.2–0.5 mg/mL may be used for infants and small children).
Infusion rate: Administer dose over 2 hr; infusion may be reduced to 1 hr if well tolerated. A ≥1-micron inline filter may be used.

AMPHOTERICIN B, LIPOSOMAL *continued*

Closely monitor renal, hepatic, electrolyte, and hematologic status. Thrombocytopenia, anemia, leukopenia, tachycardia, hypokalemia, hypomagnesemia, hypocalcemia, hyperglycemia, diarrhea, dyspnea, skin rash, low back pain, nephrotoxicity, and increases in liver enzymes and bilirubin may occur. Rhabdomyolysis has been reported. Safety and effectiveness in neonates have not been established. See conventional amphotericin for drug interactions.

Compared with conventional amphotericin B, higher concentrations found in the liver and spleen; and similar concentrations found in the lungs and kidney. CNS/CSF concentrations are higher than other amphotericin B products. Pharmacokinetics in renal and hepatic impairment have not been studied.

Common infusion-related reactions include fever, chills, rigors, nausea, vomiting, hypotension, and headache; may premedicate with acetaminophen, diphenhydramine, and meperidine (see Conventional *Amphotericin B* remarks).

False elevations of serum phosphate have been reported with the PHOSm assay (used in Beckman Coulter analyzers).

AMPICILLIN
Many generics
Antibiotic, aminopenicillin

Caps: 500 mg
Injection: 125, 250, 500 mg; 1, 2, 10 g
Contains 3 mEq Na/1 g IV drug

Neonate (IM/IV):
<7 days:
<2 kg: 100 mg/kg/24 hr ÷ Q12 hr
≥2 kg: 150 mg/kg/24 hr ÷ Q8 hr
Group B streptococcal meningitis: 200–300 mg/kg/24 hr ÷ Q8 hr
≥7 days:
<1.2 kg: 100 mg/kg/24 hr ÷ Q12 hr
1.2–2 kg: 150 mg/kg/24 hr ÷ Q8 hr
>2 kg: 200 mg/kg/24 hr ÷ Q6 hr
Group B streptococcal meningitis: 300 mg/kg/24 hr ÷ Q4–6 hr
Infant/child (see remarks):
Mild-moderate infections:
IM/IV: 100–200 mg/kg/24 hr ÷ Q6 hr
PO: 50–100 mg/kg/24 hr ÷ Q6 hr; **max. PO dose**: 4 g/24 hr
Severe infections: 200–400 mg/kg/24 hr ÷ Q4–6 hr IM/IV; **max. dose:** 12 g/24 hr
Community-acquired pneumonia in a fully immunized patient (IV/IM):
S. pneumoniae penicillin MIC ≤2.0 or H. influenzae (β-lactamase negative): 150–200 mg/kg/24 hr ÷ Q6 hr
S. pneumoniae penicillin MIC ≥4.0: 300–400 mg/kg/24 hr ÷ Q6 hr
Max. IV/IM dose: 12 g/24 hr
Adult:
IM/IV: 500–3000 mg Q4–6 hr
PO: 250–500 mg Q6 hr
Max. IV/IM dose: 14 g/24 hr

Continued

For explanation of icons, see p. 667

AMPICILLIN *continued*

SBE prophylaxis:

Moderate risk patients:

Child: 50 mg/kg/dose (**max. dose**: 2 g/dose) × 1 IV/IM 30 min before procedure

Adult: 2 g/dose × 1 IV/IM 30 min before procedure

High risk patients with GU and GI procedures: Aforementioned doses PLUS gentamicin 1.5 mg/kg × 1 (**max. dose**: 120 mg) IV within 30 min of starting procedure. Followed by ampicillin 25 mg/kg/dose IV (or PO amoxicillin) × 1, 6 hr later.

Use higher doses with shorter dosing intervals to treat CNS disease and severe infection. CSF penetration occurs only with inflamed meninges. **Adjust dose in renal failure (see Chapter 31**).

Produces the same side effects as penicillin, with cross-reactivity. Rash commonly seen at 5–10 days and rash may occur with concurrent EBV infection or allopurinol use. May cause interstitial nephritis, diarrhea, and pseudomembranous enterocolitis. Chloroquine reduces ampicillin's oral absorption.

AMPICILLIN/SULBACTAM

Unasyn and generics

Antibiotic, aminopenicillin with β-lactamase inhibitor

Injection:

1.5 g = ampicillin 1 g + sulbactam 0.5 g

3 g = ampicillin 2 g + sulbactam 1 g

15 g = ampicillin 10 g + sulbactam 5 g

Contains 5 mEq Na per 1.5 g drug combination

Dosage based on ampicillin component:

Neonate:

Premature (based on pharmacokinetic data): 100 mg/kg/24 hr ÷ Q12 hr IM/IV

Full term: 100 mg/kg/24 hr ÷ Q8 hr IM/IV

Infant ≥1 mo and child (see remarks):

Mild/moderate infections: 100–200 mg/kg/24 hr ÷ Q6 hr IM/IV; **max. dose**: 2 g ampicillin/dose

Meningitis/severe infections: 200–400 mg/kg/24 hr ÷ Q4–6 hr IM/IV; **max. dose**: 2 g ampicillin/dose

Adult: *1–2 g Q6–8 hr IM/IV*

Max. dose: 8 g ampicillin/24 hr

Similar spectrum of antibacterial activity to ampicillin with the added coverage of β-lactamase producing organisms. Total sulbactam dose **should not exceed** 4 g/24 hr.

Use higher doses with shorter dosing intervals to treat CNS disease and severe infection. Hepatic dysfunction, including hepatitis and cholestatic jaundice, has been reported. Monitor hepatic function in patients with hepatic impairment.

Adjust dose in renal failure (see Chapter 31). Similar CSF distribution and side effects to ampicillin. Postmarking adverse reactions reported include abdominal pain, melena, gastritis, stomatitis, dyspepsia, black hairy tongue, dizziness, dyspnea, TEN, and urticaria.

ANTIPYRINE AND BENZOCAINE (OTIC)

Antipyrine and Benzocaine Otic and many generics; previously available as Auralgan

Otic analgesic, cerumenolytic

Otic solution: antipyrine 5.4%, benzocaine 1.4% (15 mL); may contain oxyquinoline sulfate

Otic analgesia: Fill external ear canal (2–4 drops) Q1–2 hr PRN. After instillation of the solution, a cotton pledget should be moistened with the solution and inserted into the meatus.

Use TID for 2–3 days.

ANTIPYRINE AND BENZOCAINE (OTIC) *continued*

Benzocaine sensitivity may develop and not intended for prolonged use. **Contraindicated** if tympanic membrane perforated or PE tubes in place. Local reactions (e.g., burning, stinging) and hypersensitivity reactions may occur. Risk of benzocaine-induced methemoglobinemia may be increased in infants aged ≤3 mo.

ARGININE CHLORIDE—INJECTABLE PREPARATION
R-Gene 10
Metabolic alkalosis agent, urea cycle disorder treatment agent, growth hormone diagnostic agent

Injection: 10% (100 mg/mL) arginine hydrochloride, contains 47.5 mEq chloride per 100 mL (300 mL)
Osmolality: 950 mOsmol/L

Used as a secondary alternative agent for patients that are unresponsive or unable to receive sodium chloride and potassium chloride.

Correction of hypochloremia: Arginine chloride dose in milliequivalents (mEq) = 0.2 × patient's weight (kg) × (103 – patient's serum chloride in mEq/L). Administer ½ to ⅔ of the calculated dose and reassess.

Drug administration: Do not exceed an IV infusion rate of 1 g/kg/hr (4.75 mEq/kg/hr). Drug may be administered without further dilution but should be diluted to reduce risk of tissue irritation.

Hyperammonemia in metabolic disorders: See Chapter 13

Contraindicated in renal or hepatic failure. Use with **extreme caution** as overdosages may result in hyperchloremic metabolic acidosis, cerebral edema, and death. Hypersensitivity reactions, including anaphylaxis, and hematuria have been reported.

Arginine hydrochloride is metabolized to nitrogen-containing products for renal excretion. Excess arginine increases the production of nitric oxide (NO) to cause vasodilation/hypotension. Closely monitor acid/base status. Hyperglycemia, hyperkalemia, GI disturbances, IV extravasation, headache, and flushing may occur.

In addition to its use for chloride supplementation, arginine is used in urea cycle disorder therapy (increase arginine levels and prevent breakdown of endogenous proteins) and as a diagnostic agent for growth hormone (stimulates pituitary release of growth hormone).

ARIPIPRAZOLE
Abilify, Abilify Maintena, Abilify MyCite, and generics
Atypical antipsychotic (2nd generation)

Tabs: 2, 5, 10, 15, 20, 30 mg
Abilify MyCite: 2, 5, 10, 15, 20, 30 mg; contains an ingestible event marker sensor inside the tablet to monitor adherence
Tabs, orally disintegrating (ODT): 10, 15 mg; contains phenylalanine
Oral solution: 1 mg/mL (150, 237 mL); may contain parabens
Intramuscular suspension for injection (extended release):
Abilify Maintena: 300, 400 mg

Irritability Associated with Autistic Disorder:

6–17 yr: Start at 2 mg PO once daily × 7 days, then increase to 5 mg PO once daily. If needed, dose may be increased in 5 mg increments ≥7 days in duration up to a **maximum** dose of 15 mg/24 hr. Patients should be periodically evaluated to determine the continued need for maintenance treatment.

Continued

For explanation of icons, see p. 667

ARIPIPRAZOLE *continued*

Schizophrenia:

13–17 yr: Start at 2 mg PO once daily × 2 days, followed by 5 mg PO once daily × 2 days, then to the recommended target dose of 10 mg PO once daily. If necessary, dose may be increased in 5 mg increments up to a **maximum** of 30 mg/24 hr (30 mg/24 hr was not shown to be more effective than 10 mg/24 hr in clinical trials). Patients should be periodically evaluated to determine the continued need for maintenance treatment.

Bipolar 1 disorder (monotherapy or adjunctive therapy):

10–17 yr: Start at 2 mg PO once daily × 2 days, followed by 5 mg PO once daily × 2 days, then to the recommended target dose of 10 mg PO once daily. If necessary, dose may be increased in 5 mg increments up to a **maximum** of 30 mg/24 hr.

Tourette Disorder:

6–18 yr (Patients should be periodically evaluated to determine the continued need for maintenance treatment):

<50 kg: Start at 2 mg PO once daily × 2 days, then increase to the target dose of 5 mg PO once daily. If necessary after 7 days, dose may be increased to 10 mg PO once daily.

≥50 kg: Start at 2 mg PO once daily × 2 days, followed by 5 mg PO once daily × 5 days, and then 10 mg PO once daily. If necessary after 7 days, dose may be increased in 5 mg increments of ≥7 days in duration **up to** a **maximum** of 20 mg/24 hr.

Monitor for clinical worsening of depression and suicidal ideation/behavior after initiation of therapy or after dose changes. **Avoid** use of extended-release IM injection with CYP 450 inducers, including carbamazepine, for >14 days. Higher cumulative doses and longer treatment duration may increase risk for irreversible tardive dyskinesia.

Weight gain, constipation, GI discomfort, akathisia, dizziness, extrapyramidal symptoms, headaches, insomnia, sedation, blurred vision, and fatigue are common. May cause leukopenia, neutropenia, agranulocytosis, hiccups, hyperthermia, neuroleptic malignant syndrome, hyperglycemia, orthostatic hypotension (risk for falls), and prolongation of the QT interval (use considered contraindicated with other medications prolonging the QT interval). Rare impulse-control problems such as compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex has been reported.

Primarily metabolized by the CYP 450 2D6 and 3A4 enzymes. Dosage reduction for using half of the usual dose has been recommended for those who are either known CYP 450 2D6 poor metabolizers; or nonpoor CYP 450 2D6 metabolizers taking strong CYP 450 2D6 (e.g., quinidine, fluoxetine, paroxetine) or 3A4 (e.g., itraconazole, clarithromycin) inhibitors. Use of ¼ the usual dose has been recommended for known CYP 2D6 poor metabolizers taking either a strong 2D6 or 3A4 inhibitor; or nonpoor CYP 450 2D6 metabolizers taking both strong 2D6 AND 3A4 inhibitors.

Consult with a pediatric psychiatrist for use in ADHD, conduct disorder, and PDD-NOS. Oral doses may be administered with or without meals. Do not split orally disintegrating tablet dosage form.

ARNUITY ELLIPTA

See Fluticasone Preparations

ASCORBIC ACID
Vitamin C and many others
Water soluble vitamin

Tabs [OTC]: 100, 250, 500 mg, 1, g
Chewable tabs (Sunkist Vitamin C and others) [OTC]: 100, 250, 500 mg; some may contain aspartame
Tabs (timed release) [OTC]: 0.5, 1, 1.5 g
Caps [OTC]: 500, 1000 mg
Extended-release caps [OTC]: 500, 1000 mg
Injection: 500 mg/mL (50 mL); may contain sodium hydrosulfite or edetate disodium
Oral liquid [OTC]: 500 mg/5 mL (236, 473 mL); may contain propylene glycol, saccharin, sodium benzoate
Oral syrup [OTC]: 500 mg/5 mL (118 mL)
Crystals [OTC]: 1 g per ¼ teaspoonful (120 g, 480 g)
Some products may contain approximately 5 mEq Na/1 g ascorbic acid

Scurvy (PO/IM/IV/SC):
Child: 100–300 mg/24 hr ÷ once daily-BID for at least 2 wk
Adult: 100–250 mg once daily-BID for at least 2 wk
U.S. Recommended Daily Allowance (RDA):
See Chapter 21.

Adverse reactions: nausea, vomiting, heartburn, flushing, headache, faintness, dizziness, and hyperoxaluria. Use high doses with **caution** in G6PD patients. May cause false-negative and false-positive urine glucose determinations with glucose oxidase and cupric sulfate tests, respectively.
May increase the absorption of aluminum hydroxide and increase the adverse/toxic effects of deferoxamine. May reduce the effects of amphetamines.
Oral dosing is preferred with or without food. IM route is the preferred parenteral route. Protect the injectable dosage form from light.
Pregnancy Category changes to "C" if used in doses greater than the RDA.

ASPIRIN
ASA, various trade names and generics
Nonsteroidal antiinflammatory agent, antiplatelet agent, analgesic

Tabs/Caplet [OTC]: 325, 500 mg
Tabs, enteric-coated [OTC]: 81, 325, 500, 650 mg
Tabs, time-release [OTC]: 81, 325 mg
Tabs, buffered [OTC]: 325 mg; may contain magnesium, aluminum, and/or calcium
Caplet, buffered [OTC]: 500 mg; may contain magnesium, aluminum, and/or calcium
Tabs, chewable [OTC]: 81 mg
Suppository [OTC]: 300, 600 mg (12s)

Analgesic/antipyretic: 10–15 mg/kg/dose PO/PR Q4–6 hr up to total of 60–80 mg/kg/24 hr
Max. dose: 4 g/24 hr
Antiinflammatory: 60–100 mg/kg/24 hr PO ÷ Q6–8 hr
Kawasaki disease (see remarks): 80–100 mg/kg/24 hr PO ÷ QID during febrile phase up until defervesces for 48–72 hr then decrease to 3–5 mg/kg/24 hr PO QAM. Continue for at least 8 wk or until both platelet count and ESR are normal.

For explanation of icons, see p. 667

ASPIRIN *continued*

Do not use in children <16 yr for treatment of varicella or flulike symptoms (risk for Reye syndrome), in combination with other NSAIDs, or in severe renal failure. **Use with caution** in bleeding disorders, renal dysfunction, gastritis, and gout. May cause GI upset, allergic reactions, liver toxicity, and decreased platelet aggregation.

Drug interactions: may increase effects of methotrexate, valproic acid, and warfarin which may lead to toxicity (protein displacement). Buffered dosage forms may decrease absorption of ketoconazole and tetracycline. GI bleeds have been reported with concurrent use of SSRIs (e.g., fluoxetine, paroxetine, sertraline).

A moderate initial febrile phase dosage of 30–50 mg/kg/24 hr PO ÷ QID for Kawasaki disease is used in Japan and Western Europe because there are no data to suggest this or the higher dosage regimen is superior.

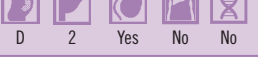
Therapeutic levels: antipyretic/analgesic: 30–50 mg/L, antiinflammatory: 150–300 mg/L. Tinnitus may occur at levels of 200–400 mg/L. Recommended serum sampling time at steady state: obtain trough level just prior to dose following 1–2 days of continuous dosing. Peak levels obtained 2 hr (for nonsustained release dosage forms) after a dose may be useful for monitoring toxicity. **Adjust dose in renal failure (see Chapter 31)**.

For breast-feeding considerations:

High-dose aspirin regimens: use an alternative drug is recommended.

Low-dose (75–162 mg/24 hr) aspirin regimens: avoid breastfeeding for 1–2 hr after a dose.

ATENOLOL
Tenormin and generics
β_1 selective adrenergic blocker



Tab: 25, 50, 100 mg
Oral suspension: 2 mg/mL

Hypertension:

Child and adolescent: 0.5–1 mg/kg/dose PO once daily–BID; **max. dose**: 2 mg/kg/24 hr up to 100 mg/24 hr.

Adult: 25–100 mg/dose PO once daily; **max. dose**: 100 mg/24 hr

Contraindicated in pulmonary edema and cardiogenic shock. May cause bradycardia, hypotension, second- or third-degree AV block, dizziness, fatigue, lethargy, and headache. **Use with caution** in diabetes and asthma. Wheezing and dyspnea have occurred when daily dosage exceeds 100 mg/24 hr. Postmarketing evaluation reports a temporal relationship for causing elevated LFTs and/or bilirubin, hallucinations, psoriatic rash, thrombocytopenia, visual disturbances, and dry mouth. **Avoid** abrupt withdrawal of the drug. Does not cross the blood-brain barrier; lower incidence of CNS side effects compared with propranolol. Neonates born to mothers receiving atenolol during labor or while breastfeeding may be at risk for hypoglycemia.

Use with disopyramide, amiodarone or digoxin may enhance bradycardic effects. **Adjust dose in renal impairment (see Chapter 31)**.

ATOMOXETINE
Strattera
Norepinephrine reuptake inhibitor, ADHD agent

Capsules: 10, 18, 25, 40, 60, 80, 100 mg

Child ≥6 yr and adolescent ≤70 kg (see remarks):
Start with 0.5 mg/kg/24 hr PO QAM and increase after a minimum of 3 days to approximately 1.2 mg/kg/24 hr PO ÷ QAM or BID (morning and late afternoon/early evening).
Max. daily dose: 1.4 mg/kg/24 hr or 100 mg, whichever is less.
If used with a strong CYP 450 2D6 inhibitor (e.g., fluoxetine, paroxetine, quinidine) or in patients with reduced CYP 450 2D6 activity: Maintain aforementioned initial dose for 4 wk and increase to a **max.** of 1.2 mg/kg/24 hr only if symptoms **do not** improve and initial dose is tolerated.

Child ≥6 yr and adolescent >70 kg (see remarks):
Start with 40 mg PO QAM and increase after a minimum of 3 days to approximately 80 mg/24 hr PO ÷ QAM or BID (morning and late afternoon/early evening). After 2–4 wk, dose may be increased to a **max**. of 100 mg/24 hr if needed.
If used with a strong CYP 450 2D6 inhibitor (e.g., fluoxetine, paroxetine, quinidine) or in patients with reduced CYP 450 2D6 activity: Maintain aforementioned initial dose for 4 wk and increase to 80 mg/24 hr only if symptoms **do not** improve and initial dose is tolerated.

Contraindicated in patients with narrow-angle glaucoma, pheochromocytoma, and severe cardiac disorders. **Do not** administer with or within 2 wk after discontinuing an MAO inhibitor; fatal reactions have been reported. **Use with caution** in hypertension, tachycardia, cardiovascular or cerebrovascular diseases, or with concurrent albuterol therapy. Increased risk of suicidal thinking has been reported; closely monitor for clinical worsening, agitation, aggressive behavior, irritability, suicidal thinking or behaviors, and unusual changes in behavior when initiating (first few months) or at times of dose changes (increases or decreases). Atomoxetine is a CYP 450 2D6 substrate; poor 2D6 metabolizers compared with normal has been reported to have higher rates of adverse effects (insomnia, weight loss, constipation, depression, tremor, and excoriation), greater improvement of ADHD symptoms with lower final dose requirements. Alopecia and hyperhidrosis have been reported.
Doses >1.2 mg/kg/24 hr in patients ≤70 kg have not been shown to be of additional benefit. Reduce dose (initial and target doses) by 50% and 75% for patients with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic insufficiency, respectively.
Major side effects include GI discomfort, vomiting, fatigue, anorexia, dizziness, and mood swings. Hypersensitivity reactions, aggression, irritability, priapism, allergic reactions, and severe liver injury have also been reported. Consider interrupting therapy in patients who are not growing or gaining weight satisfactorily.
Doses may be administered with or without food. Atomoxetine can be discontinued without tapering.

ATOVAQUONE
Mepron and generics
Antiprotozoal

Oral suspension: 750 mg/5 mL (210 mL); contains benzyl alcohol

Continued

For explanation of icons, see p. 667

ATOVAQUONE *continued*

Pneumocystis jiroveci (carinii) pneumonia (PCP):

Treatment (21-day course):

Child: 30–40 mg/kg/24 hr PO ÷ BID with fatty foods; **max. dose:** 1500 mg/24 hr. Infants 3–24 mo may require higher doses of 45 mg/kg/24 hr.

Adult: 750 mg/dose PO BID

Prophylaxis (1st episode and recurrence):

Child 1–3 mo or >24 mo: 30 mg/kg/24 hr PO once daily; **max. dose:** 1500 mg/24 hr

Child 4–24 mo: 45 mg/kg/24 hr PO once daily: **max. dose**: 1500 mg/24 hr

Adult: 1500 mg/dose PO once daily

Toxoplasma gondii:

Child:

First episode prophylaxis and recurrence prophylaxis: use *P. jiroveci* prophylaxis dosages ± pyrimethamine 1 mg/kg/dose (**max.** 25 mg/dose) PO once daily PLUS leucovorin 5 mg PO Q3 days.

Adult:

Treatment: 1500 mg/dose PO BID ± (sulfadiazine 1000–1500 mg PO Q6 hr or pyrimethamine PLUS leucovorin).

First episode prophylaxis: 1500 mg/dose PO once daily ± pyrimethamine 25 mg PO once daily PLUS leucovorin 10 mg PO once daily.

Recurrence prophylaxis: 750 mg/dose PO Q6–12 hr ± pyrimethamine 25 mg PO once daily PLUS leucovorin 10 mg PO once daily.

Not recommended in the treatment of severe *P. jiroveci* (lack of clinical data). Patients with GI disorders or severe vomiting and who cannot tolerate oral therapy should consider alternative IV therapies. Rash, pruritus, sweating, GI symptoms, LFT elevation, dizziness, headache, insomnia, anxiety, cough, and fever are common. Anemia, Stevens-Johnson syndrome, hepatitis, renal/urinary disorders, and pancreatitis have been reported.

Metoclopramide, rifampin, rifabutin, and tetracycline may decrease atovaquone levels. Shake oral suspension well before dispensing all doses. Take all doses with high-fat foods to maximize absorption.

ATROPINE SULFATE
AtroPen, and many generic products
Anticholinergic agent

C | 2 | No | No | No

Injection (vials): 0.4, 1 mg/mL
Injection (prefilled syringe): 0.25 mg/5 mL, 0.5 mg/5 mL, 1 mg/10 mL
Injection (autoinjector for IM use):
AtroPen 0.25 mg: delivers a single 0.25 mg (0.3 mL) dose (yellow colored pen)
AtroPen 0.5 mg: delivers a single 0.5 mg (0.7 mL) dose (blue colored pen)
AtroPen 1 mg: delivers a single 1 mg (0.7 mL) dose (dark red colored pen)
AtroPen 2 mg: delivers a single 2 mg (0.7 mL) dose (green colored pen)
Ophthalmic Dosage Forms:
Ointment: 1% (3.5 g)
Solution: 1% (2, 5, 15 mL)

Preintubation dose (use 1 mg/mL concentration for IM route; see remarks):
Neonate: 0.01–0.02 mg/kg/dose IV (over 1 min)/IM prior to other premedications.
Child: 0.02 mg/kg/dose IV/IO/IM; **max. dose**: 0.5 mg/dose
Adult: 0.5 mg/dose IV/IM
Cardiopulmonary resuscitation/bradycardia (see remarks):
Child: 0.02 mg/kg/dose IV/IO/IM (use 1 mg/mL for IM) Q5 min × 2–3 doses PRN; **max. single dose**: 0.5 mg in children, 1 mg in adolescents; **max total dose**: 1 mg children, 2 mg adolescents

ATROPINE SULFATE *continued*

Bronchospasm: 0.025–0.05 mg/kg/dose (**max. dose**: 2.5 mg/dose) in 2.5 mL NS Q6–8 hr via nebulizer

Nerve agent and insecticide poisoning for muscarinic symptoms (organophosphate or carbamate poisoning) (IV/IO/IM/ET; dilute in 1–2 mL NS for ET administration):

Child: 0.05–0.1 mg/kg Q 5–10 min until bronchial or oral secretions terminate.

Adolescent: 1–3 mg/dose Q 3–5 min until bronchial or oral secretions terminate.

Adult: 2–5 mg/dose Q3–5 min until bronchial or oral secretions terminate.

AtroPen device (IM route): Inject as soon as exposure is known or suspected. Give one dose for mild symptoms and two additional doses (total three doses) in rapid succession 10 min after the first dose for severe symptoms as follows:

Child <6 mo (<7 kg): 0.25 mg

Child 6 mo–4 yr (7–18 kg): 0.5 mg

Child 4–10 yr (18–41 kg): 1 mg

Child >10 yr and adult (≥41 kg): 2 mg

Ophthalmic (uveitis):

Child: (0.5% solution; prepared by diluting equal volume of the 1% atropine ophthalmic solution with artificial tears) 1–2 drops in each eye once daily-TID

Adult: (1% solution) 1–2 drops in each eye once daily-QID

Contraindicated in glaucoma, obstructive uropathy, tachycardia, and thyrotoxicosis, except for severe or life-threatening muscarinic symptoms. Use with **caution** in patients sensitive to sulfites.

Use in neonatal bradycardia is no longer recommended. Data suggest the use of a minimum 0.1-mg dose may not be warranted for the preintubation indication. Use of the minimum 0.1-mg dose could result in an overdose in younger patients.

Side effects include: dry mouth, blurred vision, fever, tachycardia, constipation, urinary retention, CNS signs (dizziness, hallucinations, restlessness, fatigue, headache).

In case of bradycardia, may give via endotracheal tube at 0.04–0.06 mg/kg (dilute with NS to volume of 1–2 mL and follow each dose with 1 mL NS). Use injectable solution for nebulized use; can be mixed with albuterol for simultaneous administration. AtroPen dosage form is designed of IM administration to the outer thigh.

Ophthalmic use is not recommended for children less than 3 mo of age due to risk for systemic absorption.

AURALGAN

See Antipyrine and Benzocaine

AZATHIOPRINE

Imuran, Azasan, and generics

Immunosuppressant

Oral suspension: 50 mg/mL

Tabs:

Imuran and generic: 50 mg (scored)

Azasan: 75, 100 mg (scored)

Injection: 100 mg

Immunosuppression (see remarks):

Child and adult:

Initial: 3–5 mg/kg/24 hr IV/PO once daily

Maintenance: 1–3 mg/kg/24 hr IV/PO once daily

For explanation of icons, see p. 667

AZATHIOPRINE *continued*

Increased risk for hepatosplenic T-cell lymphoma has been reported in adolescents and young adults. Toxicity: bone marrow suppression, rash, stomatitis, hepatotoxicity, alopecia, arthralgias, and GI disturbances.

Use ¼–⅓ dose when given with xanthine oxidase inhibitors (e.g., allopurinol). Patients with low or absent thiopurine methyl transferase (TPMT) or nucleotide diphosphatase (NUDT15) may be at increased risk for severe and life-threatening myelotoxicity. Consider alternative therapy in patients with homozygous TPMT or NUDT15 deficiency and reduced dosages in patients with heterozygous deficiency. Individuals with the low functioning alleles for NUDT15 are common among Asian ancestry and Hispanic ethnicity.

Severe anemia has been reported when used in combination with captopril or enalapril. Monitor CBC, platelets, total bilirubin, alkaline phosphatase, BUN, and creatinine. Pancytopenia and bone marrow suppression have been reported with concomitant use of pegylated interferon and ribavirin in patients with hepatitis C. Progressive multifocal leukoencephalopathy (PML) has been reported. **Adjust dose in renal failure (see Chapter 31)**.

Administer oral doses with food to minimize GI discomfort. To minimize infant exposure via breastmilk, avoid breastfeeding for 4–6 hr after administering a maternal dose.

AZELASTINE
Astelin, Astepro, and generics
Antihistamine

Nasal spray:

0.1% (Astelin, Astepro, and generics): 137 mCg/spray (200 actuations per 30 mL); contains benzalkonium chloride and EDTA

0.15% (Astepro and generics): 205.5 mCg/spray (200 actuations per 30 mL); contains benzalkonium chloride and EDTA

Ophthalmic drops (generics; previously available as Opitvar): 0.05% (0.5 mg/mL) (6 mL); contains benzalkonium chloride

Seasonal allergic rhinitis:

0.1% strength:

Child 2–11 yr: 1 spray each nostril BID

≥12 yr and adult: 1–2 sprays each nostril BID

0.15% strength:

Child 6–12 yr: 1 spray each nostril BID

≥12 yr and adult: 1–2 sprays each nostril BID or 2 sprays each nostril once daily

Perennial allergic rhinitis:

0.1% strength:

≥6 mo–<12 yr: 1 spray each nostril BID

0.15% strength:

6–<12 yr: 1 spray each nostril BID

≥12 yr and adult: 2 sprays each nostril BID

Ophthalmic:

≥3 yr and adult: Instill 1 drop into each affected eye BID

NASAL USE: Drowsiness may occur despite nasal route of administration (**avoid** concurrent use of alcohol or CNS depressants). Bitter taste, nausea, nasal burning, pharyngitis, weight gain, fatigue, nasal sores, and epistaxis may also occur. Also available in combination with fluticasone as Dymista with labeled dosing information of 1 spray each nostril BID for seasonal allergic rhinitis (≥6 yr and adult).

AZELASTINE *continued*

OPHTHALMIC USE: Eye burning and stinging have been reported in about 30% of patients receiving the ophthalmic dosage form. **Should not be used** to treat contact lens–related irritation. Soft contact lens users should wait at least 10 min after dose instillation before they insert their lenses.

AZITHROMYCIN
Zithromax, Zithromax TRI-PAK, Zithromax Z-PAK, Zmax (extended-release oral suspension), Azasite, and generics
Antibiotic, macrolide

Tablets: 250, 500, 600 mg
TRI-PAK: 500 mg (3s as unit dose pack)
Z-PAK: 250 mg (6s as unit dose pack)
Oral suspension: 100 mg/5 mL (15 mL), 200 mg/5 mL (15, 22.5, 30 mL)
Oral Powder (Sachet): 1 g (3s, 10s)
Injection: 500 mg; contains 9.92 mEq Na/1 g drug
Ophthalmic solution (Azasite): 1% (2.5 mL); contains benzalkonium chloride

Infant and child (see remarks):
Community acquired pneumonia (≥3 mo):
Tablet or oral suspension: 10 mg/kg PO on day 1 (**max. dose**: 500 mg), followed by 5 mg/kg/24 hr PO once daily (**max. dose:** 250 mg/24 hr) on days 2–5
IV and PO regimen: 10 mg/kg/dose IV once daily for at least 2 days followed by 5 mg/kg/dose PO once daily to complete a 5-day course (**max. dose**: 500 mg/24 hr)
Pharyngitis/tonsillitis (Group A streptococcal; 2–15 yr): 12 mg/kg/24 hr PO once daily × 5 days (**max. dose:** 500 mg/24 hr). Alternatively, 12 mg/kg/24 hr (**max. dose**: 500 mg/24 hr) PO once daily on day 1 followed by 6 mg/kg/dose (**max. dose:** 250 mg/dose) PO once daily on days 2–5 has been recommended by the IDSA.
Acute sinusitis (≥6 mo): 10 mg/kg/dose (**max. dose:** 500 mg) PO once daily × 3 days
Pertussis:
1–<6 mo: 10 mg/kg/dose PO once daily × 5 days
≥6 mo: 10 mg/kg/dose (**max. dose**: 500 mg) PO × 1, followed by 5 mg/kg/ (**max. dose**: 250 mg) PO once daily on days 2–5.
Mycobacterium avium complex in HIV (see www.aidsinfo.nih.gov/guidelines for most current recommendations):
Prophylaxis for first episode: 20 mg/kg/dose PO Q 7 days (**max. dose**: 1200 mg/dose); alternatively, 5 mg/kg/24 hr PO once daily (**max. dose:** 250 mg/dose) with or without rifabutin.
Prophylaxis for recurrence: 5 mg/kg/24 hr PO once daily (**max. dose**: 250 mg/dose), plus ethambutol 15 mg/kg/24 hr (**max. dose:** 900 mg/24 hr) PO once daily with or without rifabutin 5 mg/kg/24 hr (**max. dose:** 300 mg/24 hr).
Treatment: 10–12 mg/kg/24 hr PO once daily (**max. dose:** 500 mg/24 hr) × 1 mo or longer, plus ethambutol 15–25 mg/kg/24 hr (**max. dose**: 1 g/24 hr) PO once daily with or without rifabutin 10–20 mg/kg/24 hr (**max. dose**: 300 mg/24 hr).
Endocarditis prophylaxis: 15 mg/kg/dose (**max. dose:** 500 mg) PO × 1, 30–60 min before procedure.
Antiinflammatory agent in cystic fibrosis:
25–39 kg: 250 mg PO every Mondays, Wednesdays, and Fridays.
≥40 kg: 500 mg PO every Mondays, Wednesdays, and Fridays.

Continued

For explanation of icons, see p. 667

AZITHROMYCIN *continued*

Adolescent and adult:

Pharyngitis, tonsillitis, skin, and soft tissue infection: 500 mg PO day 1, then 250 mg/24 hr PO on days 2–5

Mild/moderate bacterial COPD exacerbation: aforementioned 5-day dosing regimen OR 500 mg PO once daily × 3 days

Community acquired pneumonia:

Tablets: 500 mg PO day 1, then 250 mg/24 hr PO on days 2–5

IV and tablet regimen: 500 mg IV once daily × 2 days followed by 500 mg PO once daily to complete a 7- to 10-day regimen (IV and PO)

Sinusitis:

Tablets: 500 mg PO once daily × 3 days

Uncomplicated chlamydial cervicitis or urethritis: Single 1-g dose PO

Gonococcal cervicitis or urethritis: Single 2-g dose PO

Acute PID (chlamydia): 500 mg IV once daily × 1–2 days followed by 250 mg PO once daily to complete a 7-day regimen (IV and PO).

Mycobacterium avium complex in HIV (see www.aidsinfo.nih.gov/guidelines for most recent recommendations):

Prophylaxis for first episode: 1200 mg PO Q 7 days with or without rifabutin 300 mg PO once daily

Prophylaxis for recurrence: 500 mg PO once daily, plus ethambutol 15 mg/kg/dose PO once daily, with or without rifabutin 300 mg PO once daily

Treatment: 500–600 mg PO once daily with ethambutol 15 mg/kg/dose PO once daily with or without rifabutin 300 mg PO once daily.

Endocarditis prophylaxis: 500 mg PO × 1, 30–60 min before procedure

Antiinflammatory agent in cystic fibrosis: use same dosing in children.

Ophthalmic:

≥1 yr and adult: Instill one drop into the affected eye(s) BID, 8–12 hr apart, × 2 days, followed by one drop once daily for the next 5 days.

No longer recommended for otitis media due to increased resistant pathogens.

Contraindicated in hypersensitivity to macrolides and history of cholestatic jaundice/hepatic dysfunction associated with prior use. **Use with caution** in impaired hepatic function, GFR <10 mL/min (limited data), hypokalemia, hypomagnesemia, bradycardia, arrhythmias, prolonged QT intervals, and receiving medications that can cause the aforementioned conditions of caution. May cause increase in hepatic enzymes, cholestatic jaundice, GI discomfort, and pain at injection site (IV use). Compared with other macrolides, less risk for drug interactions. Nelfinavir may increase azithromycin levels; monitor for liver enzyme abnormalities and hearing impairment. Vomiting, diarrhea, and nausea have been reported at higher frequency in otitis media with 1-day dosing regimen. Exacerbations of myasthenia gravis/syndrome, serious skin reactions (e.g., SJS and TEN), infantile hypertrophic pyloric stenosis, decreased lymphocytes, and elevated bilirubin, BUN, and creatinine have been reported. CNS penetration is poor.

Aluminum- and magnesium-containing antacids decrease absorption. Tablet and oral suspension dosage forms may be administered with or without food. Extended-release oral suspension should be taken on an empty stomach (at least 1 hr before or 2 hr following a meal). Intravenous administration is over 1–3 hr; **do not** give as a bolus or IM injection.

Ophthalmic Use: Do not wear contact lenses. Eye irritation is the most common side effect.

AZTREONAM

Azactam, Cayston, and generic intravenous products

Antibiotic, monobactam

Injection: 1, 2 g

Frozen injection (Azactam): 1 g/50 mL 3.4% dextrose, 2 g/50 mL 1.4% dextrose (iso-osmotic solutions); each 1 g drug contains approximately 780 mg L-arginine

Nebulizer solution (Cayston): 75 mg powder to be reconstituted with the supplied diluent of 1 mL 0.17% sterile sodium chloride and 8 mL of diluent.

AZTREONAM *continued*

Neonate:
30 mg/kg/dose IV/IM:
<1.2 kg and 0–4 wk age: Q12 hr
1.2–2 kg:
0–7 days: Q12 hr
>7 days: Q8 hr
>2 kg:
0–7 days: Q8 hr
>7 days: Q6 hr
Child: 90–120 mg/kg/24 hr ÷ Q6–8 hr IV/IM; **max. dose:** 8 g/24 hr
Cystic Fibrosis: 150–200 mg/kg/24 hr ÷ Q6–8 hr IV/IM (**max. dose:** 8 g/24 hr). Alternatively, higher doses have been used at 200–300 mg/kg/24 hr ÷ Q6 hr IV/IM (**max. dose:** 12 g/24 hr)
Adult:
Moderate infections: 1–2 g/dose Q8–12 hr IV/IM
Severe infections: 2 g/dose Q6–8 hr IV/IM
Max. dose: 8 g/24 hr
Inhalation:
Cystic fibrosis prophylaxis therapy:
≥7 yr and adult: 75 mg TID (minimum 4 hr between doses) administered in repeated cycles of 28 days on drug followed by 28 days off drug. Administer each dose with the Altera Nebulizer System.

Typically indicated in multidrug resistant aerobic gram-negative infections when β-lactam therapy is contraindicated. Well-absorbed IM. **Use with caution** in arginase deficiency. Low cross-allergenicity between aztreonam and other β-lactams. Adverse reactions: thrombophlebitis, eosinophilia, leukopenia, neutropenia, thrombocytopenia, elevation of liver enzymes, hypotension, seizures, and confusion. Good CNS penetration. Probenecid and furosemide increase aztreonam levels. **Adjust dose in renal failure (see Chapter 31).**

INHALATIONAL USE: Cough, nasal congestion, wheezing, pharyngolaryngeal pain, pyrexia, chest discomfort, abdominal pain, and vomiting may occur. Bronchospasm has been reported. Use the following order of administration: bronchodilator first, chest physiotherapy, other inhaled medications (if indicated), and aztreonam last.

B

BACITRACIN ± POLYMYXIN B
Various ophthalmic and topical generic products
In combination with polymyxin b: AK-Poly-Bac Ophthalmic, Double Antibiotic Topical, Polysporin Topical and others
Antibiotic, topical

BACITRACIN:
Ophthalmic ointment: 500 units/g (3.5 g)
Topical ointment (OTC): 500 units/g (1, 15, 30, 113.4, 454 g)
Topical cream (OTC): 500 units/g (14, 28 g)
BACITRACIN IN COMBINATION WITH POLYMYXIN B:
Ophthalmic ointment (AK-Poly-Bac Ophthalmic): 500 units bacitracin +10,000 units polymyxin B/g (3.5 g)
Topical ointment (OTC): 500 units bacitracin +10,000 units polymyxin B/g (15, 30 g)

For explanation of icons, see p. 667

BACITRACIN ± POLYMYXIN B *continued*

BACITRACIN

Child and adult:

Topical: Apply to affected area once daily to TID

Ophthalmic: Apply 0.25- to 0.5-inch ribbon into the conjunctival sac of the infected eye(s) Q 3–12 hr; frequency depends on severity of infection. Administer Q3–4 hr × 7–10 days for mild/moderate infections.

BACITRACIN + POLYMYXIN B

Child and adult:

Topical: Apply ointment to affected area once daily to TID

Ophthalmic: Apply 0.25- to 0.5-inch ribbon into the conjunctival sac of the infected eye(s) Q 3–12 hr; frequency depends on severity of infection. Administer Q3–4 hr × 7–10 days for mild/moderate infections.

Hypersensitivity reactions to bacitracin and/or polymyxin b can occur. **Do not use** topical ointment for the eyes or for a duration of >7 days. Side effects may include rash, itching, burning, and edema.

Ophthalmic dosage form may cause temporary blurred vision and retard corneal healing. For ophthalmic use, wash hands before use and **avoid contact** with tube tip with skin or eye.

For neomycin containing products, see Neomycin/Polymyxin B/± Bacitracin.

BACLOFEN
Lioresal, Gablofen, Kemstro, and generic tablets
Centrally acting skeletal muscle relaxant

C	2	Yes	No	No

Tabs: 5, 10, 20 mg

Disintegrating oral tabs (Kemstro): 10, 20 mg; contains phenylalanine

Oral suspension: 5, 10 mg/mL

Intrathecal injection:

Gablofen: 50 mCg/mL (1 mL), 0.5 mg/mL (20 mL), 1 mg/mL (20 mL), 2 mg/mL (20 mL); preservative free

Lioresal: 50 mCg/mL (1 mL), 0.5 mg/mL (20 mL), 2 mg/mL (5, 20 mL); preservative free

Oral: **Dosage increments, if tolerated, are made at 3-day intervals until desired effect or max. dose is achieved.** Initiate first dosage level at QHS, followed by Q12 hr and then Q8 hr. Dosage increments are made by first increasing the QHS dosage, followed by the morning dosage and then the remaining mid-day dosage.

Child (PO, see remarks):

<20 kg: Start at 2.5 mg QHS, increase in 2.5 mg increments if needed up to the recommended **max. dose**, below.

≥20–50 kg: Start at 5 mg QHS, increase in 5 mg increments if needed up to the recommended **max. dose**, below.

>50 kg: Start at 10 mg QHS, increase in 10 mg increments if needed up to the recommended **max. dose**, below.

Recommended max. PO dose:

2 yr–<8 yr: 60 mg/24 hr

8–16 yr: 80 mg/24 hr

>16 yr: 120 mg//24 hr

Adult (PO):

Start at 5 mg TID, increase in 5-mg increments if needed up to a **maximum** of 80 mg/24 hr.

BACLOFEN *continued*

Intrathecal continuous infusion maintenance therapy (not well established):

<12 yr: average dose of 274 mCg/24 hr (range: 24–1199 mCg/24 hr) has been reported.

≥12 yr and adult: most required 300–800 mCg/24 hr (range: 12–2003 mCg/24 hr with limited experience at doses >1000 mCg/24 hr)

Avoid abrupt withdrawal of drug. **Use with caution** in patients with seizure disorder or impaired renal function. Approximately 70%–80% of the drug is excreted in the urine unchanged. Administer oral doses with food or milk.

Adverse effects: Drowsiness, fatigue, nausea, vertigo, psychiatric disturbances, rash, urinary frequency, and hypotonia. **Avoid** abrupt withdrawal of intrathecal therapy to prevent potential life-threatening events (rhabdomyolysis, multiple organ-system failure, and death).

Cases of intrathecal mass at the tip of the implanted catheter leading to withdrawal symptoms have been reported. Inadvertent subcutaneous injection may occur with improper access of the reservoir refill septum and may result in an overdose. Sterile techniques must be used with intrathecal use accounting for all nonsterile external surfaces.

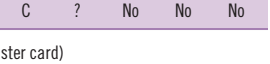
Usual maintenance oral dosage range observed from a collection of smaller prospective and retrospective studies suggest following (see dosage section for initial dose titration):

<2 yr: 10–20 mg/24 hr ÷ Q8 hr to a **maximum** of 40 mg/24 hr

2–7 yr: 20–40 mg/24 hr ÷ Q8 hr to a **maximum** of 60 mg/24 hr

≥8 yr: 30–40 mg/24 hr ÷ Q8 hr to a **maximum** of 200 mg/24 hr

BALOXAVIR MARBOXIL
Xofluza
Antiviral, endonuclease inhibitor



Tabs: 20 mg (2 or 4 tablet blister card), 40 mg (1 or 2 tablet blister card)
Oral suspension: in development

Treatment of influenza (initiate therapy within 48 hr of onset of symptoms):

Child 1–<12 yr:

<20 kg: 2 mg/kg/dose PO once

≥20 kg: 40 mg PO once

≥12 yr and adult:

40–<80 kg: 40 mg PO once

≥80 kg: 80 mg PO once

Recent pediatric phase 3 comparison trial with oseltamivir (MINISONE-2) showed comparable efficacy and baloxavir was well tolerated. Influenza prophylaxis use and human pregnancy information are currently not available.

Adverse effects reported in clinical trials include diarrhea, bronchitis, nasopharyngitis, headache, and nausea.

Baloxavir marboxil is a prodrug that is rapidly converted to the active baloxavir following oral administration. No clinically meaningful pharmacokinetics differences with moderate hepatic impairment (Child-Pugh class B) or with creatinine clearances ≥50 mL/min. Pharmacokinetics have not been evaluated in severe hepatic and/or severe renal impairment.

Primarily metabolized by UGT1A3 with minor contribution from CYP3A4. May reduce the efficacy of intranasal live attenuated influenza vaccine.

Dose may be administered with or without food. **Avoid** coadministration with dairy products, calcium, aluminum, magnesium, multivitamins with minerals, iron, selenium, or zinc, because decreased absorption of baloxavir may occur.

For explanation of icons, see p. 667

BECLOMETHASONE DIPROPIONATE
QVAR Redihaler, Beconase AQ, Qnasl Children's, Qnasl
Corticosteroid

Breath-Activated Inhalation Aerosol, oral:
QVAR Redihaler: 40 mCg/inhalation (10.6 g provides 120 inhalations), 80 mCg/inhalation (10.6 g provides 120 inhalations)
Inhalation Aerosol, nasal:
Beconase AQ: 42 mCg/inhalation (25 g provides 180 metered doses); contains benzalkonium chloride
Qnasl Children's: 40 mCg/inhalation (6.8 g provides 60 metered doses)
Qnasl: 80 mCg/inhalation (10.6 g provides 120 metered doses)

Oral inhalation (QVAR Redihaler) (see remarks):
4–11 yr: Start at 40 mCg BID. If response is inadequate after 2 wk, may increase dose to the recommended **maximum dose** of 80 mCg BID.
≥12 yr and adult:
Corticosteroid naïve: Start at 40–80 mCg BID; **max. dose**: 320 mCg BID
Previous corticosteroid use: Start at 40–160 mCg BID; **max. dose**: 320 mCg BID
Nasal inhalation:
Beconase AQ:
6–12 yr: Start with 1 spray (42 mCg) each nostril BID, may increase to the **maximum** dose of 2 sprays each nostril BID if needed. Once symptoms are controlled, decrease dose to 1 spray each nostril BID.
>12 yr and adult: 1–2 spray(s) (42–84 mCg) each nostril BID
Qnasl Children's:
4–11 yr: 1 spray (40 mCg) each nostril once daily; **max. dose**: 2 sprays total (80 mCg)/24 hr
Qnasl:
12 yr and adult: 2 sprays (160 mCg) each nostril once daily; **max. dose**: 4 sprays (320 mCg)/24 hr.

Not recommended for children <4 yr with oral inhalation and <6 yr (Becnase AQ) or <4 yr (Qnasl Children's) with the nasal administration because of unknown safety and efficacy. Dose should be titrated to lowest effective dose. **Avoid** using higher than recommended doses. **Avoid** use of nasal dosage form in recent nasal ulcers, nasal surgery or nasal trauma. Nasal septal perforation has been reported with nasal product. Psychiatric and behavioral changes have been reported in children with the oral inhalation product. Routinely monitor growth of pediatric patients with chronic use of all dosage form.

When converting from fluticasone to beclomethasone for oral inhalation use, consider the following:

Fluticasone MDI (Flovent HFA)	Fluticasone DPI (Flovent Diskus)	Beclomethasone BAI (QVAR Redihaler)
44 mCg: 2 puffs BID	50 mCg: 2 inhalations BID	40 mCg: 1 puff BID
110 mCg: 2 puffs BID	100 mCg: 2 inhalations BID	40 mCg: 2 puffs BID
220 mCg: 2 puffs BID	250 mCg: 2 inhalations BID	80 mCg: 2 puffs BID

BAI, Breath-activated inhaler; *DPI,* dry powder inhaler; *MDI,* metered dose inhaler.

CYP 450 3A4 inhibitors (e.g., ketoconazole, erythromycin, and protease inhibitors) or significant hepatic impairment may increase systemic exposure of beclomethasone.
Monitor for hypothalamic, pituitary, adrenal, or growth suppression, and hypercorticism. Rinse mouth and gargle with water after oral inhalation; may cause thrush.
QVAR Redihaler is a breath-activated inhaler device and requires the patient to have a minimum inspiratory flow rate of 30 L/min for proper dose activation and does not require priming. Do not shake the Redihaler device with the cap open, and do not use it with a tube spacer or volume holding chamber.

BENZOYL PEROXIDE
BP Wash, NeoBenz Micro, Oxy-5, Oxy-10, PanOxyl, and many other products
Topical acne product

Liquid wash [OTC]: 5% (120, 150, 200 mL), 6% (180, 360 mL), 7% (473 mL), 10% (120, 150, 240 mL)
Liquid cream wash [OTC]: 4% (170 g), 7% (180 g)
Bar [OTC]: 5% (113 g), 10% (113 g)
Lotion [OTC]: 4% (297 g), 5% (30 mL), 6% (170, 340 g), 8% (297 g), 10% (30 mL, 85, 170, 340 g)
Cream [OTC]: 5% (18 g), 10% (30 g)
Gel [OTC]: 2.5% (60 g), 5% (42.5, 60, 90 g), 6.5% (113 g), 8% (113g), 10% (42.5, 56, 60, 90 g)
NOTE: Some preparations may contain alcohol and come in combination packs of cleansers and creams at various strengths.
Combination product with erythromycin (Benzamycin and others):
Gel: 30 mg erythromycin and 50 mg benzoyl peroxide per g (23.3, 46 g); some preparations may contain 20% alcohol
Combination product with clindamycin:
Gel:
BenzaClin and generics: 10 mg clindamycin and 50 mg benzoyl peroxide per g (25, 35, 50 g); some preparations may contain methylparaben.
Duac: 12 mg clindamycin and 50 mg benzoyl peroxide per g (45 g)
Acanya: 12 mg clindamycin and 25 mg benzoyl peroxide per g (50 g)
Combination product with adapalene: see Adapalene ± Benzoyl Peroxide

Acne (child ≥12 yr and adult, see remarks):
Cleansers (liquid wash, or bar): Wet affected area prior to application. Apply and wash once daily–BID; rinse thoroughly, and pat dry. Modify dose frequency or concentration to control the amount of drying or peeling.
Lotion, cream, or gel: Cleanse skin, and apply small amounts over affected areas once daily initially; increase frequency to BID–TID, if needed. Modify dose frequency or concentration to control drying or peeling.
Combination products:
Benzamycin, BenzaClin and generics: Apply BID (morning and evening) to affected areas after washing and drying skin.
Duac: Apply QHS to affected areas after washing and drying skin.
Acanya: Apply pea-sized amount once daily.

Contraindicated in known history of hypersensitivity to product's components (benzoyl peroxide, clindamycin, or erythromycin). **Avoid** contact with mucous membranes and eyes. May cause skin irritation, stinging, dryness, peeling, erythema, edema, and contact dermatitis. Anaphylaxis have been reported with products containing clindamycin and benzoyl peroxide.
Concurrent use with tretinoin (Retin-A) will increase risk of skin irritation. Products containing clindamycin and erythromycin should not be used in combination.
Any single application resulting in excessive stinging or burning may be removed with mild soap and water. Lotion, cream, and gel dosage forms should be applied to dry skin.
Data are limited for use <12 yr of age.

For explanation of icons, see p. 667

BENZTROPINE MESYLATE
Cogentin and generics
Anticholinergic agent, drug-induced dystonic reaction antidote, anti-Parkinson agent

Injection: 1 mg/mL (2 mL)
Tabs: 0.5, 1, 2 mg

Drug-induced extrapyramidal symptoms (PO/IM/IV):
>3 yr: 0.02–0.05 mg/kg/dose once daily–BID
Adult: 1–4 mg/dose once daily–BID
Acute dystonic reaction (phenothiazines) (IM/IV):
Child: 0.02 mg/kg/dose (**max. dose:** 1 mg) × 1
Adult: 1–2 mg/dose × 1

Contraindicated in myasthenia gravis, GI/GU obstruction, untreated narrow-angle glaucoma and peptic ulcer. Use IV route **only** when PO and IM routes are not feasible. May cause anticholinergic side effects, especially constipation and dry mouth. Drug interactions include: potentiation of CNS depressant effects when used with CNS depressants; enhance CNS side effects of amantadine; and inhibit the response of neuroleptics. This medication has not been formally assigned a pregnancy category by the FDA. The Australian pregnancy ratings have deemed use in pregnancy to a limited number of women without an increase in frequency of malformation or other direct/indirect harmful effects.
Onset of action: 15 min for IV/IM and 1 hr for PO.
Oral doses should be administered with food to decrease GI upset.

BERACTANT

See Surfactant, pulmonary.

BETAMETHASONE
Injection: Celestone Soluspan, ReadySharp Betamethasone, and generics
Topical: Diprolene, Diprolene AF, Luxiq, Sernivo, and generics
Corticosteroid

Na Phosphate and Acetate:
Injection suspension (Celestone Soluspan, ReadySharp Betamethasone and generics): 6 mg/mL (3 mg/mL Na phosphate +3 mg/mL betamethasone acetate) (5 mL); may contain benzalkonium chloride and EDTA.
Dipropionate:
Topical cream: 0.05% (15, 45 g)
Topical emulsion (Sernivo): 0.05% (120 mL); contains parabens
Topical lotion: 0.05% (60 mL); may contain 46.8% alcohol and propylene glycol
Topical ointment: 0.05% (15, 45 g)
Valerate:
Topical cream: 0.1% (15, 45 g)
Topical foam (Luxiq and generics): 1.2 mg/g (50, 100 g); may contain 60.4% ethanol, cetyl alcohol, stearyl alcohol, and propylene glycol

BETAMETHASONE *continued*

Topical lotion: 0.1% (60 mL); may contain 47.5% isopropyl alcohol
Topical ointment: 0.1% (15, 45 g)
Dipropionate augmented:
Topical cream (Diprolene AF and generics): 0.05% (15, 50 g); contains propylene glycol
Topical gel: 0.05% (15, 50 g); contains propylene glycol
Topical lotion (Diprolene and generics): 0.05% (30, 60 mL); contains 30% isopropyl alcohol
Topical ointment (Diprolene and generics): 0.05% (15, 45, 50 g); contains propylene glycol

All dosages should be adjusted based on patient response and severity of condition (see remarks).
Antiinflammatory:
Child:
IM: 0.0175–0.125 mg/kg/24 hr or 0.5–7.5 mg/m²/24 hr Q6–12 hr
Adolescent and adult:
IM: 0.6–9 mg/24 hr ÷ Q12–24 hr
Topical (use smallest amount for shortest period of time to avoid adrenal suppression and reassess diagnosis if no improvement is achieved after 2 wk; see remarks):
Valerate and dipropionate forms:
Child and adult: Apply to affected areas once daily–BID
Dipropionate augmented forms (see remarks):
≥13 yr–adult: Apply to affected areas once daily–BID
Max. dose: 14 days and the following specific dosage form maximum amount
Cream, ointment and gel: 50 g/wk
Lotion: 50 mL/wk

Use with caution in hypothyroidism, cirrhosis, ulcerative colitis, and history of allergic reactions to corticosteroids. See Chapter 8 for relative steroid potencies and doses based on body surface area. Betamethasone is inadequate when used alone for adrenocortical insufficiency because its minimal mineralocorticoid properties. Like all steroids, may cause hypertension, pseudotumor cerebri, acne, Cushing syndrome, adrenal axis suppression, GI bleeding, hyperglycemia, and osteoporosis.

Betamethasone is a substrate for CYP 450 3A4, and use with a strong inhibitor (e.g., ketoconazole and itraconazole) may lead to increased exposure and side effects of betamethasone.

Na phosphate and acetate injectable suspension recommended for IM, intra-articular, intrasynovial intralesional, soft tissue use only; but **not** for IV use. Topical betamethasone dipropionate augmented (Diprolene and Diprolene AF) is **not recommended** in children ≤12 yr owing to the higher risk for adrenal suppression.

Injectable IM dosage form is used in premature labor to stimulate fetal lung maturation.

BICITRA

See Citrate Mixtures.

BISACODYL
Dulcolax, Ducodyl, Bisacodyl EC,
Fleet Bisacodyl, and various other names
Laxative, stimulant

Tabs (enteric-coated) [OTC]: 5 mg
Suppository [OTC]: 10 mg
Enema (Fleet Bisacodyl) [OTC]: 10 mg/30 mL (37.5 mL)
Delayed released tabs [OTC]: 5 mg

D com*ued* by

For explanation of icons, see p. 667

BISACODYL *continued*

Oral (administered 6 hr before desired effect):
Child (3–10 yr): 5 mg once daily
>10 yr and adolescent: 5–10 mg once daily
Adult: 5–15 mg once daily
Rectal suppository (see remarks):
2–10 yr: 5 mg once daily
>10 yr and adolescent: 5–10 mg once daily
Adult: 10 mg once daily
Rectal enema (as a single dose):
≥12 yr and adult: 10 mg (30 mL) × 1

Do not use in newborn period. Instruct patient/parent that tablets should be swallowed whole, **not** chewed or crushed; **not** to be given within 1 hr of antacids or milk. May cause abdominal cramps, nausea, vomiting, and rectal irritation. Oral usually effective within 6–10 hr; rectal usually effective within 15–60 min.

Antacids may decrease the effect of bisacodyl and may cause the premature release of the delayed-release formulation prior to reaching the large intestine. Use of suppository should be retained in the rectum for 15–20 min.

BISMUTH SUBSALICYLATE

Pepto-Bismol, Geri-Pectate, Bismatrol, Kao-Tin, Stomach Relief, Stomach Relief Max St, and many others (see remarks)

Antidiarrheal, gastrointestinal ulcer agent

D	3	Yes	No	No

Liquid [OTC]:
Pepto-Bismol, Geri-Pectate, Bismatrol, Kao-Tin, Stomach Relief, and others: 262 mg/15 mL (240, 360, 480 mL)
Stomach Relief Max St: 525 mg/15mL (240, 480 mL)
Chewable tabs [OTC]: 262 mg; may contain aspartame
Contains 102 mg salicylate per 262 mg tablet; or 129 mg salicylate per 15 mL of the 262 mg/15 mL liquid.

Diarrhea:
Child: 100 mg/kg/24 hr ÷5 equal doses for 5 days; **max. dose**: 4.19 g/24 hr
Dosage by age*: give following dose Q30 min to 1 hr PRN up to a* ***max. dose*** *of 8 doses/24 hr:*
3–5 yr: 87.3 mg (1/3 tablet or 5 mL of 262 mg/15 mL)
6–8 yr: 174.7 mg (2/3 tablet or 10 mL of 262 mg/15 mL)
9–11 yr: 262 mg (1 tablet or 15 mL of 262 mg/15 mL)
≥12 yr–adult: 524 mg (2 tablets or 30 mL of 262 mg/15 mL)
Helicobacter pylori gastric infection (as part of a 3 or 4 drug combination therapy; doses not well established for children):
Child: 8 mg/kg/24 hr PO ÷ BID × 10–14 days, or 262 mg PO QID X 7–14 days have been reported.
Adult: 300 mg PO QID × 10–14 days

Generally not recommended in children <16 yr with chicken pox or flulike symptoms (risk for Reye syndrome), in combination with other nonsteroidal antiinflammatory drugs, anticoagulants, or oral antidiabetic agents or in severe renal failure. **Use with caution** in bleeding disorders, renal dysfunction, gastritis, and gout. May cause darkening of tongue and/or black stools, GI upset, impaction, and decreased platelet aggregation.

BISMUTH SUBSALICYLATE *continued*

Drug combination appears to have antisecretory and antimicrobial effects with some antiinflammatory effects. Absorption of bismuth is negligible, whereas approximately 80% of the salicylate is absorbed. Decreases absorption of tetracycline.

DO NOT use Children's Pepto (calcium carbonate) because it does not contain bismuth subsalicylate. **Avoid use in renal failure (see Chapter 31).**

BOSENTAN
Tracleer
Endothelin receptor antagonist

Tabs: 62.5, 125 mg
Dispersible tabs (to be dissolved in water to make an oral suspension): 32 mg (scored); contains aspartame
Oral suspension: 6.25 mg/mL

Pulmonary arterial hypertension (see remarks):
2015 AHA/ATS Pediatric Pulmonary Hypertension Guidelines:
<10 kg: Start at 1 mg/kg/dose PO BID then increase to 2 mg/kg/dose PO BID
10–20 kg: Start at 15.625 mg PO BID then increase to 31.25 mg PO BID
>20–40 kg: Start at 31.25 mg PO BID then increase to 62.5 mg PO BID
>40 kg: Start at 62.5 mg PO BID then increase to 125 mg PO BID
Alternative FDA-labeled dosing by age and weight (PO):

Age	Weight (kg)	Dosage (PO)
≤12 yr	4–8	16 mg BID
	>8–16	32 mg BID
	>16–24	48 mg BID
	>24–40	64 mg BID
>12 yr	≤40	62.5 mg BID
	>40	62.5 mg BID X 4 wk, then 125 mg BID

Dosage Modification for Transaminase Elevation:

ALT/AST Levels	Dosage Adjustment
>3 to ≤5× ULN	Reconfirm by another aminotransferase test; if confirmed, modify dosage regimen (always reassess aminotransferase levels within 3 days and Q 2 wk thereafter to any dosage reintroduction or reduction): ≤12 yr, and >12 yr and ≤40 kg: Interrupt therapy. If aminotransferase returns to pretreatment levels, reintroduce with dosage prior to interruption >12 yr and >40 kg, and adult: Reduce dosage to 62.5 mg PO BID; or interrupt therapy and monitor aminotransferase levels Q 2 wk (if aminotransferase levels return to pretreatment levels, continue with most recent dosage or 62.5 mg PO BID)
>5 to ≤8× ULN	Reconfirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase at least Q 2 wk. Once aminotransferase returns to pretreatment levels, consider reintroduction of bosentan and reassess aminotransferase within 3 days and Q 2 wk thereafter to any dosage reintroduction or reduction: ≤12 yr, and >12 yr and ≤40 kg: Dosage prior to discontinuing >12 yr and >40 kg, and adult: 62.5 mg PO BID
>8× ULN	All ages: Discontinue treatment permanently

ULN, Upper limit of normal

For explanation of icons, see p. 667

BOSENTAN *continued*

Contraindicated in women who are or may become pregnant and with concurrent use of cyclosporine (increases bosentan concentrations) or glyburide (increases risk for hepatotoxicity). Due to these risks, bosentan is available only through the Tracleer REMS program where prescribers and pharmacies need to be certified. See www.tracleerrems.com or call 1-866-228-3546 for more information.

Baseline and monthly monitoring of serum aminotransferases and bilirubin; and pregnancy tests for females of reproductive potential (two forms of birth control required) are required. Use should be **avoided** in patients with preexisting hepatic impairment (baseline aminotransferases >3 times the usual normal limit).

May cause respiratory tract infections, anemia (dose related), edema, increased liver aminotransferases (see dosage modification; higher incidence in adults) and pyrexia. Decreased sperm counts, liver cirrhosis, liver failure, DRESS, thrombocytopenia, and sinusitis have been reported.

Bosentan is substrate for the CYP2C9 and 3A4 enzymes, and OATP1B1/SLCO1B1 transporter. It also induces CYP2C9 and 3A4; may decrease sildenafil levels. Reduces the effectiveness of hormonal contraceptives.

Doses may be administered orally with or without food.

BREO ELLIPTA

See Fluticasone Furoate + Vilanterol.

BROMPHENIRAMINE WITH PHENYLEPHRINE
Dimetapp Children's Cold and Allergy, Brohist D, Ru-Hist D, and many other products
Antihistamine + decongestant

Oral liquid/syrup (Dimetapp Children's Cold and Allergy and others) [OTC]: Brompheniramine 1 mg + phenylephrine 2.5 mg/5 mL (118, 237 mL); contains propylene glycol and sodium benzoate

Tabs (Brohist-D, Ru-Hist D) [OTC]: Brompheniramine 4 mg + phenylephrine 10 mg

NOTE: other combination products exist using the Dimetapp name; always check the specific ingredients with each specific product

All doses based on brompheniramine component *(see remarks).*

2 to <6 yr: 1 mg Q4 hr PRN PO up to a **max. dose** of 6 mg/24 hr

6–12 yr: 2 mg Q4 hr PRN PO up to a **max. dose** of 12 mg/24 hr

≥12 yr and adult: 4 mg Q4 hr PRN PO up to a **max. dose** of 24 mg/24 hr

Alternatively, dosing based on specific dosage forms/products. CAUTION: These products may be available in different concentrations (see remarks).

Oral, liquid/syrup (Dimetapp Children's Cold and Allergy):

6 to <12 yr: 10 mL Q4 hr PRN PO up to a **max. dose** of 60 mL/24 hr

≥12 yr and adult: 20 mL Q4 hr PRN PO up to a **max. dose** of 120 mL/24 hr

Oral, tab (Brohist-D, Ru-Hist D):

6 to <12 yr: 0.5 tab Q4 hr PRN PO not to exceed 3 tablets/24 hr

≥12 yr and adult: 1 tab Q4 hr PRN PO not to exceed 6 tablets/24 hr

Generally not recommended for treating URIs for infants. No proven benefit for infants and young children with URIs. Over the counter (OTC or nonprescription) use of this product is **not recommended** for children <6 yr old due to reports of serious adverse effects (cardiac and respiratory distress, convulsions, and hallucinations) and fatalities (from unintentional overdosages, including combined use of other OTC products containing the same active ingredients).

Contraindicated with use of MAO inhibitors (concurrent use and within 14 days after discontinuing MAO inhibitor). **Use with caution** in narrow-angle glaucoma, bladder neck obstruction, asthma, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, hypertension, coronary artery disease, diabetes mellitus, and thyroid disease. Discontinue use 48 hr prior to allergy skin testing. May cause drowsiness, fatigue, CNS excitation, xerostomia, blurred vision, and wheezing.

BUDESONIDE

Pulmicort Respules, Pulmicort Flexhaler, Rhinocort Allergy Nasal Spray, Entocort EC, Uceris, and generics

Corticosteroid

Nasal spray (Rhinocort Allergy and generics) [OTC]: 32 mCg/actuation (5 mL delivers 60 sprays, 8.43 mL delivers 120 sprays); may contain disodium EDTA and polysorbate 80

Nebulized inhalation suspension (Pulmicort Respules and generics): 0.25 mg/2 mL, 0.5 mg/2 mL (30s); may contain disodium EDTA and polysorbate 80

Oral breath activated inhalation powder (Pulmicort Flexhaler): 90 mCg/metered dose (165 mg, delivers 60 doses), 180 mCg/metered dose (225 mg, delivers 120 doses); contains lactose

Enteric coated granules in a capsule (Entocort EC and generics): 3 mg

Extended release tablet (Uceris and generics): 9 mg

Rectal foam (Uceris): 2 mg per metered dose (33.4 g, delivers 14 doses; 2 canisters per kit)

Nebulized inhalation suspension:

Child 1–8 yr:

No prior steroid use: 0.5 mg/24 hr ÷ once daily–BID; **max. dose**: 0.5 mg/24 hr

Prior inhaled steroid use: 0.5 mg/24 hr ÷ once daily–BID; **max. dose**: 1 mg/24 hr

Prior oral steroid use: 1 mg/24 hr ÷ once daily–BID; **max. dose**: 1 mg/24 hr

NIH Asthma Guideline 2007 recommendations (divide daily doses once daily–BID):

Child 0–4 yr:

Low dose: 0.25–0.5 mg/24 hr

Medium dose: >0.5–1 mg/24 hr

High dose: >1 mg/24 hr

Child 5–11 yr:

Low dose: 0.5 mg/24 hr

Medium dose: 1 mg/24 hr

High dose: 2 mg/24 hr

Oral inhalation:

Pulmicort Flexhaler (see remarks):

Child ≥6 yr: Start at 180 mCg BID; **max. dose**: 720 mCg/24 hr.

Adult: Start at 180–360 mCg BID; **max. dose**: 1440 mCg/24 hr.

Continued

For explanation of icons, see p. 667

BUDESONIDE *continued*

Nasal inhalation:

≥6 to <12 yr: Start at 1 spray in each nostril once daily. If needed, increase to 2 sprays each nostril once daily. Then reduce dose back to initial dose when symptoms improve. **Max. nasal dose**: 128 mCg/24 hr (4 sprays/24 hr).

≥12 yr to adult: Start at 2 sprays in each nostril once daily. When symptoms improve, reduce dose to 1 spray each nostril once daily. Usual **max. dose** is 128 mCg/24 hr (4 sprays/24 hr) but some may require 256 mCg/24 hr (8 sprays/24 hr) initially with a subsequent reduced dosage to improve symptoms.

Crohn disease (Encort EC and generics):

Child ≥6 yr (see remarks): Data are limited; only the following dosages have been reported. Additional studies are needed.

Active disease: 9 mg PO once daily × 7–8 wk

Maintenance of remission: 6 mg PO once daily × 3–4 wk

In addition, a report in 10–19 yr old children demonstrated higher remission rates with an induction dose of 12 mg PO once daily × 4 wk, followed by 9 mg PO once daily × 3 wk, followed by 6 mg PO once daily × 3 wk.

Adult:

Active disease: 9 mg PO QAM × 8 wk; if remission is not achieved, a second 8-wk course may be given.

Maintenance of remission: 6 mg PO once daily for up to 3 mo. If symptom control is maintained at 3 mo, taper dosage to compete cessation. Remission therapy beyond 3 mo has not shown to provide substantial clinical benefit.

Ulcerative colitis, induction of remission (Uceris and generics):

Adult:

Extended release oral tablet: 9 mg PO QAM for up to 8 wk

Rectal foam: 2 mg PR BID × 2 wk followed by 2 mg PR once daily × 4 wk

Reduce maintenance dose to as low as possible to control symptoms. May cause pharyngitis, cough, epistaxis, nasal irritation, and HPA-axis suppression. Rinse mouth after each use via the oral inhalation route. Nebulized budesonide has been shown effective in mild to moderate croup at doses of 2 mg × 1. Ref: *N Engl J Med* 331(5):285.

Hypersensitivity reactions, including anaphylaxis, have been reported with the inhaled route. Anaphylactic reactions, rectal bleeding, peripheral edema, mood swings, increased blood pressure, rash, and benign intracranial hypertension have been reported with oral route of administration.

Safety and effectiveness for mild/moderate Crohn disease have been established for children 8–17 yr old weighing ≥25 kg. Safety and efficacy have NOT been established in pediatric patients for the maintenance of clinical remission of mild/moderate Crohn disease. Although the reported safety profile in pediatric Crohn disease is consistent with adults, there may be increased risk for decreased growth velocity due to higher systemic absorption of corticosteroids in children with Crohn disease.

CYP 450 3A4 inhibitors (e.g., ketoconazole, erythromycin, protease inhibitors) or significant hepatic impairment may increase systemic exposure of budesonide (inhalation and PO routes).

Onset of action for oral inhalation and nebulized suspension is within 1 day and 2–8 days, respectively, with peak effects at 1–2 wk and 4–6 wk, respectively.

For nasal use, onset of action is seen after 1 day with peak effects after 3–7 days of ther apy. Discontinue therapy if no improvement in nasal symptoms after 3 wk of continuous therapy.

Pulmicort Flexhaler is a breath activated device which requires the patient to have an inspiratory flow rate of approximately 60 L/min for optimal drug delivery.

Pregnancy category is "B" for inhalation routes of administration and "C" for the oral and rectal routes. **Breast feeding category is "2" for inhalation routes and "?"** for the rectal route. Breast feeding with the oral route of administration may result in budesonide exposure to the infant up to 10 times higher than that by the inhalation route. **Do not** crush or chew the oral capsule dosage form.

BUDESONIDE AND FORMOTEROL
Symbicort
Corticosteroid and long-acting β_2-adrenergic agonist

Aerosol inhaler:

80 mcg budesonide + 4.5 mcg formoterol fumarate dihydrate (6.9 g delivers 60 inhalations, 10.2 g delivers approximately 120 inhalations)

160 mcg budesonide + 4.5 mcg formoterol fumarate dihydrate (6 g delivers 60 inhalations, 10.2 g delivers approximately 120 inhalations)

5–11 yr (NIH Asthma Guideline 2007 recommendations) and 6 to <12 yr (FDA labeling); see remarks: Two inhalations BID of 80 mcg budesonide + 4.5 mcg formoterol; **max. dose:** 4 inhalations/24 hr.

≥12 yr and adult:

No prior inhaled steroid use: Start with two inhalations BID of 80 mcg budesonide + 4.5 mcg formoterol ***OR*** 160 mcg budesonide + 4.5 mcg formoterol, depending on severity.

Prior low to medium doses of inhaled steroid use: Start with two inhalations BID of 80 mcg budesonide + 4.5 mcg formoterol.

Prior medium to high doses of inhaled steroid use: Start with two inhalations BID of 160 mcg budesonide + 4.5 mcg formoterol.

Max. dose: 2 inhalations of 160 mcg budesonide + 4.5 mcg formoterol BID

See Budesonide and Formoterol for remarks. Should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to-medium dose inhaled corticosteroids) or whose disease severity requires the use of two maintenance therapies. Titrate to the lowest effective strength after asthma is adequately controlled.

Reported side effects at ≥3% and more frequently compared with budesonide alone include URI, pharyngitis, headache, and rhinitis.

As needed rescue therapy with budesonide/formoterol was found to be noninferior to maintenance budesonide and PRN terbutaline for controlling symptoms in mild asthmatics ≥12 yr old (Ref. *N Engl J Med* 378[20]:1877).

Proper patient education including dosage administration technique is essential; see patient package insert for detailed instructions. Rinse mouth after each use.

For explanation of icons, see p. 667

BUMETANIDE
Generics; previously available as Bumex
Loop diuretic

Tabs: 0.5, 1, 2 mg
Injection: 0.25 mg/mL (4, 10 mL); some preparations may contain 1% benzyl alcohol

Neonate and infant (see remarks): PO/IM/IV
≤6 mo: 0.01–0.05 mg/kg/dose once daily or every other day
Infant and child: PO/IM/IV
>6 mo: 0.015–0.1 mg/kg/dose once daily-QID; **max. dose:** 10 mg/24 hr
Adult:
PO: 0.5–2 mg/dose once daily–BID
IM/IV: 0.5–1 mg over 1–2 min. May give additional doses Q2–3 hr PRN
Usual max. dose (PO/IM/IV): 10 mg/24 hr

Cross-allergenicity may occur in patients allergic to sulfonamides. Dosage reduction may be necessary in patients with hepatic dysfunction. Administer oral doses with food.
Side effects include cramps, dizziness, hypotension, headache, electrolyte losses (hypokalemia, hypocalcemia, hyponatremia, hypochloremia), and encephalopathy. May also lead to metabolic alkalosis. Serious skin reactions (e.g., Stevens-Johnson, TEN) have been reported.
Drug elimination has been reported to be slower in neonates with respiratory disorders compared with neonates without. May displace bilirubin in critically ill neonates. **Maximal** diuretic effect for infants ≤6 mo has been reported at 0.04 mg/kg/dose with greater efficacy seen at lower dosages.

BUTORPHANOL
Generics; previously available as Stadol
Narcotic, analgesic

Injection: 1 mg/mL (1 mL), 2 mg/mL (1, 2 mL)
Nasal solution: 10 mg/mL (2.5 mL); 1 mg per spray

Child (limited data): 0.01–0.02 mg/kg/dose (**max. dose**: 2 mg/dose) IV Q3–4 hr PRN. Use of a single dose of 0.03 mg/kg IV has been reported in postoperative patients.
Adult:
IV: *1 mg/dose Q3–4 hr PRN; usual dosage range*: 0.5–2 mg Q3–4 hr PRN
IM: 2 mg/dose Q3–4 hr PRN; usual dosage range: 1–4 mg Q3–4 hr PRN
Intranasal: 1 spray (1 mg) in one nostril × 1; an addition 1 mg dose may be given at 1–1.5 hr if needed. This 2-dose sequence may be repeated in 3–4 hr if needed. Alternatively, the patient may receive 2 mg initially (1 mg in each nostril) only if they remain recumbent if drowsiness or dizziness occurs; an additional dose may be given 3–4 hr later.

A synthetic mixed agonist/antagonist opioid analgesic. **Contraindicated** in patients hypersensitive to benzethonium chloride. **Use with caution** in hypotension, thyroid dysfunction, renal or hepatic impairment, and concomitant CNS depressants. **Suggested dosage reduction** in renal impairment (IV/IM): 75% of usual dose for GFR 10–50 mL/min and 50% of usual dose for GFR <10 mL/min with an increase in dosage interval based on duration of clinical effects. A 50% IV/IM dosage reduction with increased dosage interval has been recommended in hepatic dysfunction. Reduced dosage for intranasal administration for both renal and hepatic impairment: initial dose should not exceed 1 mg.
Butorphanol is a P450 3A4 substrate. Cytochrome P450 3A4 inhibitors may increase butophanol's effects and toxicity (fatal respiratory depression).

BUMETANIDE *continued*

Common side effects include drowsiness, dizziness, insomnia (nasal spray), nausea, vomiting, nasal congestion (nasal spray). Severe respiratory depression has been reported with use of nasal solutions.

Onset of action: 5–10 min (IV); 0.5–1 hr (IM); and within 15 min (intranasal). **Duration**: 3–4 hr (IV/IM) and 4–5 hr (intranasal).

C

CAFFEINE CITRATE
Cafcit and generics
Methylxanthine, respiratory stimulant

Injection: 20 mg/mL (3 mL)
Oral liquid: 20 mg/mL (3 mL), also available as powder for compounding 10 or 20 mg/mL
20 mg/mL caffeine citrate salt = 10 mg/mL caffeine base

Doses expressed in mg of caffeine citrate.
Neonatal apnea:
Loading dose: 20–25 mg/kg IV/PO × 1
Maintenance dose: 5–10 mg/kg/dose PO/IV Q24 hr, to begin 24 hr after loading dose

Avoid use in symptomatic cardiac arrhythmias. **Do not use** caffeine benzoate formulations; it has been associated with kernicterus in neonates. **Use with caution** in impaired renal or hepatic function.

Therapeutic levels: 5–25 mg/L. Cardiovascular, neurologic, or GI toxicity reported at serum levels >50 mg/L. Recommended serum sampling time: obtain trough level within 30 min prior to a dose. Steady state is typically achieved 3 wk after initiation of therapy. Levels obtained prior to steady state are useful for preventing toxicity.

For IV administration, give loading dose over 30 min and maintenance dose over 10 min.

CALCITONIN—SALMON
Miacalcin (injection) and generic nasal sprays; nasal sprays previously available as Fortical and Miacalcin
Hypercalcemia antidote, antiosteoporotic

Injection (Miacalcin): 200 U/mL (2 mL); contains phenol
Nasal spray: 200 U/metered dose (3.7 mL provides at least 30 doses); may contain benzyl alcohol

Osteogenesis imperfecta:
>6 mo-adolescent: 2 U/kg/dose IM/SC 3 times per week
Hypercalcemia (see remarks):
Adult: Start with 4 U/kg/dose IM/SC Q12 hr; if response is unsatisfactory after 1 or 2 days, may increase dose to 8 U/kg/dose Q12 hr. If response remains unsatisfactory after 2 more days, increase to a **max. dose** of 8 U/kg/dose Q6 hr.
Paget disease (see remarks):
Adult: Start with 100 U IM/SC once daily initially, followed by lower maintenance dose of 50 U 3 times per week if sufficient.

Continued

For explanation of icons, see p. 667

CALCITONIN—SALMON *continued*

Contraindicated in patients sensitive to salmon protein or gelatin. Because of hypersensitivity risk (e.g., bronchospasm, airway swelling, anaphylaxis), skin test is recommended before initiating IM/SC therapy. For skin test, prepare a 10-U/mL dilution with normal saline (NS), administer 0.1 mL intradermally, and observe for 15 min for wheal or significant erythema. Tachyphylaxis has been reported after 2–3 days of use for the treatment of hypercalcemia of malignancy.

Nausea, abdominal pain, diarrhea, flushing, and inflammation/urticaria at the injection site have been reported with IM/SC route of administration. May decrease lithium levels via enhanced urinary clearance. Hypocalcemia and increased risk for malignancies have been reported in a meta-analysis.

Intranasal use currently indicated for postmenopausal osteoporosis in adults. Nasal irritation (alternate nostrils to reduce risk), rhinitis, and epistaxis may occur with the intranasal product.

Tremors have been reported with both intranasal and injectable routes of administration.

If the injection volume exceeds 2 mL, use IM route and multiple sites of injection.

CALCITRIOL

1,25-dihydroxycholecalciferol, Rocaltrol, and generics

Active form vitamin D, fat soluble

Caps (Rocaltrol and generics): 0.25, 0.5 mCg; may contain parabens

Oral solution (Rocaltrol and generics): 1 mCg/mL (15 mL)

Injection (generics; previously available as Calcijex): 1 mCg/mL (1 mL); contains EDTA

Hypoparathyroidism (evaluate dosage at 2- to 4-wk intervals):

Child >1 yr and adult: Initial dose of 0.25 mCg/dose PO once daily. May increase daily dosage by 0.25 mCg at 2- to 4-wk intervals. Usual maintenance dosage as follows:

<1 yr (limited data): 0.02–0.06 mCg/kg/dose PO once daily

1–5 yr: 0.25–0.75 mCg/dose PO once daily

>6 yr and adult: 0.5–2 mCg/dose PO once daily

Renal failure: See the National Kidney Foundation guidelines at https://www.kidney.org/professionals/guidelines/guidelines_commentaries/bone-metabolism-ckd

Most potent vitamin D metabolite available. Should not be used to treat 25-OH vitamin D deficiency; use cholecalciferol or ergocalciferol. Monitor serum calcium and phosphorus, and parathyroid hormone (PTH) in dialysis patients. **Avoid** concomitant use of Mg^{2+}-containing antacids. IV dosing applies if patient is undergoing hemodialysis.

Contraindicated in patients with hypercalcemia or vitamin D toxicity. Side effects include: weakness, headache, vomiting, constipation, hypotonia, polydipsia, polyuria, myalgia, metastatic calcification, etc. Allergic reactions, including anaphylaxis, have been reported. May increase serum creatinine in predialysis patients.

CALCIUM ACETATE

Calphron, Eliphos, Phoslyra, and generics (previously available as PhosLo); 25% elemental Ca

Calcium supplement, phosphorous-lowering agent

Tabs (Calphron, Eliphos, and generics): 667 mg (169 mg elemental Ca)

Capsules (Generics; previously available as PhosLo): 667 mg (169 mg elemental Ca)

Oral solution (Phoslyra): 667 mg/5 mL (473 mL) (169 mg elemental Ca per 5 mL); contains methylparabens and propylene glycol

Each 1 g of salt contains 12.7 mEq or 6.34 mmol (250 mg) elemental Ca.

D

CALCIUM ACETATE *continued*

Doses expressed in mg of calcium acetate.

Hyperphosphatemia (see remarks):

Child and adolescent: Start with 667–1000 mg PO with each meal. If needed, dosage may be titrated every 2–4 wk up to the recommended limits from the KDOQI guidelines:

Calcium intake as phosphate binders: 1500 mg elemental calcium/24 hr

Total calcium intake from all sources: 2000 mg elemental calcium/24 hr

Adult: Start with 1334 mg PO with each meal. Dosage may be increased gradually every 2–3 wk to bring serum phosphorous levels below 6 mg/dL, as long as hypercalcemia does not occur. Most patients require 2001–2668 mg PO with each meal.

Contraindicated in ventricular fibrillation. **Use with caution** in renal impairment, as hypercalcemia may develop in end-stage renal failure. Nausea and hypercalcemia may occur. Approximately 40% of dose is systemically absorbed under fasting conditions and up to 30% in nonfasting conditions. May reduce absorption of fluoroquinolones, tetracyclines, iron, and effectiveness of polystyrene sulfonate. May potentiate effects of digoxin.

1 g calcium acetate binds to 45 mg phosphorus.

Administer with meals and plenty of fluids for use as a phosphorus-lowering agent. Calcium is excreted in breast milk and is not expected to harm the infant provided maternal serum calcium is appropriately monitored.

CALCIUM CARBONATE

Tums, Children's Pepto, and many others including generics; 40% elemental Ca

Calcium supplement, antacid

Tab, chewable [OTC]: 400, 500, 600, 750, 1000, 1250 mg; may contain aspartame

Children's Pepto [OTC]: 400 mg

Tab [OTC]: 648, 1250, 1500 mg

Oral suspension [OTC]: 1250 mg/5 mL; may contain parabens

Powder [OTC]: 800 mg/2 g (480 g)

Each 1 g of salt contains 20 mEq or 10 mmol (400 mg) elemental Ca.

Some products may be combined with vitamin D; check package labeling.

Hypocalcemia (Doses expressed in mg of elemental calcium. To convert to mg of salt, divide elemental dose by 0.4.):

Neonate: 50–150 mg/kg/24 hr ÷ Q4–6 hr PO; **max. dose:** 1 g/24 hr

Child: 45–65 mg/kg/24 hr PO ÷ QID

Adult: 1–2 g/24 hr PO ÷ TID–QID

Antacid (Doses expressed in mg of calcium carbonate; chronic use NOT recommended in GERD):

2–5 yr and ≥10.9 kg: 375–400 mg PO as symptoms occur; **max. dose**: 1500 mg/24 hr

>6–11 yr: 750–800 mg PO as symptoms occur; **max. dose**: 3000 mg/24 hr

>11 yr and adult: 500–3000 mg PO as symptoms occur; **max. dose**: 7500 mg/24 hr.

See *Calcium acetate* for **contraindications, precautions,** and drug interactions. Side effects: constipation, hypercalcemia, hypophosphatemia, hypomagnesemia, nausea, vomiting, headache, and confusion. Some products may contain trace amounts of sodium. Administer with plenty of fluids. For use as a phosphorus-lowering agent, administer with meals. Calcium is excreted in breast milk and is not expected to harm the infant, provided maternal serum calcium is appropriately monitored.

For explanation of icons, see p. 667

CALCIUM CHLORIDE
Various generics; 27% elemental Ca
Calcium supplement

Injection: 100 mg/mL (10%) (1.36 mEq Ca/mL) (10 mL)
Prefilled syringe for injection: 100 mg/mL (10%) (1.36 mEq Ca/mL) (10 mL)
Each 1 g of salt contains 13.6 mEq or 6.8 mmol (273 mg) elemental Ca.

Doses expressed in mg of calcium chloride.
Cardiac arrest or calcium channel blocker toxicity:
Neonate, infant, and child: 20 mg/kg/dose (**max. dose:** 1000 mg/dose) IV/IO Q10 min PRN, if effective, an infusion of 20–50 mg/kg/hr may be used
Adult: 500–1000 mg/dose IV Q10 min PRN or 2–4 mg/kg/dose Q10 min PRN
MAXIMUM IV ADMINISTRATION RATES:
IV push: **Do not exceed** 100 mg/min (over 10–20 sec in cardiac arrest)
IV infusion: **Do not exceed** 45–90 mg/kg/hr with a **max. concentration** of 20 mg/mL.

Contraindicated in ventricular fibrillation. **Not recommended** for asystole and electromechanical dissociation. **Use with caution** in renal impairment, as hypercalcemia may develop in end stage renal failure. May potentiate effects of digoxin.
Use IV with extreme caution. Extravasation may lead to necrosis. Hyaluronidase may be helpful for extravasation. Central line administration is preferred IV route of administration. **Do not use** scalp veins. **Do not administer IM or SC routes.**
Rapid IV infusion associated with bradycardia, hypotension, and peripheral vasodilation. May cause hyperchloremic acidosis.
Calcium is excreted in breast milk and is not expected to harm the infant, provided maternal serum calcium is appropriately monitored.

CALCIUM CITRATE
Calcitrate, Citracal, Viactiv, and generics; 21% elemental Ca
Calcium supplement

Tabs:
Calcitrate, Citracal, and generics [OTC]: 950 mg (200 mg elemental Ca)
Generics [OTC]: 1040 mg (218 mg elemental Ca)
Some products may be combined with vitamin D; check package labeling
Chewable tabs:
Citracal [OTC]: 950 mg (200 mg elemental Ca) and 500 IU vitamin D3
Viactiv [OTC]: 650 mg elemental Ca and 500 IU vitamin D3 with 40 mCg vitamin K, and 10 mg sodium
Each 1 g of salt contains 10.5 mEq or 5.25 mmol (211 mg) elemental Ca.

Doses expressed as mg of elemental calcium. To convert to mg of salt, divide elemental dose by 0.21.
Hypocalcemia:
Neonate: 50–150 mg/kg/24 hr ÷ Q4–6 hr PO; **max. dose**: 1 g/24 hr
Child: 45–65 mg/kg/24 hr PO ÷ QID
Adult: 1–2 g/24 hr PO ÷ TID-QID

CALCIUM CITRATE *continued*

See Calcium Acetate for **contraindications, precautions,** and drug interactions. Side effects: constipation, hypercalcemia, hypophosphatemia, hypomagnesemia, nausea, vomiting, headache, and confusion.

Administer with meals for use as a phosphorus-lowering agent. For hypocalcemia, do not administer with or before meals/food and take plenty of fluids.

Calcium is excreted in breast milk and is not expected to harm the infant, provided maternal serum calcium is appropriately monitored.

CALCIUM GLUCONATE

Cal-Glu and generics; 9.3% elemental Ca

Calcium supplement

Tabs [OTC]: 50 mg

Caps (Cal-Glu) [OTC]: 500 mg

Injection: 100 mg/mL (10%) (0.465 mEq Ca/mL) (10, 50, 100 mL); may contain 400 mCg aluminum per 1000 mL (0.4 mCg per 100 mg calcium gluconate); see remarks

Each 1 g of salt contains 4.65 mEq or 2.33 mmol (93 mg) elemental Ca

Doses expressed in mg calcium gluconate.

Maintenance/hypocalcemia:

Neonate: IV: 200–800 mg/kg/24 hr ÷ Q6 hr

Infant:

IV: 200–500 mg/kg/24 hr ÷ Q6 hr

PO: 400–800 mg/kg/24 hr ÷ Q6 hr

Child: 200–500 mg/kg/24 hr IV or PO ÷ Q6 hr

Adult: 0.5–8 g/24 hr IV or PO ÷ Q6 hr

For cardiac arrest:

Infant and child: 100 mg/kg/dose (**max.** 3000 mg/dose) IV Q10 min PRN

Adult: 1.5–3 g/dose IV Q10 min PRN

Max. dose: 3 g/dose

For tetany:

Neonate, infant, child: 100–200 mg/kg dose IV over 5–10 min, repeat dose 6 hr later if needed; **max. dose**: 500 mg/kg/24 hr

Adult: 0.5–2 g IV over 10–30 min, repeat dose 6 hr later if needed.

MAXIMUM IV ADMINISTRATION RATES:

IV push: **Do not exceed** 100 mg/min (over 10–20 sec in cardiac arrest)

IV infusion: **Do not exceed** 200 mg/min with a **maximum** concentration of 50 mg/mL

Contraindicated in ventricular fibrillation. **Use with caution** in renal impairment, as hypercalcemia may develop in end-stage renal failure. **Avoid** peripheral infusion because extravasation may cause tissue necrosis. IV infusion associated with hypotension and bradycardia. Also associated with arrhythmias in digitalized patients. May reduce absorption of fluoroquinolones, tetracyclines, iron, and effectiveness of polystyrene sulfonate with oral route of administration.

Do not administer IV dosage form via scalp veins and the IM or SC routes. IV dosage form may precipitate when mixed with bicarbonate or ceftriaxone. IV dosage form may also contain aluminum (see how supplied section), and patients with renal impairment (including premature infants) receiving >4–5 mCg/kg/24 hr aluminum have been associated with CNS and bone toxicities.

Calcium is excreted in breast milk and is not expected to harm the infant provided maternal serum calcium is appropriately monitored.

For explanation of icons, see p. 667

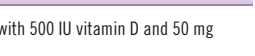
CALCIUM LACTATE
Cal-Lac and various generics; 13% elemental Ca
Calcium supplement

Tabs [OTC]: 100, 648 mg
Caps (Cal-Lac) [OTC]: 500 mg
Each 1 g salt contains 6.48 mEq or 3.24 mmol (130 mg) elemental Ca.

Doses expressed in mg of calcium lactate.
Hypocalcemia:
Neonate/Infant: 400–500 mg/kg/24 hr PO ÷ Q4–6 hr
Child: 500 mg/kg/24 hr PO ÷ Q6–8 hr
Adult: 1.5–3 g PO Q8 hr
Max. dose: 9 g/24 hr

See *Calcium Acetate* for **contraindications, precautions,** and drug interactions. May cause constipation, headache, and hypercalcemia.
Administer with or following meals and with plenty of fluids. **Do not** dissolve tablets in milk.
Calcium is excreted in breast milk and is not expected to harm the infant, provided maternal serum calcium is appropriately monitored.

CALCIUM PHOSPHATE, TRIBASIC
Posture-D; 39% elemental Ca
Calcium supplement



Tabs [OTC]: 600 mg elemental calcium and 280 mg phosphorus; with 500 IU vitamin D and 50 mg magnesium
Oral suspension: 20 mg elemental calcium/1 mL
NOTE: Pharmacy may crush tablets into a powder to enhance drug delivery for children unable to swallow tablets and to accommodate smaller doses.
Each 1 g of salt contains 19.3 mEq or 9.65 mmol (390 mg) elemental Ca.

Doses expressed as mg of elemental calcium.
Hypocalcemia:
Neonate: 20–80 mg/kg/24 hr ÷ Q4–6 hr PO; **max. dose:** 1 g/24 hr
Child: 45–65 mg/kg/24 hr PO ÷ Q6 hr
Adult: 1–2 g/24 hr PO ÷ Q6–8 hr

Contraindicated in ventricular fibrillation. **Use with caution** in renal impairment, because hypercalcemia may develop in end-stage renal failure **(avoid use** in dialysis with hypercalcemia), history of kidney stones, and parathyroid disorders. May cause constipation, GI disturbances, and hypercalcemia. See *Calcium Acetate* for drug interactions.
Give with or following meals and with plenty of fluids. Keep in mind the amounts of vitamin D and magnesium your respective dosage may provide.
Calcium is excreted in breast milk and is not expected to harm the infant, provided maternal serum calcium is appropriately monitored.

CALFACTANT

See Surfactant, pulmonary

CANNABIDIOL
Epidiolex
Anticonvulsant

Oral solution: 100 mg/mL (100 mL); contains ethanol and sesame oil

Lennox-Gastaut syndrome or Dravet syndrome (see remarks):

Child ≥2 yr and adult: Start at 2.5 mg/kg/dose PO BID × 1 wk, dosage may be increased to a maintenance dose of 5 mg/kg/dose PO BID. Dose may be further increased after 1 wk if needed and tolerated at weekly increments of 2.5 mg/kg/dose BID (5 mg/kg/24 hr) up to the **maximum** of 20 mg/kg/24 hr. Those requiring a more rapid titration from 10 mg/kg/24 hr to 20 mg/kg/24 hr may be titrated no more frequent than Q48 hr.

Dosage reduction in moderate and severe hepatic impairment prior to initiation of therapy (slower dose titration has been suggested):

Child-Pugh Category for Hepatic Impairment	Initial PO Dose (mg/kg/dose BID)	Maintenance PO Dose (mg/kg/dose BID)	Maximum PO Dose (mg/kg/dose BID)
B (moderate)	1.25	2.5	5
C (severe)	0.5	1	2

Epidiolex is a schedule V controlled substance. Common side effects include somnolence, decreased appetite, diarrhea, elevated transaminase (dose related), fatigue, malaise and asthenia, rash, insomnia, and sleep disorder. Suicidal behavior and ideation and respiratory failure have been reported.

Monitor ALT, AST, and total bilirubin at baseline and 1, 3, 6 mo initially and periodically thereafter. More frequent monitoring is recommended with concurrent valproic acid or clobazam. Reduce dose or discontinue use in the presence of hepatic impairment.

Epidiolex is a substrate for CYP 450 2C19 and 3A4; other moderate/strong inducers or inhibitors for these enzymes may affect its overall exposure. May increase the effects/toxicity of clobazam and diazepam because it may inhibit CYP 450 1A2, 2B6, 2C8, 2C9, and 2C19. May inhibit the UGT 1A9 and 2B7 transporters.

Teratogen data limited only to animal studies with evidence of developmental toxicities at similar exposure concentrations in humans receiving therapeutic doses. Patients exposed to cannabidiol during pregnancy are encouraged to register with the North American Antiepileptic Drug Pregnancy Registry at www.aedpregnancyregistry.org.

Administration with high-fat or high-calorie meals may increase absorption. Gradually taper when discontinuing medication; **avoid** abrupt discontinuation.

Each bottle of oral solution must be stored in the original bottle in the upright position at 59–86°F. Discard the unused portion of each bottle 12 wk after first opening.

CAPTOPRIL
Various generics; previously available as Capoten
Angiotensin-converting enzyme inhibitor, antihypertensive

Tabs: 12.5, 25, 50, 100 mg
Oral suspension: 1 mg/mL

Neonate: 0.01–0.05 mg/kg/dose PO Q8–12 hr
Infant aged <6 mo: Initially 0.01–0.5 mg/kg/dose PO BID–TID; titrate upward if needed; **max. dose:** 6 mg/kg/24 hr.

Continued

For explanation of icons, see p. 667

CAPTOPRIL *continued*

Child: Initially, 0.3–0.5 mg/kg/dose PO BID–TID; titrate upward if needed; **max. dose:** 6 mg/kg/24 hr up to 450 mg/24 hr.

Adolescent and adult: Initially, 12.5–25 mg/dose PO BID–TID; increase weekly if necessary by 25 mg/dose to **max. dose:** 450 mg/24 hr. Usual dosage range: 25–100 mg/24 hr ÷ BID.

Onset within 15–30 min of administration. Peak effect within 1–2 hr. **Adjust dose with renal failure (see Chapter 31)**. Should be administered on an empty stomach 1 hr before or 2 hr after meals. Titrate to minimal effective dose. Lower doses should be used in patients with sodium and water depletion because of diuretic therapy.

Use with caution in collagen vascular disease and concomitant potassium sparing diuretics. **Avoid use** with dialysis with high-flux membranes as anaphylactoid reactions have been reported. May cause rash, proteinuria, neutropenia, cough, angioedema (head, neck and intestine), hyperkalemia, hypotension, or diminution of taste perception (with long term use). Known to decrease aldosterone and increase renin production. **Do not** coadminister with angiotensin receptor blockers or aliskiren as use has been associated with increased risks for hypotension, hyperkalemia, and acute renal failure. Captopril is a CYP 450 2D6 substrate. Use with sirolimus, everolimus, temsirolimus, or sacubitril may increase risk for angioedema.

Captopril should be discontinued as soon as possible when pregnancy is detected.

CARBAMAZEPINE
Epitol, Tegretol, Tegretol-XR, Carbatrol, Equetro, Carnexiv, and various generics
Anticonvulsant

Tabs: 200 mg
Chewable tabs: 100 mg
Extended-release tabs (Tegretol-XR and generics): 100, 200, 400 mg
Extended-release caps (Carbatrol, Equetro, and generics): 100, 200, 300 mg
Oral suspension: 100 mg/5 mL (450 mL); may contain propylene glycol
Injection (Carnexiv): 10 mg/mL (20 mL); contains betadex sulfobutyl ether sodium (preservative-free)

See remarks regarding dosing intervals for specific dosage forms:

<6 yr:

Initial: 10–20 mg/kg/24 hr PO ÷ BID–TID (QID for suspension)

Increment: Q5–7 days up to **max. dose** of 35 mg/kg/24 hr PO

6–12 yr:

Initial: 10 mg/kg/24 hr PO ÷ BID up to **max. dose**: 100 mg/dose BID

Increment: 100 mg/24 hr at 1-wk intervals (÷ TID–QID) until desired response is obtained

Maintenance: 20–30 mg/kg/24 hr PO ÷ BID-QID; usual maintenance dose is 400–800 mg/24 hr; **max. dose:** 1000 mg/24 hr

>12 yr and adult:

Initial: 200 mg PO BID

Increment: 200 mg/24 hr at 1-wk intervals (÷ BID-QID) until desired response is obtained

Maintenance: 800–1200 mg/24 hr PO ÷ BID–QID

Max. dose:

Child 12–15 yr: 1000 mg/24 hr

Child >15 yr: 1200 mg/24 hr

Adult: 1.6–2.4 g/24 hr

Intravenous dosage form (Carnexiv; see remarks):

Child: pediatric PK, efficacy, and safety data currently not available

CARBAMAZEPINE *continued*

Intravenous dosage form (Carnexiv; see remarks) cont.:

Adult (IV; indicated as replacement therapy for PO carbamazepine when PO route is not feasible): Determine IV daily dose by taking 70% of the established total daily oral dosage and dividing into 4 equal doses to be administered Q6 hr. Each dose is further diluted in 100 mL of compatible fluid and infused over 30 min. **Use is NOT recommended** >7 days.

Contraindicated for patients taking monoamine oxidase (MAO) inhibitors or who are sensitive to tricyclic antidepressants. Should not be used in combination with clozapine, owing to increased risk for bone marrow suppression and agranulocytosis. Increased risk for severe dermatologic reactions (e.g., Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]) has been associated with the HLA-B*1502 (prevalent among Asian descent) and HLA-A*3101 (prevalent among Japanese, Native American, Southern Indian, and some Arabic ancestry) alleles.

Erythromycin, diltiazem, verapamil, cefixime, cimetidine, itraconazole, aprepitant, and INH may increase serum levels. Carbamazepine may decrease activity of warfarin, direct-acting oral anticoagulants (e.g., rivaroxaban, apixaban), doxycycline, oral contraceptives, cyclosporine, theophylline, phenytoin, benzodiazepines, ethosuximide, and valproic acid. Carbamazepine is a CYP 450 3A3/4 substrate and inducer of CYP 450 1A2, 2C, and 3A3/4. The enzyme-inducing effects may increase effects/toxicity of cyclophosphamide. CYP 450 3A4 inhibitors may increase carbamazepine levels/toxicity.

Suggested dosing intervals for specific dosage forms: extended-release tabs or caps (BID); chewable and immediate-release tablets (BID–TID); suspension (QID).

Doses may be administered with food. **Do not** crush or chew extended-release dosage forms. Shake bottle well prior to dispensing oral suspension dosage form, and **do not** administer simultaneously with other liquid medicines or diluents.

Drug metabolism typically increases after the first month of therapy initiation due to hepatic autoinduction.

Therapeutic blood levels for seizures: 4–12 mg/L. Recommended serum sampling time: obtain trough level within 30 min prior to an oral dose. Steady state is typically achieved 1 mo following the initiation of therapy (following enzymatic autoinduction). Levels obtained prior to steady state are useful for preventing toxicity. Blood trough levels of 7–10 mg/L have been recommended for bipolar disorders.

Side effects include sedation, dizziness, diplopia, aplastic anemia, neutropenia, urinary retention, nausea, SIADH, and SJS. Suicidal behavior or ideation, hypogammaglobulinemia, and onychomadesis have been reported. Approximately one-third of patients who had hypersensitivity reactions will also experience the hypersensitivity to oxcarbazepine. Pretreatment complete blood counts (CBCs) and liver function tests (LFTs) are suggested. Patient should be monitored for hematologic and hepatic toxicity. Most common side effects with the IV route, dizziness, somnolence, blurred vision, diplopia, headache, infusion-related reaction, infusion site pain, and anemia.

Adjust dose in renal impairment (see Chapter 31). Do not use IV dosage form in moderate/severe renal impairment (GFR <30 mL/min) due to accumulation of betadex sulfobutyl ether sodium, which may be nephrotoxic.

CARBAMIDE PEROXIDE

Otic solution: Debrox, Auraphene-B, Earwax Removal Drops, and many generic products
Oral liquid: Gly-Oxide
Cerumenolytic, topical oral analgesic

Otic solution (OTC): 6.5% (15 mL); may contain propylene glycol or alcohol
Oral liquid (OTC): 10% (Gly-Oxide) (15, 60 mL)

Continued

For explanation of icons, see p. 667

Carbamide Peroxide *continued*

Cerumenolytic:

<12 yr: Tilt head sideways and instill 1–5 drops (according to patient size) into affected ear; retain drops in ear for several minutes. Remove wax by gently flushing the ear with warm water, using a soft rubber bulb ear syringe. Dose may be repeated BID PRN for up to 4 days.

≥12 yr: Following the same instructions as aforementioned, instill 5–10 drops into affected ear BID PRN for up to 4 days.

Oral analgesic (see remarks):

≥2 yr (able to follow instructions): Instill several drops of the oral liquid to affected area and expectorate after 2–3 min, ***OR*** place 10 drops on tongue and mix with saliva, swish for several minutes, and expectorate. Administer up to QID, after meals and QHS, for **up to 7 days.**

Otic solution: Contraindicated if tympanic membrane perforated; following otic surgery; ear discharge, drainage, pain, irritation, or rash; or PE tubes in place. Tip of applicator should not enter ear canal when used as a cerumenolytic.

Oral liquid: Prolonged use may result in fungal overgrowth. **Do not** rinse the mouth or drink for at least 5 min when using oral preparation.

Pregnancy category has not been formally assigned by the FDA.

CARBINOXAMINE

Karbinal ER, RyVent, and many generics

Antihistamine

Oral liquid: 4 mg/5 mL (473 mL); may contain propylene glycol

Extended-release oral suspension (Karbinal ER): 4 mg/5 mL (480 mL); contains parabens and metasulfite

Tabs: 4, 6 mg

RyVent: 6 mg

Child (PO; see remarks):

Immediate-release dosage forms: 0.2–0.4 mg/kg/24 hr PO ÷ TID-QID; alternative dosing by age (**do not exceed** 0.4 mg/kg/24 hr):

2–5 yr: 1–2 mg TID–QID

6–11 yr: 2–4 mg TID–QID

≥12 yr: 4–8 mg TID–QID

Extended-release oral suspension (Karbinal ER; approximately 0.2–0.4 mg/kg/24 hr):

2–3 yr: 3–4 mg Q12 hr

4–5 yr: 3–8 mg Q12 hr

6–11 yr: 6–12 mg Q12 hr

≥12 yr: 6–16 mg Q12 hr

Adult (PO):

Immediate-release dosage forms: 4–8 mg TID–QID

Extended-release oral suspension (Karbinal ER): 6–16 mg Q12 hr

Generally not recommended for treating upper respiratory tract infections (URIs) for infants. No proven benefit for infants and young children with URIs. **The FDA does not recommend use for URIs in children <2 yr because of reports of increased fatalities.** Karbinal ER use is **contraindicated** in <2 yr and in nursing mothers.

Contraindicated in acute asthma, hypersensitivity with other ethanolamine antihistamines, MAO inhibitors, severe hypertension, narrow-angle glaucoma, severe coronary artery disease, and urinary retention. Be aware that combination products containing a decongestant may exist.

May cause drowsiness, vertigo, dry mucus membranes, and headache. Paradoxical excitation reactions more likely in younger children. Contact dermatitis and GI irritation have been reported.

CARNITINE
Levocarnitine, Carnitor, Carnitor SF, L-Carnitine, and generics
Nutritional supplement, amino acid

Tabs: 330 mg
Caps: 250 mg
Oral solution: 100 mg/mL (118 mL); contains methylparabens and propylparabens; Carnitor SF is a sugar-free product
Injection: 200 mg/mL (5 mL); preservative free

Primary carnitine deficiency:
Oral:
Child: 50–100 mg/kg/24 hr PO ÷ Q8–12 hr; increase slowly as needed and tolerated to **max. dose** of 3 g/24 hr
Adult: 330 mg to 1 g/dose BID–TID PO; **max. dose:** 3 g/24 hr
IV:
Child and adult: 50 mg/kg as loading dose; may follow with 50 mg/kg/24 hr IV infusion (for severe cases); maintenance: 50 mg/kg/24 hr ÷ Q4–6 hr; increase to **max. dose** of 300 mg/kg/24 hr if needed.

May cause nausea, vomiting, abdominal cramps, diarrhea, and body odor. Seizures have been reported in patients with or without a history of seizures.
Safety in end-stage renal disease (ESRD) has not been established. High doses to severely compromised renal function or ESRD on dialysis may result in accumulation of potentially toxic metabolites (trimethylamine and trimethylamine-*N*-oxide). Serious hypersensitivity reactions, including anaphylaxis, have been reported with IV use mostly in ESRD patients undergoing dialysis.
Give bolus IV infusion over 2–3 min.

CARVEDILOL
Coreg, Coreg CR, and generics
Adrenergic antagonist (α and β), antihypertensive

Tabs: 3.125, 6.25, 12.5, 25 mg
Extended-release caps (Coreg CR and generics): 10, 20, 40, 80 mg
Oral suspension: 0.1, 1.25, 1.67 mg/mL

Heart failure:
Immediate-release dosage forms (tablets and oral suspension; see remarks):
Infant, child, adolescent (2013 Canadian Cardiovascular Society Guidelines):
<62.5 kg: Start at 0.1 mg/kg/24 hr PO ÷ Q12 hr. Dose may be doubled every 2 wk if needed and tolerated up to 0.8–1 mg/kg/24 hr ÷ Q12 hr. Divide daily dosage by Q8 hr if child is <4 yr old due to altered pharmacokinetics.
≥***62.5 kg:*** Start at 3.125 mg PO BID. Dose by be doubled every 2 wk if needed and tolerated up to 25 mg BID. 25 mg PO TID may be needed for patients weighing >75 kg.
Adult: Start at 3.125 mg PO BID × 2 wk, if needed and tolerated, may increase to 6.25 mg BID. Dose may be doubled every 2 wk if needed to the following **max. doses:**
<85 kg: 25 mg BID
≥***85 kg:*** 50 mg BID
Extended-release capsules:
Adult: Start at 10 mg PO once daily × 2 wk, if needed and tolerated, double the dose every 2 wk up to a **maximum** of 80 mg once daily.

D cont'd by

For explanation of icons, see p. 667

CARVEDILOL *continued*

Hypertension:

Adult:

Immediate-release dosage forms: Start at 6.25 mg PO BID; dose may be doubled every 1–2 wk up to a **maximum** of 25 mg PO BID.

Extended-release capsules: Start at 20 mg PO once daily × 1–2 wk, if needed and tolerated, increase to 40 mg PO once daily. If needed, dose may be further increased in 2-wk intervals up to a **maximum** of 80 mg/24 hr.

Immediate-release and extended-release products are NOT interchangeable on a mg-to-mg basis.

Contraindicated in asthma or related bronchospastic disease, sick sinus syndrome, 2nd- or 3rd-degree heart block, severe bradycardia, cardiogenic shock, decompensated cardiac failure requiring IV inotropic therapy, and severe hepatic impairment (Child-Pugh class C).

Use with caution mild/moderate hepatic impairment (Child-Pugh class A or B), renal insufficiency, thyrotoxicosis, ischemic heart disease, diabetes, and cataract surgery. **Avoid abrupt withdrawal** of medication.

Children <3.5 yr old may have faster carvedilol clearance and may require higher dosages or TID dosing. Carvedilol is a CYP 450 2D6 substrate. Digoxin, disopyramide, and dipyridamole may increase bradycardic effects.

Bradycardia, postural hypotension, peripheral edema, weight gain, hyperglycemia, diarrhea, dizziness, and fatigue are common. Hypersensitivity reactions have been reported. Chest pain, headache, vomiting, edema, and dyspnea have also been reported in children. Administering doses with food can reduce risk for orthostatic hypotension.

CASPOFUNGIN
Cancidas and generics
Antifungal, echinocandin

Injection: 50, 70 mg; contains sucrose (39 mg in 50 mg vial and 54 mg in 70 mg vial) and mannitol (26 mg in 50 mg vial and 36 mg in 70 mg vial)

Preterm neonate to <3 mo infant:

BSA dosing (based on a small pharmacokinetic study, achieving similar plasma exposure as seen in adults receiving 50 mg/24 hr): 25 mg/m^2/dose IV once daily.

Weight-based dosing (based on a prospective, randomized, double-blinded, controlled, and case series data): 2 mg/kg/dose IV once daily for at least 2 wk after first negative blood culture and resolution of signs/symptoms for invasive candidiasis have been reported to be more efficacious with fewer side effects than conventional amphotericin B.

3 mo infant–17 yr (see remarks): 70 mg/m^2/dose IV loading dose on day 1 followed by 50 mg/m^2/dose IV once daily maintenance dose. Increase the maintenance dose to 70 mg/m^2/dose if response is inadequate or if the patient is receiving an enzyme-inducing medication (see remarks).

Maximum loading and maintenance dose: 70 mg/dose.

Adult (see remarks):

Loading dose: 70 mg IV × 1

Maintenance dose:

Usual: 50 mg IV once daily. If tolerated and response is inadequate or if patient is receiving an enzyme-inducing medication (see remarks), increase to 70 mg IV once daily.

Hepatic insufficiency (Child-Pugh score 7–9): 35 mg IV once daily.

Use with caution in hepatic impairment and concomitant enzyme-inducing drugs. Higher maintenance doses (70 mg/m^2/dose in children and 70 mg in adults) are recommended for concomitant use of enzyme inducers such as carbamazepine, dexamethasone, phenytoin, nevirapine, efavirenz, or rifampin. Use Mosteller formula for calculating body surface area (BSA).

CASPOFUNGIN *continued*

Most common adverse effects (>10%) in children include fever, diarrhea, rash, elevated aspartate transaminase/alanine transaminase (ALT/AST), hypokalemia, hypotension, and chills. May also cause facial swelling, nausea/vomiting, headache, infusion site phlebitis, and LFT elevation. Anaphylaxis, TEN, SJS, and possible histamine-related reactions (angioedema, bronchospasm, and warmth sensation) have been reported. Hepatobiliary adverse effects have been reported in pediatric patients with serious underlying medical conditions.

Reduce daily dose by 30% in moderate hepatic impairment (Child-Pugh score 7–9).

Use with cyclosporine may cause transient increase in LFTs and caspofungin level elevations. May decrease tacrolimus levels.

Administer doses by slow IV infusion over 1 hr. **Do not** mix or co-infuse with other medications, and **avoid** using dextrose-containing diluents (e.g., D_5W).

CEFACLOR
Generics; previously available as Ceclor
Antibiotic, cephalosporin (second generation)

Caps: 250, 500 mg
Extended-release tabs: 500 mg
Oral suspension: 125 mg/5 mL (150 mL); 250 mg/5 mL (150 mL); 375 mg/5 mL (100 mL)

Child >1 mo old (use regular-release dosage forms): 20–40 mg/kg/24 hr PO ÷ Q8 hr; **max. dose:** 1 g/24 hr
Q12 hr dosage interval option for pharyngitis (use oral suspension dosage form): 20 mg/kg/24 hr PO ÷ Q12 hr; **max. dose:** 1 g/24 hr
Adult: 250–500 mg/dose PO Q8 hr
Extended-release tablets: 500 mg/dose PO Q12 hr

Not recommended for otitis media or pharyngitis/tonsillitis. **Use with caution** in patients with penicillin allergy or renal impairment. Side effects include elevated LFTs, bone marrow suppression, and moniliasis. Probenecid may increase cefaclor concentrations. May cause positive Coombs test or false-positive test for urinary glucose. Serum sickness reactions have been reported in patients receiving multiple courses of cefaclor.

Do not crush, cut, or chew extended-release tablets. Doses should be given on an empty stomach. **Extended-release tablets not recommended for children. Adjust dose in renal failure (see Chapter 31).**

CEFADROXIL
Generics; previously available as Duricef
Antibiotic, cephalosporin (first generation)

Oral suspension: 250 mg/5 mL (50, 100 mL), 500 mg/5 mL (75, 100 mL)
Tabs: 1 g
Caps: 500 mg

Infant and child: 30 mg/kg/24 hr PO ÷ Q12 hr (daily dose may be administered once daily for group A β-hemolytic streptococci pharyngitis/tonsillitis); **max. dose**: 2 g/24 hr
Bacterial endocarditis prophylaxis for dental and upper airway procedures: 50 mg/kg/dose (***max. dose:*** 2 g) × 1 PO 1 hr before procedure.

Continued

For explanation of icons, see p. 667

CEFADROXIL *continued*

Adolescent and adult: 1–2 g/24 hr PO ÷ Q12–24 hr (administer Q12 hr for complicated UTIs); **max. dose:** 2 g/24 hr

Bacterial endocarditis prophylaxis for dental and upper airway procedures: 2 g × 1 PO 1 hr before procedure.

See *Cephalexin* for **precautions** and interactions. Rash, nausea, vomiting, and diarrhea are common. Transient neutropenia and vaginitis have been reported. **Adjust dose in renal failure (see Chapter 31).**

CEFAZOLIN

Generics; previously available as Ancef

Antibiotic, cephalosporin (first generation)

B	1	Yes	Yes	No

Injection: 0.5, 1, 10, 20, 100 g

Frozen injection: 1 g/50 mL (contains 2 g dextrose to make an iso-osmotic solution), 2 g/100 mL (contains 4 g dextrose to make an iso-osmotic solution)

Contains 2.1 mEq Na/g drug

Neonate (IM/IV):

Postnatal age ≤7 days:

≤2000 g: 50 mg/kg/24 hr ÷ Q12 hr

>2000 g: 100 mg/kg/24 hr ÷ Q12 hr

Postnatal age >7–28 days:

≤2000 g: 75 mg/kg/24 hr ÷ Q8 hr

>2000 g: 150 mg/kg/24 hr ÷ Q8 hr

Infant >1 mo and child (IM/IV):

Mild/moderate infection: 25–100 mg/kg/24 hr ÷ Q6–8 hr; **max. dose**: 6 g/24 hr

Severe infection: 100–150 mg/kg/24 hr ÷ Q6–8 hr (**max. dose**: 12 g/24 hr); 150 mg/kg/24 hr ÷ Q6–8 hr has been recommended for bone/joint infections

Adult: 2–6 g/24 hr ÷ Q6–8 hr IV/IM; **max. dose**: 12 g/24 hr

Bacterial endocarditis prophylaxis for dental and upper respiratory procedures:

Infant and child: 50 mg/kg IV/IM (**max. dose**: 1 g) 30 min before procedure

Adult: 1 g IV/IM 30 min before procedure

Use with caution in renal impairment or in penicillin-allergic patients. Does not penetrate well into cerebrospinal fluid (CSF). May cause phlebitis, leukopenia, thrombocytopenia, transient liver enzyme elevation, and false-positive urine-reducing substance (Clinitest) and Coombs test.

For dosing in obese patients, use higher end of the dosing recommendation. **Adjust dose in renal failure (see Chapter 31).**

CEFDINIR

Generics; previously available as Omnicef

Antibiotic, cephalosporin (third generation)

B	1	Yes	Yes	No

Caps: 300 mg

Oral suspension: 125 mg/5 mL (60, 100 mL), 250 mg/5 mL (60, 100 mL)

6 mo–12 yr:

Otitis media, sinusitis (not recommended as empiric monotherapy), pharyngitis/tonsillitis: 14 mg/kg/24 hr PO ÷ Q12–24 hr; **max. dose:** 600 mg/24 hr

Uncomplicated skin infections (see remarks): 14 mg/kg/24 hr PO ÷ Q12 hr; **max. dose:** 600 mg/24 hr

CEFDINIR *continued*

≥13 yr and adult:

Bronchitis, sinusitis, pharyngitis/tonsillitis: 600 mg/24 hr PO ÷ Q12–24 hr

Community-acquired pneumonia, uncomplicated skin infections (see remarks): 600 mg/24 hr PO ÷ Q12 hr

Use with caution in penicillin-allergic patients or in presence of renal impairment. Good gram-positive cocci activity but may be inadequate for penicillin-resistant pneumococci. May cause diarrhea (especially in children <2 yr), headache, vaginitis, and false-positive urine-reducing substance (Clinitest) and Coombs test. Eosinophilia and abnormal LFTs have been reported with higher than usual doses.

Once-daily dosing has not been evaluated in pneumonia and skin infections. Probenecid increases serum cefdinir levels. **Avoid** concomitant administration with iron and iron-containing vitamins and antacids containing aluminum or magnesium (space 2 hr apart) to reduce the risk for decreasing antibiotic's absorption. May cause red stools when administered with iron and iron-containing products. Doses may be taken without regard to food. **Adjust dose in renal failure (see Chapter 31).**

CEFEPIME
Maxipime and generics
Antibiotic, cephalosporin (fourth generation)

Injection: 1, 2 g
Premixed injection: 1 g/50 mL, 2 g/100 mL (iso-osmotic dextrose solutions)
Each 1 g drug contains 725 mg L-Arginine.

Neonate (IV/IM):

<14 days old: 60 mg/kg/24 hr ÷ Q12 hr

≥14 days old: 100 mg/kg/24 hr ÷ Q12 hr

Meningitis or Pseudomonas infections:

<1 kg and 0–14 days old, or 1–2 kg and <0–7 days old: 100 mg/kg/24 hr ÷ Q12 hr

<1 kg and >14 days old, or 1–2 kg and >7 days old, or >2 kg and 0–30 days old: 150 mg/kg/24 hr ÷ Q8 hr

Child ≥2 mo (IV/IM): 100 mg/kg/24 hr ÷ Q12 hr

Meningitis, fever, and neutropenia, or serious infections: 150 mg/kg/24 hr ÷ Q8 hr

Max. dose: 2 g/single dose or 6 g/24 hr

Cystic fibrosis: 150 mg/kg/24 hr ÷ Q8 hr IV/IM, up to a **max. dose** of 6 g/24 hr. Higher dose of 200 mg/kg/24 hr ÷ Q6 hr (**max. dose**: 8 g/24 hr) has been recommended for resistant pseudomonas isolates.

Adult: 1–4 g/24 hr ÷ Q12 hr IV/IM

Severe infections: 6 g/24 hr ÷ Q8 hr IV/IM

Max. dose: 6 g/24 hr

Use with caution in patients with penicillin allergy or renal impairment. Good activity against *Pseudomonas aeruginosa* and other gram-negative bacteria plus most gram-positives (methicillin-sensitive *Staphylococcus aureus*). Extended/continuous infusion administration is an option for treating resistant isolates.

May cause thrombophlebitis, GI discomfort, transient increases in liver enzymes, and false-positive urine-reducing substance (Clinitest) and Coombs test. Probenecid increases serum cefepime levels. Encephalopathy, myoclonus, seizures (including nonconvulsive status epilepticus), aphasia, transient leukopenia, neutropenia, agranulocytosis, and thrombocytopenia have been reported. **Adjust dose in renal failure (see Chapter 31).**

For explanation of icons, see p. 667

CEFIXIME
Suprax and generics
Antibiotic, cephalosporin (third generation)

Oral suspension: 100 mg/5 mL (50 mL), 200 mg/5 mL (50, 75 mL), 500 mg/5 mL (10, 20 mL)
Chewable tabs: 100, 200 mg; contains aspartame
Caps: 400 mg

Infant (>6 mo) and child: 8 mg/kg/24 hr ÷ Q12–24 hr PO; **max. dose:** 400 mg/24 hr. May be used in infants ≥3 mo old for community-acquired pneumonia.
Alternative dosing for acute UTI: 16 mg/kg/24 hr ÷ Q12 hr on day 1, followed by 8 mg/kg/24 hr Q24 hr PO × 13 days. **Max. dose**: 400 mg/24 hr
Adolescent and adult: 400 mg/24 hr ÷ Q12–24 hr PO
Uncomplicated cervical, urethral, or rectal infections due to Neisseria gonorrhoeae (not recommended as first-line cephalosporin by the CDC; ceftriaxone is preferred, use only when ceftriaxone is not available): 400 mg × 1 PO plus azithromycin 1 g PO × 1 OR doxycycline 100 mg PO BID × 7 days.

Use with caution in patients with penicillin allergy or renal failure. Adverse reactions include diarrhea (16% incidence reported in clinical trials), abdominal pain, nausea, and headaches. Transient increase in AST/ALT has been reported. Activity is inadequate against penicillin-resistant pneumococci.
Because of reduced bioavailability, do not use tablets for the treatment of otitis media. Probenecid increases serum cefixime levels. Unlike most cephalosporins, drug is excreted unchanged in the bile (5%–10%) and urine (50%). May increase carbamazepine serum concentrations. May cause false-positive urine-reducing substance (Clinitest), Coombs test, and nitroprusside test for ketones. **Adjust dose in renal failure (see Chapter 31).**

CEFOTAXIME
Generics; previously available as Claforan
Antibiotic, cephalosporin (third generation)

Injection: 0.5, 1, 2, 10 g
Contains 2.2 mEq Na/g drug

Neonate, IV/IM:
Postnatal age ≤7 days (all weights): 100 mg/kg/24 hr ÷ Q12 hr
Postnatal age 8–28 days:
<1000 g:
8–14 days postnatal: 100 mg/kg/24 hr ÷ Q12 hr
15–28 days postnatal: 150 mg/kg/24 hr ÷ Q8 hr
≥1000 g: 150 mg/kg/24 hr ÷ Q8 hr
Meningitis (minimum 21 days of therapy):
Postnatal age ≤7 days and ≥2 kg: 100–150 mg/kg/24 hr ÷ Q8–12 hr
Postnatal age >7 days and ≥2 kg: 150–200 mg/kg/24 hr ÷ Q6–8 hr.
Infant and child (1 mo–12 yr and <50 kg): 150–200 mg/kg/24 hr ÷ Q6–8 hr IV/IM. Higher doses of 150–225 mg/kg/24 hr ÷ Q6–8 hr have been recommended for infections outside the CSF due to penicillin-resistant pneumococci.
Meningitis: 200 mg/kg/24 hr ÷ Q6 hr IV/IM. Higher doses of 225–300 mg/kg/24 hr ÷ Q6–8 hr (some recommend 300 mg/kg/24 hr ÷ Q4–6 hr), in combination with vancomycin (dosed at CNS target levels), have been recommended for meningitis due to penicillin-resistant pneumococci.
Max. dose: 12 g/24 hr

CEFOTAXIME *continued*

Child (>12 yr or ≥50 kg) and adult: 1–2 g/dose Q6–8 hr IV/IM
Severe infection: 2 g/dose Q4–6 hr IV/IM
Max. dose: 12 g/24 hr

Use with caution in penicillin allergy and renal impairment (reduce dosage). Toxicities similar to other cephalosporins: allergy, neutropenia, thrombocytopenia, eosinophilia, false-positive urine-reducing substance (Clinitest) and Coombs test, elevated BUN, creatinine, and liver enzymes. Probenecid increases serum cefotaxime levels.
Good CNS penetration. **Adjust dose in renal failure (see Chapter 31).**

CEFOTETAN
Cefotan and generics
Antibiotic, cephalosporin (second generation)

Injection: 1, 2, 10 g
Frozen injection: 1 g/50 mL 3.8% dextrose, 2 g/50 mL 2.2% dextrose (iso-osmotic solutions)
Contains 3.5 mEq Na/g drug

Infant and child (IV/IM, limited data):
Mild/moderate infection: 60 mg/kg/24 hr ÷ Q12 hr; max. single dose: 2 g/dose
Severe infection: 100 mg/kg/24 hr ÷ Q12 hr; max. single dose: 2–3 g/dose
Intra-abdominal infection: 40–80 mg/kg/24 hr ÷ Q12 hr
Adolescent and adult: 2–4 g/24 hr ÷ Q12 hr IV/IM; **max. dose:** 6 g/24 hr
PID: 2 g Q12 hr IV × 24–48 hr after clinical improvement. Doxycycline 100 mg Q12 hr PO/IV × 14 days is also initiated at the same time.
Max. dose (all ages): 6 g/24 hr
Preoperative prophylaxis (30–60 min before procedure; may repeat dose in 6 hr if lengthy procedure or excessive blood loss):
Child: 40 mg/kg/dose (**max. dose:** 2 g/dose) IV
Adult: 1–2 g IV

Use with caution in penicillin-allergic patients or in presence of renal impairment. May cause disulfiram-like reaction with ethanol, increase effects/toxicities of anticoagulants, false-positive urine-reducing substance (Clinitest), and false elevations of serum and urine creatinine (Jaffe method). Hemolytic anemia and liver enzyme elevations have been reported. Good anaerobic activity but poor CSF penetration. **Adjust dose in renal failure (see Chapter 31).**

CEFOXITIN
Generics; previously available as Mefoxin
Antibiotic, cephalosporin (second generation)

Injection: 1, 2, 10 g
Frozen injection: 1 g/50 mL 4% dextrose, 2 g/50 mL 2.2% dextrose (iso-osmotic solutions)
Contains 2.3 mEq Na/g drug

Neonate (limited data): 90–100 mg/kg/24 hr ÷ Q8 hr IM/IV
Infant and child:
Mild/moderate infections: 80–100 mg/kg/24 hr ÷ Q6–8 hr IM/IV
Severe infections: 100–160 mg/kg/24 hr ÷ Q4–6 hr IM/IV

For explanation of icons, see p. 667

CEFOXITIN *continued*

Adult: 1–2 g/dose Q6–8 hr IM/IV

PID: 2 g IV Q6h × 24–48 hr after clinical improvement. Doxycycline 100 mg Q12 hr PO/IV × 14 days is also initiated at the same time.

Max. dose (all ages): 12 g/24 hr

Preoperative prophylaxis (30–60 min before procedure; may repeat dose in 2 hr for lengthy procedure or excessive blood loss):

Child: 40 mg/kg/dose (**max. dose:** 2 g/dose) IV

Adult: 2 g IV

Use with caution in penicillin-allergic patients or in presence of renal impairment. Has good anaerobic activity but poor CSF penetration. May cause injection site reaction and thrombophlebitis. Transient increases in LFTs have been reported.

Probenecid increases serum cefoxitin levels. May cause false-positive urine-reducing substance (Clinitest and other copper reduction method tests) and false elevations of serum and urine creatinine (Jaffe and KDA methods).

Adjust dose in renal failure (see Chapter 31).

CEFPODOXIME PROXETIL

Generics; previously available as Vantin

Antibiotic, cephalosporin (third generation)

Tabs: 100, 200 mg

Oral suspension: 50, 100 mg/5 mL (50, 100 mL)

2 mo–11 yr:

Otitis media: 10 mg/kg/24 hr PO ÷ Q12 hr × 5 days; **max. dose:** 400 mg/24 hr

Pharyngitis/tonsillitis: 10 mg/kg/24 hr PO ÷ Q12 hr × 5–10 days; **max. dose:** 200 mg/24 hr

Acute maxillary sinusitis: 10 mg/kg/24 hr PO ÷ Q12 hr × 10 days; **max. dose:** 400 mg/24 hr

≥12 yr–adult:

Exacerbation of chronic bronchitis, community-acquired pneumonia, and sinusitis: 400 mg/24 hr PO ÷ Q12 hr × 10 days (14 days for pneumonia)

Pharyngitis/tonsillitis: 200 mg/24 hr PO ÷ Q12 hr × 5–10 days

Skin/skin structure infection: 800 mg/24 hr PO ÷ Q12 hr × 7–14 days

Uncomplicated UTI: 200 mg/24 hr PO ÷ Q12 hr × 7 days

Use with caution in penicillin-allergic patients or in presence of renal impairment. May cause diarrhea, nausea, vomiting, vaginal candidiasis, and false-positive Coombs test. Transient elevation of ALT/SGPT has been reported in clinical trials.

Tablets should be administered with food to enhance absorption. Suspension may be administered without regard to food. High doses of antacids or H_2 blockers may reduce absorption. Probenecid increases serum cefpodoxime levels.

Cefpodoxime proxetil is a prodrug that is deesterified in the GI tract to the active cefpodoxime. **Adjust dose in renal failure (see Chapter 31).**

CEFPROZIL

Generics; previously available as Cefzil

Antibiotic, cephalosporin (second generation)

Tabs: 250, 500 mg

Oral suspension: 125 mg/5 mL, 250 mg/5 mL (50, 75, 100 mL); contains aspartame and

CEFPROZIL *continued*

Otitis media:
6 mo–12 yr: 30 mg/kg/24 hr PO ÷ Q12 hr; **max. dose:** 1 g/24 hr
Pharyngitis/tonsillitis:
2–12 yr: 15 mg/kg/24 hr PO ÷ Q12 hr; **max. dose:** 1 g/24 hr
≥13 yr: 500 mg PO Q24 hr
Acute sinusitis:
6 mo–12 yr: 15–30 mg/kg/24 hr PO ÷ Q12 hr; **max. dose:** 1 g/24 hr
>12 yr: 250 or 500 mg PO Q12 hr
Uncomplicated skin infections:
2–12 yr: 20 mg/kg/24 hr PO Q24 hr; **max. dose:** 500 mg/dose
>12 yr: 250 mg PO Q12 hr or 500 mg PO Q12–24 hr
UTI:
2–24 mo: 30 mg/kg/24 hr PO ÷ Q12 hr

Use with caution in penicillin-allergic patients or in presence of renal impairment. Oral suspension contains aspartame and phenylalanine and should not be used by phenylketonurics. May cause nausea, vomiting, diarrhea, liver enzyme elevations, and false-positive urine-reducing substance (Clinitest and other copper reduction method tests) and Coombs test. Probenecid increases serum cefprozil levels. Absorption is not affected by food. **Adjust dose in renal failure (see Chapter 31).**

CEFTAROLINE FOSAMIL
Teflaro
Antibiotic, cephalosporin (fifth generation)

Injection: 400, 600 mg; contains L-arginine

Child (2 mo–<18 yr):
Acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP):
2 mo–<2 yr: 8 mg/kg/dose IV Q8 hr
≥2 yr–<18 yr:
≤33 kg: 12 mg/kg/dose IV Q8 hr
>33 kg: 400 mg IV Q8 hr or 600 mg IV Q12 hr
Adult: 600 mg IV Q12 hr
Cystic fibrosis (limited data):
Child ≥6 yr and adolescent: 15 mg/kg/dose IV Q8 hr (**max. dose:** 600 mg/dose) infused over 2 hr in 7 patients (mean age: 20.3 ± 8.0) achieved the targeted serum concentration time greater than the MIC of 60%.
Adult: pharmacokinetic simulations in 8 patients revealed dosages of 600 mg IV Q8 hr infused over 1 hr or 600 mg IV Q12 hr infused over 3 hr would achieve the targeted serum concentration time greater than the MIC of 60%.

Use with caution in penicillin allergy and renal impairment. Common side effects from pediatric trials include diarrhea, rash, vomiting, pyrexia, and nausea. Leukopenia and liver enzyme elevations have been reported.
Probenecid increases serum ceftaroline levels. Direct Coombs test seroconversion has been reported with use.
Adjust dose in renal failure (see Chapter 31).

For explanation of icons, see p. 667

CEFTAZIDIME
Fortaz, Tazicef, and generics
Antibiotic, cephalosporin (third generation)

Injection: 0.5, 1, 2, 6 g
Frozen injection: 1 g/50 mL 4.4% dextrose, 2 g/50 mL 3.2% dextrose (iso-osmotic solutions)
Contains 2.3 mEq Na/g drug

Neonate (IV/IM):
Postnatal age ≤7 days: 50 mg/kg/dose Q12 hr
Postnatal age >7–28 days:
<1000 g:
Postnatal age 8–14 days: 50 mg/kg/dose Q12 hr
Postnatal age 15–28 days: 50 mg/kg/dose Q8–12 hr
1000–2000 g: 50 mg/kg/dose Q8–12 hr
>2000 g: 50 mg/kg/dose Q8 hr
Meningitis:
Postnatal age ≤7 days: 50 mg/kg/dose Q8–12 hr
Postnatal age >7 days: 50 mg/kg/dose Q8 hr
Infant (>1 mo) and child (IV/IM): 100–150 mg/kg/24 hr ÷ Q8 hr; **max. dose:** 6 g/24 hr
Cystic fibrosis and meningitis (IV/IM): 150–200 mg/kg/24 hr ÷ Q6–8 hr (**max. dose:** 6 g/24 hr). Higher dosage of 200–400 mg/kg/24 hr ÷ Q6–8 hr (**max. dose:** 12 g/24 hr) has been used for cystic fibrosis.
Adult (IV/IM): 1–2 g/dose Q8–12 hr; **max. dose:** 6 g/24 hr

Use with caution in penicillin-allergic patients or in presence of renal impairment. Good *Pseudomonas* coverage and CSF penetration. May cause rash, liver enzyme elevations, and false-positive urine-reducing substance (Clinitest and other copper reduction method tests) and Coombs test. Probenecid increases serum ceftazidime levels. **Adjust dose in renal failure (see Chapter 31).** Nonconvulsive status epilepticus, neuromuscular excitability, and myoclonia may occur with elevated levels of ceftazidime.

CEFTAZIDIME WITH AVIBACTAM
Avycaz
Antibiotic, cephalosporin
(third generation with β-lactamase inhibitor)

Injection: 2 g ceftazidime and 0.5 g avibactam
Contains 3.2 mEq Na/g ceftazidime

All doses based on ceftazidime component and are infused over 2 hr.
Complicated UTI (including pyelonephritis; treat for 7–14 days):
≥3 mo to <6 mo: 40 mg/kg/dose IV Q8 hr
≥6 mo, child, and adolescent: 50 mg/kg/dose (**max.** 2 g/dose) IV Q8 hr
Adult: 2 g IV Q8 hr
Complicated intra-abdominal infections: use same dosage for complicated UT in combination with metronidazole and treat for 5–14 days.
Nosocomial pneumonia (including VAP):
Adult: 2 g IV Q8 hr × 7–14 days

See ceftazidime for additional remarks. Avibactam is a novel β-lactamase inhibitor of serine β-lactamases to improve ceftazidime's susceptibility to Enterobacteriaceae.
Clinical trial safety profile in children and adults are similar, which include common side effects of vomiting, diarrhea, rash, and infusion site reactions.

CEFTAZIDIME WITH AVIBACTAM *continued*

eGFR (mL/min/1.73m²)	Dosage Based on Ceftazidime Component	Maximum Ceftazidime Dose
31–50	25 mg/kg/dose IV Q8 hr	1000 mg/dose
16–30	19 mg/kg/dose IV Q12 hr	750 mg/dose
6–15	19 mg/kg/dose IV Q24 hr	750 mg/dose
≤5	19 mg/kg/dose IV Q48 hr	750 mg/dose

If receiving hemodialysis (HD), administer doses after dialysis with a dosage schedule of 19 mg ceftazidime/kg/dose (**max. dose:** 750 mg) IV Q24 hr. Approximately 55% of drug is removed after a 4-hr dialysis session.

Australian Therapeutic Goods Administration reports animal reproductive toxicity without evidence of teratogenic effects with avibactam. Human studies of ceftazidime/avibactam are incomplete.

CEFTIBUTEN
Generics; previously available as Cedax
Antibiotic, cephalosporin (third generation)

Oral suspension: 90 mg/5 mL (60, 90, 120 mL); contains sodium benzoate
Caps: 400 mg

Child (>6 mo): 9 mg/kg/24 hr (**max. dose:** 400 mg/24 hr) PO once daily
≥***12 yr and adult:*** 400 mg PO once daily; **max. dose:** 400 mg/24 hr

Not recommended as a treatment option for otitis media or pharyngitis/tonsillitis. **Use with caution** in penicillin-allergic patients or in presence of renal impairment. May cause GI symptoms and elevations in eosinophils and BUN. SJS and elevated liver enzymes have been reported. Gastric acid–lowering medications (e.g., ranitidine and omeprazole) may enhance bioavailability of ceftibutin.

Oral suspension should be administered 2 hr before or 1 hr after a meal. **Adjust dose in renal failure (see Chapter 31).**

CEFTRIAXONE
Generics; previously available as Rocephin
Antibiotic, cephalosporin (third generation)

Injection: 0.25, 0.5, 1, 2, 10 g
Frozen injection: 1 g/50 mL 3.8% dextrose, 2 g/50 mL 2.4% dextrose (iso-osmotic solutions)
Contains 3.6 mEq Na/g drug

Neonate:
Gonococcal ophthalmia or prophylaxis: 25–50 mg/kg/dose IM/IV × 1; **max. dose:** 125 mg/dose

Infant (>1 mo) and child:
Mild/moderate infections: 50–75 mg/kg/24 hr ÷ Q12–24 hr IM/IV; **max. dose:** 2 g/24 hr
Severe infections/meningitis (including penicillin-resistant pneumococci): 100 mg/kg/24 hr IM/IV ÷ Q12 hr; **max. dose:** 2 g/dose and 4 g/24 hr
Penicillin-resistant pneumococci outside of the CSF: 80–100 mg/kg/24 hr ÷ Q12–24 hr (**max. dose:** 2 g/dose and 4 g/24 hr)
Lyme disease: 50–75 mg/kg/dose (**max. dose:** 2 g/dose) IV once daily

For explanation of icons, see p. 667

CEFTRIAXONE *continued*

Infant (>1 mo) and child (cont.):

Acute otitis media: 50 mg/kg IM/IV (**max. dose:** 1 g) × 1; for persistent or relapse cases use 50 mg/kg IM/IV (**max. dose:** 1 g) Q24 hr × 3 doses.

Adult: 1–2 g/dose Q12–24 hr IV/IM; **max. dose:** 2 g/dose and 4 g/24 hr

Uncomplicated gonorrhea or chancroid: 250 mg IM × 1

Bacterial endocarditis prophylaxis for dental and upper respiratory procedures:

Infant and child: 50 mg/kg IV/IM (**max. dose:** 1 g) 30 min before procedure

Adult: 1 g IV/IM 30 min before procedure

Contraindicated in neonates with hyperbilirubinemia. **Do not** administer with IV calcium-containing solutions or products (mixed or administered simultaneously via different lines) in neonates (<28 days old) because of risk of precipitation of ceftriaxone-calcium salt. Cases of fatal reactions with calcium-ceftriaxone precipitates in lung and kidneys in preterm and full-term neonates have been reported. **Do not** administer simultaneously with IV calcium-containing solutions via a Y-site for any age group. IV calcium-containing products may be administered sequentially only when the infusion lines are thoroughly flushed between infusions with a compatible fluid.

Use with caution in penicillin allergy; patients with gallbladder, biliary tract, liver, or pancreatic disease; presence of renal impairment; or in neonates with continuous dosing (risk for hyperbilirubinemia). In neonates, consider using an alternative third-generation cephalosporin with similar activity. Unlike other cephalosporins, ceftriaxone is significantly cleared by the biliary route (35%–45%).

Rash, injection site pain, diarrhea, and transient increase in liver enzymes are common. May cause reversible cholelithiasis, sludging in gallbladder, and jaundice. May interfere with serum and urine creatinine assays (Jaffe method) and cause false-positive urinary protein and urinary reducing substances (Clinitest).

For IM injections, dilute drug with either sterile water for injection or 1% lidocaine to a concentration of 250 or 350 mg/mL (250 mg/mL has lower incidence of injection site reactions). Assess the potential risk/benefit for using lidocaine as a diluent; see Lidocaine for additional remarks especially risk for methemoglobinemia.

CEFUROXIME (IV, IM)/CEFUROXIME AXETIL (PO)

IV: Generics; previously available as Zinacef
PO: Generics; previously available as Ceftin
Antibiotic, cephalosporin (second generation)

Injection: 0.75, 1.5, 7.5 g
Injectable dosage forms contain 2.4 mEq Na/g drug
Tabs: 250, 500 mg

IM/IV:

Neonate:

Postnatal age ≤7 days: 100 mg/kg/24 hr ÷ Q12 hr

Postnatal age >7 days:

<1 kg:

8 to ≤14 days old: 100 mg/kg/24 hr ÷ Q12 hr

≥15 days old: 150 mg/kg/24 hr ÷ Q8 hr

≥1 kg: 150 mg/kg/24 hr ÷ Q8 hr

Infant (>3 mo)/child:

Mild/moderate infection: 75–100 mg/kg/24 hr ÷ Q8 hr; **max. dose:** 1500 mg/dose

Severe infection: 100–200 mg/kg/24 hr ÷ Q6–8 hr; **max. dose:** 1500 mg/dose

Adult: 750–1500 mg/dose Q8 hr; **max. dose:** 9 g/24 hr

PO (see remarks):

CEFUROXIME (IV, IM)/CEFUROXIME AXETIL (PO) *continued*

Pharyngitis and tonsillitis (oral suspension): 20 mg/kg/24 hr ÷ Q12 hr; **max. dose:** 500 mg/24 hr
Impetigo (oral suspension): 30 mg/kg/24 hr ÷ Q12 hr; **max. dose:** 1 g/24 hr
Otitis media and sinusitis:
Oral suspension: 30 mg/kg/24 hr ÷ Q12 hr; **max. dose:** 1 g/24 hr
Oral tablet: 250 mg BID
Lyme disease (alternative to doxycycline or amoxicillin):
Oral suspension: 30 mg/kg/24 hr (**max. dose:** 1 g/24 hr) ÷ Q12 hr × 14–28 days.
Child (≥13 yr):
Sinusitis, otitis media, pharyngitis, and tonsillitis:
Tab: 250 mg Q12 hr
Adult: 250–500 mg BID; **max. dose:** 1 g/24 hr

Use with caution in penicillin-allergic patients or in presence of renal impairment. May cause GI discomfort; thrombophlebitis at the infusion site; false-positive urine-reducing substance (Clinitest and other copper reduction method tests) and Coombs test; and may interfere with serum and urine creatinine determinations by the alkaline picrate method. Transient increases in liver enzymes have been reported. Not recommended for meningitis.

Oral suspension dosage form currently not available. Tablets and oral suspension are NOT bioequivalent and CANNOT be substituted on a mg/mg basis. Concurrent use of antacids, H_2 blockers, and proton pump inhibitors may decrease oral absorption. **Adjust dose in renal failure (see Chapter 31).**

CELECOXIB
Celebrex and generics
Nonsteroidal antiinflammatory agent (COX-2 selective)

Capsules: 50, 100, 200, 400 mg

Juvenile rheumatoid arthritis (JRA; ≥2 yr and adolescent; see remarks):
10–25 kg: 50 mg PO BID
>25 kg: 100 mg PO BID
Adult (see remarks): 100–200 mg PO BID

Contraindicated for perioperative pain with coronary artery bypass graft (CABG) surgery. **Use with caution** in patients with systemic-onset JRA due to risk for serious adverse reactions (e.g., disseminated intravascular coagulation). In adults, serious cardiovascular and GI risks reported include thrombosis, myocardial infarction (MI), stroke, GI bleed, GI ulceration, and GI perforation. Common adverse effects include headache, diarrhea, nausea, and hypertension. TEN, SJS, acute kidney injury, and hyperkalemia have also been reported.

Celecoxib is a substrate of CYP 450 2C9. Poor metabolizers of 2C9 should start with half the lowest recommended dose and use with caution, or consider alternative therapy. Angiotensin-converting enzyme (ACE) inhibitors, loop diuretics, and sodium phosphates may increase risk for renal dysfunction. Oral corticosteroids, antiplatelet drugs (e.g., aspirin), anticoagulants, SSRIs, smoking, alcohol use, older age, and poor health status may increase risk for GI bleeds with prolonged treatment courses. Celecoxib may reduce the antihypertensive effects of ACE inhibitors and increase the levels/toxicity of lithium, metoprolol, and methotrexate.

Not recommended for use in severe renal dysfunction and severe hepatic impairment (Child-Pugh Class C). Reduce dose by 50% and monitor patient closely in moderate hepatic impairment (Child-Pugh Class B).

Pregnancy category is "C" for prior to 30 wk's gestation and "D" for 30 wk and greater.

If unable to swallow capsules whole, contents of the capsule may be added to applesauce (stable for

For explanation of icons, see p. 667

CEPHALEXIN
Keflex and generics
Antibiotic, cephalosporin (first generation)

Caps: 250, 500, 750 mg
Tabs: 250, 500 mg
Oral suspension: 125 mg/5 mL, 250 mg/5 mL (100, 200 mL)

Infant and child:
Mild/moderate infection: 25–50 mg/kg/24 hr PO ÷ Q6 hr; **max. dose:** 2 g/24 hr. Less frequent dosing (Q8–12 hr) may be used for uncomplicated infections.
Severe infection: 75–100 mg/kg/24 hr PO ÷ Q6 hr; **max. dose:** 4 g/24 hr
Streptococcal pharyngitis and skin infections: 25–50 mg/kg/24 hr PO ÷ Q6–12 hr. Total daily dose may be divided Q12 hr for streptococcal pharyngitis (>1 yr).
UTI: 50–100 mg/kg/24 hr PO ÷ Q6 hr
Adult: 1–4 g/24 hr PO ÷ Q6 hr
Max. dose (all ages): 4 g/24 hr
Bacterial endocarditis prophylaxis for dental and upper respiratory procedures:
Infant and child: 50 mg/kg PO (**max. dose:** 2 g) 1 hr before procedure
Adult: 2 g PO 1 hr before procedure

Some cross-reactivity with penicillins. **Use with caution** in renal insufficiency. May cause GI discomfort, false-positive urine-reducing substance (Clinitest and other copper reduction method tests) and Coombs test; false elevation of serum theophylline levels (HPLC method); and false urinary protein test. Hemolytic anemia and slight increases in AST and ALT have been reported.
Probenecid increases serum cephalexin levels, and concomitant administration with cholestyramine may reduce cephalexin absorption. May increase the effects of metformin.
Administer doses on an empty stomach; 2 hr prior or 1 hr after meals. **Adjust dose in renal failure (see Chapter 31).**

CETIRIZINE ± PSEUDOEPHEDRINE
Zyrtec, Zyrtec Allergy, Zyrtec Children's Allergy, Zerviate, and generics
In combination with pseudoephedrine:
Zyrtec-D 12 hr and generics
Antihistamine, less-sedating

Oral solution or syrup (OTC): 5 mg/5 mL (120, 473 mL); contains parabens
Tabs (OTC): 5, 10 mg
Capsule (Liquid filled; OTC): 10 mg
Dispersible/disintegrating tabs (OTC): 10 mg
Ophthalmic solution (Zerviate): 2.4 mg/1 mL (0.2 mL; 5 single use vials per box)
In combination with pseudoephedrine (PE):
Extended-release tabs (OTC): 5 mg cetirizine + 120 mg PE

Cetirizine (see remarks for dosing in hepatic impairment):
6 mo and <2 yr: 2.5 mg PO once daily; dose may be increased for children 12–23 mo to a **max. dose** of 2.5 mg PO Q12 hr.
2–5 yr: Initial dose: 2.5 mg PO once daily; if needed, may increase dose to a **max. dose** of 5 mg/24 hr once daily or divided BID.

CETIRIZINE ± PSEUDOEPHEDRINE *continued*

≥6 yr–adult: 5–10 mg PO once daily

Ophthalmic use:

≥2 yr and adult: Instill 1 drop to affected eye(s) BID (approximately 8 hr apart)

Cetirizine in combination with pseudoephedrine (PE) (see remarks for dosing in hepatic impairment):

≥12 yr and adult:

Zyrtec-D 12 hr: 1 tablet PO BID

Generally not recommended for treating URIs for infants. No proven benefit for infants and young children with URIs. The FDA does not recommend use for URIs in children <2 yr because of reports of increased fatalities.

May cause headache, pharyngitis, GI symptoms, dry mouth, and sedation. Aggressive reactions and convulsions have been reported. Has NOT been implicated in causing cardiac arrhythmias when used with other drugs that are metabolized by hepatic microsomal enzymes (e.g., ketoconazole, erythromycin).

In hepatic impairment, the following doses have been recommended:

Cetirizine:

<6 yr: Use not recommended

6–11 yr: <2.5 mg PO once daily

≥12 yr–adult: 5 mg PO once daily

Cetirizine in combination with pseudoephedrine:

≥12 yr–adult: 1 tablet PO once daily

Doses may be administered regardless to food. For Zyrtec-D 12 Hr, see Pseudoephedrine for additional remarks. Pregnancy category is "B" for cetirizine and "C" when combined with pseudoephedrine.

Dosage adjustment is recommended in renal impairment (see Chapter 31).

OPHTHALMIC USE: Common side effects include application site pain, ocular hyperemia, and reduced visual acuity. Oculogyric crisis has been reported. Do not touch dropper tip to anything, and remove contact lenses prior to administration (wait 10 min before inserting lenses).

CHARCOAL, ACTIVATED

See Chapter 3

CHLORAMPHENICOL

Generics

Antibiotic

Injection: 1 g

Contains 2.25 mEq Na/g dru

Neonate IV:

Loading dose: 20 mg/kg

Maintenance dose (first dose should be given 12 hr after loading dose):

≤7 days: 25 mg/kg/24 hr Q24 hr

>7 days:

≤2 kg: 25 mg/kg/24 hr Q24 hr

>2 kg: 50 mg/kg/24 hr ÷ Q12 hr

Infant/child/adult: 50–75 mg/kg/24 hr IV ÷ Q6 hr

Meningitis: 75–100 mg/kg/24 hr IV ÷ Q6 hr

For explanation of icons, see p. 667

CHLORAMPHENICOL *continued*

Max. dose (all ages): 4 g/24 hr

Dose recommendations are just guidelines for therapy; monitoring of blood levels is essential. Follow hematologic status for dose-related or idiosyncratic marrow suppression. "Gray baby" syndrome may be seen with levels >50 mg/L. **Use with caution** in G6PD deficiency, renal or hepatic dysfunction, and neonates.

Concomitant use of phenobarbital and rifampin may lower chloramphenicol serum levels. Phenytoin may increase chloramphenicol serum levels. Chloramphenicol may increase the effects/toxicity of phenytoin, chlorpropamide, cyclosporine, tacrolimus, and oral anticoagulants and decrease absorption of vitamin B_{12}. Chloramphenicol is an inhibitor of CYP 450 2C9.

Therapeutic levels: Peak: 15–25 mg/L for meningitis and 10–20 mg/L for other infections. Trough: 5–15 mg/L for meningitis and 5–10 mg/L for other infections. Recommended serum sampling time: trough within 30 min prior to next dose; peak 30 min after the end of infusion. Time to achieve steady state: 2–3 days for newborns; 12–24 hr for children and adults.

CHLOROQUINE PHOSPHATE

Generics; previously available as Aralen

Amebicide, antimalarial

Tabs: 250, 500 mg as phosphate (150, 300 mg base, respectively)

Oral suspension: 16.67 mg/mL as phosphate (10 mg/mL base), 15 mg/mL as phosphate (9 mg/mL base)

Doses expressed in mg of chloroquine base:

Malaria prophylaxis (start 1–2 wk prior to exposure and continue for 4 wk after leaving endemic area):

Infant and child: 5 mg/kg/dose PO every week; **max. dose**: 300 mg/dose

Adult: 300 mg/dose PO every week

Malaria treatment (chloroquine sensitive strains):

For treatment for malaria, consult with ID specialist or see the latest edition of the AAP Red Book.

Infant and child: 10 mg/kg/dose (**max. dose**: 600 mg/dose) PO × 1; followed by 5 mg/kg/dose (**max. dose**: 300 mg/dose) 6, 24, and 48 hr after the initial dose.

Adult: 600 mg/dose PO × 1; followed by 300 mg/dose 6, 24, and 48 hr after the initial dose.

Contraindicated in the presence of retinal or visual field changes and known hypersensitivity to 4-aminoquinoline compounds. **Use with caution** in liver disease, preexisting auditory damage or seizures, G6PD deficiency, psoriasis, porphyria, or concomitant hepatotoxic drugs. May cause nausea, vomiting, electrocardiogram (ECG) abnormalities, prolonged QT interval, blurred vision, retinal and corneal changes (reversible corneal opacities), headaches, confusion, skeletal muscle weakness, increased liver enzymes, and hair depigmentation. SJS, TEN, anaphylactic reactions, and maculopathy and macular degeneration have been reported. False-positive test for urine amphetamine screen may occur.

Antacids, ampicillin, and kaolin may decrease the absorption of chloroquine (allow 4-hr interval between these drugs and chloroquine). Cimetidine may increase effects/toxicity of chloroquine. May increase serum cyclosporine levels. Coadministration with mefloquine may increase risk of convulsions. May reduce the antibody response to intradermal human diploid-cell rabies vaccine.

Monitor CBCs periodically with therapies of prolonged duration. **Adjust dose in renal failure (see Chapter 31).**

CHLOROTHIAZIDE
Diuril and generics
Thiazide diuretic

Tabs: 250, 500 mg
Oral suspension: 250 mg/5 mL (237 mL); contains 0.5% alcohol, 0.12% methylparaben, 0.02% propylparaben, and 0.1% benzoic acid
Injection: 500 mg; contains 5 mEq Na/1 g drug

<6 mo:
PO: 20–40 mg/kg/24 hr ÷ Q12 hr
IV: Start at 5–10 mg/kg/24 hr ÷ Q12 hr, may increase to 20–40 mg/kg/24 hr ÷ Q12 hr if needed.
≥6 mo:
PO: 10–40 mg/kg/24 hr ÷ Q12 hr; **maximum PO** dose by age:
6 mo–2 yr: 375 mg/24 hr
2–12 yr: 1 g/24 hr
>12 yr: 2 g/24 hr
IV: Start at 5–10 mg/kg/24 hr ÷ Q12–24 hr, may increase to 20 mg/kg/24 hr ÷ Q12 hr if needed.
Adult: 500–2000 mg/24 hr ÷ Q12–24 hr PO/IV; alternative IV dosing, some may respond to intermittent dosing on alternate days or on 3–5 days each week.
Adjunct therapy for neonatal hyperinsulinemia/hypoglycemia (limited data): 7–10 mg/kg/24 hr ÷ BID PO with diazoxide PO

Contraindicated in anruia. **Use with caution** in liver and severe renal disease and sulfonamide hypersensitivity. May increase serum calcium, bilirubin, glucose, and uric acid. May cause alkalosis, pancreatitis, dizziness, hypokalemia, and hypomagnesemia.
Avoid IM or subcutaneous administration.
Pregnancy category changes to "D" if used in pregnancy-induced hypertension.

CHLORPHENIRAMINE MALEATE
Chlor-Trimeton and generics
Antihistamine

Tabs [OTC]: 4 mg
Sustained-release tabs [OTC]: 12 mg
Syrup [OTC]: 2 mg/5 mL (120, 473 mL); may contain 5% alcohol and/or parabens

Doses may be administered as scheduled or PRN (see remarks).
Child <12 yr: 0.35 mg/kg/24 hr PO ÷ Q4–6 hr or dose based on age as follows:
2–5 yr: 1 mg/dose PO Q4–6 hr; **max. dose**: 6 mg/24 hr
6–11 yr: 2 mg/dose PO Q4–6 hr; **max. dose** 12 mg/24 hr
≥12 yr–adult: 4 mg/dose Q4–6 hr PO; **max. dose:** 24 mg/24 hr
Sustained release: 12 mg PO Q 12 hr

Use with caution in asthma. May cause sedation, dry mouth, blurred vision, urinary retention, polyuria, and disturbed coordination. Young children may be paradoxically excited.
Found in many combinations over-the-counter (OTC, or nonprescription) cough and cold products and are **not recommended** for children <6 yr old due to reports of serious adverse effects (cardiac and respiratory distress, convulsions, and hallucinations) and fatalities (from unintentional overdosages, including combined use of other OTC products containing the same active ingredients).
Administer doses with food. Sustained-release forms are **NOT** recommended in children <6 yr and should **NOT** be crushed, chewed, or dissolved.

For explanation of icons, see p. 667

CHLORPROMAZINE
Generics; previously available as Thorazine
Antiemetic, antipsychotic, phenothiazine derivative

Tabs: 10, 25, 50, 100, 200 mg
Oral suspension: 30 mg/mL
Injection: 25 mg/mL (1, 2 mL); may contain sodium metabisulfite and sodium sulfite.

Psychosis:
Child >6 mo:
PO: 2.5–6 mg/kg/24 hr ÷ Q4–6 hr; **max. PO dose:** 500 mg/24 hr
IM/IV: 2.5–4 mg/kg/24 hr ÷ Q6–8 hr
Max. IM/IV dose:
<5 yr: 40 mg/24 hr
5–12 yr: 75 mg/24 hr
Adult:
PO: 10–25 mg/dose Q4–6 hr; **max. dose:** 2 g/24 hr
IM/IV: Initial: 25 mg; repeat with 25–50 mg/dose, if needed, Q1–4 hr up to a **max. dose** of 400 mg/dose Q4–6 hr

Antiemetic:
Child (≥6 mo):
IV/IM/PO: 0.5–1 mg/kg/dose Q6–8 hr PRN
Max. IM/IV/PO dose:
<5 yr: 40 mg/24 hr
5–12 yr: 75 mg/24 hr
Adult:
IV/IM: 25–50 mg/dose Q4–6 hr PRN
PO: 10–25 mg/dose Q4–6 hr PRN

Adverse effects include drowsiness, jaundice, lowered seizure threshold, extrapyramidal/anticholinergic symptoms, hypotension (more with IV), arrhythmias, agranulocytosis, and neuroleptic malignant syndrome. May potentiate effect of narcotics, sedatives, and other drugs. Monitor BP closely. ECG changes include prolonged PR interval, flattened T waves, and ST depression; **do not use** in combination with fluoxetine, haloperidol, citalopram, and other drugs that can prolong the QT interval. **Do not administer oral liquid dosage form simultaneously with carbamazepine oral suspension;** an orange rubbery precipitate may form.

CHOLECALCIFEROL
D–3, D3–5, D3–50, Decara, D Drops, Emfamil D-Vi-Sol, Replesta, and many others
Vitamin D3

Tablet (OTC): 400; 1000; 2000; 3000; 5000; 50,000 IU
Caps (OTC): 1000; 2000; 5000; 10,000; 25,000; 50,000 IU
D3-5: 5000 IU
Decara: 25,000; 50,000 IU
D3-50: 50,000 IU
Chewable tablet (OTC): 400; 1000; 2000; 5000 IU
Chewable wafer (Replesta; OTC): 50000 IU (8)

CHOLECALCIFEROL *continued*

Oral drops (D Drops and others) [OTC]: 400 IU/drop (2.5, 10.3 mL), 600 IU/drop (2.8 mL), 1000 IU/drop (5, 10.3 mL), 2000 IU/drop (5, 10.3 mL), 4000 IU/drop (10.3 mL), 6000 IU/drop (10.3 mL)
Oral liquid: (Emfamil D-Vi-Sol and generics) [OTC]: 400 IU/mL (50 mL)
Conversion: 1000 IU is equivalent to 25 mCg of cholecalciferol

Dietary supplementation (see Chapter 21 for additional information):
Preterm: 200–400 IU/24 hr PO
Infant (<1 yr): 400 IU/24 hr PO
Breastfed neonate and infant: 400 IU/24 hr PO
Child (≥1 yr) and adolescent: 400–600 IU/24 hr PO

Vitamin D deficiency:
Non–cystic fibrosis patients:

	Vitamin D (25-OH) Level		
Age	**>20–<30 ng/mL (Insufficiency)**	**10–20 ng/mL (Deficiency)**	**<10 ng/mL (Severe Deficiency)**
<6 mo	1000 IU once daily	1000 IU once daily	Contact Pediatric Endocrinologist and assess for rickets
>6–<12 mo	400–1000 IU once daily	2000 IU once daily	50,000 IU once daily × 3 days followed by 2000 IU once daily[a]
1–2 yr	600–1000 IU once daily	2000 IU once daily	50,000 IU once daily × 3 days followed by 2000 IU once daily[a]
>2 yr with no risk factors[b]	1000–2000 IU once daily	5000 IU once daily	50,000 IU once daily × 3 days followed by 5000 IU once daily[a]
>2 yr with any risk factor[b]	2000–4000 IU once daily	10,000 IU once daily	50,000 IU once daily × 3 days followed by 10,000 IU once daily[a]

[a]50,000 IU daily loading dose may be avoided for patients with hyperphosphatemia.
[b]Risk factors include malabsorption syndromes, obesity (BMI ≥95th percentile), chronic use of antiepileptics, glucocorticoids, antifungals (systemic), or antiretrovirals.

Cystic fibrosis patients (supplementation in addition to cystic fibrosis specialty multivitamin unless indicated):

	Vitamin D (25-OH) Level			
Age	**≥30 ng/mL (Sufficiency)**	**21–29 ng/mL (Insufficiency)**	**≤20 ng/mL (Deficiency)**	**<10 ng/mL (Severe Deficiency)**
<12 mo	CF multivitamin only (to provide 600 IU once daily)	2000 IU once daily	5000 IU once daily	5000 IU once daily[a]
≥1–<10 yr	CF multivitamin (to provide 1200 IU once daily) plus 2000 IU once daily	6000 IU once daily	10,000 IU once daily	50,000 IU once daily × 1 mo followed by 10,000 IU once daily
≥10 yr	CF multivitamin only (to provide 6000 IU once daily)	10,000 IU once daily	50,000 IU once daily × 1 mo followed by 10,000 IU once daily	50,000 IU once daily × 1 mo followed by 10,000 IU once daily

[a]Assess for rickets.

For explanation of icons, see p. 667

CHOLECALCIFEROL *continued*

Rickets (with calcium supplementation; decrease to maintenance dosage when radiologically proven healing is achieved):

Infant: 2000 IU PO once daily × ≥3 mo, followed by 400 IU once daily maintenance

Child: 3000–6000 IU PO once daily × ≥3 mo, followed by 600 IU once daily maintenance

Adolescent: 6000 IU PO once daily × ≥3 mo, followed by 400 IU once daily maintenance.

Renal failure (CKD stages 2–5) and 25-OH vitamin D levels ≤30 ng/mL (monitor serum 25-OH vitamin D and corrected calcium/phosphorus 1 mo after initiation and Q 3 mo thereafter):

Child (PO):

25-OH vitamin D <5 ng/mL: 8000 IU/24 hr × 4 wk followed by 4000 IU/24 hr × 2 mo; OR 50,000 IU weekly × 4 wk followed by 50,000 IU twice monthly for 3 mo

25-OH vitamin D 5–15 ng/mL: 4000 IU/24 hr × 12 wk; OR 50,000 IU every other week × 12 wk

25-OH vitamin D 16–30 ng/mL: 2000 IU/24 hr × 3 mo; OR 50,000 IU monthly × 3 mo

Maintenance dose (after repletion): 200–1000 IU once daily

Biologic potency and oral absorption may be greater than ergocalciferol (vitamin D_2). Requires activation by the liver (25-hydroxylation) and kidney (1-hydroxylation) to the active form, calcitriol. Recommended time period to recheck serum 25-OH vitamin D is 3 mo after initiation or change in dosage.

Monitor serum Ca^{2+}, PO_4, 25-OH vitamin D (goal level for infant and child: ≥20 ng/mL) and alkaline phosphate. Serum Ca^{2+}, PO_4 product should be <70 mg/dL to avoid ectopic calcification. Serum 25-OH vitamin D level of ≥35 ng/mL has been used in cystic fibrosis patients to decrease the risk of hyperparathyroidism and bone loss.

Serum 25-OH vitamin D levels ≥100 ng/mL is considered toxic. Toxic effects in infants may result in nausea, vomiting, constipation, abdominal pain, loss of appetite, polydipsia, polyuria, muscle weakness, muscle/joint pain, confusion, and fatigue; renal damage may also occur.

Pregnancy category changes to "D" if used in doses above the U.S. RDA.

CHOLESTYRAMINE

Questran, Questran Light, Cholestyramine Light, Prevalite, and generics

Antilipemic, binding resin

Powder for oral suspension:

Questran and generics: 4 g anhydrous resin per 9 g powder (9 g—box of 60 packets, 378 g can)

Questran Light: 4 g anhydrous resin per 5 g powder (5 g—box of 60 packets, 210 g can)

Cholestyramine Light: 4 g anhydrous resin per 5.7 g powder with aspartame (5.7 g—box of 60 packets, 239 g can)

Prevalite: 4 g anhydrous resin per 5.5 g powder with aspartame (5.5 g—box of 42 or 60 packets, 231 g can)

All doses based in terms of anhydrous resin. Titrate dose based on response and tolerance.

Hypercholesterolemia:

Child and adolescent: 240 mg/kg/24 hr ÷ TID PO; doses normally do not exceed 8 g/24 hr (higher doses do not provide additional benefit). Give PO as slurry in water, juice, or milk before meals.

Adult: 4 g once daily–BID PO; **max. dose**: 24 g/24 hr

Pruritis associated with cholestasis:

Child: 240 mg/kg/24 hr ÷ BID–TID PO; suggested **max. dose:**

≤10 yr: 4–10 g/24 hr; higher doses may cause steatorrhea

>10 yr and adolescent: 16 g/24 hr

Adult: 4 g once daily or BID PO; may gradually increase dose to 16 g/24 hr.

CHOLESTYRAMINE *continued*

In addition to the use for managing hypercholesterolemia, drug may be used for itching associated with elevated bile acids, and diarrheal disorders associated with excess fecal bile acids or *Clostridium difficile* (pseudomembranous colitis). May also be applied topically for diaper dermatitis by preparing a 5% or 10% topical product with hydrophilic topical ointment (Aquaphor); other compounded topical formulations exist (e.g., Butt paste: Cholestyramine, sucralfate, zinc oxide, and Eucerin).

May cause constipation, abdominal distention, vomiting, vitamin deficiencies (A, D, E, K), and rash. Hyperchloremic acidosis may occur with prolonged use.

Give other oral medications 4–6 hr after cholestyramine or 1 hr before dose to avoid decreased absorption.

CHOLINE MAGNESIUM TRISALICYLATE
Generic; previously available as Trilisate
Nonsteroidal antiinflammatory agent

Combination of choline salicylate and magnesium salicylate (1:1.24 ratio, respectively); strengths expressed in terms of mg salicylate:
Oral liquid: 500 mg/5 mL (240 mL); may contain methylparaben

Dose based on total salicylate content.
Child: 30–60 mg/kg/24 hr PO ÷ BID–TID
Adult: 500 mg–1.5 g/dose PO once daily–TID

Avoid use in patients with suspected varicella or influenza due to concerns of Reye syndrome. **Use with caution** in severe hepatic or renal (hypermagnesemia risk) failure, asthma, or peptic ulcer disease. Less GI irritation than aspirin and other NSAIDs. No antiplatelet effects.

Pregnancy category changes to "D" if used during the third trimester.

Therapeutic salicylate levels, see *Aspirin*. 500 mg choline magnesium trisalicylate is equivalent to 650 mg aspirin. May be mixed with fruit juices just before ingestion. Do not administer with antacids.

CICLESONIDE
Alvesco, Omnaris, Zetonna
Corticosteroid

Aerosol inhaler (Alvesco): 80 mCg/actuation (6.1 g = 60 doses), 160 mCg/actuation (6.1 g = 60 doses)
Nasal spray:
Omnaris (nasal suspension): 50 mCg/actuation (12.5 g = 120 doses)
Zetonna (nasal aerosol solution): 37 mCg/actuation (6.1 g = 60 doses)

Intranasal (allergic rhinitis):
Omnaris:
2–11 yr (limited data): 1 or 2 sprays (50 or 100 mCg) per nostril once daily. **Max. dose**: 200 mCg/24 hr. 2 sprays (100 mCg) per nostril once daily is FDA approved for use in children ≥6 yr for seasonal allergic rhinitis.
≥***12 yr and adult:*** 2 sprays (100 mCg) per nostril once daily. **Max. dose**: 200 mCg/24 hr.
Zetonna:
≥***12 yr and adult:*** 1 spray (37 mCg) per nostril once daily. **Max. dose**: 74 mCg/24 hr.

Continued

For explanation of icons, see p. 667

CICLESONIDE *continued*

Oral inhalation (asthma; Alvesco):

Dosage recommended by the Global Initiative for Asthma (GINA) guidelines (current FDA labeled dosage information is for ≥12 yr and is listed below). All daily doses divided BID:

Age	Low Dose (mCg/24 hr)	Medium Dose (mCg/24 hr)	High Dose (mCg/24 hr)
6–11 yr	80	>80–160	>160 up to 640 mCg/24 hr
≥12 yr and adult	80–160	>160–320	>320 up to 640 mCg/24 hr

≥12 yr and adult (FDA labeling):

Prior use with bronchodilator only: 80 mCg/dose BID; **max. dose:** 320 mCg/24 hr

Prior use with inhaled corticosteroid: 80 mCg/dose BID; **max. dose:** 640 mCg/24 hr

Prior use with oral corticosteroid: 320 mCg/dose BID; **max. dose:** 640 mCg/24 hr

Ciclesonide is a prodrug hydrolyzed to an active metabolite, des-ciclesonide via esterases in nasal mucosa and lungs; further metabolism via hepatic CYP3A4 and 2D6. Concurrent use with ketoconazole and other CYP 450 3A4 inhibitors may increase systemic des-ciclesonide levels. **Use with caution** and monitor in hepatic impairment.

Oral inhalation (asthma): Rinse mouth after each use. May cause headache, arthralgia, nasal congestion, nasopharyngitis, and URIs. Routinely monitor growth of pediatric patients. Maximum therapeutic benefit may not be achieved until 4 wk after initiation; consider dose increase if response is inadequate after 4 wk after initial dosage.

Intranasal (allergic rhinitis): Clear nasal passages prior to use. May cause otalgia, epistaxis, nasopharyngitis, and headache. Nasal septal perforation has been reported. Patients should be free of nasal disease, except for allergic rhinitis, before starting therapy. Monitor linear growth of pediatric patients routinely. Onset of action: 24–48 hr; further improvement observed over 1–2 wk in seasonal allergic rhinitis or 5 wk in perennial allergic rhinitis. Discontinue use if nasal erosion, ulceration, or perforation occurs.

CIDOFOVIR

Generics; previously available as Vistide

Antiviral

Injection: 75 mg/mL (5 mL); preservative free

Safety and efficacy have not been established in children.

CMV retinitis:

Adolescent and adult:

Induction: 5 mg/kg IV once weekly × 2 with probenecid and hydration

Maintenance: 5 mg/kg IV Q2 weeks with probenecid and hydration

Adenovirus infection in immunocompromised oncology patients (limited data and other regimens exist; see remarks):

Child:

Induction: 5 mg/kg/dose IV once weekly until PCR negative. Administer oral probenecid 1–1.25 g/m^2/dose (rounded to the nearest 250-mg interval) 3 hr before and 1 hr and 8 hr after each dose of cidofovir. Also give IV NS via IV at maintenance fluid concentration, 3 times, 1 hr before and 1 hr after cidofovir, followed by 2 times maintenance fluid for an additional 2 hr. For patients with renal dysfunction (see remarks), give 1 mg/kg/dose IV three times weekly until PCR negative.

Maintenance: 5 mg/kg/dose IV Q2 weeks with probenecid and hydration.

CIDOFOVIR *continued*

BK virus hemorrhagic cystitis (limited data and other regimens exist): 1 mg/kg/dose IV once weekly WITHOUT probenecid.

Contraindicated in hypersensitivity to probenecid or sulfa-containing drugs; sCr >1.5 mg/dL, CrCl ≤55 mL/min, urine protein ≥100 mg/dL (2+ proteinuria), direct intraocular injection of cidofovir, and concomitant nephrotoxic drugs. **Renal impairment is the major dose-limiting toxicity.** IV NS prehydration and probenecid must be used (unless not indicated) to reduce risk of nephrotoxicity. May also cause nausea, vomiting, headache, rash, metabolic acidosis, uveitis, decreased intraocular pressure, and neutropenia.

Reported criteria for defining renal dysfunction in children include a sCr >1.5 mg/dL, GFR <90 mL/min/1.73 m^2, and >2+ proteinuria. For adults, reduce dose to 3 mg/kg if sCr increases 0.3–0.4 mg/dL from baseline. Discontinue therapy if sCr increases ≥0.5 mg/dL from baseline or development of ≥3+ proteinuria.

Administer doses via IV infusion over 1 hr at a concentration ≤8 mg/mL.

CIMETIDINE
Tagamet HB and generics
Histamine-2 antagonist

Tabs: 200, 300, 400, 800 mg
OTC (Tagamet HB and generics): 200 mg
Oral solution: 300 mg/5 mL (237 mL); may contain 2.8% alcohol, propylene glycol, and parabens

Neonate: 5–20 mg/kg/24 hr PO ÷ Q6–12 hr
Infant: 10–20 mg/kg/24 hr PO ÷ Q6–12 hr
Child: 20–40 mg/kg/24 hr PO ÷ Q6 hr
Adult: 300 mg/dose PO QID OR 400 mg/dose PO BID OR 800 mg/dose PO QHS
Ulcer prophylaxis: 400–800 mg PO QHS

Diarrhea, rash, myalgia, confusion, neutropenia, gynecomastia, elevated LFTs, or dizziness may occur. **Use with caution** in hepatic and renal impairment **(adjust dose in renal failure; see Chapter 31).**

Inhibits CYP 450 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 isoenzymes, therefore increases levels and effects of many hepatically metabolized drugs (i.e., theophylline, phenytoin, lidocaine, nicardipine, diazepam, warfarin). Cimetidine may decrease the absorption of iron, ketoconazole, and tetracyclines.

CIPROFLOXACIN
Cipro, Cipro XR, Ciloxan ophthalmic, Cetraxal, Ciprodex, Cipro HC Otic, Otovel Otic, and generics
Antibiotic, quinolone

Tabs: 100, 250, 500, 750 mg
Extended-release tabs (Cipro XR and generics): 500, 1000 mg
Oral suspension: 250 mg/5 mL (100 mL), 500 mg/5 mL (100 mL)
Premixed injection: 200 mg/100 mL 5% dextrose, 400 mg/200 mL 5% dextrose (iso-osmotic solutions)
Ophthalmic solution (Ciloxan and generics): 0.3% (2.5, 5, 10 mL); may contain benzalkonium chloride

For explanation of icons, see p. 667

CIPROFLOXACIN *continued*

Ophthalmic ointment (Ciloxan): 0.3% (3.5 g)

Otic suspension:

Cetraxal and generics: 0.5 mg/0.25 mL or 0.2% (14s)

With dexamethasone (Ciprodex): 3 mg/mL (0.3%) ciprofloxacin + 1 mg/mL (0.1%) dexamethasone (7.5 mL); contains benzalkonium chloride

With hydrocortisone (Cipro HC Otic): 2 mg/mL (0.2%) ciprofloxacin + 10 mg/mL (1%) hydrocortisone (10 mL); contains benzyl alcohol

With fluocinolone (Otovel Otic): 3 mg/mL (0.3%) ciprofloxacin + 0.25 mg/mL (0.025%) fluocinolone acetonide (0.25 mL; carton of 14s)

Neonate:

32–37 weeks' gestation: 10 mg/kg/dose IV Q12 hr

≥38 weeks' gestation: 15 mg/kg/dose IV Q12 hr

Child:

PO:

Mild/moderate infection: 20 mg/kg/24 hr ÷ Q12 hr; **max. dose**: 1 g/24 hr

Severe infection: 30–40 mg/kg/24 hr ÷ Q12 hr; **max. dose:** 1.5 g/24 hr

IV:

Severe infection: 10 mg/kg/dose Q8–12 hr; **max. dose**: 400 mg/dose

Complicated UTI or pyelonephritis (× 10–21 days):

PO: 20–40 mg/kg/24 hr ÷ Q12 hr; **max. dose:** 1.5 g/24 hr

IV: 18–30 mg/kg/24 hr ÷ Q8 hr; **max. dose:** 1.2 g/24 hr

Cystic fibrosis:

PO: 40 mg/kg/24 hr ÷ Q12 hr; **max. dose:** 2 g/24 hr

IV: 30 mg/kg/24 hr ÷ Q8 hr; **max. dose:** 1.2 g/24 hr

Anthrax (see remarks):

Inhalational/systemic/cutaneous: Start with 20–30 mg/kg/24 hr ÷ Q12 hr IV (**max. dose:** 800 mg/24 hr) and convert to oral dosing with clinical improvement at 20–30 mg/kg/24 hr ÷ Q12 hr PO (**max. dose:** 1 g/24 hr). Duration of therapy: 60 days (IV and PO combined)

Post exposure prophylaxis: 20–30 mg/kg/24 hr ÷ Q12 hr PO × 60 days; **max. dose:** 1 g/24 hr

Adult:

PO:

Immediate release: 250–750 mg/dose Q12 hr

Extended-release tabs (Cipro XR and generics):

Uncomplicated UTI/Cystitis: 500 mg/dose Q24 hr

Complicated UTI/Uncomplicated pyelonephritis: 1000 mg/dose Q24 hr

IV: 400 mg/dose Q12 hr; 400 mg/dose Q8 hr for more severe/complicated infections

Anthrax (see remarks):

Inhalational/systemic/cutaneous: Start with 400 mg/dose Q12 hr IV and convert to oral dosing with clinical improvement at 500 mg/dose Q12 hr PO. Duration of therapy: 60 days (IV and PO combined).

Post exposure prophylaxis: 500 mg/dose Q12 hr PO × 60 days.

Ophthalmic solution:

≥1 yr and adult: 1–2 drops Q2 hr while awake × 2 days, then 1–2 drops Q4 hr while awake × 5 days. Clinical efficacy for bacterial conjunctivitis has been demonstrated for neonates <31 days old in a randomized, double-blinded, multicenter, parallel-group clinical trial.

Ophthalmic ointment:

≥2 yr and adult: Apply 0.5-inch ribbon TID × 2 days, then BID × 5 days

Otic:

Cetraxal and generics:

Acute otitis externa (≥1 yr and adult): 0.25 mL to affected ear(s) BID × 7 days

CIPROFLOXACIN *continued*

Ciprodex:

Acute otitis media with tympanostomy tubes or acute otitis externa (≥6 mo and adult): 4 drops to affected ear(s) BID × 7 days

Cipro HC Otic:

Otitis externa (>1 yr and adult): 3 drops to affected ear(s) BID × 7 days

Otovel Otic:

Acute otitis media with tympanostomy tubes (≥6 mo): 0.25 mL to affected ear(s) BID × 7 days

Systemic fluoroquinolones are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system.

Can cause GI upset, renal failure, and seizures. GI symptoms, headache, restlessness, and rash are common side effects. Peripheral neuropathy, pseudotumor cerebri, severe hepatic necrosis, and psychiatric reactions have been reported. **Use with caution** in children <18 yr (like other quinolones, tendon rupture can occur during or after therapy, especially with concomitant corticosteroid use), alkalinized urine (crystalluria), seizures, excessive sunlight (photosensitivity), and renal dysfunction **(adjust systemic dose in renal failure; see Chapter 31).** Blood glucose disturbances (hypoglycemia and hyperglycemia) have been reported in diabetic patients receiving insulin or oral hypoglycemic agent.

Do not use otic suspension with perforated tympanic membranes and with viral infections of the external ear canal.

For dosing in obese patients, use an adjusted body weight (ABW). ABW = ideal body weight + 0.45 (total body weight − ideal body weight).

Combinational antimicrobial therapy is recommended for anthrax. For penicillin-susceptible strains, consider changing to high-dose amoxicillin (25–35 mg/kg/dose TID PO). See www.bt.cdc.gov for the latest information.

Inhibits CYP 450 1A2. Ciprofloxacin can increase effects and/or toxicity of caffeine, methotrexate, theophylline, warfarin, tizanidine (excessive sedation and dangerous hypotension), and cyclosporine. Probenecid increases ciprofloxacin levels.

Do not administer antacids or other divalent salts with or within 2–4 hr of oral ciprofloxacin dose. **Do not** administer oral suspension through feeding tubes, because this dosage form adheres to the tube.

CITRATE MIXTURES
Alkalinizing agent, electrolyte supplement

Oral liquid:

Each mL of oral solution contains the following mEq of electrolyte:

	Na	K	Citrate or HCO_3
Tricitrates[a] or Sodium Citrate/Potassium Citrate and Citric Acid (473 mL)	1	1	2
Potassium Citrate and Citric Acid[a] (473 mL)	0	2	2
Sodium Citrate and Citric Acid[a] (30, 473 mL)	1	0	1
Oracit (15, 30, 500 mL)	1	0	1

[a]Sugar free.

Oral powder for oral solution:

Cytra-K: each packet of sugar-free powder contains 30 mEq each of potassium and citrate/HCO_3 (100 packets per box) and must be diluted in at least 6 ounces of cold water or juice.

For explanation of icons, see p. 667

CITRATE MIXTURES *continued*

Dilute dose in water or juice.
All mEq doses based on citrate.
Infant and child (PO): 2–3 mEq/kg/24 hr ÷ Q6–8 hr or 5–15 mL/dose Q6–8 hr (after meals and before bedtime) and adjust dose to desired serum bicarbonate level
Adult (PO): 100–200 mEq/24 hr ÷ Q6–8 hr or 15–30 mL/dose Q6–8 hr (after meals and before bedtime)

Contraindicated in severe renal impairment and acute dehydration. **Use with caution** in patients already receiving potassium supplements or who are sodium restricted. May have laxative effect and cause hypocalcemia and metabolic alkalosis.
Adjust dose to maintain desired pH. 1 mEq of citrate is equivalent to 1 mEq HCO_3 in patients, as citrate is converted to CO_2 via the citric acid cycle in the mitochondria.
Potassium citrate has a pregnancy category of "C"; otherwise the pregnancy category is unknown for the other components to this medication.

CLARITHROMYCIN
Generics; previously available as Biaxin and Biaxin XL
Antibiotic, macrolide

Film tablets: 250, 500 mg
Extended-release tablets: 500 mg
Granules for oral suspension: 125, 250 mg/5 mL (50, 100 mL)

Infant and child:
Acute otitis media, pharyngitis/tonsillitis, pneumonia, acute maxillary sinusitis, or uncomplicated skin infections: 15 mg/kg/24 hr PO ÷ Q12 hr; **max. dose:** 1 g/24 hr
Pertussis (≥1 mo): 15 mg/kg/24 hr PO ÷ Q12 hr × 7 days; **max. dose:** 1 g/24 hr
Bacterial endocarditis prophylaxis: 15 mg/kg (**max. dose:** 500 mg) PO 1 hr before procedure
Helicobacter pylori: 20 mg/kg/24 hr PO ÷ Q12 hr × 7–14 days; **max. dose:** 1 g/24 hr with amoxicillin and proton pump inhibitor with/without metronidazole
Mycobacterium avium complex (MAC):
Prophylaxis (1st episode and recurrence): 15 mg/kg/24 hr PO ÷ Q12 hr
Treatment: 15 mg/kg/24 hr PO ÷ Q12 hr with other antimycobacterial drugs
Max. dose (prophylaxis and treatment): 1 g/24 hr
Adolescent and adult:
Pharyngitis/tonsillitis, acute maxillary sinusitis, bronchitis, pneumonia, or uncomplicated skin infections:
Immediate release: 250–500 mg/dose Q12 hr PO
Extended-release tablet: 1000 mg Q24 hr PO (currently not indicated for pharyngitis/tonsillitis or uncomplicated skin infections)
Adult:
Pertussis: 500 mg (immediate release)/dose Q12 hr PO × 7 days
Bacterial endocarditis prophylaxis: 500 mg PO 1 hr before procedure
MAC:
Prophylaxis (1st episode and recurrence): 500 mg/dose Q12 hr PO
Treatment: 500 mg Q12 hr PO with other antimycobacterial drugs
Helicobacter pylori *GI infection:* 500 mg Q12 hr PO with proton pump inhibitor (lansoprazole or omeprazole) and amoxicillin

CLARITHROMYCIN *continued*

Contraindicated in patients allergic to erythromycin and history of cholestatic jaundice/hepatic dysfunction with prior use. As with other macrolides, clarithromycin has been associated with QT prolongation (**avoid use** with other drugs known to prolong QT interval) and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes. May cause cardiac arrhythmias in patients also receiving cisapride. Side effects: diarrhea, nausea, abnormal taste, dyspepsia, abdominal discomfort (less than erythromycin but greater than azithromycin), and headache. Anaphylaxis, angioedema, hepatic dysfunction, rhabdomyolysis, SJS, and TEN have been reported.

May increase effects/toxicity of carbamazepine, theophylline, cyclosporine, digoxin, ergot alkaloids, fluconazole, midazolam, selected oral hypoglycemic agents, tacrolimus, triazolam, quetiapine, and warfarin. Substrate and inhibitor of CYP 450 3A4, and inhibits CYP 1A2.

Adjust dose in renal failure (see Chapter 31). Doses, regardless of dosage form, may be administered with food.

CLINDAMYCIN
Cleocin-T, Cleocin, Clindagel, Evoclin, Clindesse, and generics
Antibiotic, lincomycin derivative

Caps: 75, 150, 300 mg
Oral solution: 75 mg/5 mL (100 mL); may contain ethyl parabens
Injection: 150 mg/mL (2, 4, 6, 60 mL); contains 9.45 mg/mL benzyl alcohol
Premixed injection in 5% dextrose or NS: 300 mg/50 mL, 600 mg/50 mL, 900 mg/50 mL; contains edetate disodium and may contain benzyl alcohol
Solution, topical (Cleocin-T and generics): 1% (30, 60 mL); may contain 50% isopropyl alcohol and propylene glycol
Gel, topical (Cleocin-T, Clindagel, and generics): 1% (30, 60 g); may contain methylparaben and propylene glycol
Lotion, topical (Cleocin-T and generics): 1% (60 mL); may contain methylparaben
Foam, topical (Evoclin): 1% (50, 100 g); contains 58% ethanol
See *benzoyl peroxide* for combination topical product (clindamycin and benzoyl peroxide)
See tretinoin for combination topical product (clindamycin and tretinoin)
Vaginal cream (Cleocin, Clindesse, and generics): 2% (40 g); may contain benzyl alcohol
Vaginal suppository: 100 mg (3s)

Neonate:
IV/IM: 5 mg/kg/dose with the following dosage intervals:
≤7 days:
≤2 kg: Q12 hr
>2 kg: Q8 hr
>7–28 days:
<1 kg: Q12 hr for 8–14 days old and Q8 hr for ≥15–28 days old
1–2 kg: Q8 hr
>2 kg: Q6 hr
Child and adolescent:
PO: 10–40 mg/kg/24 hr ÷ Q6–8 hr; **max. dose**: 1.8 g/24 hr
IM/IV: 20–40 mg/kg/24 hr ÷ Q6–8 hr; **max. dose**: 2.7 g/24 hr
Bacterial endocarditis prophylaxis: 20 mg/kg (**max. dose:** 600 mg) × 1 PO, IV or IM; 1 hr before procedure with PO route and 30 min before procedure with IV or IM route.

For explanation of icons, see p. 667

CLINDAMYCIN *continued*

Adult:

PO: 150–450 mg/dose Q6–8 hr; **max. dose**: 1.8 g/24 hr

IM/IV: 1200–2700 mg/24 hr IM/IV ÷ Q6–12 hr; **max. IV dose:** 4.8 g/24 hr. **Max. IM dose:** 600 mg/dose

Bacterial endocarditis prophylaxis: 600 mg × 1 PO, IV or IM; 1 hr before procedure with PO route and 30 min before procedure with IV or IM route.

Topical for acne (≥12 yr and adult; administer after washing and fully dry the affected skin):

Solution, lotion, or gel (Cleocin-T and generics): apply to affected area BID.

Clindagel or Evoclin (foam): apply to affected area once daily.

Bacterial vaginosis (adolescent and adult):

Suppositories: 100 mg/dose QHS × 3 days

Vaginal cream (2%): 1 applicator dose (5 g) QHS for 3 or 7 days in nonpregnant patients and for 7 days in pregnant patients in second and third trimesters.

Not indicated in meningitis; CSF penetration is poor.

Pseudomembranous colitis may occur up to several weeks after cessation of therapy.

May cause diarrhea, rash, granulocytopenia, thrombocytopenia, or sterile abscess at injection site. Anaphylaxis, DRESS, SJS, severe taste alterations including metallic taste (with high IV doses), and TEN have been reported with systemic use. Eye pain and contact dermatitis have been reported with topical use.

Clindamycin may increase the neuromuscular blocking effects of tubocurarine and pancuronium.

Do not exceed IV infusion rate of 30 mg/min because hypotension and cardiac arrest have been reported with rapid infusions. May diminish the effects of erythromycin when administered together. In vitro studies indicate clindamycin is a substrate and inhibitor for CYP 450 3A4.

Dosage reduction may be required in severe renal or hepatic disease but not necessary in mild/moderate conditions. Oral liquid preparation may not be palatable; consider use of oral capsules as a sprinkle onto applesauce or pudding.

CLOBAZAM

Onfi, Sympazan, and generics

Benzodiazepine, anticonvulsant

Tabs (Onfi and generics): 10, 20 mg

Oral film (Sympazan): 5, 10, 20 mg (60s)

Oral suspension (Onfi and generics): 2.5 mg/mL (120 mL); contains parabens, polysorbate 80, and propylene glycol

Lennox-Gastaut (adjunctive therapy; see remarks):

Child (≥2 yr) and adult (PO): Dosage increments (if needed) should not be more rapid than every 7 days.

Weight (kg)	Initial Dose	Dose at Day 8, if Needed	Dose at Day 15, if Needed
≤30 kg	5 mg once daily	5 mg BID	10 mg BID (**max. dose**)
>30 kg	5 mg BID	10 mg BID	20 mg BID (**max. dose**)

CLOBAZAM *continued*

Dosage adjustment for mild/moderate hepatic impairment (Child-Pugh score 5–9) and individuals with poor CYP 450 2C19 activity (PO):

Weight (kg)	Initial Dose	First Dose Increment, If Needed	Second Dose Increment, If Needed	Third Dose Increment, If Needed
≤30 kg	5 mg once daily × ≥14 days	5 mg BID × ≥7 days	10 mg BID (**max. dose**)	N/A
>30 kg	5 mg once daily × ≥7 days	5 mg BID × ≥7 days	10 mg BID × ≥7 days	20 mg BID (**max. dose**)

N/A, Not applicable.

Seizures (generalized or partial, as monotherapy or adjunctive therapy; limited data and prescribing information from Canada and the United Kingdom):

Infant and child (<2 yr): Start at 0.5–1 mg/kg/24 hr (**max. dose:** 5 mg/24 hr) PO ÷ BID, if needed and tolerated, slowly increase dosage at 5–7 days intervals up to the **maximum** of 10 mg/kg/24 hr.

2–16 yr: Start at 5 mg PO once daily, if needed and tolerated, slowly increase dosage at 5–7 day intervals up to the **maximum** of 40 mg/kg/24 hr. Usual dosage range: 10–20 mg/24 hr or 0.3–1 mg/kg/24 hr ÷ BID.

Use with caution in hepatic impairment (dose adjustment may be needed). Do not discontinue use abruptly, as seizures/withdrawal symptoms may occur. Common side effects include constipation, drooling, ataxia, drowsiness, insomnia, aggressive behavior, cough, and fever. SJS, TEN, urinary retention, hypothermia, leukopenia, and thrombocytopenia have been reported.

Do not use in combination with azelastine, olanzapine, sodium oxybate, and thioridazine; increased risk of adverse events. Proton pump inhibitors, azole antifungal agents (e.g., itraconazole and ketoconazole), St. John's Wort, grapefruit juice, CNS depressants, cimetidine, and calcium channel blockers may increase the effects/toxicity of clobazam. Use with opioids may result in profound sedation, respiratory depression, coma, and mortality. Carbamazepine, rifamycin derivatives (e.g., rifampin), and theophylline may decrease the effects of clobazam. Clobazam is a major substrate for CYP 450 2C19 and P-glycoprotein, minor substrate for CYP 450 2B6 and 3A4, inhibitor of CYP 450 2D6, and inducer of CYP 3A4. Carefully review the patient's medication profile for other drug interactions each time clobazam is initiated or when a new drug is added to a regimen containing clobazam.

Doses may be taken with or without food. Tablets may be crushed and mixed with applesauce.

Oral film (Sympazan) uses same PO dosage with the following method for administration: apply film on top of the tongue, allow it to dissolve, and swallow saliva in a normal manner. **Do not** chew, spit, or talk while film is dissolving. Doses may be taken with or without food but **do not** administer with liquids.

CLONAZEPAM
Klonopin and generics
Benzodiazepine, anticonvulsant

Tabs: 0.5, 1, 2 mg
Disintegrating oral tabs: 0.125, 0.25, 0.5, 1, 2 mg; contains phenylalanine
Oral suspension: 100 mCg/mL

Continued

For explanation of icons, see p. 667

CLONAZEPAM *continued*

Infant and child: <10 yr or <30 kg:
Initial: 0.01–0.03 mg/kg/24 hr PO ÷ BID–TID; **maximum initial dose:** 0.05 mg/kg/24 hr.
Increment: 0.25–0.5 mg/24 hr Q3 days, up to **maximum maintenance dose** of 0.1–0.2 mg/kg/24 hr ÷ TID
Child ≥10 yr or ≥30 kg and adult:
Initial: 1.5 mg/24 hr PO ÷ TID
Increment: 0.5–1 mg/24 hr Q3 days; **max. dose:** 20 mg/24 hr

Contraindicated in severe liver disease and acute narrow-angle glaucoma. Drowsiness, behavior changes, increased bronchial secretions, GI, CV, GU, and hematopoietic toxicity (thrombocytopenia, leukopenia) may occur. Monitor for depression, suicidal behavior/ideation, and unusual changes in behavior/mood. **Use with caution** in patients with compromised respiratory function, porphyria, and renal impairment. **Do not discontinue abruptly.** $T_{½}$ = 24–36 hr.

Proposed therapeutic levels (not well established): 20–80 ng/mL. Recommended serum sampling time: Obtain trough level within 30 min prior to an oral dose. Steady state is typically achieved after 5–8 days continuous therapy using the same dose.

Carbamazepine, phenytoin, and phenobarbital may decrease clonazepam levels and effect. Drugs that inhibit CYP-450 3A4 isoenzymes (e.g., erythromycin) may increase clonazepam levels and effects/toxicity.

CLONIDINE
Catapres, Kapvay, Catapres TTS, Duraclon, and generics
Central α-adrenergic agonist, antihypertensive

Tabs (Catapres and generics): 0.1, 0.2, 0.3 mg
Extended-release oral tab (Kapvay and generics): 0.1 mg
Oral suspension: 20, 100, 1000 mCg/mL
Transdermal patch (Catapres TTS and generics): 0.1, 0.2, 0.3 mg/24 hr (7-day patch); contains metallic components (see remarks)
Injection, epidural (Duraclon and generics): 100, 500 mCg/mL (10 mL); preservative free

Hypertension (use immediate-release products unless noted):
Child (PO): 5–10 mCg/kg/24 hr ÷ Q8–12 hr initially; if needed, increase at 5- to 7-day intervals to 5–25 mCg/kg/24 hr ÷ Q6 hr; **max. dose:** 25 mCg/kg/24 hr up to 0.9 mg/24 hr.
≥12 yr and adult (PO): 0.1 mg BID initially; increase in 0.1 mg/24 hr increments at weekly intervals until desired response is achieved (usual range: adolescent: 0.2–0.6 mg/24 hr ÷ BID; adult: 0.1–0.8 mg/24 hr ÷ BID), **max. dose:** 2.4 mg/24 hr
Transdermal patch (each patch lasts 7 days by rotating application sites but more frequent patch change at every 5 days may be needed for children):
Child: conversion to patch only after establishing an optimal oral dose first. Use a transdermal dosage closest to the established total oral daily dose.
Adult: Initial 0.1 mg/24 hr patch for first week. May increase dose by 0.1 mg/24 hr at 1–2 wk intervals PRN. Usual range: 0.1–0.3 mg/24 hr. Doses >0.6 mg/24 hr do not provide additional benefit.
ADHD (Child ≥6 yr and adolescent):
Immediate-release product (PO):
≤45 kg: Start with 0.05 mg QHS; if needed, increase by 0.05 mg/24 hr every 3–7 days as increments with BID, TID, and then QID dosing up to the following **max. dose:**
27–40.5 kg: 0.2 mg/24 hr
40.5–45 kg: 0.3 mg/24 hr

CLONIDINE *continued*

>45 kg: Start with 0.1 mg QHS; if needed, increase by 0.1 mg/24 hr every 3–7 days as increments with BID, TID, and then QID dosing up to the **max. dose** of 0.4 mg/24 hr.

Extended-release product (Kapvay and generics, PO): Start with 0.1 mg QHS; if needed, increase by 0.1 mg every 7 days by administering the dose BID up to a **maximum** of 0.4 mg/24 hr. Depending on dosage level, BID dosing should be either the same amount or with the higher dosage given at bedtime. If therapy is to be discontinued, slowly reduce dosage at ≤0.1 mg every 3 to 7 days to avoid withdrawal.

Neonatal abstinence syndrome, adjunctive therapy (use immediate-release product; limited data): 0.5–1 mCg/kg/dose Q4–6 hr PO; use Q6 hr interval for preterm neonates.

Side effects: Dry mouth, dizziness, drowsiness, fatigue, constipation, anorexia, arrhythmias, and local skin reactions with patch. Somnolence, fatigue, URIs irritability, throat pain, insomnia, nightmares, and emotional disorder were reported as common side effects in ADHD clinical trials. May worsen sinus node dysfunction and AV block especially for patients taking other sympatholytic drugs. **Do not abruptly discontinue;** signs of sympathetic overactivity may occur; taper gradually over >1 wk.

β-blockers may exacerbate rebound hypertension during and following the withdrawal of clonidine. If patient is receiving both clonidine and a β-blocker and clonidine is to be discontinued, the β-blocker should be withdrawn several days prior to tapering the clonidine. If converting from clonidine over to a β-blocker, introduce the β-blocker several days after discontinuing clonidine (after taper).

Monitor heart rate when used with digitalis, calcium channel blockers, and β-blockers. Use with diltiazem or verapamil may result in sinus bradycardia. Use with neuroleptics may induce/exacerbate orthostatic hypotension, dizziness, and fatigue. Consider using lower dosages in renal impairment because the drug is primarily eliminated unchanged in the urine and signs of bradycardia, sedation, and hypotension may occur.

$T_{½}$: 44–72 hr (neonate), 6–20 hr (adult). Onset of action (antihypertensive): 0.5–1 hr for oral route, 2–3 days for transdermal route. **Do not** use transdermal route while patient is undergoing a magnetic resonance imaging (MRI) procedure; transdermal patches contains metals and may result in serious patient burns when undergoing MRI.

CLOTRIMAZOLE
Alevazol, Lotrimin AF, Gyne-Lotrimin 3, Gyne-Lotrimin 7, and generics
Antifungal, imidazole

Oral troche: 10 mg
Cream, topical (Lotrimin AF and generics; OTC): 1% (15, 30, 45 g); may contain benzyl alcohol
Ointment, topical (Alevazol; OTC): 1% (56.7 g)
Solution, topical (OTC): 1% (10, 30 mL)
Vaginal cream (OTC):
Gyne-Lotrimin 7 and generics: 1% (45 g)
Gyne-Lotrimin 3 and generics: 2% (21 g)

Topical (cream, ointment, or solution):
≥2 yr–adult: Apply to affected skin areas BID; × 2 wk for cutaneous candidiasis, × 4–8 wk for tinea corporis/pedis.

Vaginal cream (>12 yr and adult; in addition to intravaginal use, may also apply to external vaginal area BID × 7 days PRN for itching and irritation):
1 applicator dose (5 g) of 1% cream intravaginally QHS × 7–14 days, or
1 applicator dose of 2% cream intravaginally QHS × 3 days

For explanation of icons, see p. 667

CLOTRIMAZOLE *continued*

Thrush:

>3 yr–adult: Dissolve slowly (15–30 min) one troche in the mouth 5 times/24 hr × 14 days

***Systemic use*: Do not use** troches for systemic infections. Liver enzyme elevation, nausea, and vomiting may occur with troches.

Topical use: May cause erythema, blistering, or urticaria with topical use. **Avoid use** of tampons, douches, spermicides, other vaginal products, condoms, and diaphragms with vaginal cream. Vaginal cream can weaken latex.

Pregnancy code is a "B" for topical and vaginal dosage forms and "C" for troches.

CORTICOTROPIN
Acthar Gel, ACTH
Adrenocorticotropic hormone

Injection, repository gel: 80 U/mL (5 mL); contains phenol
1 unit = 1 mg

Infantile spasms (many regimens exist):

20–40 U/24 hr IM once daily × 6 wk or 150 U/m²/24 hr ÷ BID for 2 wk, followed by a gradual 2 wk taper of 30 U/m²/dose QAM × 3 days, followed by 15 U/m²/dose QAM × 3 days, followed by 10 U/m²/dose QAM × 3 days and 10 U/m²/dose every other morning × 6 days.

Antiinflammatory:

≥2 yr and adolescent: 0.8 U/kg/24 hr ÷ Q12–24 hr IM

Contraindicated in acute psychoses, CHF, Cushing disease, TB, peptic ulcer, ocular herpes, fungal infections, recent surgery, and sensitivity to porcine products. **Use with caution** in osteoporosis. Repository gel dosage form is only for IM route.

Hypersensitivity reactions and injection site reactions may occur. Similar adverse effects as corticosteroids.

CORTISONE ACETATE
Various generics
Corticosteroid

Tabs: 25 mg

Antiinflammatory/immunosuppressive:

Child: 2.5–10 mg/kg/24 hr ÷ Q6–8 hr PO
Adult: 25–300 mg/24 hr ÷ Q12–24 hr PO

May produce glucose intolerance, Cushing syndrome, edema, hypertension, adrenal suppression, cataracts, hypokalemia, skin atrophy, peptic ulcer, osteoporosis, and growth suppression.

Pregnancy category changes to "D" if used in the first trimester.

CO-TRIMOXAZOLE

See SULFAMETHOXAZOLE AND TRIMETHOPRIM

CROMOLYN
Nasalcrom, Gastrocrom, and generics; previously available as Intal
Antiallergic agent, mast cell stabilizer

Nebulized solution: 10 mg/mL (2 mL)
Oral concentrate (Gastrocrom and generics): 100 mg/5 mL (5 mL)
Ophthalmic solution: 4% (10 mL)
Nasal spray (NasalCrom and generics) [OTC]: 4% (5.2 mg/spray) (100 sprays, 13 mL; 200 sprays, 26 mL); contains benzalkonium chloride and EDTA

Nebulization:
Child ≥2 yr and adult: 20 mg Q6–8 hr
Exercise-induced asthma: 20 mg × 1, 10–15 min prior to and no longer than 1 hr before exercise.
Nasal:
Child ≥2 yr and adult: 1 spray each nostril TID–QID; **max. dose**: 1 spray 6 times/24 hr.
Ophthalmic:
Child >4 yr and adult: 1–2 gtts 4–6 times/24 hr
Food allergy/inflammatory bowel disease:
2–12 yr: 100 mg PO QID; give 15–20 min AC and QHS; **max. dose**: 40 mg/kg/24 hr
>12 yr and adult: 200–400 mg PO QID; give 15–20 min AC and QHS
Systemic mastocytosis (taper to lowest effective maintenance dose once desired effect is achieved):
Infant and child <2 yr: 20 mg/kg/24 hr ÷ QID PO; **max. dose:** <6 mo: 20 mg/kg/24 hr, ≥6 mo to <2 yr: 40 mg/kg/24 hr
2–12 yr: 100 mg PO QID; give 30 min AC and QHS; **max. dose:** 40 mg/kg/24 hr
>12 yr and adult: 200 mg PO QID; give 30 min AC and QHS; **max. dose:** 40 mg/kg/24 hr

May cause rash, cough, bronchospasm, and nasal congestion. May cause headache, diarrhea with oral use. **Use with caution** in patients with renal or hepatic dysfunction because cromolyn is equally excreted unchanged in the urine and feces (bile).
Therapeutic response often occurs within 2 wk; however, a 4- to 6-wk trial may be needed to determine maximum benefit. Oral concentrate can only be diluted in water. Nebulized solution can be mixed with albuterol nebs.

CYANOCOBALAMIN/VITAMIN B_{12}
B-12 Compliance, Physicians EZ Use B-12, Nascobal, vitamin B_{12}, and generics
Vitamin (synthetic), water soluble

Tabs (OTC): 100, 250, 500, 1000 mCg
Extended-release tabs: 1000 mCg
Sublingual tabs: 2500 mCg
Sublingual liquid: 3000 mCg/mL (52 mL)
Lozenges (OTC): 50, 100, 250, 500 mCg
Nasal spray (Nascobal): 500 mCg/spray (1.3 mL delivers 4 doses); contains benzalkonium chloride
Injection: 1000 mCg/mL (1, 10, 30 mL); may contain benzyl alcohol
Injection kit (B-12 Compliance, Physicians EZ Use B-12, and generics): 1000 mCg/mL (1 mL); may contain benzyl alcohol
Contains cobalt (4.35%)

Continued

For explanation of icons, see p. 667

CYANOCOBALAMIN/VITAMIN B_{12} *continued*

U.S. RDA: See Chapter 21.

Vitamin B_{12} deficiency, treatment:

Child (IM or deep SC): 100 mCg/24 hr × 10–15 days followed by 100 mCg once or twice weekly for several months

Maintenance: At least 60 mCg/mo

Adult (IM or deep SC): 100 mCg/24 hr × 6–7 days, if improvement, 100 mCg/dose every 3–4 days × 2–3 wk. Use maintenance dose when hematologic values return to normal.

Maintenance: 100 mCg/mo

Pernicious anemia:

Child (IM or deep SC): 30–50 mCg/24 hr for at least 14 days to a total dose of 1000–5000 mCg

Maintenance: 100 mCg/mo

Adult (IM or deep SC): 100 mCg/24 hr × 6–7 days, if improvement, 100 mCg/dose every 3–4 days × 2–3 wk. Use maintenance dose when hematologic values return to normal.

Maintenance:

IM/deep SC: 100 mCg/mo

Intranasal: 500 mCg in one nostril once weekly

Sublingual: 1000–2000 mCg/24 hr

Contraindicated in optic nerve atrophy. May cause hypokalemia, hypersensitivity (anaphylaxis shock and death reported with parenteral use), pruritis, and vascular thrombosis. Vitamin B_{12} use may mask folate deficiency and unmask polycythemia vera.

Prolonged use of acid-suppressing medications may reduce cyanocobalamin oral absorption.

Pregnancy category changes to "C" if used in doses greater than the RDA or if administered by the intranasal route.

Protect product from light. Some products may contain aluminum and may accumulate in renal impairment. Oral route of administration is generally **not recommended** for pernicious anemia and B_{12} deficiency due to poor absorption. IV route of administration is **NOT recommended** because of a more rapid elimination. See Chapter 21 for multivitamin preparations.

CYCLOPENTOLATE

Cyclogyl and generics

Anticholinergic, mydriatic agent

Ophthalmic solution: 0.5% (15 mL), 1% (2, 5, 15 mL), 2% (2, 5, 15 mL); may contain benzalkonium chloride

Administer dose approximately 40–50 min prior to examination/procedure.

Infant: Use of cyclopentolate/phenylephrine (Cyclomydril) due to lower cyclopentolate concentration and reduced risk of systemic side effects.

Child and adolescent: 1 drop of 0.5%–1% solution OU, followed by repeat drop, if necessary, in 5 min. Use 2% solution for heavily pigmented iris.

Adult: 1 drop of 1% solution OU followed by another drop OU in 5 min. Use 2% solution for heavily pigmented iris.

Do not use in narrow-angle glaucoma. May cause a burning sensation, behavioral disturbance, tachycardia, and loss of visual accommodation. Psychotic reactions and behavioral disturbances have been reported in children. To minimize absorption, apply pressure over nasolacrimal sac for at least 2 min. CNS and cardiovascular side effects are common with the 2% solution in children. **Avoid** feeding infants within 4 hr of dosing to prevent potential feeding intolerance.

Onset of action: 15- to 60-min duration of action: 6–24 hr; complete recovery of accommodation may

CYCLOPENTOLATE WITH PHENYLEPHRINE
Cyclomydril
Anticholinergic/sympathomimetic, mydriatic agent

Ophthalmic solution: 0.2% cyclopentolate and 1% phenylephrine (2, 5 mL); contains 0.1% benzalkonium chloride, EDTA, and boric acid

Neonate (administer dose approximately 40–50 min prior to examination/procedure; see remarks): 1 drop OU Q5–10 min; **max. dose:** 3 drops per eye
Infant, child, and adolescent (administer dose at least 15 min prior to examination; see remarks): 1 drop OU Q5–10 min PRN

Used to induce mydriasis. See *cyclopentolate* for additional remarks.
Onset of action: 15–60 min. Duration of action: 4–12 hr.
Apply pressure over the nasolacrimal sac for 2–3 min after administration to minimize systemic absorption.

CYCLOSPORINE, CYCLOSPORINE MICROEMULSION, CYCLOSPORINE MODIFIED
Sandimmune, Gengraf, Neoral, Restasis, Cequa, and generics
Immunosuppressant

CYCLOSPORINE (Sandimmune and generics):
Injection: 50 mg/mL (5 mL); contains 32.9% alcohol and 650 mg/mL polyoxyethylated castor oil
Oral solution: 100 mg/mL (50 mL); contains 12.5% alcohol
Caps: 25, 50, 100 mg; contains 12.8% alcohol
CYCLOSPORINE MICROEMULSION (Neoral):
Caps: 25, 100 mg
Oral solution: 100 mg/mL (50 mL)
Neoral products contain 11.9% alcohol
CYCLOSPORINE MODIFIED (Gengraf):
Caps: 25, 100 mg; contains 12.8% alcohol
Oral solution: 100 mg/mL (50 mL): contains propylene glycol
Ophthalmic emulsion (Restasis): 0.05% (0.4 mL as 30 single-use vials/box, 1.5 mL, 5.5 mL); contains polysorbate 80
Ophthalmic solution/drops (Cequa): 0.09% (0.25 mL in boxes of 60s); preservative free

Neoral manufacturer recommends a 1:1 conversion ratio with Sandimmune. Because of its better absorption, lower doses of Neoral and Gengraf may be required. Exact dosing will vary depending on transplant type.
Oral: 15 mg/kg/24 hr as a single dose given 4–12 hr pretransplantation; give same daily dose ÷ Q12–24 hr for 1–2 wk posttransplantation, then reduce by 5% per week to 3–10 mg/kg/24 hr ÷ Q12–24 hr
IV: 5–6 mg/kg/24 hr as a single dose given 4–12 hr pretransplantation; administer over 2–6 hr; give same daily dose posttransplantation until patient able to tolerate oral form
Ophthalmic:
≥16 yr and adult: Instill one drop onto affected eye(s) Q12 hr.

May cause nephrotoxicity, hepatotoxicity, hypomagnesemia, hyperkalemia, hyperuricemia, hypertension, hirsutism, acne, GI symptoms, tremor, leukopenia, sinusitis, gingival

For explanation of icons, see p. 667

CYCLOSPORINE, CYCLOSPORINE MICROEMULSION, CYCLOSPORINE MODIFIED *continued*

hyperplasia, and headache. Encephalopathy, convulsions, lower extremity pain, vision and movement disturbances, and impaired consciousness have been reported, especially in liver transplant patients. Psoriasis patients previously treated with PUVA and, to a lesser extent, methotrexate or other immunosuppressive agents, UVB, coal tar, or radiation therapy are at increased risk for skin malignancies when taking Neoral or Gengraf.

Opportunistic infections and activation of latent viral infections have been reported.

BK virus–associated nephropathy has been observed in renal transplant patients.

Use caution with concomitant use of other nephrotoxic drugs (e.g., amphotericin B, aminoglycosides, nonsteroidal antiinflammatory drugs, and tacrolimus).

Plasma concentrations increased with the use of boceprevir, telaprevir, fluconazole, ketoconazole, itraconazole, erythromycin, clarithromycin, voriconazole, nefazodone, diltiazem, verapamil, nicardipine, carvedilol, and corticosteroids. Plasma concentrations decreased with the use of carbamazepine, nafcillin, rifampin, oxcarbazepine, bosentan, phenobarbital, octreotide, and phenytoin. May increase bosentan, dabigatran, methotrexate, repaglinide, and anthracycline antibiotics (e.g., doxorubicin, mitoxantrone, daunorubicin) levels/effects/toxicity. Use with nifedipine may result in gingival hyperplasia. Cyclosporine is a substrate and inhibitor for CYP 450 3A4 and P-glycoprotein.

Children may require dosages 2–3 times higher than adults. Plasma half-life 6–24 hr.

Monitor trough levels (just prior to a dose at steady state). Steady state is generally achieved after 3–5 days of continuous dosing. Interpretation will vary based on treatment protocol and assay methodology (RIA monoclonal vs. RIA polyclonal vs. HPLC), as well as whole blood vs. serum sample. Additional monitoring and dosage adjustments may be necessary in renal and hepatic impairment or when changing dosage forms.

For ophthalmic use: Ocular burning may occur. Remove contact lens prior to use; lens may be inserted 15 min after dose administration. May be used with artificial tears but need to be separated by 15 min for one another.

CYPROHEPTADINE
Various generics; previously available as Periactin
Antihistamine

Tabs: 4 mg
Syrup: 2 mg/5 mL (473 mL); may contain alcohol 5%

Antihistaminic uses:
Child: 0.25 mg/kg/24 hr or 8 mg/m²/24 hr ÷ Q8–12 hr PO or by age:
2–6 yr: 2 mg Q8–12 hr PO; **max. dose**: 12 mg/24 hr
7–14 yr: 4 mg Q8–12 hr PO; **max. dose**: 16 mg/24 hr
≥***15 yr:*** 4 mg Q8 hr PO; usual range 12–16 mg/24 hr; **max. dose:** 0.5 mg/kg/24 hr
Adult: Start with 12 mg/24 hr ÷ TID PO; dosage range: 12–32 mg/24 hr ÷ TID PO; **max. dose:** 0.5 mg/kg/24 hr
Migraine prophylaxis: 0.25–0.4 mg/kg/24 hr ÷ BID–TID PO up to following **max. doses:**
2–6 yr: 12 mg/24 hr
7–14 yr: 16 mg/24 hr
Adult: 0.5 mg/kg/24 hr or 32 mg/24 hr
Appetite stimulation (see remarks):
≥***2 yr and adolescent:*** 0.25 mg/kg/24 hr ÷ Q12 hr PO up to the following **max. dose** by age: 2–6 yr: 12 mg/24 hr, 7–14 yr: 16 mg/24 hr, ≥15 yr: 32 mg/24 hr.

CYPROHEPTADINE *continued*

Alternative dosing by age:

4–8 yr (limited data): 2 mg Q8 hr PO

>13 yr and adult: Start with 2 mg Q6 hr PO; dose may be gradually increased to 8 mg Q6 hr over a 3-wk period.

Contraindicated in neonates, patients currently on MAO inhibitors, and patients suffering from asthma, glaucoma, or GI/GU obstruction. May produce anticholinergic side effects including sedation and appetite stimulation. Consider reducing dosage with hepatic insufficiency.

Allow 4 to 8 wk of continuous therapy for assessing efficacy in migraine prophylaxis. For use as an appetite stimulant, a dosing cycle of 3 wk on therapy followed by 1 wk off of therapy may enhance efficacy.

D

DANTROLENE
Dantrium, Revonto, Ryanodex, and generics
Skeletal muscle relaxant

Cap: 25, 50, 100 mg
Oral suspension: 5 mg/mL
Injection:
Dantrium and Revonto: 20 mg; injectable solution containing 3 g mannitol per 20 mg drug
Ryanodex : 250 mg; injectable suspension containing 125 mg mannitol, 25 mg polysorbate 80, 4 mg povidone K12 per 250 mg drug

Chronic spasticity:

Child: (≥5 yr)

Initial: 0.5 mg/kg/dose (**max. dose**: 25 mg/dose) PO BID

Increment: Increase frequency to TID–QID at 4- to 7-day intervals, then increase doses by 0.5 mg/kg/dose

Max. dose: 3 mg/kg/dose PO BID–QID, up to 400 mg/24 hr

Malignant hyperthermia:

Prevention:

PO: 4–8 mg/kg/24 hr ÷ Q6 hr ×1–2 days before surgery with last dose administered 3–4 hr prior to surgery

IV (see remarks for specific dosage form administration rates): 2.5 mg/kg beginning 1.25 hr before anesthesia, additional doses PRN

Treatment (see remarks for specific dosage form administration rates): 1 mg/kg IV, repeat PRN to **maximum cumulative dose** of 10 mg/kg, followed by a post-crisis regimen of 4–8 mg/kg/24 hr PO ÷ Q6 hr for 1–3 days

Contraindicated in active hepatic disease. Monitor transaminases for hepatotoxicity. **Use with caution** with cardiac or pulmonary impairment. May cause change in sensorium, drowsiness, weakness, diarrhea, constipation, incontinence, and enuresis. Rare cardiovascular collapse has been reported in patients receiving concomitant verapamil. May potentiate vecuronium-induced neuromuscular block.

Continued

For explanation of icons, see p. 667

DANTROLENE *continued*

Avoid unnecessary exposure of medication to sunlight. **Avoid** extravasation into tissues. A decrease in spasticity sufficient to allow daily function should be therapeutic goal. Discontinue if benefits are not evident in 45 days.

IV administration rates for malignant hyperthermia:

Dosage Form	Prevention Use	Treatment Use
Injectable solution	Over 1 hr	IV push
Injectable suspension	Over at least 1 min	IV push

DAPSONE

Aczone, Diaminodiphenylsulfone, DDS, and generics

Antibiotic, sulfone derivative

Tabs: 25, 100 mg

Oral suspension: 2 mg/mL

Topical gel: 5% (60, 90 g)

Aczone: 7.5% (60, 90 g)

Pneumocystis jiroveci (formerly carinii) treatment:

Child and adult: 2 mg/kg/24 hr PO once daily (**max. dose**: 100 mg/24 hr) with trimethoprim 15 mg/kg/24 hr PO ÷ TID ×21 days

P. jiroveci (formerly carinii) prophylaxis (first episode and recurrence):

Child ≥1 mo: 2 mg/kg/24 hr PO once daily; **max. dose**: 100 mg/24 hr. Alternative weekly dosing, 4 mg/kg/dose PO Q7 days; **max. dose**: 200 mg/dose

Adult: 100 mg/24 hr PO ÷ once daily–BID with or without pyrimethamine 50 mg PO Q7 days and leucovorin 25 mg PO Q 7 days; other combination regimens with pyrimethamine and leucovorin may be used (see https://www.aidsinfo.gov).

Toxoplasma gondii prophylaxis (prevent first episode):

Child ≥1 mo: 2 mg/kg/24 hr (**max. dose**: 25 mg/24 hr) PO once daily with pyrimethamine 1 mg/kg/24 hr (**max.** 25 mg/dose) PO once daily and leucovorin 5 mg PO Q3 days

Adult: 50 mg PO once daily with pyrimethamine 50 mg PO Q7 days and leucovorin 25 mg PO Q 7 days; other combination regimens with pyrimethamine and leucovorin may be used (see https://www.aidsinfo.gov).

Leprosy (See www.who.int/en/ for the WHO latest recommendations including combination regimens such as rifampin ± clofazimine):

Child: 1–2 mg/kg/24 hr PO once daily; **max. dose**: 100 mg/24 hr

Adult: 100 mg PO once daily

Acne vulgaris (topical gel):

≥12 yr:

5% gel: Apply small amount (pea size) of topical gel onto clean, acne-affected areas BID.

7.5% gel: Apply small amount (pea size) of topical gel onto clean, acne-affected areas once daily

Patients with HIV, glutathione deficiency, or G6PD deficiency may be at increased risk for developing methemoglobinemia. Side effects include hemolytic anemia (dose related), agranulocytosis, methemoglobinemia, aplastic anemia, nausea, vomiting, hyperbilirubinemia, headache, nephrotic syndrome, and hypersensitivity reaction (sulfone syndrome). Cholestatic jaundice, hepatitis, peripheral neuropathy, and suicidal intent have been reported with systemic use.

DAPSONE *continued*

Didanosine, rifabutin, and rifampin decrease dapsone levels. Trimethoprim increases dapsone levels. Pyrimethamine, nitrofurantoin, primaquine, and zidovudine increase risk for hematological side effects.

Oral suspension may not be absorbed as well as tablets.

TOPICAL USE: Dry skin, erythema, and peeling of the skin may occur. Use of topical gel, followed by benzoyl peroxide for acne, has resulted in temporary local discoloration (yellow/orange) of the skin and facial hair. **Avoid use** of topical gel in G6PD deficiency or congenital/idiopathic methemoglobinemia.

DARBEPOETIN ALFA
Aranesp
Erythropoiesis stimulating protein

Injection: 25, 40, 60, 100, 200, 300 mCg/1 mL (1 mL)

Single dose pre-filled injection syringe (27 gauge ½-inch needle): 10 mCg/0.4 mL (0.4 mL), 25 mCg/0.42 mL (0.42 mL), 40 mCg/0.4 mL (0.4 mL), 60 mCg/0.3 mL (0.3 mL), 100 mCg/0.5 mL (0.5 mL), 150 mCg/0.3 mL (0.3 mL), 200 mCg/0.4 mL (0.4 mL), 300 mCg/0.6 mL (0.6 mL), 500 mCg/1 mL (1 mL)

Both dosage forms contain polysorbate 80 (0.05 mg/mL), albumin free and preservative free.

Anemia in chronic renal failure (see remarks):

Receiving dialysis (initial dosage and adjust dose according to the table that follows; IV route is recommended for patients on hemodialysis):

Infant, child, and adolescent: Start with 0.45 mCg/kg/dose IV/SC once weekly

Adult: Start with 0.45 mCg/kg/dose IV/SC once weekly, ***OR*** 0.75 mCg/kg/dose IV/SC once every 2 wk

Not receiving dialysis (initial dosage; adjust dose according to the table that follows):

Infant, child, and adolescent: Start with 0.45 mCg/kg/dose IV/SC once weekly, ***OR*** 0.75 mCg/kg/dose IV/SC once every 2 wk

Adult: Start with 0.45 mCg/kg/dose IV/SC once every 4 wk

DARBEPOETIN ALFA DOSE ADJUSTMENT IN ANEMIA ASSOCIATED WITH CHRONIC RENAL FAILURE

Response to Dose	Dose Adjustment
<1 g/dL increase in hemoglobin and below target range after 4 wk of therapy	Increase dose by 25% not more frequently than once monthly. Further increases, if needed, may be done at 4-wk intervals. Among those who do not adequately respond over a 12-wk escalation period, further dose increase is unlikely to improve response and may increase risks.
>1 g/dL increase in hemoglobin in any 2-wk period, or if hemoglobin exceeds and approaches 11 g/dL	Decrease dose by 25% or more
Hemoglobin continues to increase despite dosage reduction	Discontinue therapy; reinitiate therapy at a 25% lower dose of the previous dose after the hemoglobin starts to decrease

Continued

For explanation of icons, see p. 667

DARBEPOETIN ALFA *continued*

Anemia associated with chemotherapy (patients with nonmyeloid malignancies):

Child (limited data) and adult (see remarks): Start with 2.25 mCg/kg/dose SC once weekly and adjust dose according to the table that follows:

DARBEPOETIN ALFA DOSE ADJUSTMENT IN ANEMIA ASSOCIATED WITH CHEMOTHERAPY

Response to Dose	Dose Adjustment
<1 g/dL increase in hemoglobin and remains below 10 g/dL after 6 wk of therapy	Increase dose to 4.5 mCg/kg/dose once weekly SC/IV
>1 g/dL increase in hemoglobin in any 2-wk period, or when hemoglobin reaches a level needed to avoid transfusion	Decrease dose by 40%
If hemoglobin exceeds a level needed to avoid transfusion	Hold therapy until hemoglobin approaches a level where transfusions may be required and restart at a reduced dose by 40%
Lack or response after 8 wk or completion of chemotherapy	Discontinue therapy

Conversion from epoetin alfa to darbepoetin alfa (see table below):

Previous Weekly Epoetin Alfa Dose (units/wk)[a]	Pediatric Weekly Darbepoetin Alfa Dose (mCg/wk) Administered SC/IV Once Weekly[b]	Adult Weekly Darbepoetin Alfa Dose (mCg/wk) Administered SC/IV Once Weekly[b]	Adult Once Every 2 wk Darbepoetin Alfa Dose (mCg Every 2 wk) Administered SC/IV Once Every 2 wk[c]
<1,500	Insufficient data	6.25	12.5
1,500–2,499	6.25	6.25	12.5
2,500–4,999	10	12.5	25
5,000–10,999	20	25	50
11,000–17,999	40	40	80
18,000–33,999	60	60	120
34,000–89,999	100	100	200
≥90,000	200	200	400

[a]200 units of epoetin alfa is equivalent to 1 mCg darbepoetin alfa.

[b]If patient was receiving epoetin alfa 2–3 times weekly, darbepeotin alfa should be administered once weekly.

[c]If patient was receiving epoetin alfa once weekly, darbepoetin alfa should be administered once every 2 wk.

Contraindicated in uncontrolled hypertension and patients hypersensitive to albumin/polysorbate 80 or epoetin alfa. Darbepoetin alfa is not intended for patients requiring acute correction of anemia. **Use with caution** in seizures and liver disease. Erythema multiforme, SJS, and TEN have been reported. Evaluate serum iron, feritin, and TIBC; concurrent iron supplementation may be necessary. Red cell aplasia and severe anemia associated with neutralizing antibodies to erythropoietin have been reported.

USE IN CHRONIC RENAL FAILURE: Higher doses may be needed for pediatric patients being switched from epoetin alfa than those for naïve patients. May cause edema, fatigue, GI disturbances, headache, blood pressure changes, fever, cardiac arrhythmia/arrest, infections and myalgia. Higher risk for mortality and serious cardiovascular events have been reported with higher targeted hemoglobin levels (>11 g/dL). If hemoglobin levels do not increase or reach targeted levels despite appropriate dose titrations over a 12 wk period, (1) **do not** administer higher doses and use the lowest dose that will maintain hemoglobin levels to avoid the need for recurrent blood transfusions; (2) evaluate and

DARBEPOETIN ALFA *continued*

treat other causes of anemia; (3) always follow the dose adjustment instructions; and (4) discontinue use if patient remains transfusion dependent.

USE IN CANCER: Use only for anemia due to myelosuppressive chemotherapy; not effective in reducing the need for transfusions in patients with anemia not due to chemotherapy. Shortened survival and time to tumor progression have been reported in patients with various cancers. May cause fatigue, fever, edema, dizziness, headache, GI disturbances, arthralgia/myalgia, and rash. Use lowest dose to avoid transfusions and **do not exceed hemoglobin levels >12 g/dL**; increased frequency of adverse events, including mortality and thrombotic vascular events, have been reported. **Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense this drug to cancer patients.**

Monitor hemoglobin, BP, serum chemistries, and reticulocyte count. Increases in dose should not be made more frequently than once a mo. For IV administration, infuse over 1–3 min.

DEFEROXAMINE MESYLATE
Desferal and generics
Chelating agent

Injection: 500, 2000 mg

Acute iron poisoning (if using IV route, convert to IM as soon as the patient's clinical condition permits; see remarks):

Child:

IV: 15 mg/kg/hr

IM: 50 mg/kg/dose Q6 hr

Max. IV or IM dose: 6 g/24 hr

Adult:

IV: 15 mg/kg/hr

IM: 1 g ×1, then 0.5 g Q4 hr ×2; may repeat 0.5 g Q4–12 hr

Max. dose: 6 g/24 hr

Chronic iron overload (see remarks):

Child and adolescent:

IV: 20–40 mg/kg/dose over 8–12 hr once daily ×5–7 days per week; usual **max. dose**: 40 mg/kg/24 hr (child) or 60 mg/kg/24 hr (adolescent)

SC: 20–40 mg/kg/dose once daily as infusion over 8–12 hr ×3–7 days per week; **max. dose**: 2 g/24 hr

Adult:

IV: 40–50 mg/kg/dose over 8–12 hr once daily ×5–7 days per week; **max. dose**: 6 g/24 hr

IM: 0.5–1 g/dose once daily; **max. dose**: 1 g/24 hr

SC: 1–2 g/dose once daily as infusion over 8–24 hr

Contraindicated in severe renal disease or anuria. **Not approved** for use in primary hemochromatosis. May cause flushing, erythema, urticaria, hypotension, tachycardia, diarrhea, leg cramps, fever, cataracts, hearing loss, nausea, and vomiting. Iron mobilization may be poor in children <3 yr. Serum creatinine elevation, acute renal failure, renal tubular disorders, and hepatic dysfunction have been reported.

Avoid use if glomerular filtration rate (GFR) <10 mL/min and administer 25%–50% of usual dose if GFR is 10–50 mL/min or patient is receiving continuous renal replacement therapy (CRRT).

High doses and concomitant low ferritin levels have also been associated with growth retardation. Growth velocity may resume to pretreatment levels by reducing the dosage. Acute respiratory distress

Continued

For explanation of icons, see p. 667

DEFEROXAMINE MESYLATE *continued*

syndrome (ARDS) has been reported following treatment with excessively high IV doses in patients with acute iron intoxication or thalassemia. Toxicity risk has been reported with infusions >8 mg/kg/hr for >4 days for thalassemia, and with infusions of 15 mg/kg/hr for >1 day for acute iron toxicity. Pulmonary toxicity was not seen in 193 courses.

For IV infusion, **maximum rate:** 15 mg/kg/hr. Infuse IV infusion over 6–12 hr for mild/moderate iron intoxication and over 24 hr for severe cases, then reassess. SC route is via a portable controlled-infusion device and is **not recommended** in acute iron poisoning.

DESMOPRESSIN ACETATE

DDAVP, Stimate, and generics

Vasopressin analog, synthetic; hemostatic agent

Tabs: 0.1, 0.2 mg

Nasal solution (with rhinal tube): 100 mCg/mL (2.5, 5 mL); contains 9 mg NaCl/mL and 5 mg chlorbutanol/mL

Injection: 4 mCg/mL (1, 10 mL); contains 9 mg NaCl/mL

Nasal spray:

100 mCg/mL, 10 mCg/spray (50 sprays, 5 mL); contains 7.5 mg NaCl/mL and 0.2 mg benzalkonium chloride/mL

Stimate: 1500 mCg/mL, 150 mCg/spray (25 sprays, 2.5 mL); contains 7.5 mg NaCl/mL and 0.1 mg benzalkonium chloride/mL

Conversion: 100 mCg = 400 IU arginine vasopressin

Diabetes insipidus (see remarks):

Oral:

Child ≤12 yr: Start with 0.05 mg/dose BID; titrate to effect; usual dose range: 0.1–0.8 mg/24 hr.

Child >12 yr and adult: Start with 0.05 mg/dose BID; titrate dose to effect; usual dose range: 0.1–1.2 mg/24 hr ÷ BID–TID.

Intranasal (titrate dose to achieve control of excessive thirst and urination. Morning and evening doses should be adjusted separately for diurnal rhythm of water turnover):

3 mo–12 yr: 5–30 mCg/24 hr ÷ once daily–BID

>12 yr and adult: 5–40 mCg/24 hr ÷ once daily–TID

IV/SC:

<12 yr (limited data): 0.1–1 mCg/24 hr ÷ once daily–BID; start with lower dose and increase as needed.

≥12 yr and adult: 2–4 mCg/24 hr ÷ BID

Hemophilia A and von Willebrand disease:

Intranasal: 2–4 mCg/kg/dose 2 hr before procedure

IV: 0.2–0.4 mCg/kg/dose over 15–30 min, administered 30 min before procedure

Nocturnal enuresis (≥6 yr; see remarks):

Oral: 0.2 mg at bedtime, if needed, titrate to achieve desired effect by 0.2 mg Q3 days up to a **max. dose** of 0.6 mg/24 hr.

Use with caution in hypertension, patients at risk for water intoxication with hyponatremia, and coronary artery disease. May cause headache, nausea, seizures, blood pressure changes, hyponatremia, nasal congestion, abdominal cramps, and hypertension.

Desmopressin is primarily excreted in the urine, and renal impairment may increase the elimination half-life (some consider use contraindicated when GFR is <50 mL/min).

NOCTURNAL ENURESIS: Intranasal formulations are no longer indicated by the FDA for primary **nocturnal enuresis** (children are susceptible for severe hyponatremia and seizures) or in patients with a

DESMOPRESSIN ACETATE *continued*

history of hyponatremia. Patients using tablets should reduce their fluid intake to prevent potential water intoxication and hyponatremia, and have their therapy interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance.

Injection may be used SC or IV at approximately 10% of intranasal dose. Adjust fluid intake to decrease risk of water intoxication and monitor serum sodium.

If switching stabilized patient from intranasal route to IV/SC route, use 10% of intranasal dose. Peak effects: 1–5 hr with intranasal route; 1.5–3 hr with IV route; and 2–7 hr with PO route.

DEXAMETHASONE

Decadron, Dexpak Taperpak, Maxidex, and generics; previously available as Hexadrol

Corticosteroid

Tabs (Decadron and other generics): 0.5, 0.75, 1, 1.5, 2, 4, 6 mg

Dexpak Taperpak, and generics: 1.5 mg [21 tabs (6 days), 35 tabs (10 days), 51 tabs (13 days)]

Injection (sodium phosphate salt): 4, 10 mg/mL (some preparations contain benzyl alcohol or methyl/propyl parabens)

Elixir: 0.5 mg/5 mL (237 mL); some preparations contain 5% alcohol

Oral solution: 0.1, 1 mg/mL; some preparations contain 30% alcohol

Ophthalmic solution: 0.1% (5 mL)

Ophthalmic suspension (Maxidex): 0.1% (5 mL)

Airway edema: 0.5–2 mg/kg/24 hr IV/IM ÷ Q6 hr (begin 24 hr before extubation and continue for 4–6 doses after extubation)

Asthma exacerbation: 0.6 mg/kg/dose (max. 16 mg/dose) PO/IV/IM Q24 hr ×1 or 2 doses; use beyond 2 days increases risk for metabolic adverse effects

Croup: 0.6 mg/kg/dose PO/IV/IM ×1

Antiemetic (chemotherapy induced):

Initial: 10 mg/m^2/dose IV; **max. dose**: 20 mg

Subsequent: 5 mg/m^2/dose Q6 hr IV

Anti-inflammatory:

Child: 0.08–0.3 mg/kg/24 hr PO, IV, IM ÷ Q6–12 hr

Adult: 0.75–9 mg/24 hr PO, IV, IM ÷ Q6–12 hr

Brain tumor associated cerebral edema:

Loading dose: 1–2 mg/kg/dose IV/IM ×1

Maintenance: 1–1.5 mg/kg/24 hr ÷ Q4–6 hr; **max. dose**: 16 mg/24 hr

Ophthalmic use (child and adult):

Solution: Instill 1–2 drops into the conjunctival sac(s) of the affected eye(s) Q1 hr during the day and Q2 hr during the night as initial therapy. When a favorable response is achieved, reduce dosage to Q3–4 hr. Further dose reduction to 1 drop TID–QID may be sufficient to control symptoms.

Suspension: Shake well before using. Instill 1–2 drops in the conjunctival sac(s) of the affected eye(s) up to 4–6 times/24 hr. For severe disease, drops may be used Q1 hr, being tapered to discontinuation as inflammation subsides. For mild disease, drops may be used ≤4–6 times/24 hr.

Not recommended for systemic therapy in the prevention or treatment of chronic lung disease in infants with very low birth weight because of increased risk for adverse events. Dexamethasone is a substrate of CYP P450 3A3/4 and P-glycoprotein, and a moderate inducer of CYP P450 3A4.

Compared to prednisone, dexamethasone has no mineralocorticoid effects with greater glucocorticoid effects. Consider use of alternative low glucocorticoid systemic steroid for patients with hyperglycemia.

Contraindicated in active untreated infections and fungal, viral, and mycobacterial ocular infections.

For explanation of icons, see p. 667

DEXAMETHASONE *continued*

Oral peak serum levels occur 1–2 hr and within 8 hr following IM administration. **For other uses, doses based on body surface area, and dose equivalence to other steroids, see Chapter 10.**

OPHTHALMIC USE: Use ophthalmic preparation only in consultation with an ophthalmologist. **Use with caution** in corneal/scleral thinning and glaucoma. Consider the possibility of persistent fungal infections of the cornea after prolonged use. Ophthalmic solution/suspension may be used in otitis externa.

DEXMEDETOMIDINE
Precedex and generics
Alpha-Adrenergic agonist, sedative

Injection (Precedex and generics): 200 mCg/2 mL (2 mL); preservative free
Multidose injection: 400 mCg/4 mL (4 mL); contains methyl- and propyl-parabens
Pre-mixed injection in NS (Precedex and generics): 80 mCg/20 mL (20 mL), 200 mCg/50 mL (50 mL), 400 mCg/100 mL (100 mL); preservative free

NOTE: Maintenance infusion rate dosing metric is mCg/kg/HR
ICU sedation:

Child (limited data): 0.5–1 mCg/kg/dose IV ×1 over 10 min followed by 0.2–1 mCg/kg/hr infusion titrated to effect. Children <1 yr of age may require higher dosages.

Adult: 1 mCg/kg/dose IV ×1 over 10 min, followed by 0.2–0.7 mCg/kg/hr infusion and titrated to effect.

Procedural sedation:

Child (limited data):

IV: 2 mCg/kg/dose ×1 IV followed by 1.5 mCg/kg/hr was administered to children with autism/pervasive developmental disorders for sedation for electroencephalography (EEG).

IM: 1–4.5 mCg/kg/dose ×1 IM was administered to children for sedation for EEG. Extremely anxious, inconsolable, aggressive, and noncompliant children received doses >2.5 mCg/kg; and calm and relatively compliant children received doses ≤2.5 mCg/kg. A second lower repeat dose (~2 mCg/kg/dose IM) was administered adequate sedation was not achieved after 10 min of the first dose.

Intranasal route (limited data): 1–2 mCg/kg/dose ×1 for premedication 30–60 min prior to anesthesia induction.

Adult: 0.5–1 mCg/kg/dose IV ×1 over 10 min, followed by 0.6 mCg/kg/hr titrated to effect; dosage has ranged from 0.2–1 mCg/kg/hr.

Use with caution with other vasodilating or negative chronotropic agents (additive pharmacodynamic effects), hepatic impairment (decrease drug clearance; consider dose reduction), advanced heart block, hypovolemia, diabetes mellitus, chronic hypertension, and severe ventricular dysfunction. Prolonged use >24 hr may be associated with tolerance and tachyphylaxis and dose-related side effects (ARDS, respiratory failure and agitation). Withdrawal symptoms within 24 hr after discontinuing dexmedetomidine have been reported in ~5% of adults receiving the medication up to 7 days regardless of dosage; no withdrawal symptoms were seen in adults after discontinuing therapy lasting <6 hr in duration.

Hypotension and bradycardia are common side effects; may be more pronounced in hypovolemia, diabetes or chronic hypertension. Transient hypertension has been observed during loading doses. QT prolongation, hypernatremia, sinus arrest, and polyuria have been reported. **Do not** abruptly withdraw therapy, as withdrawal symptoms (nausea, vomiting, and agitation) are possible; taper the dose when discontinuing use.

DEXMEDETOMIDINE *continued*

Use with anesthetics, sedatives, hypnotics, and opioids may lead to enhanced effects; consider dosage reduction of dexmedetomidine. Dexmedetomidine is a CYP 450 2A6 substrate and a weak inhibitor of CYP 450 1A2, 2C9, and 3A4.

Onset of action for procedural sedation: IV or IM: 15 min, intranasal: 15–30 min. Duration of action for procedural sedation: IM: 1 hr, intranasal: 1–1.5 hr.

This drug should be administered by individuals skilled in the management of patients in the ICU and OR. Concentrated IV solution (100 mCg/1 mL) must be diluted with NS to a concentration of 4 mCg/mL prior to administration. See Chapter 6 for additional information.

DEXMETHYLPHENIDATE
Focalin, Focalin XR, and generics
CNS stimulant

Tab, immediate release (Focalin and generics): 2.5, 5, 10 mg
Extended release caps (Focalin XR and generics): 5, 10, 15, 20, 25, 30, 35, 40 mg

Attention deficit/hyperactivity disorder:

METHYLPHENIDATE NAIVE:

Age/Dosage Form	Initial Dose	Dosage Increase at Weekly Intervals, if Needed	Daily Maximum Dose
≥6 YR AND ADOLESCENT			
Immediate-Release Tabs[a]	2.5 mg PO BID	2.5–5 mg/24 hr	20 mg/24 hr (10 mg BID)
Extended-Release Caps[b]	5 mg PO once daily	5 mg/24 hr	30 mg/24 hr (some may require and able to tolerate up to 50 mg/24 hr)
ADULT			
Immediate-Release Tabs[a]	2.5 mg PO BID	2.5–5 mg/24 hr	20 mg/24 hr (10 mg BID)
Extended-Release Caps[b]	10 mg PO once daily	10 mg/24 hr	40 mg/24 hr

[a]BID dosing (at least 4 hr apart).
[b]Once-daily dosing.

CONVERTING FROM METHYLPHENIDATE:

≥6 yr and adult: Start at 50% of the total daily dose of racemic methylphenidate with the following **max. doses:**

Immediate release tabs (BID dosing): 20 mg/24 hr; some may require and able to tolerate 50 mg/24 hr

Extended release caps (once daily dosing): 30 mg/24 hr for ≥6 yr–adolescents (some may require and able to tolerate 50 mg/24 hr); 40 mg/24 hr for adults.

COVERTING FROM IMMEDIATE RELEASE TABS (BID) TO EXTENDED RELEASE CAPS (once daily)

DEXMETHYLPHENIDATE: Use the equivalent mg dosage amount.

Dexmethylphenidate is the d-enantiomer of methylphenidate and accounts for the majority of clinical effects for methylphenidate. **Contraindicated** in glaucoma, anxiety disorders, motor tics, and Tourette syndrome. **Do not** use with monoamine oxidase (MAO) inhibitor; hypertensive crisis may occur if used within 14 days of discontinuance of MAO inhibitor. See methylphendate for additional warnings and drug interactions.

Continued

For explanation of icons, see p. 667

DEXMETHYLPHENIDATE *continued*

Common side effects include abdominal pain, indigestion, appetite suppression, nausea, headache, insomnia, and anxiety. Peripheral vasculopathy, including Raynaud phenomenon, and priapism have been reported. Monitor for long-term growth suppression in children and assess for risk of abuse and dependence prior to prescribing.

Immediate-release tablets are dosed BID (minimum 4 hr between doses) and extended-release capsules are dosed once daily. Contents of the extended-release capsule may be sprinkled on a spoonful of applesauce and consumed immediately for those who are unable to swallow capsules.

DEXTROAMPHETAMINE ± AMPHETAMINE

Dexedrine, ProCentra, Zenzedi, Mydayis, and many generics

In combination with amphetamine: Adderall, Adderall XR, and generics

CNS stimulant, amphetamine

Tabs, immediate release:

Generics: 5, 10 mg

Zenzedi: 2.5, 5, 7.5, 10, 15, 20, and 30 mg

Sustained-release caps (Dexedrine and generics): 5, 10, 15 mg

Oral solution (ProCentra and generics): 1 mg/mL (473 mL)

In combination with amphetamine (Adderall): Available as 1:1:1:1 mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate salts (e.g., 5 mg tablet contains 1.25 mg dextroamphetamine sulfate, 1.25 mg dextroamphetamine saccharate, 1.25 mg amphetamine aspartate, and 1.25 mg amphetamine sulfate; 5 mg of the mixture is equivalent to 3.1 mg amphetamine base):

Tabs (Adderall and generics): 5, 7.5, 10, 12.5, 15, 20, 30 mg

Caps, extended-release:

Adderal XR and generics: 5, 10, 15, 20, 25, 30 mg

Mydayis: 12.5, 25, 37.5, 50 mg

Oral suspension: 1 mg/mL

Dosages are in terms of mg of dextroamphetamine when using dextroamphetamine alone OR in terms of mg of the total dextroamphetamine and amphetamine salts when using Adderall. Non-extended-release dosage forms are usually given BID–TID (first dose on awakening and subsequent doses at intervals of 4–6 hr later). Extended/sustained-released dosage forms are usually given PO once daily, sometimes BID (6–8 hr between doses).

Attention deficit/hyperactivity disorder:

3–5 yr: 2.5 mg/24 hr QAM; increase by 2.5 mg/24 hr at weekly intervals to a **max. dose** of 40 mg/24 hr ÷ once daily–BID (some may require TID dosing).

≥6 yr: 5 mg/24 hr QAM; increase by 5 mg/24 hr at weekly intervals to a **max. dose** of 40 mg/24 hr ÷ once daily–BID (some may require TID dosing). **Max. dose** of 60 mg/24 hr has been used patients >50 kg.

Narcolepsy (divide daily dosage once daily–TID for immediate release dosage form and once daily–BID for extended release dosage form):

6–12 yr: 5 mg/24 hr ÷ once daily-TID; increase by 5 mg/24 hr at weekly intervals to a **max. dose** of 60 mg/24 hr

>12 yr and adult: 10 mg/24 hr ÷ once daily-TID; increase by 10 mg/24 hr at weekly intervals to a **max. dose** of 60 mg/24 hr

DEXTROAMPHETAMINE ± AMPHETAMINE *continued*

Use with caution in presence of hypertension, cardiovascular disease, and renal or hepatic impairment (drug elimination may be decreased). **Avoid** use in known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that may increase risk of sympathomimetic effects of amphetamines (sudden death, stroke, and MI have been reported). **Do not** give with MAO inhibitors (also within 14 days of discontinuance) or general anesthetics. Use with proton pump inhibitors (PPIs) may reduce the effectiveness of either dextroamphetamine or the combination with amphetamine.

DEXTROAMPHETAMINE AND AMPHETAMINE: Serotonin syndrome may occur when used with serotonergic neurotransmitter medications such as MAO inhibitors, SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), triptans, and TCAs. CYP 450 2D6 inhibitors may increase the effects/toxicity of the combination medication.

Not recommended for <3 yr. Medication should generally **not** be used in children <5 yr old, as diagnosis of attention deficit and hyperactivity disorder (ADHD) in this age group is extremely difficult (use in consultation with a specialist). Interrupt administration occasionally to determine need for continued therapy. Many side effects, including insomnia (**avoid** dose administration within 6 hr of bedtime), restlessness/irritability, anorexia, psychosis, visual disturbances, headache, vomiting, abdominal cramps, dry mouth, and growth failure. Paranoia, mania, peripheral vasculopathy (including Raynaud phenomenon), priapism, bruxism, and auditory hallucination have been reported. Assess for risk of abuse and dependence prior to prescribing. Tolerance develops. Same guidelines as for methylphenidate apply. See Amphetamine for amphetamine-containing products.

DIAZEPAM

Valium, Diastat, Diastat AcuDial, and generics

Benzodiazepine; anxiolytic, anticonvulsant

Tabs: 2, 5, 10 mg

Oral solution: 1 mg/mL, 5 mg/mL; contains 19% alcohol

Injection: 5 mg/mL (2, 10 mL); contains 40% propylene glycol, 10% alcohol, 5% sodium benzoate, and 1.5% benzyl alcohol

Intramuscular auto-injector: 5 mg/mL (2 mL); contains 40% propylene glycol, 10% alcohol, 5% sodium benzoate, and 1.5% benzyl alcohol

Rectal gel:

Pediatric rectal gel (Diastat and generics): 2.5 mg (5 mg/mL concentration with 4.4 cm rectal tip delivery system; contains 10% alcohol, 1.5% benzyl alcohol, sodium benzoate, and propylene glycol); in twin packs.

Pediatric/Adult rectal gel (Diastat AcuDial and generics):

4.4 cm rectal tip delivery system (Pediatric/Adult): 10 mg (5 mg/mL, delivers set doses of either 5, 7.5, or 10 mg); contains 10% alcohol, 1.5% benzyl alcohol, sodium benzoate, and propylene glycol; in twin packs.

6 cm rectal tip delivery system (Adult): 20 mg (5 mg/mL, delivers set doses of either 12.5, 15, 17.5, 20 mg); contains 10% alcohol, 1.5% benzyl alcohol, sodium benzoate, and propylene glycol; in twin packs.

Sedative/muscle relaxant:

Child:

IM or IV: 0.04–0.2 mg/kg/dose Q2–6 hr; **max. dose**: 0.6 mg/kg within an 8-hr period.

PO: 0.12–0.8 mg/kg/24 hr ÷ Q6–8 hr

Continued

For explanation of icons, see p. 667

DIAZEPAM *continued*

Sedative/muscle relaxant (cont.):

Adult:

IM or IV: 5–10 mg/dose Q3–4 hr PRN

PO: 2–10 mg/dose Q6–8 hr PRN

Status epilepticus:

Neonate (use only after failed therapy of other agents; note the excipients of the IV dosage forms): 0.1–0.3 mg/kg/dose IV Q15–30 min ×2–3 doses up to **max. total dose** of 2 mg.

Child >1 mo–<5 yr: 0.2–0.5 mg/dose IV Q2–5 min up to **max. total dose** of 5 mg. May repeat dosing in 2–4 hr as needed.

Child ≥5 yr: 1 mg/dose IV Q2–5 min up to **max. total dose** of 10 mg. May repeat dosing in 2–4 hr as needed.

Adult: 5–10 mg/dose IV Q10–15 min; **max. total dose**: 30 mg in an 8-hr period. May repeat dosing in 2–4 hr as needed.

Rectal dose (using IV dosage form): 0.5 mg/kg/dose followed by 0.25 mg/kg/dose in 10 min PRN; **max. dose**: 20 mg/dose.

Rectal gel: all doses rounded to the nearest available dosage strength; repeat dose in 4–12 hr PRN.

Do not use >5 times per month or > once every 5 days.

2–5 yr: 0.5 mg/kg/dose

6–11 yr: 0.3 mg/kg/dose

≥12 yr: and adult: 0.2 mg/kg/dose

Max. dose (all ages): 20 mg/dose

Contraindicated in myasthenia gravis, severe respiratory insufficiency, severe hepatic failure, and sleep apnea syndrome. Hypotension and respiratory depression may occur. **Use with caution** in hepatic and renal dysfunction, glaucoma, shock, and depression. **Do not** use in combination with protease inhibitors. Concurrent use with CNS depressants, cimetidine, erythromycin, itraconazole, and valproic acid may enhance the effects of diazepam. Use with opioids may result in profound sedation, respiratory depression, coma and mortality. Diazepam is a substrate for CYP 450 2B6, 2C8, 2C9, and 3A5-7, and minor substrate and inhibitor for CYP 450 2C19 and 3A3/4. The active desmethyldiazepam metabolite is a CYP 450 2C19 substrate.

Administer the conventional IV product undiluted no faster than 2 mg/min and **do not** mix with IV fluids.

In status epilepticus, diazepam must be followed by long-acting anticonvulsants. Onset of anticonvulsant effect: 1–3 min with IV route; 2–10 min with rectal route. **For management of status epilepticus, see Chapter 1.**

DIAZOXIDE
Proglycem
Antihypoglycemic agent, antihypertensive agent

Oral suspension: 50 mg/mL (30 mL); contains 7.25% alcohol

Hyperinsulinemic hypoglycemia (due to insulin-producing tumors; start at the lowest dose; see remarks):

Newborn and infant: Start at 5 mg/kg/24 hr ÷ Q8–12 hr PO and gradually titrate if needed; usual range of 8–15 mg/kg/24 hr with reported range of 5–20 mg/kg/24 hr ÷ Q8–12 hr

Child and adolescent: Start at 5 mg/kg/24 hr ÷ 8 hr PO and gradually titrate if needed; usual range: 3–8 mg/kg/24 hr ÷ Q8–12 hr PO

DIAZOXIDE *continued*

Hypoglycemia should be treated initially with IV glucose; diazoxide should be introduced only if refractory to glucose infusion. Should **not** be used in patients hypersensitive to thiazides unless benefit outweighs risk. Thiazides may enhance diazoxide's hyperglycemic effects. **Use with caution** in renal impairment (clearance of drug is reduced); consider dosage reduction.

Sodium and fluid retention is common in young infants and adults and may precipitate congestive heart failure (CHF) in patients with compromised cardiac reserve (usually responsive to diuretics). Hirsutism (reversible), GI disturbances, transient loss of taste, tachycardia, ketoacidosis, palpitations, rash, headache, weakness, and hyperuricemia may occur. Pulmonary hypertension in newborns/infant treated for hypoglycemia has been reported as resolution/improvement of the condition was achieved after discontinuance of diazoxide. Monitor BP closely for hypotension.

Hyperglycemic effect with PO administration occurs within 1 hr, with a duration of 8 hr.

DICLOXACILLIN SODIUM
Generics; previously available as Dycill and Pathocil
Antibiotic, penicillin (penicillinase-resistant)

Caps: 250, 500 mg
Contains 0.6 mEq Na/250 mg drug

Child (<40 kg) (see remarks):
Mild/moderate infections: 12.5–25 mg/kg/24 hr PO ÷ Q6 hr; **max. dose**: 1 g/24 hr
Skin and soft tissue infection (MSSA): 25–50 mg/kg/24 hr PO ÷ Q6 hr; **max. dose**: 2 g/24 hr
Severe infections: 50–100 mg/kg/24 hr PO ÷ Q6 hr; **max. dose**: 2 g/24 hr
Child (≥40 kg) and adult: 125–500 mg/dose PO Q6 hr; **max. dose:** 2 g/24 hr

Contraindicated in patients with a history of penicillin allergy. **Use with caution** in cephalosporin hypersensitivity. May cause nausea, vomiting, and diarrhea. Immune hypersensitivity has been reported.

Limited experience in neonates and very young infants. Higher doses (50–100 mg/kg/24 hr) are indicated following IV therapy for osteomyelitis. CNS penetration is poor.

May decrease the effects of oral contraceptives and warfarin. Administer 1 hr before meals or 2 hr after meals.

DIGOXIN
Lanoxin, Lanoxin Pediatric, Digitek, and generics
Antiarrhythmic agent, inotrope

Tabs: 62.5, 125, 187.5, 250 mCg
Oral solution: 50 mCg/mL (60 mL); may contain 10% alcohol
Injection:
Lanoxin Pediatric: 100 mCg/mL (1 mL); may contain propylene glycol and alcohol
Lanoxin and generics: 250 mCg/mL (2 mL); may contain propylene glycol and alcohol

Continued

For explanation of icons, see p. 667

DIGOXIN *continued*

Digitalizing: Total digitalizing dose (TDD) and maintenance doses in mCg/kg/24 hr (see the table that follows):

DIGOXIN DIGITALIZING AND MAINTENANCE DOSES

	TDD		Daily Maintenance	
Age	**PO**	**IV/IM**	**PO**	**IV/IM**
Premature neonate	20	15	5	3–4
Full term neonate	30	20	8–10	6–8
1 mo– <2 yr	40–50	30–40	10–12	7.5–9
2–10 yr	30–40	20–30	8–10	6–8
>10 yr and <100 kg	10–15	8–12	2.5–5	2–3

TDD, Total digitalizing dose.

Initial: 1/2 TDD, then 1/4 TDD Q8–18 hr ×2 doses; obtain electrocardiogram (ECG) 6 hr after dose to assess for toxicity

Maintenance:

<10 yr: Give maintenance dose ÷ BID

≥10 yr: Give maintenance dose once daily

Contraindicated in patients with ventricular dysrhythmias. Use should be **avoided** in patients with preserved left ventricular systolic function. **Use with caution** in renal failure, with calcium channel blockers (may result in heart block), and with adenosine (enhanced depressant effects on sinoatrial [SA] and atrioventricular [AV] nodes). May cause AV block or dysrhythmias. In patients treated with digoxin, cardioversion, or calcium infusion, may lead to ventricular fibrillation (pretreatment with lidocaine may prevent this). Patients with beri beri heart disease may not respond to digoxin if underlying thiamine deficiency is not treated concomitantly. Decreased serum potassium and magnesium, or increased magnesium and calcium may increase risk for digoxin toxicity. For signs and symptoms of toxicity, see Chapter 3.

Excreted via the kidney; **adjust dose in renal failure (see Chapter 31).** Therapeutic concentration: 0.8–2 ng/mL. Higher doses may be required for supraventricular tachycardia. Neonates, pregnant women, and patients with renal, hepatic, or heart failure may have falsely elevated digoxin levels, due to the presence of digoxin-like substances.

Digoxin is a CYP450 3A4 and P-glycoprotein substrate. Calcium channel blockers, captopril, carvedilol, amiodarone, quinidine, cyclosporine, itraconazole, tetracycline, and macrolide antibiotics may increase digoxin levels. Use with β-blockers and ivabradine may increase risk for bradycardia. Succinylcholine may cause arrhythmias in digitalized patients.

$T_{1/2}$: Premature infants, 61–170 hr; full-term neonates, 35–45 hr; infants, 18–25 hr; and children, 35 hr.

Recommended serum sampling at steady state: Obtain a single level from 6 hr postdose to just before the next scheduled dose following 5–8 days of continuous dosing. Levels obtained prior to steady state may be useful in preventing toxicity.

DIGOXIN IMMUNE FAB (OVINE)
DigiFab
Antidigoxin antibody

Injection: 40 mg

Dosing based on known amounts of digoxin acutely ingested:

First determine total body digoxin load (TBL):

TBL (mg) = mg digoxin ingested ×0.8

Then, calculate digoxin immune Fab dose:

Dose in number of digoxin immune Fab vials (DigiFab): # of vials = TBL ÷ 0.5

Dosing based on steady-state serum digoxin levels:

Digifab dose (mg) from steady-state digoxin levels

	Serum Digoxin Concentration (ng/mL)						
Patient Weight (kg)	**1**	**2**	**4**	**8**	**12**	**16**	**20**
1	0.4 mg[a]	1 mg[a]	1.5 mg[a]	3 mg[a]	5 mg	6.5 mg	8 mg
3	1 mg[a]	2.5 mg[a]	5 mg	10 mg	14 mg	19 mg	24 mg
5	2 mg[a]	4 mg	8 mg	16 mg	24 mg	32 mg	40 mg
10	4 mg	8 mg	16 mg	32 mg	48 mg	64 mg	80 mg
20	8 mg	16 mg	32 mg	64 mg	96 mg	128 mg	160 mg
40	20 mg	40 mg	80 mg	120 mg	200 mg	280 mg	320 mg
60	20 mg	40 mg	120 mg	200 mg	280 mg	400 mg	480 mg
70	40 mg	80 mg	120 mg	240 mg	360 mg	440 mg	560 mg
80	40 mg	80 mg	120 mg	280 mg	400 mg	520 mg	640 mg
100	40 mg	80 mg	160 mg	320 mg	480 mg	640 mg	800 mg

[a]Use 1 mg/mL DigiFab concentration for dose accuracy

Dosage Administration:

Reconstitute each vial with 4 mL NS for a 10 mg/mL concentration and infuse IV dose over 30 min. If an infusion rate reaction occurs, stop infusion and restart at a slower rate. In situations of cardiac arrest, DigiFab can be administered as a bolus injection, but expect an increased risk for infusion-related reactions. For smaller doses, vials may be reconstituted with 36 mL NS for a 1 mg/mL concentration.

Contraindicated if hypersensitive to sheep products. **Use with caution** in renal **or** cardiac failure. May cause rapidly developing severe hypokalemia, decreased cardiac output (from withdrawal of digoxin's inotropic effects), rash, edema, and phlebitis. Digoxin therapy may be reinstituted in 3–7 days, when toxicity has been corrected. Digoxin-immune FAB will interfere with digitalis immunoassay measurements to result in misleading concentrations.

For explanation of icons, see p. 667

DILTIAZEM
Cardizem, Cardizem CD, Cardizem LA, Cartia XT, Matzim LA, Taztia XT, Tiazac, and many others including generics
Calcium channel blocker, antihypertensive

Tabs: 30, 60, 90, 120 mg
Extended-release tabs (for Q24 hr dosing):
Various generics: 180, 240, 300, 360, 420 mg
Cardizem LA: 120, 180, 240, 300, 360, 420 mg
Matzim LA: 180, 240, 300, 360, 420 mg
Extended-release caps (for Q12 hr dosing): 60, 90, 120 mg
Extended-release caps (for Q24 hr dosing):
Various generics: 120, 180, 240, 300, 360, 420 mg
Cardizem CD, Taztia XT: 120, 180, 240, 300, 360 mg
Cartia XT: 120, 180, 240, 300 mg
Tiazac: 120, 180, 240, 300, 360, 420 mg
Oral liquid: 12 mg/mL
Injection: 5 mg/mL (5, 10, 25 mL)

Hypertension:
Child: 1.5–2 mg/kg/24 hr PO ÷ TID–QID; **max. dose:** 3.5 mg/kg/24 hr, alternative **max. dose** of 6 mg/kg/24 hr up to 360 mg/24 hr have been recommended
Adolescent and adult:
Immediate release: 30–120 mg/dose PO TID–QID; usual range 180–360 mg/24 hr
Extended release: 120–360 mg/24 hr PO ÷ once daily–BID (BID dosing with Q12 hr extended release generic capsule; once daily dosing with extended-release tabs, Cardizem CD, Cartia XT, Cardizem LA, Matzim LA, Taztia XT, Tiazac and Q24 hr generic extended release capsule or tab); **max. dose:** 540 mg/24 hr

Contraindicated in acute myocardial infarction (MI) with pulmonary congestion, second- or third-degree heart block, and sick sinus syndrome**. Use with caution** in CHF or renal and hepatic impairment. Dizziness, headache, edema, nausea, vomiting, heart block, and arrhythmias may occur. Acute hepatic injury and severe skin reactions have been reported. Monitor heart rate with concurrent clonidine use (sinus bradycardia has been reported).
Diltiazem is a substrate and inhibitor of the CYP 450 3A4 enzyme system. May increase levels and effects/toxicity of buspirone, cyclosporine, carbamazepine, fentanyl, digoxin, ivabradine, quinidine, tacrolimus, benzodiazepines, and β-blockers. Cimetidine and statins may increase diltiazem serum levels. Rifampin may decrease diltiazem serum levels.
Maximal antihypertensive effect seen within 2 wk. Extended-release dosage forms should be swallowed whole and NOT crushed or chewed. Cardizem immediate-release tablets should be swallowed whole, as crushing or chewing them may alter their pharmacokinetics.

DIMENHYDRINATE
Dramamine, Driminate, and generics
Antiemetic, antihistamine

Tabs (OTC): 50 mg
Chewable tabs (OTC): 50 mg; contains 1.5 mg phenylalanine
Injection: 50 mg/mL; contains benzyl alcohol and propylene glycol

DIMENHYDRINATE *continued*

Child (<12 yr): 5 mg/kg/24 hr ÷ Q6 hr PO/IM/IV; alternative oral dosing by age:
2–5 yr: 12.5–25 mg/dose Q6–8 hr PRN PO with the max. dosage below
6–12 yr: 25–50 mg/dose Q6–8 hr PRN PO with the max. dosage below
≥12 yr and adult: 50–100 mg/dose Q4–6 hr PRN PO/IM/IV
MAX. PO DOSE:
2–5 yr: 75 mg/24 hr
6–12 yr: 150 mg/24 hr
≥12 yr and adult: 400 mg/24 hr
MAX. IM DOSE:
Child: 300 mg/24 hr

Causes drowsiness and anticholinergic side effects. May mask vestibular symptoms and cause CNS excitation in young children. **Caution** when taken with ototoxic agents or history of seizures. **Use should be limited to management of prolonged vomiting of known etiology. Not recommended** in children <2 yr. Toxicity resembles anticholinergic poisoning.

DIPHENHYDRAMINE
Benadryl, many other brand names, and generics
Antihistamine

Elixir (OTC): 12.5 mg/5 mL; may contain 5.6% alcohol
Oral liquid/solution (OTC): 12.5 mg/5 mL
Caps/Tabs (OTC): 25, 50 mg
Chewable tabs (OTC): 12.5 mg; contains aspartame, phenylalanine
Injection: 50 mg/mL
Topical cream (OTC): 1, 2% (30 g)
Topical gel (OTC): 2% (118 mL); contains parabens
Topical stick (OTC): 2% (14 mL); contains alcohol

Severe allergic reaction (anaphylaxis) and dystonic reactions (including phenothiazine toxicity) (PO/IM/IV):
Child: 1–2 mg/kg/dose Q6 hr; usual dose: 5 mg/kg/24 hr ÷ Q6 hr. **Max. dose**: 50 mg/dose and 300 mg/24 hr
Adult: 25–50 mg/dose Q4–8 hr; **max. dose**: 400 mg/24 hr
Sleep aid (PO/IM/IV): Administer dose 30 min before bedtime.
2–11 yr: 0.5–1 mg/kg/dose; **max. dose**: 50 mg/dose
≥12 yr: 50 mg
Topical (cream, gel, stick):
≥2 yr–adult: Apply 1% or 2% to affected area no more than TID–QID.

Contraindicated with concurrent MAO inhibitor use, acute attacks of asthma, GI or urinary obstruction. **Use with caution** in infants and young children, and **do not use** in neonates due to potential CNS effects. Side effects include sedation, nausea, vomiting, xerostoma, blurred vision, and other reactions common to antihistamines. CNS side effects more common than GI disturbances. May cause paradoxical excitement in children. False-positive test for urine phencyclidine (PCP) screen may occur. **Adjust dose in renal failure (see Chapter 31).**
TOPICAL USE: side effects include rash, urticaria, and photosensitivity.

For explanation of icons, see p. 667

DIVALPROEX SODIUM
Depakote, Depakote Sprinkles, Depakote ER, and generics
Anticonvulsant

Delayed-release tabs: 125, 250, 500 mg
Extended-release tabs (Depakote ER and generics): 250, 500 mg
Sprinkle caps (Depakote Sprinkles and generics): 125 mg

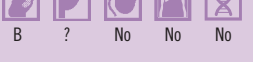
Dose: see Valproic Acid

See Valproic Acid. Preferred over valproic acid for patients on ketogenic diet. **Contraindicated** with known urea cycle disorders. Depakote ER is prescribed by a once-daily interval, whereas Depakote is typically prescribed BID. Depakote and Depakote ER are not bioequivalent; see package insert for dose conversion.

Efficacy was not established in separate randomized double-blinded, placebo-controlled trials for the treatment of pediatric bipolar disorder (10–17 yr old) and migraine prophylaxis (12–17 yr old).

Pregnancy category is "X" when used for migraine prophylaxis and is a "D" for all other indications.

DOBUTAMINE
Various generics; previously available as Dobutrex
Sympathomimetic agent



Injection: 12.5 mg/mL (20, 40 mL); contains sulfites
Prediluted injection in D_5W: 1 mg/mL (250 mL), 2 mg/mL (250 mL), 4 mg/mL (250 mL)

Continuous IV infusion (all ages): 2–20 mCg/kg/min
Max. dose: 40 mCg/kg/min
To prepare infusion: see IV infusions on page i

Contraindicated in idiopathic hypertrophic subaortic stenosis (IHSS). Tachycardia, arrhythmias (premature ventricular contractions [PVCs]), and hypertension may occasionally occur (especially at higher infusion rates). Correct hypovolemic states before use. Increases AV conduction, and may precipitate ventricular ectopic activity.

Dobutamine has been shown to increase cardiac output and systemic pressure in pediatric patients of every age group. However, in premature neonates, dobutamine is less effective than dopamine in raising systemic blood pressure without causing undue tachycardia, and dobutamine has not been shown to provide any added benefit when given to such infants already receiving optimal infusions of dopamine.

Monitor BP and vital signs. $T_{1/2}$: 2 min. Peak effects in 10–20 min. Use with linezolid may potentially increase blood pressure. Use with catechol-O-methyltransferase (COMT) inhibitors (e.g., entacapone) may increase heart rate, arrhythmias, and changes in blood pressure.

DOCUSATE
Colace, DocuSol Kids, DocuSol, Kao-Tin, Enemeez Mini, and many other brands
Stool softener, laxative

Available as docusate sodium:
Caps (OTC): 100, 250 mg; sodium content (100 mg cap: ~5 mg)
Tabs (OTC): 100 mg
Syrup (OTC): 20 mg/5 mL (473 mL); may contain alcohol
Oral liquid (OTC): 10 mg/mL (118, 473 mL); contains 1 mg/mL sodium
Rectal enema:
DocuSol Kids (OTC): 100 mg/5 mL (5 mL); contains polyethylene glycol
Enemeez Mini, and DocuSol (OTC): 283 mg/5 mL (5 mL); DocuSol Plus product contains benzocaine
Available as docusate calcium:
Caps (Kao-Tin and generics; OTC): 240 mg

PO (take with liquids; see remarks):
<3 yr: 10–40 mg/24 hr ÷ once daily–QID
3–6 yr: 20–60 mg/24 hr ÷ once daily–QID
6–12 yr: 40–150 mg/24 hr ÷ once daily–QID
>12 yr and adult: 50–400 mg/24 hr ÷ once daily–QID
Rectal (see remarks):
2–<12 yr: 100 mg/5 mL or 283 mg/5 mL PR once daily
≥12 yr and adult: 283 mg/5 mL PR once daily–TID. Alternatively, 50–100 mg of oral liquid (not syrup) mixed in enema fluid (saline or oil retention enemas) may be used.

Oral dosage effective only after 1–3 days of therapy, whereas the enema has an onset of action in 2–15 min. Reassess therapy if no response seen after 7 days of continuous use.
Incidence of side effects is exceedingly low. Rash, nausea, and throat irritation have been reported. Oral liquid is bitter; give with milk, fruit juice, or formula to mask taste.
A few drops of the 10 mg/mL oral liquid may be used in the ear as a cerumenolytic. Effect is usually seen within 15 min.

DOLASETRON
Anzemet
Antiemetic agent, 5-HT3 antagonist

Tabs: 50, 100 mg
Oral suspension: 10 mg/mL

Chemotherapy-induced nausea and vomiting prevention:
2 yr–adult: 1.8 mg/kg/dose PO up to a **max. dose** of 100 mg. Administer PO dose 60 min prior to chemotherapy. IV route of administration is considered contraindicated for this indication due to increased risk for QTc prolongation.
Postoperative nausea and vomiting prevention: Administer PO dose 2 hr prior to surgery and IV dose 15 min prior to cessation of anesthesia.
2–16 yr:
PO: 1.2 mg/kg/dose ×1 (**max. dose**: 100 mg) ×1
IV: 0.35 mg/kg/dose (**max. dose**: 12.5 mg) ×1
Adult:
IV: 12.5 mg/dose ×1

For explanation of icons, see p. 667

DOLASETRON *continued*

Postoperative nausea and vomiting treatment: Administer IV at onset of nausea and vomiting.
2–16 yr: 0.35 mg/kg/dose (**max. dose**: 12.5 mg) IV
>16 yr–adult: 12.5 mg/dose IV

May cause hypotension and prolongation of cardiac conduction intervals, particularly QTc interval (dose-dependent effect). Common side effects include dizziness, headache, sedation, blurred vision, fever, chills, and sleep disorders. Rare cases of sustained supraventricular and ventricular arrhythmias, fatal cardiac arrest, and MI have been reported in children and adolescents.

Avoid use in patients with congenital long QTc syndrome, hypomagnesemia, hypokalemia, or with concurrent use with other drugs that increase QTc interval (e.g., erythromycin, cisapride). Drug's active metabolite (hydrodolasetron) is a substrate for CYP 450 2D6 and 3A3/4 isoenzymes; concomitant use of enzyme inhibitors (e.g., cimetidine) may increase risk for side effects, and use of enzyme inducers (e.g., rifampin) may decrease dolasetron's efficacy. Serotonin syndrome has been associated with concurrent use of SSRIs (e.g., fluoxetine, sertraline), SNRIs (e.g., duloxetine, venlafaxine), MAO inhibitors, mirtazapine, fentanyl, lithium, tramadol, and IV methylene blue.

Although no dosage adjustments are necessary, hydrodolasetron's clearance decreases 42% with severe hepatic impairment and 44% with severe renal impairment.

ECG monitoring is recommended in patients with electrolyte abnormalities, CHF, bradyarrhythmias or renal impairment.

IV doses may be administered undiluted over 30 sec.

DOPAMINE
Various generics; previously available as Intropin
Sympathomimetic agent

Injection: 40 mg/mL (5, 10 mL)
Prediluted injection in D_5W: 0.8, 1.6, 3.2 mg/mL (250, 500 mL)

All ages:

Low dose: 2–5 mCg/kg/min IV; increases renal blood flow; minimal effect on heart rate and cardiac output
Intermediate dose: 5–15 mCg/kg/min IV; increases heart rate, cardiac contractility, cardiac output, and to a lesser extent, renal blood flow.
High dose: >15 mCg/kg/min IV; α adrenergic effects are prominent; decreases renal perfusion.
Max. dose recommended: 20–50 mCg/kg/min IV
To prepare infusion: see IV infusions on page i.

Do not use in pheochromocytoma, tachyarrhythmias, or hypovolemia. Monitor vital signs and blood pressure continuously. Correct hypovolemic states. Tachyarrhythmias, ectopic beats, hypertension, vasoconstriction, and vomiting may occur. **Use with caution** with phenytoin because hypotension and bradycardia may be exacerbated. Use with linezolid may potentially increase blood pressure.

Newborn infants may be more sensitive to the vasoconstrictive effects of dopamine. Children <2 yr of age clear dopamine faster, and high variability in neonates is exhibited.

Should be administered through a central line or large vein. Extravasation may cause tissue necrosis; treat with phentolamine. **Do not** administer into an umbilical arterial catheter.

DORNASE ALFA/DNASE
Pulmozyme
Inhaled mucolytic

Inhalation solution: 1 mg/mL (2.5 mL; in boxes of 30s)

Cystic fibrosis:
Child ≥5 yr and adult: 2.5 mg via nebulizer once daily. Some patients may benefit from 2.5 mg BID.

Contraindicated in patients with hypersensitivity to epoetin alfa. Voice alteration, pharyngitis, laryngitis may result. These are generally reversible without dose adjustment. Safety and efficacy have not been demonstrated in patients >1 yr of continuous use.

Do not mix with other nebulized drugs. An inhaled β-agonist may be useful before administration to enhance drug distribution. Chest physiotherapy should be incorporated into treatment regimen. The following nebulizer compressor systems have been recommended for use: Pulmo-Aide, Pari-Proneb, Mobilaire, Porta-Neb, or PariBaby. Use of the "Sidestream" nebulizer cup can significantly reduce the medication administration time.

DOXAPRAM HCL
Dopram
CNS stimulant

Injection: 20 mg/mL (20 mL); contains 0.9% benzyl alcohol

Methylxanthine-refractory neonatal apnea (see remarks): Load with 2.5–3 mg/kg IV over 15 min, followed by a continuous IV infusion of 1 mg/kg/hr titrated to the lowest effective dose; **max. dose**: 2.5 mg/kg/hr

Contraindicated in seizures, proven or suspected pulmonary embolism, head injuries, cerebral vascular accident, cerebral edema, cardiovascular or coronary artery disease, severe hypertension, pheochromocytoma, hyperthyroidism, and in patients with mechanical disorders of ventilation. **Do not** use with general anesthetic agents that can sensitize the heart to catecholamines (e.g., halothane, cyclopropane, and enflurane) to reduce the risk of cardiac arrhythmias, including ventricular tachycardia and ventricular fibrillation. **Do not** initiate doxapram until the general anesthetic agent has been completely excreted.

Assess the benefit-risk of benzyl alcohol exposure to neonates. Hypertension occurs with higher doses (>1.5 mg/kg/hr). May also cause tachycardia, arrhythmias, seizure, hyperreflexia, hyperpyrexia, abdominal distension, bloody stools, and sweating. **Avoid** extravasation into tissues.

DOXYCYCLINE
Acticlate, Vibramycin, Doryx, Monodox, Oracea, many others and generics
Antibiotic, tetracycline derivative

Caps: 50, 75, 100, 150 mg
Tabs (Acticlate and generics): 20, 50, 75, 100, 150 mg
Delayed release caps (Oracea and generics): 40 mg
Delayed release tabs (Doryx and generics): 50, 75, 100, 150, 200 mg
Syrup: 50 mg/5 mL (473 mL); contains parabens and propylene glycol
Oral suspension: 25 mg/5 mL (60 mL)
Injection: 100 mg

For explanation of icons, see p. 667

DOXYCYCLINE *continued*

General Dosing, Lyme Disease, Rickettsial Disease, and Skin/Soft-Tissue Infection: (see remarks):
≤45 kg: 2.2 mg/kg/dose BID PO/IV; **max. dose**: 200 mg/24 hr
>45 kg: 100 mg/dose BID PO/IV
Max. dose: 200 mg/24 hr

PID:
Inpatient: 100 mg IV Q12 hr with cefotetan or cefoxitin, or ampicillin/sulbactam. Convert to oral therapy 24 hr after patient improves on IV to complete a 14-day total course (IV and PO).
Outpatient: 100 mg PO Q12 hr ×14 days with ceftriaxone, cefoxitin + probenecid, or other parenteral third-generation cephalosporin with or without metronidazole

Anthrax (inhalation/systemic/cutaneous; see remarks): Initiate therapy with IV route and convert to PO route when clinically appropriate. Duration of therapy is 60 days (IV and PO combined):
≤8 yr or ≤45 kg: 2.2 mg/kg/dose BID IV/PO; **max. dose**: 200 mg/24 hr
>8 yr and >45 kg: 100 mg/dose BID IV/PO

Malaria prophylaxis (start 1–2 days prior to exposure and continue for 4 wk after leaving endemic area):
>8 yr: 2.2 mg/kg/24 hr PO once daily; **max. dose**: 100 mg/24 hr and max. duration of 4 mo.
Adult: 100 mg PO once daily

Periodontitis:
Adult: 20 mg BID PO × ≤9 mo

Use with caution in hepatic and renal disease. Generally **not recommended** for use in children <8 yr due to risk for tooth enamel hypoplasia and discoloration. However, the AAP Redbook recommends doxycycline as the drug of choice for rickettsial disease regardless of age and the use in children <8 yr for short treatment courses (≤21 days). May cause GI symptoms, photosensitivity, hemolytic anemia, rash, and hypersensitivity reactions. Increased intracranial pressure (pseudotumor cerebri), TEN, DRESS, erythema multiforme, and Stevens-Johnson syndrome have been reported.

Doxycycline is approved for the treatment of anthrax (Bacillus anthracis) in combination with one or two other antimicrobials. If meningitis is suspected, consider using an alternative agent because of poor CNS penetration. Consider changing to high-dose amoxicillin (25–35 mg/kg/dose TID PO) for penicillin-susceptible strains. See www.bt.cdc.gov for the latest information.

Rifampin, barbiturates, phenytoin, and carbamazepine may increase clearance of doxycycline. Doxycycline may enhance the hypoprothrombinemic effect of warfarin. See Tetracycline for additional drug/food interactions and remarks.

Infuse IV over 1–4 hr. **Avoid** prolonged exposure to direct sunlight.

For periodontitis, take tablets ≥1 hr prior or 2 hr after meals.

DRONABINOL
Marinol, Syndros, Tetrahydrocannabinol, THC, and generics
Antiemetic

Caps (Marinol and generics): 2.5, 5, 10 mg; may contain sesame oil
Oral solution (Syndros): 5 mg/mL (30 mL); contains alcohol (50% w/w), parabens, and polyethylene glycol

Oral capsule and solution dosage forms are NOT bioequivalent and should not be used interchangeably.

ORAL CAPSULES:
Antiemetic:
Child and adult (PO capsules): 5 mg/m²/dose 1–3 hr prior to chemotherapy, then Q2–4 hr up to a **max. dose** of 4–6 doses/24 hr; doses may be gradually increased by 2.5 mg/m²/dose as needed and tolerated.

DRONABINOL *continued*

Appetite stimulant:

Adult (PO capsules): 2.5 mg BID 1 hr before lunch and dinner; if not tolerated, reduce dose to 2.5 mg once daily 1 hr before dinner or QHS. **Max dose**: 20 mg/24 hr (use **caution** when increasing doses because of increased risk of dose-related adverse reactions at higher dosages)

ORAL SOLUTION:

Antiemetic:

Adult (PO oral solution): 4.2 mg/m^2/dose 1–3 hr prior to chemotherapy, then Q2–4 hr up to a **max. dose** of 4–6 doses/24 hr; doses may be gradually increased by 2.1 mg/m^2/dose increments up to a **max. dose** of 12.6 mg/m^2/dose if needed and tolerated.

Appetite stimulant:

Adult (PO oral solution): 2.1 mg BID 1 hr before lunch and dinner; if not tolerated, reduce dose to 2.1 mg once daily 1 hr before dinner or QHS. Dose may be gradually increased, if needed and tolerated, by increasing the pre-dinner dose to 4.2 mg 1 hr before dinner. Further increase to 4.2 mg BID 1 hr before lunch and dinner if needed and tolerated. **Max. dose**: 16.8 mg/24 hr.

Contraindicated in patients with history of substance abuse and mental illness and allergy to sesame oil (capsules only). **Use with caution** in heart disease, seizures, hepatic disease (reduce dose if severe), and in patients who operate motor vehicles or dangerous machinery. Side effects: euphoria, dizziness, difficulty concentrating, anxiety, mood change, sedation, hallucinations, ataxia, paresthesia, hypotension, excessively increased appetite, and habit-forming potential. Exacerbation of mania, depression, schizophrenia, and seizures have been reported. **Avoid use** with other medications that can produce similar side effects.

Dronabinol is a substrate for CYP 450 2C9 and 3A4. Individuals with poor CYP 450 2C9 activity may have reduced clearance of dronabinol which may increase effects/toxicity.

Onset of action: 0.5–1 hr; duration of psychoactive effects 4–6 hr, appetite stimulation 24 hr.

DROPERIDOL

Generics; previously available as Inapsine

Sedative, antiemetic

C	3	Yes	Yes	No

Injection: 2.5 mg/mL (2 mL)

Antiemetic/sedation:

Child: 0.03–0.07 mg/kg/dose IM or IV over 2–5 min; if needed, may give 0.1–0.15 mg/kg/dose; **initial max. dose**: 0.1 mg/kg/dose and subsequent **max. dose**: 2.5 mg/dose.

Dosage interval:

Antiemetic: PRN Q4–6 hr

Sedation: Repeat dose in 15–30 min if necessary

Adult: 2.5–5 mg IM or IV over 2–5 min; **initial max. dose** is 2.5 mg.

Dosage interval:

Antiemetic: PRN Q3–4 hr

Sedation: Repeat dose in 15–30 min if necessary.

Use with caution in renal and hepatic impairment; 75% of metabolites are excreted renally, and drug is extensively metabolized in the liver. Side effects include hypotension, tachycardia, extrapyramidal side effects such as dystonia, feeling of motor restlessness, laryngospasm, bronchospasm. May lower seizure threshold. **Fatal arrhythmias and QT interval prolongation has been associated with use.**

Onset in 3–10 min. Peak effects within 10–30 min. Duration of 2–4 hr. Often given as adjunct to other agents.

For explanation of icons, see p. 667

E

ELEXACAFTOR/TEZACAFTOR/IVACAFTOR

Trikafta

Cystic Fibrosis Transmembrane Conductance Regulator Corrector and Potentiator

Tabs:

Morning dose (orange colored): elexacaftor 100 mg + tezacaftor 50 mg + ivacaftor 75 mg

Evening dose (light blue colored): ivacaftor 150 mg

Available as an 84-tablet carton containing 4 wallets for a 28-day supply; each wallet contains 14 morning-dose tablets and 7 evening-dose tablets for a 7-day supply

Child ≥12 yr and adult (PO, morning and evening dose should be taken ~12 hr apart with fat-containing food; see remarks):

Morning dose: 2 morning-dose tablets (elexacaftor 100 mg + tezacaftor 50 mg + ivacaftor 75 mg each tablet) every morning

Evening dose: 1 evening-dose tablet (150 mg ivacaftor) every evening

Dose Adjustment for Hepatic Impairment:

	Mild (Child-Pugh Class A)	[a]Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
Morning dose	Use regular dosage	Use regular dosage	Should not be used
Evening dose	Use regular dosage	No evening dosage	Should not be used

[a]Use not recommended unless benefit exceeds risk

Dose Adjustment for Moderate CYP 450 3A inhibitors (e.g., fluconazole, erythromycin):
Administer doses in the morning only.

Day 1: 2 morning-dose tablets (elexacaftor 100 mg + tezacaftor 50 mg + ivacaftor 75 mg each tablet)

Day 2: 1 evening-dose tablet (ivacaftor 150 mg) in the morning

Day 3: 2 morning-dose tablets

Day 4: 1 evening-dose tablet (ivacaftor 150 mg) in the morning, then continue with 2 morning-dose tablets and one evening-dose tablet (administered in the mornings) on alternate days

Dose Adjustment for Strong CYP 450 3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin): Morning doses only.

Day 1: 2 morning-dose tablets (elexacaftor 100 mg + tezacaftor 50 mg + ivacaftor 75 mg each tablet)

Days 2 and 3: no dose

Day 4: 2 morning-dose tablets, then continue with 2 morning-dose tablets twice a week (approximately 3–4 days apart)

Works on CFTR trafficking defects with two correctors (elexacaftor and tezacaftor) and a potentiator (ivacaftor). Indicated for individuals with at least one F508del CFTR mutation.

Common side effects include headache, URI, abdominal pain, diarrhea, rash, nasal congestion, rhinorrhea, rhinitis, influenza sinusitis, and increases in liver enzymes (ALT/AST, bilirubin) and serum creatine phosphokinase. Monitor baseline ALT/AST and bilirubin at baseline and repeat every 3 mo for the first year followed by annual assessments. Ocular exams should be obtained at baseline and annually as cataracts have been reported in children. May cause a false-positive urine drug screen for cannabinoids.

Do not use in severe hepatic impairment (Child-Pugh C) and use is not recommended, unless the benefit outweighs the risk, for moderate hepatic impairment (Child-Pugh B). **Use with caution** with

ELEXACAFTOR/TEZACAFTOR/IVACAFTOR *continued*

All three components of this medication are substrates of CYP 450 3A. **Avoid use** in combination with strong inducers of CYP 450 3A (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort). Use with moderate and strong CYP 3A inhibitors requires dose reductions; see dosing section. Elexacaftor/tezacaftor/ivacaftor may increase the effects/toxicity of digoxin, cyclosporine, everolimus, glimepiride, glipizide, glyburide, nateglinide, repaglinide, sirolimus, tacrolimus, and warfarin. Always evaluate the potential drug-drug interactions.

Avoid food or drink containing grapefruit or Seville oranges.

Administer all doses with high-fat foods to assure absorption. If a dose is missed within 6 hr of a scheduled dose, administer the respective morning or evening dose immediately and resume usual dosing. However, if the missed dose is >6 hr, the following is recommended:

Missed morning dose: take missed dose as soon as possible and do not take evening dose for that day; then resume usual dosing the next day.

Missed evening dose: do not take the missed dose; then resume usual dosing the next day.

Never take a double dose for a missed dose.

EMLA

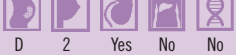
See Lidocaine and Prilocaine

ENALAPRIL MALEATE (PO), ENALAPRILAT (IV)

Enalapril: Vasotec, Epaned, and generics

Enalaprilat: generics; previously available as Vasotec IV

Angiotensin converting enzyme inhibitor, antihypertensive



D 2 Yes No No

Enalapril:

Tabs (Vasotec and generics): 2.5, 5, 10, 20 mg (scored)

Oral solution (Epaned): 1 mg/mL (150 mL); contains sodium benzoate

Oral suspension: 0.1, 1 mg/mL

Enalaprilat:

Injection: 1.25 mg/mL (1, 2 mL); contains benzyl alcohol

Hypertension:

Infant and child:

PO: 0.08 mg/kg/24 hr up to 5 mg/24 hr once daily; increase PRN over 2 wk.

Max. dose (higher doses have not been evaluated): 0.58 mg/kg/24 hr up to 40 mg/24 hr

IV: 0.005–0.01 mg/kg/dose Q8–24 hr; **max. dose**: 1.25 mg/dose

Adolescent and adult:

PO: 2.5–5 mg/24 hr once daily initially to **max. dose** of 40 mg/24 hr ÷ once daily–BID

IV: 0.625–1.25 mg/dose IV Q6 hr; doses as high as 5 mg Q6 hr is reported to be tolerated for up to 36 hr.

Contraindicated with hypersensitivity to ACE inhibitors and use in combination with a neprilysin inhibitor (e.g., sacubitril). **Use with caution** in bilateral renal artery stenosis. **Avoid use** in dialysis with high-flux membranes because anaphylactoid reactions have been reported. Side effects: nausea, diarrhea, headache, dizziness, hyperkalemia, hypoglycemia, hypotension, and hypersensitivity. Cough is a reported side effect of ACE inhibitors.

Risk for angioedema increases with enalapril and coadministration of rapamycin or sacubitril.

Enalapril (PO) is converted to its active form (Enalaprilat) by the liver. Administer IV over 5 min. **Adjust dose in renal impairment (see Chapter 31).**

For explanation of icons, see p. 667

EMLA *continued*

Nitritoid reactions have been seen in patients receiving concomitant IV gold therapy. Enalapril/enalaprilat should be discontinued as soon as possible when pregnancy is detected. If oliguria or hypotension occurs in a neonate with in utero exposure with enalapril/enalaprilat, exchange transfusions or dialysis may be needed to reverse hypotension and/or support renal function.

ENOXAPARIN
Lovenox and generics
Anticoagulant, low-molecular-weight heparin

Injection: 100 mg/mL (3 mL); contains pork proteins and 15 mg/mL benzyl alcohol
Injection (pre-filled syringes with 27-gauge × ½-inch needle): 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL, 120 mg/0.8 mL, 150 mg/1 mL; preservative free and may contain pork proteins
Approximate anti–factor Xa activity: 100 IU per 1 mg

Initial empiric dosage; patient-specific dosage defined by therapeutic drug monitoring when indicated (see remarks).

DVT treatment:
<2 mo: 1.5 mg/kg/dose Q12 hr SC; higher doses of 1.7–2 mg/kg/dose Q12 hr SC have been recommended for neonates
≥2 mo—adult: 1 mg/kg/dose Q12 hr SC; alternatively, 1.5 mg/kg/dose Q24 hr SC can be used in adults.
Dosage adjustment for DVT treatment to achieve target anti–factor Xa low molecular weight heparin (LMWH) levels of 0.5–1 units/mL (see the following table).

Anti-factor Xa Level LMWH (units/mL)	Hold Next Dose?	Dose Change	Repeat Anti-factor Xa Level LMWH?
<0.4	No	Increase by 25%	4 hr post next new AM dose
0.4	No	Increase by 10%	4 hr post next new AM dose
0.5	No	No	4 hr post next AM dose; if within therapeutic range recheck 1 wk later at 4 hr post dose
0.6–0.7	No	No	1 wk later at 4 hr post dose
0.8–1	No	No	4 hr post next AM dose; if within therapeutic range recheck 1 wk later at 4 hr post dose
1.1–1.5	No	Decrease by 20%	4 hr post next new AM dose
1.6–2	3 hr and measure trough level (goal <0.5 units/mL) prior to next new dose	Decrease by 30%	4 hr post next new AM dose
>2	Until anti-factor Xa LMWH reaches 0.5 units/mL (levels can be measured Q12 hr until it reaches ≤0.5 units/mL).	When anti-factor Xa LMWH reaches ≤0.5 units/mL, dose may be restarted at a dose 40% less than originally prescribed.	4 hr post next new AM dose

ENOXAPARIN *continued*

DVT prophylaxis:

Infant <2 mo: 0.75 mg/kg/dose Q12 hr SC

Infant ≥2 mo—child 18 yr: 0.5 mg/kg/dose Q12 hr SC; **max. dose**: 30 mg/dose

Patients with indwelling epidural catheters/neuraxial anesthesia (≥2 mo–child 18 yr): 1 mg/kg/dose Q24 hr SC; **max. dose**: 40 mg/dose. Twice-daily dosing is contraindicated for these patients. See remarks.

Adjust dosage for DVT prophylaxis to achieve target anti–factor Xa levels of 0.1–0.3 units/mL for all children.

Adult:

Knee or hip replacement surgery: 30 mg BID SC ×7–14 days; initiate therapy 12–24 hr after surgery provided hemostasis is established. Alternatively, for hip replacement surgery, 40 mg once daily SC ×7–14 days initially up to 3 wk thereafter; initiate therapy 9–15 hr prior to surgery.

Inhibits thrombosis by inactivating factor Xa without significantly affecting bleeding time, platelet function, PT, or aPTT at recommended doses. Dosages of enoxaparin, heparin, or other LMWHs **CANNOT** be used interchangeably on a unit-for-unit (or mg-for-mg) basis because of differences in pharmacokinetics and activity. Peak anti–factor Xa LMWH activity is achieved 4 hr after a SC dose**. Anti–factor Xa LMWH is NOT THE SAME as unfractionated heparin anti–factor Xa level (used for monitoring heparin therapy).**

Contraindicated in major bleeding, drug-induced thrombocytopenia, and pork hypersensitivity. **Use with caution** in uncontrolled arterial hypertension, bleeding diathesis, history of recurrent GI ulcers, diabetic retinopathy, and severe renal dysfunction (reduce dose by increasing the dosage interval from Q12 hr to Q24 hr if GFR <30 mL/min). Prophylactic use is not recommended in patients with prosthetic heart valves (especially in pregnant women) due to reports of fatalities in patients and fetuses. **Concurrent use with spinal or epidural anesthesia or spinal puncture has resulted in long-term or permanent paralysis; potential benefits must be weighed against the risks.** May cause fever, confusion, edema, nausea, hemorrhage, thrombocytopenia (including heparin-induced thrombocytopenia ± thrombosis [HIT/HITTS]), hypochromic anemia, and pain/erythema at injection site. Allergic reactions, headache, eosinophilia, alopecia, hepatocellular and cholestatic liver injury, and osteoporosis (long-term use) have been reported. **Protamine sulfate is the antidote**; 1 mg protamine sulfate neutralizes 1 mg enoxaparin.

DVT prophylaxis for patients with epidural catheters/neuraxial anesthesia: If placing needle, hold anticoagulation for 12 hr and restart dosing no sooner than 4 hr after needle insertion. If removing catheter, hold anticoagulation for 12 hr and restart dosing no sooner than 2 hr after catheter removal.

Recommended anti–factor Xa LMWH levels obtained 4 hr after subcutaneous dose after the third consecutive dose for children (anti–factor Xa LMWH response in children is highly variable compared to adults):
DVT treatment: 0.5–1 units/mL
DVT prophylaxis: 0.1–0.3 units/mL

Administer by deep SC injection by having the patient lie down. Alternate administration between the left and right anterolateral and left and right posterolateral abdominal wall. See package insert for detailed SC administration recommendations. To minimize bruising, do not rub the injection site. IM route of administration is not recommended.

For additional information, see *Chest* 2008;133:887–968 and *Regional Anesthesia and Pain Medicine* 2003;28(3):172–197.

For explanation of icons, see p. 667

EPINEPHRINE HCL
Adrenalin, EpiPen, Auvi-Q, Symjepi, Adrenaclick, Adyphren, Epinephrine SNAP, Primatene Mist, and generics
Sympathomimetic agent

Injection:
1:1000 (aqueous): 1 mg/mL (1, 30 mL); may contain chlorobutanol and metabisulfite
1:10,000 (aqueous): 0.1 mg/mL (10 mL pre-filled syringes with either 18-G 3.5 inch or 20-G 1.5-inch needles)

Autoinjector:
EpiPen and generics: Delivers a single 0.3 mg (0.3 mL) dose (2 pack; EpiPen and some generic products include a training device)
EpiPen Jr and generics: Delivers a single 0.15 mg (0.3 mL) dose (2 pack; EpiPen Jr and some generic products include a training device)
Auvi-Q: Delivers a single 0.1 mg (0.1 mL) dose, 0.15 mg (0.15 mL) dose, or 0.3 mg (0.3 mL) dose (2 pack with training device; each unit provides voice instructions when activated)
Symjepi: Delivers a single 0.15 mg (0.3 mL) dose or 0.3 mg (0.3 mL) dose (1 or 2 pack)
Adrenaclick: Delivers a single 0.15 mg (0.15 mL) dose, or 0.3 mg (0.3 mL) dose (2 pack)

Syringe Kit for Anaphylaxis (for specific weight-based dosages for any size patient):
Adyphren, EpinephrineSNAP: 1 mg/mL (1 mL single use vial in a box of 25 vials, 30 mL multi-use vial as a single vial or box of 10 vials)

Many preparations may contain sulfites.

Aerosol inhaler (HFA; Primatene Mist [OTC]): 0.125 mg per spray (160 sprays per inhaler) (11.7 g); contains 1% alcohol and polysorbate 80

CARDIAC USE:

Neonate:

Asystole and bradycardia: 0.01–0.03 mg/kg of 1:10,000 solution (0.1–0.3 mL/kg) IV/ET Q3–5 min PRN.

Infant and child:

Bradycardia/asystole and pulseless arrest: See page ii and PALS algorithms in the back of the book.

Bradycardia, asystole, and pulseless arrest (see remarks):

First dose: 0.01 mg/kg of 1:10,000 solution (0.1 mL/kg) IO/IV; **max. dose**: 1 mg (10 mL). Subsequent doses Q3–5 min PRN should be the same. High-dose epinephrine after failure of standard dose has not been shown to be effective (see remarks). Must circulate drug with CPR. For ET route, see below.

All ET doses: 0.1 mg/kg of 1:1000 solution (0.1 mL/kg) ET Q3–5 min.

Adult:

Asystole: 1 mg IV or 2–2.5 mg ET Q3–5 min.

IV drip (all ages): 0.1–1 mCg/kg/min; titrate to effect; to prepare infusion, see inside front cover.

HYPERSENSITIVITY/ANAPHYLACTIC REACTIONS (recommended IM administration via the anterolateral aspect of the thigh through clothing if necessary; see remarks for IV dosing):

Infant, child, and adolescent: 0.01 mg/kg/dose IM (**max. dose**: 0.3 mg/dose for prepubertal child, 0.5 mg/dose for adolescent) Q5–15 min PRN.

Auvi-Q (administer the following dosage IM ×1; an additional dose may be repeated in 5–15 min):

7.5 to <15 kg: 0.1 mg

15 to <30 kg: 0.15 mg

≥30 kg: 0.3 mg

EpiPen/EpiPen Jr, Adrenaclick, Symjepi, or equivalent generic autoinjector (administer the following dosage IM ×1; an additional dose may be repeated in 5–15 min):

15 to <30 kg: 0.15 mg

≥30 kg: 0.3 mg

EPINEPHRINE HCL *continued*

Adult: Start with 0.2–0.5 mg IM Q5–15 min PRN. If using EpiPen, Adrenaclick, Symjepi, or equivalent generic autoinjector, use 0.3 mg IM ×1; an additional dose may be repeated in 5–15 min.

RESPIRATORY BRONCHODILATOR USE:

SC Injection (use 1:1000 or 1 mg/mL aqueous injection):

Infant and child: 0.01 mL/kg/dose SC (**max. single dose** 0.5 mL); repeat Q15 min ×3–4 doses or Q4 hr PRN

Adult: 0.3–0.5 mg (0.3–0.5 mL)/dose SC Q20 min ×3 doses.

Nebulization (alternative to racemic epinephrine): 0.5 mL/kg of 1:1000 solution diluted in 3 mL NS; **max. doses**: ≤4 yr: 2.5 mL/dose; >4 yr: 5 mL/dose

Aerosol inhaler (Primatene Mist):

≥12 yr and adult: 1–2 inhalation(s) PO Q4 hr PRN; **max. dose**: 8 inhalations/24 hr

High-dose rescue therapy for in-hospital cardiac arrest in children after failure of an initial standard dose has been reported to be of no benefit compared to standard dose (*N Engl J Med* 2004;350:1722–1730).

May produce arrhythmias, tachycardia, hypertension, headaches, nervousness, nausea, vomiting, and rare cases of stress cardiomyopathy. Necrosis may occur at site of repeated local injection. Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis, have been reported with IM or deep SC injections.

Concomitant use of noncardiac selective β-blockers, MAO inhibitors, COMT inhibitors, clonidine, or tricyclic antidepressants may enhance epinephrine's pressor response. Chlorpromazine, diuretics, nitrates, or α-blockers may reverse the pressor response. **Do not** use products containing chlorobutanol for ophthalmic use, as it may be harmful to the corneal endothelium.

ETT doses should be diluted with NS to a volume of 3–5 mL before administration. Follow with several positive pressure ventilations.

Hypersensitivity reactions: For bronchial asthma and certain allergic manifestations (e.g., angioedema, urticaria, serum sickness, anaphylactic shock), use epinephrine SC. Patients with anaphylaxis may benefit from IM administration. The adult IV dose for hypersensitivity reactions or to relieve bronchospasm usually ranges from 0.1 to 0.25 mg injected slowly over 5–10 min Q5–15 min as needed. Neonates may be given a dose of 0.01 mg/kg body weight; for infants, 0.05 mg is an adequate initial dose, and this may be repeated at 20- to 30-min intervals in the management of asthma attacks.

Due to the inconsistent availability of autoinjector products, periodic reeducation of available device may be necessary. See respective autoinjector product for proper dose administration methods including methods to prevent injury and/or inadvertent dose administration to the individual administering the dose. Accidental injection into the digits, hand, or feet may result in the loss of blood flow to the affected area. **Do not** inject into the buttock area.

EPINEPHRINE, RACEMIC
Asthmanefrin, and S-2
Sympathomimetic agent

Solution for inhalation (OTC): 2.25% (1.25% epinephrine base) (0.5 mL) (30s)
Contains edetate disodium and may contain sulfites.

<4 yr:

Croup (using 2.25% solution): 0.05 mL/kg/dose up to a **max. dose** of 0.5 mL/dose diluted to 3 mL with NS. Given via nebulizer over 15 min PRN but **not** more frequently than Q1–2 hr.

≥4 yr: 0.5 mL/dose diluted to 3 mL with NS via nebulizer over 15 min Q3–4 hr PRN

Tachyarrhythmias, headache, nausea, palpitations have been reported. Rebound symptoms may occur. Cardiorespiratory monitoring should be considered if administered more frequently

For explanation of icons, see p. 667

EPOETIN ALFA
Epogen, Procrit, and Erythropoietin
Recombinant human erythropoietin

Injection (single-dose, preservative-free vials): 2000, 3000, 4000, 10,000, 40,000 U/mL (1 mL)
Injection (multi-dose vials): 10,000 U/mL (2 mL), 20,000 U/mL (1 mL); contains 1% benzyl alcohol
All dosage forms contain 2.5 mg albumin per 1 mL.
NOTE: Epoetin alfa-epbx (Retacrit) is a biosimilar product available as single-dose preservative-free vials at 2000, 3000, 4000, 10,000, 40,000 U/mL (1 mL) and contains phenylalanine.

Anemia in chronic renal failure (see remarks for dosage adjustment and withholding therapy): SC/IV (IV preferred for hemodialysis patients)
Initial dose:
Child and adolescent: Start at 50 U/kg/dose 3 times per week. Reported dosage range for children (3 mo–20 yr) not requiring dialysis, 50–250 U/kg/dose 3 times per week. Reported dosage range for children receiving hemodialysis, 50–450 U/kg/dose 2–3 times per week.
Adult: Start at 50–100 U/kg/dose 3 times per week
Maintenance dose: Dose is individualized to achieve and maintain the lowest Hgb level sufficient to avoid transfusions and **not to exceed** 11 g/dL.

Anemia in cancer (use until chemotherapy is completed; see remarks for dosage reduction and withholding therapy):
Initial dose:
Child (5–18 yr): Start at 600 U/kg (**max. dose**: 40,000 U) IV once weekly.
Adult: Start at 150 U/kg/dose SC 3 times per week or 40,000 U SC once every week.
Increasing doses (if needed):
Three-times-a-week dosing regimen (adult): If no increase in Hgb >1 g/dL and Hgb remains <10 g/dL after initial 4 wk of therapy, increase dosage to 300 U/kg/dose 3 times per week.
Weekly dosing regimen: If no increase in Hgb >1 g/dL and Hgb remains <10 g/dL after initial 4 wk of therapy:
Child: Increase dose to 900 U/kg/dose IV (**max. dose**: 60,000 U) once weekly.
Adult: 60,000 U SC once weekly.
For all ages, discontinue use after 8 wk of therapy if transfusions are still required or no hemoglobin response is observed.

AZT-treated HIV patients (Hgb should not exceed 12 g/dL): SC/IV
Child: Reported dosage range in children (≥3 mo–17 yr), 50–400 U/kg/dose 2–3 times per wk.
Adult (with serum erythropoietin ≤500 milliunits/mL and receiving ≤4200 mg AZT per week): Start at 100 U/kg/dose 3 times per wk ×8 wk. If response is NOT satisfactory in reducing transfusion requirements or increasing Hgb levels after 8 wk of therapy, dose may be increased by 50–100 U/kg/dose given 3 times per wk and reevaluated every 4–8 wk thereafter. Patients are unlikely to respond to doses >300 U/kg/dose 3 times per wk.
For all ages, withhold therapy if Hgb >12 g/dL and resume therapy by decreasing dosage by 25% once Hgb falls below 11 g/dL. For adults, discontinue therapy if Hgb does not increase after 8 wk of the 300 U/kg/dose 3 times per wk dosage.

Anemia of prematurity (many regimens exist):
250 U/kg/dose SC 3 times per wk ×10 doses; alternatively, 200–400 U/kg/dose IV/SC 3–5 times per wk for 2–6 wk (total dose per wk is 600–1400 U/kg). Administer with supplemental iron at 3–6 mg elemental iron/kg/24 hr.

Use the lowest dose to avoid transfusions.
Increased risk for death, serious cardiovascular events, and thrombosis/stroke have been reported in patients treated with chronic kidney disease and hemoglobin levels >11 g/dL.
Increased risk for death, shortened survival and/or shortened time to tumor progression/regression,

EPOETIN ALFA *continued*

serious cardiovascular events, and thrombosis in various cancer patients, especially with Hgb levels >12 g/dL, have been reported with epoetin alfa and other erythropoiesis-stimulating agents.

Evaluate serum iron, ferritin, TIBC before therapy. Iron supplementation recommended during therapy unless iron stores are already in excess. Monitor Hct, BP, clotting times, platelets, BUN, serum creatinine. Peak effect in 2–3 wk.

DOSAGE ADJUSTMENT FOR ANEMIA IN CHRONIC RENAL FAILURE:

Reduce dose by ≥25%: when Hgb increases >1 g/dL in any 2-wk period. Dose reductions can be made more frequently than once every 4 wk if needed.

Increase dose by 25%: when Hgb does not increase by 1 g/dL after 4 wk of therapy. Dosage increments should not be made more frequently than once every 4 wk.

Withholding therapy: when Hgb >11 g/dL; restart therapy at a 25% lower dose after Hgb decreases to target levels or <11 g/dL.

Inadequate response after a 12-week dose escalation: Use minimum effective dosage that will maintain hemoglobin levels to avoid the need for recurrent blood transfusions and evaluate other causes of anemia. Discontinue use if patient remains transfusion dependent.

DOSAGE REDUCTION ADJUSTMENT/WITHHOLDING THERAPY FOR ANEMIA IN CANCER:

If Hgb exceeds a level needed to avoid blood transfusion: Withhold dose and resume therapy at a reduced dosage by 25% when Hgb approaches a level where blood transfusions may be needed.

If Hgb increases >1 g/dL in any 2-wk period or Hgb reaches a level to avoid blood transfusion: Reduce dose by 25%.

May cause hypertension, seizure, hypersensitivity reactions, headache, edema, dizziness. SC route provides sustained serum levels compared to IV route. For IV administration, infuse over 1–3 min.

Do not use multi-dose vial preparation for breastfeeding mothers because of concerns for benzyl alcohol.

EPOPROSTENOL

Flolan, Veletri, and generic, PGI_2, PGX, prostacyclin

Prostaglandin I_2, vasodilator

Injection: 0.5, 1.5 mg

Flolan: reconstitute with provided pH 12 sterile diluent for Flolan (50 mL)

Veletri (available only via designated specialty outpatient pharmacies): reconstitute with sterile water for injection or 0.9% sodium chloride

Generic: reconstitute with provided sterile diluent for epoprostenol sodium (50 mL)

Pulmonary Hypertension (limited data):

IV Infusion via central-line and 0.22-micron filter: Start at 1–2 **nanograms**/kg/min IV. Increase by 0.5–2 **nanograms**/kg/min Q45 min as needed and tolerated. **Avoid** abrupt withdrawal, interruptions in delivery, or sudden large decreases in dosage.

Usual effective dose:

Neonate: 20–40 **nanograms**/kg/min

Infant, child, and adolescent: 40 to >150 **nanograms**/kg/min (average 80 **nanograms**/kg/min)

Down-titration of dosage is required in the presence of high-output state (hyperdynamic right ventricle).

Inhalation route (very limited data):

Neonate: 50 **nanograms**/kg/min via continuous nebulization at a rate of 8 mL/hr, OR 50 **nanograms**/kg/min diluted in 3 mL Q2 hr via intermittent nebulization has been reported.

Child: 20–50 **nanograms**/kg/min via continuous nebulization has been reported

For explanation of icons, see p. 667

EPOPROSTENOL *continued*

Contraindicated in heart failure caused by decreased left ventricular ejection fraction. **Use with caution** in bleeding disorders; inhibits platelet aggregation.

Dose-dependent side effects of nausea, diarrhea, jaw pain, bone pain, and headaches are common. Other common side effects include hypotension, flushing, diarrhea, loss of appetite, and chest and musculoskeletal pain. Reported complications include sepsis, local site infection, and catheter dislodgement resulting in severe sepsis or rebound pulmonary hypertension (**avoid** abrupt dose withdrawal and monitor for IV line interruptions). Hypoxia, flushing, and tachycardia may suggest an overdose.

Use with medications exhibiting antiplatelet effects (e.g., SSRI antidepressants, desvenlafaxine, venlafaxine, duloxetine, NSAIDs, and anticoagulants) may increase risk for bleeding. May increase digoxin levels.

Systemic $T_{1/2}$ is 2–5 min. Continuous IV infusion is administered via central venous catheter with a 0.22-micron filter. Medication temperature stability requirements and the use of icepacks are product specific; consult with a pharmacist.

ERGOCALCIFEROL

Calciferol, Calcidol, Drisdol, and generics

Vitamin D2

Caps:

Generics [OTC]: 2000 IU

Drisdol and generics: 50,000 IU (1.25 mg)

Tabs [OTC]: 400, 2000, 2400 IU

Drops: 8000 IU/mL (200 mCg/mL) (60 mL); contains propylene glycol

Conversion: 1 mg = 40,000 IU vitamin D activity

Dietary supplementation (see Chapter 21 for additional information):

Preterm: 200–400 IU/24 hr PO

Infant (<1 yr): 400 IU/24 hr PO

Child (≥1 yr) and adolescent: 400–600 IU/24 hr PO

Renal failure (CKD stages 2–5) and 25-OH vitamin D levels <30 ng/mL (monitor serum 25-OH vitamin D and corrected calcium/phosphorus 1 mo after initiation and Q 3 mo thereafter):

25-OH vitamin D <5 ng/mL:

Child: 8000 IU/24 hr ×4 wk followed by 4000 IU/24 hr ×2 mo; or 50,000 IU weekly ×4 wk followed by 50,000 IU twice monthly for 2 mo

25-OH vitamin D 5–15 ng/mL:

Child: 4000 IU/24 hr PO ×12 wk or 50,000 IU every other wk ×12 wk.

25-OH vitamin D 16–30 ng/mL:

Child: 2000 IU/24 hr PO ×3 mo or 50,000 IU every mo ×3 mo.

Vitamin D dependent rickets:

Child: 3000–5000 IU/24 hr PO; **max. dose**: 60,000 IU/24 hr

Nutritional rickets:

Child and adult with normal GI absorption: 2000–5000 IU/24 hr PO ×6–12 wk

Malabsorption:

Child: 10,000–25,000 IU/24 hr PO

Adult: 10,000–300,000 IU/24 hr PO

Vitamin D resistant rickets (with phosphate supplementation):

Child: initial dose 40,000–80,000 IU/24 hr PO; increase daily dose by 10,000–20,000 IU PO Q3–4 mo if needed.

Adult: 10,000–60,000 IU/24 hr PO

ERGOCALCIFEROL *continued*

Hypoparathyroidism (with calcium supplementation):
Child: 50,000–200,000 IU/24 hr PO
Adult: 25,000–200,000 IU/24 hr PO

Consider using cholecalciferol instead; cholecalciferol has shown to be more biologically potent with better absorption than ergocalciferol. Vitamin D_2 is activated by 25-hydroxylation in liver and 1-hydroxylation in kidney to the active form, calcitriol.

Monitor serum $Ca^{(2+)}$, PO_4, 25-OH vitamin D (goal level for infant and child: ≥20 ng/mL), and alkaline phosphate. Serum $Ca^{(2+)}$, PO_4 product should be <70 mg/dL to avoid ectopic calcification. Titrate dosage to patient response. Watch for symptoms of hypercalcemia: weakness, diarrhea, polyuria, metastatic calcification, nephrocalcinosis.

Serum 25-OH vitamin D level of ≥35 ng/mL has been suggested in cystic fibrosis patients to decrease the risk of hyperparathyroidism and bone loss.

Pregnancy category changes to "C" if used in doses above the US RDA.

ERGOTAMINE TARTRATE ± CAFFEINE
Ergomar
In combination with caffeine: Cafergot, Migergot, and generics
Ergot alkaloid

Sublingual tabs (Ergomar): 2 mg
In combination with caffeine:
Tabs (Cafergot and generics): 1 mg and 100 mg caffeine
Suppository (Migergot): 2 mg and 100 mg caffeine (12s)

ERGOTAMINE:
Adolescent and adult:
SL: 2 mg at onset of migraine attack, then 2 mg Q30 min PRN up to **max. dose** of 6 mg/24 hr; **do not exceed** 10 mg/wk.

ERGOTAMINE PLUS CAFFEINE
Doses based on mg of ergotamine.
Oral tablet:
Adolescent and adult: 1 or 2 mg PO at onset of migraine attack, then 1 mg Q30 min up to 6 mg per attack, **not to exceed** 10 mg/wk.
Suppository:
Adolescent: 1 mg (0.5 suppository) at first sign of attack; follow with second 1 mg dose after 45 min if needed; **max. dose**: 2 mg per attack, 4 mg/24 hr, **not to exceed** 8 mg/wk.
Adult: 2 mg at first sign of attack; follow with second 2 mg dose after 1 hr if needed; **max. dose**: 4 mg per attack, not to exceed 10 mg/wk.

Use with caution in renal or hepatic disease. May cause paresthesias, GI disturbance, angina-like pain, rebound headache with abrupt withdrawal, or muscle cramps. **Contraindicated** in pregnancy and has **not been recommended** in breast feeding. Concurrent administration with protease inhibitors, clarithromycin, erythromycin, other CYP 450 3A4 inhibitors, and nitroglycerin are **contraindicated** owing to risk of ergotism (nausea, vomiting, vasospastic ischemia leading to cerebral and peripheral ischemia).

For sublingual administration, place tablet under the tongue and do not crush.

For explanation of icons, see p. 667

ERTAPENEM
Invanz and generics
Antibiotic, carbapenem

Injection: 1 g
Contains ~6 mEq Na/g drug

≥1 mo–12 yr: 15 mg/kg/dose IV/IM Q12 hr; **max. dose**: 1 g/24 hr
Adolescent and adult: 1 g IV/IM Q24 hr
- ***Recommended duration of therapy (all ages):***
  - ***Complicated intra-abdominal infection:*** 5–14 days
  - ***Complicated skin/subcutaneous tissue infections:*** 7–14 days
  - ***Diabetic foot infection without osteomyelitis:*** 14–28 days
  - ***Community-acquired pneumonia, complicated UTI/pyelonephritis:*** 10–14 days
  - ***Acute pelvic infection:*** 3–10 days

Surgical prophylaxis:
- ***Child and adolescent:*** 15 mg/kg (**max. dose:** 1 g/dose) IV 1 hr before procedure
- ***Adult (colorectal surgery):*** 1 g IV 1 hr before procedure

Ertapenem has poor activity against P. aeruginosa, Acinetobacter, MRSA, and Enterococcus. **Do not use** in meningitis due to poor CSF penetration. **Use with caution** with CNS disorders including seizures. **Adjust dosage in renal impairment; see Chapter 31.**

Diarrhea, infusion complications, nausea, headache, vaginitis, phlebitis/thrombophlebitis, and vomiting are common. Seizures (primarily with renal insufficiency and/or CNS disorders such as brain lesions and seizures), decreased consciousness, muscle weakness, gait disturbance, abnormal coordination, teeth staining, and DRESS syndrome have been reported. Increased ALT, AST, and neutropenia have been reported in pediatric clinical trials. Decreases valproic acid levels. Probenecid may increase ertapenem levels.

IM route requires reconstitution with 1% lidocaine and **should not** be administered by IV. **Do not** reconstitute or co-infuse with dextrose containing solutions.

ERYTHROMYCIN PREPARATIONS
Erythromycin, EES, E-Mycin, EryPed, Ery-Tab, and generics
Ophthalmic ointment: Generics; previously available as Ilotycin
Topical gel: Ery, Erygel, and generics
Antibiotic, macrolide

Erythromycin base:
- **Tabs:** 250, 500 mg
- **Delayed-release tabs (Ery-Tab and generics):** 250, 333, 500 mg
- **Delayed-release caps:** 250 mg
- **Topical gel (Erygel and generics):** 2% (30, 60 g); contains alcohol 92%
- **Topical solution:** 2% (60 mL); may contain 44%–66% alcohol
- **Topical pad/swab (Ery and generics):** 2% (60s); may contain propylene glycol and alcohol
- **Ophthalmic ointment:** 0.5% (1, 3.5 g)

Erythromycin ethyl succinate (EES):
- **Oral suspension (EES, EryPed, and generics):** 200 mg/5 mL (100, 200 mL), 400 mg/5 mL (100 mL)
- **Tabs (EES and generics):** 400 mg

Erythromycin stearate (Erythrocin):
- **Tabs:** 250 mg

Erythromycin lactobionate (Erythrocin):

ERYTHROMYCIN PREPARATIONS *continued*

Oral:

Neonate (use EES preparation):

<1.2 kg: 20 mg/kg/24 hr ÷ Q12 hr PO

≥1.2 kg:

0–7 days: 20 mg/kg/24 hr ÷ Q12 hr PO

>7 days:

1.2–2 kg: 30 mg/kg/24 hr ÷ Q8 hr PO

≥2 kg: 30–40 mg/kg/24 hr ÷ Q6–8 hr PO

Chlamydial conjunctivitis and pneumonia: 50 mg/kg/24 hr ÷ Q6 hr PO ×14 days; **max. dose:** 2 g/24 hr.

Child (use base, EES, or stearate preparation): 30–50 mg/kg/24 hr ÷ Q6–8 hr; **max. dose:** 4 g/24 hr

Pertussis: 40–50 mg/kg/24 hr ÷ Q6 hr PO ×14 days (**max. dose:** 2 g/24 hr); use azithromycin for infants <1 mo old.

Adult: 2 g/24 hr ÷ Q6 hr PO ×14 days

Parenteral:

Child and adult: 15–20 mg/kg/24 hr ÷ Q6 hr IV; **max. dose**: 4 g/24 hr

Ophthalmic:

Neonatal gonococcal ophthalmia prophylaxis: Apply 1-inch ribbon to both eyes ×1.

Conjunctivitis:

Infant, child, and adolescent: Apply 1-inch ribbon to affected eye(s) several times a day up to 6 times daily.

Preoperative bowel prep: 20 mg/kg/dose (**max. dose**: 1000 mg/dose) PO erythromycin base ×3 doses, with neomycin, 1 day before surgery

Prokinetic agent:

Infant and child: 10–20 mg/kg/24 hr PO ÷ TID–QID (QAC or QAC and QHS)

Topical (administer doses after washing skin with warm water and soap and patting it dry):

Acne (≥7 yr–adolescent; typically not used as monotherapy):

Topical gel: Apply to affected area once daily–BID; discontinue use after 8 wk if no improvement or worsening of condition.

Topical solution or pad: Apply to affected area BID (morning and evening).

Avoid use in patients with known QT prolongation, proarrhythmic conditions (e.g., hypokalemia, hypomagnesemia, significant bradycardia), and receiving class IA or class III antiarrhythmic agents, HMG CoA reductase inhibitors metabolized by CYP 450 3A4 (e.g., lovastatin or simvastatin; increases risk for myopathy and rhabdomyolysis), cisapride, or pimozide. Hypertrophic pyloric stenosis in neonates receiving prophylactic therapy for pertussis; life-threatening episodes of ventricular tachycardia associated with prolonged QTc interval; and exacerbation of myasthenia gravis have been reported. May produce false-positive urinary catecholamines, 17-hydroxycorticosteroids, and 17-ketosteroids.

GI side effects common (nausea, vomiting, abdominal cramps). Cardiac dysrhythmia, anaphylaxis, interstitial nephritis, and hearing loss have been reported. Use with **caution** in liver disease. Estolate formulation may cause cholestatic jaundice, although hepatotoxicity is uncommon (2% of reported cases). Inhibits CYP 450 1A2, 3A3/4 isoenzymes. May produce elevated digoxin, theophylline, carbamazepine, clozapine, cyclosporine, and methylprednisolone levels. **Adjust dose in renal failure (see Chapter 31).** Use ideal body weight for obese patients when calculating doses.

Oral therapy should replace IV as soon as possible. Give oral doses after meals. Because of different absorption characteristics, higher oral doses of EES are needed to achieve therapeutic effects. **Avoid** IM route (pain, necrosis). For ophthalmic use, **avoid** contact of ointment tip with eye or skin.

ERYTHROPOIETIN

For explanation of icons, see p. 667

ESCITALOPRAM
Lexapro and generics
Antidepressant, selective serotonin reuptake inhibitor

Tabs: 5, 10, 20 mg
Oral solution: 1 mg/mL (240 mL); contains parabens and propylene glycol

Depression:
<12 yr: Limited data, only one placebo-controlled RCT did not demonstrate efficacy.
≥12 yr and adolescent: Start with 10 mg PO once daily. If needed after 3 wk, dose may be increased to 20 mg once daily.
Adult: Start with 10 mg PO once daily. If needed after 1 wk, dose may be increased to 20 mg once daily.

Autism and Pervasive Developmental Disorders (PDD; limited data)
6–17 yr: A 10-wk open-label trial in which 28 subjects were given a weekly PRN increasing PO dosage regimen of 2.5, 5, 10, 15, and 20 mg/24 hr. Mean dosage of responders with significant improvement at 11.1 ± 6.5 mg/24 hr. 25% of subjects responded at doses <10 mg/24 hr and 36% responded at doses ≥ 10 mg/24 hr. Seven of the 17 (41%) responders and 25% of all treated subjects could not tolerate the 10-mg/24 hr dose.

Social Anxiety Disorder (limited data):
10–17 yr: A 12-wk open-label trial in which 20 subjects were given an initial PO dosage of 5 mg once daily × 7 days followed by 10 mg once daily. If needed and tolerated, increase by 5 mg/24 hr at weekly intervals up to a **maximum** of 20 mg/24 hr. Two subjects did not complete the trial due to lack of efficacy and tolerability. Sixty-five percent of the remaining subjects met the response criteria with a mean final dose of 13 ± 4.1 mg/24 hr. Common adverse events included somnolence (25%), insomnia (20%), flu symptoms (15%), increased appetite (15%), and decreased appetite (15%).

Increased risk for serotonin syndrome when used with MAO inhibitors (or within 14 days of discontinuance), linezolid, or methylene blue; concurrent use considered **contraindicated. Do not use** with pimozide because of risk for increased QTc interval. **Use with caution** with hepatic or severe renal impairment; dosage adjustment may be needed. **Avoid** abrupt discontinuation to prevent withdrawal symptoms.

Diaphoresis, GI discomfort, xerostomia, dizziness, headache, insomnia, somnolence, sexual dysfunction, and fatigue are common side effects. Abnormal bleeding, depression, QTc prolongation, and suicidal ideation have been reported.

Primarily metabolized by the CYP 450 2C19 and 3A4 enzymes and is a weak inhibitor for CYP 450 2D6 enzyme. Consider an alternative medication (not significantly metabolized by CYP 450 2C19) for individuals with ultrarapid CYP 450 2C19 activity. Poor CYP450 2C19 metabolizers can either initiate therapy at 50% the usual dose and titrate to response or consider alternative therapy.

Taking with other medications with QTc prolongation may further increase that risk. Omeprazole may increase the toxicity of escitalopram. Doses may be administered with or without food.

ESMOLOL HCL
Brevibloc and generics
β-1-selective adrenergic blocking agent, antihypertensive agent, class II antiarrhythmic

Injection: 10 mg/mL (10 mL)
Injection, premixed infusion in iso-osmotic sodium chloride: 2000 mg/100 mL (100 mL), 2500 mg/250 mL (250 mL)

D

ESMOLOL HCL *continued*

Postoperative hypertension: Titrate to response (limited information):

Loading dose: 500 mCg/kg IV over 1 min.

Maintenance dose: 50–250 mCg/kg/min IV as infusion. Titrate doses upward 50–100 mCg/kg/min Q 5–10 min as needed. Heart surgery patients may require higher doses (~700 mCg/kg/min). Dosages as high as 1000 mCg/kg/min have been administered to children 1–12 yr.

SVT: Titrate to response (limited information).

Loading dose: 100–500 mCg/kg IV over 1 min.

Maintenance dose: 25–100 mCg/kg/min IV as infusion. Titrate doses upward 50–100 mCg/kg/min Q5–10 min as needed. Dosages as high as 1000 mCg/kg/min have been administered.

Contraindicated in sinus bradycardia, >first-degree heart block, and cardiogenic shock or heart failure. Short duration of action; $T_{1/2}$ = 2.9–4.7 min for children and 9 min for adults. May cause bronchospasm, congestive heart failure, hypotension (at doses >200 mCg/kg/min), nausea, and vomiting. May increase digoxin (by 10%–20%) and theophylline levels. Morphine may increase esmolol level by 46%. Theophylline may decrease esmolol's effects.

Administer only in a monitored setting. Concentration for administration is typically ≤10 mg/mL, but 20 mg/mL has been administered in pediatric patients.

ESOMEPRAZOLE
Nexium, Nexium 24HR, and generics
Gastric acid proton pump inhibitor

Caps, delayed-released (Nexium and generics): 20, 40 mg; contains magnesium (some generic products may contain strontium instead)

Nexium 24 HR [OTC]: 20 mg

Tab, delayed-released (Nexium 24HR; [OTC]): 20 mg; contains magnesium

Powder for oral suspension (Nexium): 2.5, 5, 10, 20, 40 mg packets (30s); contains magnesium

Injection (Nexium and generics): 20, 40 mg; contains EDTA

Child (PO):

GERD:

1–11 yr: 10 mg once daily for up to 8 wk

≥12–17 yr: 20 mg once daily for 4 wk

Erosive esophagitis in GERD:

Infant (1 mo to <1 yr; use for up to 6 wk):

3–5 kg: 2.5 mg once daily

>5 to 7.5 kg: 5 mg once daily

>7.5 to 12 kg: 10 mg once daily

1–11 yr (use for 8 wk):

<20 kg: 10 mg once daily

≥20 kg: 10 or 20 mg once daily

12–17 yr: 20 or 40 mg once daily for 4–8 wk

Child (IV):

GERD with erosive esophagitis:

Infant: 0.5–1 mg/kg/dose once daily

Child 1–17 yr:

<55 kg: 10 mg once daily

≥55 kg: 20–40 mg once daily

Adult (PO/IV):

GERD: 20 mg once daily

GERD with erosive esophagitis: 20 or 40 mg once daily ×4–8 wk.

For explanation of icons, see p. 667

ESOMEPRAZOLE *continued*

Prevention of NSAID-induced gastric ulcers: 20 or 40 mg once daily for up to 6 mo

Pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome): 40 mg BID; doses up to 240 mg/24 hr have been used.

Hepatic impairment: Patients with severe hepatic function impairment (Child-Pugh class C) should not exceed 20 mg/24 hr.

Cross-allergic reactions with other proton pump inhibitors (e.g., lansoprazole, pantoprazole, rabeprazole). **Use with caution** in liver impairment (see dosage adjustment recommendation in dosing section). GI disturbances and headache are common. Hypomagnesemia may occur with continuous use. Anaphylaxis, angioedema, bronchospasm, acute interstitial nephritis, erythema multiforme, urticaria, Stevens-Johnson syndrome, TEN, pancreatitis, and fractures of the hip, wrist, and spine (in adults >50 yr old receiving high doses or prolonged therapy >1 yr) have been reported. Fundic gland polyps have been associated with long-term use of >1 yr.

Drug is a substrate and inhibitor of CYP 450 2C19 and substrate of CYP 450 3A4. May decrease the absorption or effects of atazanavir, clopidogrel, ketoconazole, itraconazole, mycophenolate mofetil, and iron salts. May increase the effect/toxicity of diazepam, midazolam, digoxin, carbamazepine, and warfarin. Voriconazole may increase the effects of esomeprazole.

May be used in combination with clarithromycin and amoxicillin for *Helicobacter pylori* infections.

Pregnancy category is a "B" for the magnesium-containing product and a "C" for the strontium-containing product.

Administer all oral doses before meals and 30 min before sucralfate (if receiving). **Do not** crush or chew capsules. IV doses may be given as fast as 3 min or infused over 10–30 min.

ETANERCEPT

Enbrel, Enbrel SureClick, Enbrel Mini

Antirheumatic, immuno-modulatory agent, tumor necrosis factor receptor p75 Fc fusion protein

Pre-filled injection (single use): 25 mg (0.5 mL), 50 mg (1 mL); contains sucrose, L-arginine (preservative free) (carton of 4 pre-filled syringes)

Injection (powder; multi-dose vial): 25 mg with diluent (1 mL bacteriostatic water containing 0.9% benzyl alcohol); contains mannitol, sucrose, tromethamine

Auto-injector:

Enbrel SureClick (single use): 50 mg (1 mL); contains sucrose, L-arginine (preservative free) (carton of 4 auto-injectors)

Pre-filled injection cartridge to be used with Auto Touch reusable autoinjector device:

Enbrel Mini: 50 mg (1 mL); contains sucrose, L-arginine (preservative free) (carton of 4 cartridges)

Juvenile idiopathic arthritis:

Child 2–17 yr: 0.4 mg/kg/dose SC twice weekly administered 72–96 hr apart; **max. dose**: 25 mg. Alternative once weekly dose of 0.8 mg/kg/dose SC (**max. dose**: 50 mg/wk and **max. single injection site dose** of 25 mg) may be used.

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis:

Adult: 25 mg SC twice weekly administered 72–96 hr apart. Alternative once weekly dose of 50 mg SC (**max. single injection site dose** of 25 mg) may be used.

Plaque psoriasis:

Child and adolescent (4–17 yr): 0.8 mg/kg/dose (**max. dose**: 50 mg) SC once weekly.

Adult: Start with 50 mg SC twice weekly administered 72–96 hr apart × 3 mo, followed by a reduced maintenance dose of 50 mg SC per wk. Starting doses of 25 mg or 50 mg/wk have also been shown to be effective.

Max. single injection site dose: 25 mg.

ETANERCEPT *continue*d

Contraindicated in serious infections, sepsis, or hypersensitivity to any of medication components. **Use with caution** in patients with history of recurrent infections (including hepatitis B) or underlying conditions that may predispose them to infections (including concomitant immunosuppressive therapy), CNS demyelinating disorders, malignancies, immune-related diseases, and latex allergy. Common adverse effects in children include headache, abdominal pain, vomiting, and nausea. Injection site reactions (e.g., discomfort, itching, swelling), rhinitis, dizziness, rash, depression, infections (varicella, aseptic meningitis, rare cases of TB, and fatal/serious infections and sepsis), bone marrow suppression (e.g., aplastic anemia), sarcoidosis, vertigo, and CNS demyelinating disorder have also been reported. Malignancies (some fatal and ~50% were lymphomas) have been reported in children and adolescents.

Do not administer live vaccines concurrently with this drug. In JRA, it is recommended that before initiating therapy, the patient be brought up to date with all immunizations in agreement with current immunization guidelines.

Onset of action is 1–4 wk, with peak effects usually within 3 mo.

Patients must be properly instructed on preparing and administering the medication (see specific product information). For multi-dose vial, reconstitute vial by gently swirling its contents with the supplied diluent **(do not** shake or vigorously agitate), as some foaming will occur. Reconstituted solutions should be clear and colorless; unused portions must be stored in the refrigerator and used within 14 days. Do not store Auto Touch auto-injector device in the refrigerator.

Drug is administered subcutaneously by rotating injection sites (thigh, abdomen, or upper arm) with a **max. single injection site dose** of 25 mg. Administer new injections ≥1 inch from an old site and NEVER where the skin is tender, bruised, red, or hard.

ETHAMBUTOL HCL
Myambutol and generics
Antituberculosis drug

Tabs: 100, 400 mg; 400-mg tabs may be scored
Oral suspension: 50, 100 mg/mL

Tuberculosis (use in combination with other medications; see remarks):
Infant, child, adolescent, and adult:
<15 yr and < 40 kg: 15–25 mg/kg/dose (**max. dose**: 1 g/24 hr) PO once daily or 50 mg/kg/dose PO twice weekly (**max. dose**: 2.5 g/week)
<15 yr and ≥40 kg, or ≥15 yr:
40–55 kg: 800 mg PO once daily or 5 times weekly
56–75 kg: 1200 mg PO once daily or 5 times weekly
76–90 kg: 1600 mg PO once daily or 5 times weekly

Nontuberculous mycobacterial infection; and Mycobacterium avium complex in AIDS (recurrence prophylaxis or treatment; use in combination with other medications):
Infant, child, and adolescent: 15–25 mg/kg/24 hr PO once daily; **max. dose**: 2.5 g/24 hr

May cause reversible optic neuritis, especially with larger doses. Obtain baseline ophthalmologic studies before beginning therapy and then monthly. Follow visual acuity, visual fields, and (red-green) color vision. **Do not use** in optic neuritis and in children whose visual acuity cannot be assessed. **Discontinue** if any visual deterioration occurs. Monitor uric acid, liver function, heme status, and renal function. Hyperuricemia, GI disturbances, and mania are common. Erythema multiforme and hepatotoxicity have been reported.

Dosing should be based on lean body weight. Coadministration with aluminum hydroxide can reduce ethambutol's absorption; space administration by 4 hr. Give with food. **Adjust dose with renal failure**

For explanation of icons, see p. 667

ETHOSUXIMIDE
Zarontin and generics
Anticonvulsant

Caps: 250 mg
Oral solution: 250 mg/5 mL (473 mL); may contain sodium benzoate

Oral:
≤ 6 yr:
Initial: 15 mg/kg/24 hr ÷ BID; **max. dose**: 500 mg/24 hr; increase as needed Q4–7 days.
Usual maintenance dose: 15–40 mg/kg/24 hr ÷ BID
>6 yr and adult: 250 mg BID; increase by 250 mg/24 hr as needed Q4–7 days.
Usual maintenance dose: 20–40 mg/kg/24 hr ÷ BID
Max. dose (all ages): 1500 mg/24 hr

Drug of choice for absence seizures. **Use with caution** in hepatic and renal disease. Ataxia, anorexia, drowsiness, sleep disturbances, rashes, and blood dyscrasias are rare idiosyncratic reactions. May cause lupus-like syndrome; may increase frequency of grand mal seizures in patients with mixed-type seizures. Serious dermatological reactions (e.g., Stevens Johnson and DRESS) has been reported. May increase risk of suicidal thoughts/behavior. Cases of birth defects have been reported; ethosuximide crosses the placenta.

Carbamazepine, phenytoin, primidone, phenobarbital, valproic acid, nevirapine, and ritonavir may decrease ethosuximide levels.

Therapeutic levels: 40–100 mg/L. $T_{1/2}$ = 24–42 hr. Recommended serum sampling time at steady state: obtain trough level within 30 min prior to the next scheduled dose after 5–10 days of continuous dosing.

To minimize GI distress, may administer with food or milk. Abrupt withdrawal of drug may precipitate absence status.

ETOMIDATE
Amidate and generics
General anesthetic

Injection: 2 mg/mL (10, 20 mL); may contain propylene glycol

Rapid Sequence Intubation (infuse dose over 30–60 sec):
Normotensive patient: 0.3 mg/kg/dose IV/IO ×1; **max. dose:** 20 mg/dose
Hypotensive patient (see remarks): 0.15 mg/kg/dose IV/IO ×1; **max. dose**: 20 mg/dose

Not recommended for patients in septic shock due to transient adrenocortical suppression and increased risk for mortality. **Avoid use** with benznidazole and metronidazole due to the risk for disulfiram-like reaction. **Use with caution** in renal impairment (higher risk for toxicity) and in heart failure (may exacerbate condition).

Injection site pain, myoclonus (pretreatment with midazolam may reduce risk), nausea, and vomiting are reported common side effects for indications other than rapid-sequence intubation.

F

FAMCICLOVIR

Generics; previously available as Famvir

Antiviral

Tabs: 125, 250, 500 mg

Adult:

Herpes zoster: 500 mg Q8 hr PO × 7 days; initiate therapy promptly as soon as diagnosis is made (initiation within 48 hr after rash onset is ideal; currently no data for starting treatment >72 hr after rash onset).

Genital herpes (first episode): 250 mg Q8 hr PO × 7–10 days

Recurrent genital herpes:

Immunocompetent: 1000 mg Q12 hr PO × 1 day or 125 mg Q12 hr PO × 5 days; initiate therapy at first sign or symptom. Efficacy has not been established when treatment is initiated >6 hr after onset of symptoms or lesions.

Immunocompromised: 500 mg Q12 hr PO × 7 days

Suppression of recurrent genital herpes (immunocompetent): 250 mg Q12 hr PO up to 1 yr, then reassess for HSV infection recurrence

Recurrent herpes labialis:

Immunocompetent: 1500 mg PO × 1

Immunocompromised: 500 mg Q12 hr PO × 7 days

Recurrent mucocutaneous herpes in HIV: 500 mg Q12 hr PO × 7 days

Drug is converted to its active form (penciclovir). Hepatic impairment may impair/reduce the conversion of famciclovir to penciclovir. Better absorption than PO acyclovir.

May cause headache, diarrhea, nausea, and abdominal pain. Serious skin reactions (e.g., TEN and Stevens-Johnson), angioedema, hypersensitivity vasculitis, seizure, palpitations, cholestatic jaundice, and abnormal LFTs have been reported. Concomitant use with probenecid and other drugs eliminated by active tubular secretion may result in decreased penciclovir clearance. **Reduce dose in renal impairment (see Chapter 31).**

Safety and efficacy in suppression of recurrent genital herpes have not been established beyond 1 yr. No efficacy data is available for children 1–<12 yr to support its use for genital herpes, recurrent herpes labialis, and varicella. Furthermore, efficacy has not been established for recurrent herpes labialis for children 12–<18 yr. May be administered with or without food.

FAMOTIDINE

Pepcid, Pepcid AC [OTC], Pepcid AC Maximum Strength [OTC], Pepcid Complete [OTC], and generics

Histamine-2-receptor antagonist

Injection: 10 mg/mL (2, 4, 20 mL); multidose vials contain 0.9% benzyl alcohol

Premixed injection: 20 mg/50 mL in iso-osmotic sodium chloride

Oral suspension: 40 mg/5 mL (50 mL); may contain parabens and sodium benzoate

Tabs: 10 (OTC), 20 (OTC), 40 mg

Chewable tabs:

Pepcid Complete (OTC): 10 mg famotidine with 800 mg calcium carbonate and 165 mg magnesium hydroxide (25s, 50s)

Continued

For explanation of icons, see p. 667

FAMOTIDINE *continued*

Neonate and <3 mo:
IV: 0.25–0.5 mg/kg/dose Q24 hr
PO: 0.5–1 mg/kg/dose Q24 hr
≥3 mo–1 yr (GERD): 0.5 mg/kg/dose PO Q12 hr
Child (1–12 yr):
IV: initial: 0.5–1 mg/kg/24 hr ÷ Q12 hr up to a **max.** of 40 mg/24 hr
PO: initial: 1–1.2 mg/kg/24 hr ÷ Q12 hr up to a **max.** of 40 mg/24 hr
Peptic ulcer: 0.5–1 mg/kg/24 hr PO QHS or ÷ Q12 hr up to a **max. dose** of 40 mg/24 hr
GERD: 1–2 mg/kg/24 hr PO ÷ Q 12 hr up to a **max. dose** of 80 mg/24 hr
Adolescent and adult:
Duodenal ulcer:
PO: 20 mg BID or 40 mg QHS × 4–8 wk, then maintenance therapy at 20 mg QHS
IV: 20 mg BID
GERD: 20 mg BID PO × 6 wk
Esophagitis: 20–40 mg BID PO × 12 wk

A Q12-hr dosage interval is generally recommended; however, infants and young children may require a Q8-hr interval because of enhanced drug clearance. Headaches, dizziness, constipation, diarrhea, and drowsiness have occurred. **Dosage adjustment is required in severe renal failure (see Chapter 31)**; prolonged QT interval has been reported very rarely in patients with renal impairment whose dosage had not been adjusted appropriately. Rhabdomyolysis has been reported.
Shake oral suspension well prior to each use. Oral doses may be administered with or without food.

FELBAMATE
Felbatol and generics
Anticonvulsant

Tabs: 400, 600 mg
Oral suspension: 600 mg/5 mL (240, 473 mL)

Lennox-Gastaut for child 2–14 yr (adjunctive therapy):
Start at 15 mg/kg/24 hr PO ÷ TID–QID; increase dosage by 15 mg/kg/24 hr increments at weekly intervals up to a **max. dose** of 45 mg/kg/24 hr or 3600 mg/24 hr (whichever is less). See remarks for adjusting concurrent anticonvulsants.
Child ≥14 yr–adult:
Adjunctive therapy: Start at 1200 mg/24 hr PO ÷ TID–QID; increase dosage by 1200 mg/24 hr at weekly intervals up to a **max. dose** of 3600 mg/day. See remarks for adjusting concurrent anticonvulsants.
Monotherapy (as initial therapy): Start at 1200 mg/24 hr PO ÷ TID–QID. Increase dose under close clinical supervision at 600 mg increments Q2 wk to 2400 mg/24 hr. **Max. dose**: 3600 mg/24 hr.
Conversion to monotherapy: Start at 1200 mg/24 hr ÷ PO TID–QID for 2 wk; then increase to 2400 mg/24 hr for 1 wk. At wk 3, increase to 3600 mg/24 hr. Reduce dose of other anticonvulsants by 33% at the initiation of felbamate, then an additional 33% of original dose at wk 2 and continue to reduce other anticonvulsants as clinically indicated at wk 3 and beyond.

Drug should be prescribed under strict supervision by a specialist. **Contraindicated** in blood dyscrasias or hepatic dysfunction (prior or current), and hypersensitivity to meprobamate. Aplastic anemia and hepatic failure leading to death have been associated with drug. May cause headache, fatigue, anxiety, GI disturbances, gingival hyperplasia, increased liver enzymes, and bone marrow suppression. Suicidal behavior or ideation have been reported.

FELBAMATE *continued*

Obtain serum levels of concurrent anticonvulsants. Monitor liver enzymes, bilirubin, CBC with differential, platelets at baseline, and every 1–2 wk. Doses should be decreased by 50% in renally impaired patients.

When initiating adjunctive therapy (all ages), doses of other antiepileptic drugs (AEDs) are reduced by 20% to control plasma levels of concurrent phenytoin, valproic acid, phenobarbital, and carbamazepine. Further reductions of concomitant AED dosage may be necessary to minimize side effects caused by drug interactions.

When converting to monotherapy, reduce other AEDs by one-third at the start of felbamate therapy. Then after 2 wk and at the start of increasing the felbamate dosage, reduce other AEDs by an additional one-third. At wk 3, continue to reduce other AEDs as clinically indicated.

Carbamazepine levels may be decreased; however, phenytoin and valproic acid levels may be increased. Phenytoin and carbamazepine may increase felbamate clearance; valproic acid may decrease its clearance.

Doses can be administered with or without food.

FENTANYL
Sublimaze, Duragesic, Fentora, Actiq, and generics
Narcotic; analgesic, sedative

Injection: 50 mCg/mL (2, 5, 10, 20, 50 mL)
SR transdermal patch (Duragesic and generics): 12.5, 25, 50, 75, 100 mCg/hr (5s)
Tabs for buccal administration:
Fentora and generics: 100, 200, 400, 600, 800 mCg (28s)
Lozenge on a stick:
Actiq and generics: 200, 400, 600, 800, 1200, 1600 mCg (30s)

Titrate dose to effect.
Neonate and younger infant:
Sedation/analgesia: 1–4 mCg/kg/dose (**max. dose:** 100 mCg/dose) IV Q2–4 hr PRN
Continuous IV infusion: 1–5 mCg/kg/hr; tolerance may develop
Older infant and child:
Sedation/analgesia: 1–2 mCg/kg/dose (**max. dose:** 100 mCg/dose) IV/IM Q30–60 min PRN
Continuous IV infusion: 1 mCg/kg/hr; titrate to effect; usual infusion range 1–3 mCg/kg/hr
To prepare infusion, use the following formula:

$$50 \times \frac{\text{Desired dose (mCg/kg/hr)}}{\text{Desired infusion rate (mL/hr)}} \times \text{Wt (kg)} \frac{\text{mCg Fentanyl}}{\text{50 mL fluid}}$$

Oral, breakthrough cancer pain for opioid-intolerant patients (see remarks):
Buccal tabs (≥18 yr NOT previously using Actiq): Start with 100 mCg by placing tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) and letting the tablet dissolve for 15–25 min. A second 100 mCg dose, if needed, may be administered 30 min after the start of the first dose. If needed, increase dose initially in multiples of 100 mCg tablet when patients require >1 dose per breakthrough pain episode for several consecutive episodes. Must wait at least 4 hr before treating another episode with buccal tabs. If titration requires >400 mCg/dose, use 200 mCg tabs.
Lozenges (≥16 yr): Start with 200 mCg by placing lozenge in the mouth between the cheek and lower gum. If needed, may repeat dose 15 min after the completion of the first dose (30 min after start of prior dose). If therapy requires >1 lozenge per episode, consider increasing the dose to the next higher strength. **Do not** give more than 2 doses for each episode of breakthrough pain and reevaluate long-acting opioid therapy if patient requires >4 doses/24 hr. **Must wait at least 4 hr before treating another episode with lozenges.**

For explanation of icons, see p. 667

FENTANYL *continued*

Transdermal (see remarks): Safety has not been established in children <2 yr and should be administered in children ≥2 yr who are opioid tolerant. Use is **contraindicated** in acute or postoperative pain in opiate-naïve patients.

Opioid-tolerant child receiving at least 60 mg morphine equivalents/24 hr: Use 25 mCg/hr patch Q72 hr. Patch titration should not occur before 3 days of administration of the initial dose or more frequently than every 6 days thereafter.

See Chapter 6 for equianalgesic dosing and PCA dosing.

Intranasal route for acute and pre-procedure analgesia (use IV dosage form; see remarks):

≥1 yr–adolescent: 1–2 mCg/kg/dose intranasally via an automizer (**max. dose**: 100 mCg/dose) Q1 hr PRN

Use with caution in bradycardia, respiratory depression, and increased intracranial pressure. **Adjust dose in renal failure (see Chapter 31).** Fatalities and life-threatening respiratory depression have been reported with inappropriate use (overdoses, use in opioid-naïve patients, changing the patch too frequently, and exposing the patch to a heat source) of the transdermal route.

Highly lipophilic and may deposit into fat tissue. IV onset of action 1–2 min with peak effects in 10 min. IV duration of action 30–60 min. Give IV dose over 3–5 min. Rapid infusion may cause respiratory depression and chest wall rigidity. Respiratory depression may persist beyond the period of analgesia. Transdermal onset of action 6–8 hr with a 72-hr duration of action. See Chapter 6 for pharmacodynamic information with transmucosal and transdermal routes.

Buccal tabs and oral lozenges are indicated only for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to opioid therapy. Buccal tabs (Fentora), transdermal patches (Duragesic), and lozenge (Actiq) dosage forms are available through a restricted distribution program (REMS) and are NOT bioequivalent (see package insert for conversion).

Intranasal route of administration for analgesia has an onset of action at 10–30 min. Pediatric studies has demonstrated that the intranasal fentanyl is equivalent to and better than morphine (PO/IV/IM) and equivalent to intravenous fentanyl for providing analgesia.

Fentanyl is a substrate for the CYP 450 3A4 enzyme. Be aware of medications that inhibit or induce this enzyme, for it may increase or decrease the effects of fentanyl, respectively.

Pregnancy category changes to "D" if drug is used for prolonged periods or in high doses at term.

FERRIC GLUCONATE

See Iron—Injectable Preparations

FERROUS SULFATE

See Iron—Oral Preparations

FEXOFENADINE ± PSEUDOEPHEDRINE

Allegra, Allegra ODT, Allegra-D 12 Hour, Allegra-D 24 Hour, and generics

Antihistamine, less-sedating ± decongestant

Tabs: 60 mg [OTC], 180 mg [OTC]

Tabs, orally disintegrating (Allegra Allergy Children's**; ODT) [OTC]:** 30 mg; contains phenylalanine

FEXOFENADINE ± PSEUDOEPHEDRINE *continued*

Extended-release tab in combination with pseudoephedrine (PE):
Allegra-D 12 Hour [OTC]: 60 mg fexofenadine + 120 mg pseudoephedrine
Allegra-D 24 Hour [OTC]: 180 mg fexofenadine + 240 mg pseudoephedrine

Fexofenadine:
6 mo–<2 yr: 15–30 mg PO BID
2–11 yr: 30 mg PO BID
≥12 yr–adult: 60 mg PO BID; 180 mg PO once daily may be used in seasonal rhinitis.
Extended-release tabs of fexofenadine and pseudoephedrine:
≥12 yr–adult:
Allegra-D 12 Hour: 1 tablet PO BID
Allegra-D 24 Hour: 1 tablet PO once daily

May cause drowsiness, fatigue, headache, dyspepsia, nausea, and dysmenorrhea. Has not been implicated in causing cardiac arrhythmias when used with other drugs that are metabolized by hepatic microsomal enzymes (e.g., ketoconazole, erythromycin). **Reduce dose to 15 mg PO once daily for child 6 mo–<2 yr, 30 mg PO once daily for child 6–11 yr old, and 60 mg PO once daily for ≥12 yr old for any degree of renal impairment. For use of Allegra-D 12 Hour and decreased renal function (CrCl <80 mL/min)**, an initial dose of 1 tablet PO once daily is recommended. **Avoid use** of Allegra-D 24 Hour in renal impairment. See Pseudoephedrine for additional remarks if using the combination product.
Medication as the single agent may be administered with or without food. Do **not** administer antacids with or within 2 hr of fexofenadine dose. The extended-release combination product should be swallowed whole without food.

FILGRASTIM
Neupogen, G-CSF
Colony stimulating factor

Injection: 300 mCg/mL (1, 1.6 mL vials)
Injection, prefilled syringes with 27-gauge 1/2-inch needles: 600 mCg/mL (300 mCg per 0.5 mL and 480 mCg per 0.8 mL) (10s)
All dosage forms contain polysorbate 80 and are preservative free.
NOTE: the following biosimilar products are available (all contain polysorbate 80 and are preservative-free).
Single dose vials [Nivestym (filgrastim-aafi), Granix (tbo-filgrastim)]: 300 mCg/1 mL and 480 mCg/1.6 mL (10s)
Prefilled syringes [Nivestym (filgrastim-aafi), Zarxio (filgrastim-sndz)]: 300 mCg/0.5 mL and 480 mCg/0.8 mL (1 or 10s)

Individual protocols may direct dosing.
Myelosuppressive chemotherapy recipients with non-myeloid malignancies:
IV/SC: 5 mCg/kg/dose once daily × 14 days or until ANC >10,000/mm^3. Dosage may be increased by 5 mCg/kg/24 hr if desired effect is not achieved within 7 days.
Discontinue therapy when ANC >10,000/mm^3.

May cause bone pain, fever, and rash. Monitor CBC, uric acid, and LFTs. Aortis, sickle cell crisis, serious allergic reactions, glomerulonephritis, and thrombocytopenia have been reported. Decreased bone density/osteoporosis has been reported in pediatric patients with severe chronic neutropenia. **Use with caution** in patients with malignancies with myeloid

Continued

For explanation of icons, see p. 667

FILGRASTIM *continued*

characteristics. **Contraindicated** for patients sensitive to *E. coli*–derived proteins. Avoid simultaneous administration with chemotherapy and radiation and do not administer 24 hr before or after administration of chemotherapy.

Safety and effectiveness have been established for nonmyeloid malignancies receiving myelosuppressive chemotherapy in children ≥1 mo–<17 yr old. The safety profile was similar to adults.

SC routes of administration are preferred because of prolonged serum levels over IV route. If used via IV route and G-CSF final concentration <15 mCg/mL, add 2 mg albumin/1 mL of IV fluid to prevent drug adsorption to the IV administration set.

FLECAINIDE ACETATE
Generics; previously available as Tambocor
Antiarrhythmic, class Ic

Tabs: 50, 100, 150 mg
Oral suspension: 20 mg/mL

Child: Initial: 1–3 mg/kg/24 hr ÷ Q8 hr PO; usual range: 3–6 mg/kg/24 hr ÷ Q8 hr PO, monitor serum levels to adjust dose if needed.

Adult:

Sustained V tach: 100 mg PO Q12 hr; may increase by 50 mg Q12 hr (100 mg/24 hr) every 4 days to **max. dose** of 400 mg/24 hr.

Paroxysmal SVT/paroxysmal AF: 50 mg PO Q12 hr; may increase dose by 50 mg Q12 hr every 4 days to **max. dose** of 300–400 mg/24 hr.

May aggravate LV failure, sinus bradycardia, preexisting ventricular arrhythmias. May cause AV block, dizziness, blurred vision, dyspnea, nausea, headache, and increased PR or QRS intervals. **Reserve for life-threatening cases. Use with caution** in renal and/or hepatic impairment.

Flecainide is a substrate for the CYP P-450 2D6 enzyme. Be aware of medications that inhibit (e.g., certain SSRIs) or induce this enzyme, for it may increase or decrease the effects of flecainide, respectively.

Therapeutic trough level: 0.2–1 mg/L. Recommended serum sampling time at steady state: Obtain trough level within 30 min prior to the next scheduled dose after 2–3 days of continuous dosing for children; after 3–5 days for adults. **Adjust dose in renal failure (see Chapter 31).**

FLUCONAZOLE
Diflucan and generics
Antifungal agent

Tabs: 50, 100, 150, 200 mg
Injection: 2 mg/mL (100, 200 mL); contains 9 mEq Na/2 mg drug
Oral suspension: 10 mg/mL (35 mL), 40 mg/mL (35 mL)

Neonate (IV/PO):

Loading dose: 12–25 mg/kg

Thrush: 6 mg/kg

Maintenance dose: 6–12 mg/kg with the following dosing intervals (see following table); use higher doses for severe infections of Candida strains with MICs >4–8 mCg/mL.

Thrush: 3–6 mg/kg/dose with the following dosing intervals (see following table) for at least 2 wk

FLUCONAZOLE *continued*

Postconceptional Age (wk)	Postnatal Age (days)	Dosing Interval (hr) and Time (hr) to Start First Maintenance Dose After Load
≤29	0–14	48
	>14	24
≥30	0–7	48
	>7	24

Child ≥1 mo (IV/PO):

Indication	Loading Dose × 1	Maintenance Dose (Q24 hr) to Begin 24 hr After Loading Dose
Oropharyngeal candidiasis	6 mg/kg (**max. dose:** 400 mg)	3 mg/kg (**max. dose:** 200 mg/dose)
Esophageal candidiasis	12 mg/kg (**max. dose:** 800 mg)	6 mg/kg (**max. dose:** 400 mg/dose)
Invasive systemic candidiasis and Cryptococcal meningitis	12 mg/kg (**max. dose:** 800 mg)	6–12 mg/kg (**max. dose:** 400–800 mg/dose)
Suppressive therapy for HIV infected with Cryptococcal meningitis	6 mg/kg (**max. dose:** 200 mg)	6 mg/kg (**max. dose:** 200 mg/dose)

Adult:

Oropharyngeal and esophageal candidiasis: Loading dose of 200 mg PO/IV followed by 100 mg Q24 hr (24 hr after load); doses up to **max. dose** of 400 mg/24 hr should be used for esophageal candidiasis

Systemic candidiasis and cryptococcal meningitis: Loading dose of 400 mg PO/IV, followed by 200–800 mg Q24 hr (24 hr after load)

Bone marrow transplant prophylaxis: 400 mg PO/IV Q24 hr

Suppressive therapy in for HIV infected with cryptococcal meningitis: 200 mg PO/IV Q24 hr

Vaginal candidiasis: 150 mg PO × 1

Use with other medications known to prolong the QT interval and which are metabolized via the CYP 450 3A4 enzyme (e.g., erythromycin) are considered **contraindicated.** May cause nausea, headache, rash, vomiting, abdominal pain, hepatitis, cholestasis, and diarrhea. Neutropenia, agranulocytosis, thrombocytopenia, exfoliative skin disorders (e.g., SJS, TEN, DRESS), and adrenal insufficiency (reversible) have been reported. **Use with caution** in hepatic or renal dysfunction and in patients with hypokalemia, proarrhythmic conditions, or advanced cardiac failure.

Inhibits CYP 450 2C9/10 and CYP 450 3A3/4 (weak inhibitor). May increase effects, toxicity, or levels of cyclosporine, midazolam, phenytoin, rifabutin, tacrolimus, theophylline, warfarin, oral hypoglycemics, and AZT. Rifampin increases fluconazole metabolism.

Consider using higher doses in morbidly obese patients. **Adjust dose in renal failure (see Chapter 31).**

Pregnancy category is "C" for single 150 mg use for vaginal candidiasis, but a Danish study reports a higher risk for miscarriages for during weeks 7–22 of gestation. Pregnancy category "D" is for all other indications (high-dose use during first trimester of pregnancy may result in birth defects).

For explanation of icons, see p. 667

FLUCYTOSINE
Ancobon, 5-FC, 5-Fluorocytosine, and generics
Antifungal agent

Caps: 250, 500 mg
Oral suspension: 10, 50 mg/mL

Neonate (monitor serum concentrations):
<1 kg:
≤14 days old: 75 mg/kg/24 hr ÷ Q8 hr PO
15–28 days old: 75 mg/kg/24 hr ÷ Q6 hr PO
1–2 kg:
≤7 days old: 75 mg/kg/24 hr ÷ Q8 hr PO
8–28 days old: 75 mg/kg/24 hr ÷ Q6 hr PO
>2 kg and ≤60 days old: 75 mg/kg/24 hr ÷ Q6 hr PO
Dosages of 75–100 mg/kg/24 hr have been used in neonates (preterm and term) for candidal meningitis.
Child and adult (monitor serum concentrations): 50–150 mg/kg/24 hr ÷ Q6 hr PO

Monitor CBC, BUN, serum creatinine, alkaline phosphatase, AST, and ALT. Common side effects: nausea, vomiting, diarrhea, rash, CNS disturbance, anemia, leukopenia, and thrombocytopenia. **Use with caution** in hepatic and renal impairment and in hematologic disorders. Use is **contraindicated** in the first trimester of pregnancy.
Therapeutic levels: 25–100 mg/L. Recommended serum sampling time at steady state: Obtain peak level 2–4 hr after oral dose following 4 days of continuous dosing. Peak levels of 40–60 mg/L have been recommended for systemic candidiasis. Maintain trough levels above 25 mg/L. Prolonged levels above 100 mg/L can increase risk for bone marrow suppression. Bone marrow suppression in immunosuppressed patients can be irreversible and fatal.
Flucytosine interferes with creatinine assay tests using the dry-slide enzymatic method (Kodak Ektachem analyzer). **Adjust dose in renal failure (see Chapter 31).**

FLUDROCORTISONE ACETATE
Generics (previously available as Florinef);
9-fluorohydrocortisone
Corticosteroid

Tabs: 0.1 mg
Oral suspension: 0.1 mg/mL

Infant and child: 0.05–0.1 mg/24 hr once daily PO
Congenital adrenal hyperplasia: 0.05–0.3 mg/24 hr once daily PO
Adult: 0.05–0.2 mg/24 hr once daily PO

Contraindicated in CHF and systemic fungal infections. Has primarily mineralocorticoid activity. **Use with caution** in hypertension, edema, or renal dysfunction. May cause hypertension, hypokalemia, acne, rash, bruising, headaches, GI ulcers, and growth suppression.
Monitor BP and serum electrolytes. See Chapter 10 for steroid potency comparison.
Drug interactions: Drug's hypokalemic effects may induce digoxin toxicity; phenytoin and rifampin may increase fludrocortisone metabolism.
Doses 0.2–2 mg/24 hr has been used in the management of severe orthostatic hypotension in adults. Use a gradual dosage taper when discontinuing therapy.

FLUMAZENIL
Generics; previously available as Romazicon
Benzodiazepine antidote

Injection: 0.1 mg/mL (5, 10 mL); contains parabens

Benzodiazepine overdose (IV, see remarks):

Child (limited data): 0.01 mg/kg (**max. dose**: 0.2 mg) Q1 min PRN to a **max. total cumulative dose** of 1 mg. As an alternative for repeat bolus doses, a continuous infusion of 0.005–0.01 mg/kg/hr have been used.

Adult: Initial dose: 0.2 mg over 30 sec, if needed, give 0.3 mg 30 sec later over 30 sec. Additional doses of 0.5 mg given over 30 sec Q1 min PRN up to a cumulative dose of 3 mg (usual cumulative dose: 1–3 mg). Patients with only partial response to 3 mg may require additional slow titration to a total of 5 mg.

Reversal of benzodiazepine sedation (IV):

Child: Initial dose: 0.01 mg/kg (**max dose**: 0.2 mg) given over 15 sec, if needed after 45 sec, 0.01 mg/kg (**max. dose**: 0.2 mg) Q1 min to a **max. total cumulative dose** of 0.05 mg/kg or 1 mg, whichever is lower. Usual total dose: 0.08–1 mg (average 0.65 mg).

Adult: Initial dose: 0.2 mg over 15 sec, if needed after 45 sec, give 0.2 mg Q1 min to a **max. total cumulative dose** of 1 mg. Doses may be repeated at 20 min interval (**max. dose** of 1 mg per 20 min interval) up to a **max. dose** of 3 mg in 1 hr.

Does not reverse narcotics. Onset of benzodiazepine reversal occurs in 1–3 min. Reversal effects of flumazenil ($T_{1/2}$ approximately 1 hr) may wear off sooner than benzodiazepine effects. If patient does not respond after cumulative 1–3 mg dose, suspect agent other than benzodiazepines.

May precipitate seizures, especially in patients taking benzodiazepines for seizure control or in patients with tricyclic antidepressant overdose. Fear and panic attacks in patients with history of panic disorders have been reported.

Use with caution in liver dysfunction; flumazenil's clearance is significantly reduced. Use normal dose for initial dose and decrease the dosage and frequency for subsequent doses.

See Chapter 3 for complete management of suspected ingestions.

FLUNISOLIDE
Generics; previously available as Nasarel or Nasalide
Corticosteroid

Nasal solution: 25 mCg/spray (200 sprays/bottle) (25 mL); contains propylene glycol and benzalkonium chloride

After symptoms are controlled, reduce to lowest effective maintenance dose (e.g., 1 spray each nostril once daily) to control symptoms.

Nasal solution:

Child (6–14 yr):

Initial: 1 spray per nostril TID or 2 sprays per nostril BID; **max. dose**: 4 sprays per nostril/24 hr.

≥15 yr and adult:

Initial: 2 sprays per nostril BID; if needed in 4–7 days, increase to 2 sprays per nostril TID; **max. dose**: 8 sprays per nostril/24 hr.

Nasal burning and stinging is common. Nasal congestion, sneezing, epistaxis, watery eyes, sore throat, nausea/vomiting, and headaches may also occur. May cause a reduction in growth velocity. Nasal septal perforations have been reported. Flunisolide is a minor substrate of CYP 450 3A4.

nasal passages before use.

For explanation of icons, see p. 667

FLUORIDE

Fluorabon, Fluor-A-Day, Fluoritab, many others, and generics

Mineral

Concentrations and strengths based on fluoride ion:

Oral drops: 0.125 mg/drop (30 mL), 0.25 mg/drop (24 mL)
Fluorabon: 0.42 mg/mL (60 mL)

Chewable tabs (Fluor-A-Day, Fluoritab, and generics): 0.25, 0.5, 1 mg

All doses/24 hr (see table below):

Recommendations from American Academy of Pediatrics and American Dental Association for prevention of dental caries.

	Concentration of Fluoride in Drinking Water (ppm)		
Age	**<0.3**	**0.3–0.6**	**>0.6**
Birth–6 mo	0	0	0
6 mo–3 yr	0.25 mg	0	0
3–6 yr	0.5 mg	0.25 mg	0
6–16 yr	1 mg	0.5 mg	0

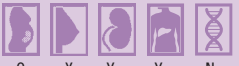
Contraindicated in areas where drinking water fluoridation is >0.7 ppm. **Acute overdose**: GI distress, salivation, CNS irritability, tetany, seizures, hypocalcemia, hypoglycemia, and cardiorespiratory failure. Chronic excess use may result in mottled teeth or bone changes.

Take with food, but **not** milk, to minimize GI upset. The doses have been decreased owing to concerns over dental fluorosis.

FLUOXETINE HYDROCHLORIDE

Prozac, Sarafem, and generics

Antidepressant, selective serotonin reuptake inhibitor



Oral solution: 20 mg/5 mL (120 mL); may contain alcohol

Caps: 10, 20, 40 mg

Delayed-released caps: 90 mg

Tabs: 10, 20, 60 mg

Depression:

Child, 8–18 yr: Start at 10–20 mg once daily PO. If started on 10 mg/24 hr, may increase dose to **max. dose** of 20 mg/24 hr after 1 wk. Use lower 10 mg/24 hr initial dose for lower-weight children; if needed, increase to 20 mg/24 hr after several weeks.

Adult: Start at 20 mg once daily PO. May increase after several weeks by 20 mg/24 hr increments to **max. dose** of 80 mg/24 hr. Doses >20 mg/24 hr should be divided BID.

Obsessive-compulsive disorder:

Child, 7–18 yr:

Lower weight child: Start at 10 mg once daily PO. May increase after several weeks. Usual dose range: 20–30 mg/24 hr. There is very minimal experience with doses >20 mg/24 hr and no experience with doses >60 mg/24 hr.

Higher weight child and adolescent: Start at 10 mg once daily PO and increase dose to 20 mg/24 hr after 2 wk. May further increase dose after several weeks. Usual dose range: 20–60 mg/24 hr.

FLUOXETINE HYDROCHLORIDE *continued*

Bulimia:

Adolescent (PO; limited data): 20 mg QAM × 3 days, then 40 mg QAM × 3 days, then 60 mg QAM.

Adult: 60 mg QAM PO; it is recommended to titrate up to this dose over several days.

Premenstrual dysphoric disorder:

Adult: Start at 20 mg PO once daily continuously or intermittently (starting 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle) using the Sarafem product. **Max. dose**: 80 mg/24 hr. Systematic evaluation has shown that efficacy is maintained for periods of 6 mo at a dose of 20 mg/day. Reassess patients periodically to determine the need for continued treatment.

Contraindicated in patients taking MAO inhibitors (e.g., linezolid) due to possibility of seizures, hyperpyrexia, and coma. **Use with caution** in patients with angle-closure glaucoma, receiving diuretics, or with liver (reduce dose with cirrhosis) or renal impairment. May increase the effects of tricyclic antidepressants. May cause headache, insomnia, nervousness, drowsiness, GI disturbance, and weight loss. Increased bleeding diathesis with unaltered prothrombin time may occur with warfarin. Hyponatremia has been reported. Monitor for clinical worsening of depression and suicidal ideation/behavior following the initiation of therapy or after dose changes.

May displace other highly protein-bound drugs. Inhibits CYP 450 2C19, 2D6, and 3A3/4 drug metabolism isoenzymes, which may increase the effects or toxicity of drugs metabolized by these enzymes. For example, use with pimozide or thioridazine may increase the risk for prolonged cardiac QTc interval and is considered **contraindicated.** Use with serotonergic drugs (e.g., triptans, methylene blue) and drugs that impair serotonin metabolism (MAOIs) may increase the risk for serotonin syndrome. Carefully review the patients' medication profile for potential interactions.

Delayed-release capsule is currently indicated for depression and is dosed at 90 mg Q7 days. It is unknown if weekly dosing provides the same protection from relapse as does daily dosing.

Breastfeeding is not recommended by the manufacturer, as adverse events to nursing infants have been reported. Fluoxetine and metabolite are variable and are higher when compared with other SSRIs. Maternal use of SSRIs during pregnancy and postpartum may result in more difficult breastfeeding. Infants exposed to SSRIs during pregnancy may also have an increased risk for persistent pulmonary hypertension of the newborn.

FLUTICASONE FUROATE + VILANTEROL

Breo Ellipta

Corticosteroid and long-acting β_2-adrenergic agonist

Breath-activated aerosol powder for inhalation (Breo Ellipta; contains lactose):

100 mCg fluticasone furoate + 25 mCg vilanterol per actuation (28, 60 doses)

200 mCg fluticasone furoate + 25 mCg vilanterol per actuation (28, 60 doses)

For Fluticasone Furoate (Arnuity Ellipta) as a single agent, see Fluticasone Preparations.

Asthma:

Adult: one inhalation of 100 mCg fluticasone furoate + 25 mCg vilanterol OR 200 mCg fluticasone furoate + 25 mCg vilanterol once daily

Max. dose: one inhalation/24 hr for either dosage strength (25 mCg vilanterol/24 hr)

Contraindicated with hypersensitivity to milk proteins. See Fluticasone Preparations for remarks. Vilanterol is a long-acting β_2-adrenergic agonist with a faster onset and longer duration of action compared to salmeterol.

Hypersensitivity reactions, hyperglycemia, muscle spasms, and tremor have been reported.

Titrate to the lowest effective strength after asthma is adequately controlled. This dosage form's breath-activated device requires a minimum inspiratory flow rate of 60 mL/min for proper dose activation. Proper patient education including dosage administration technique is essential; see

For explanation of icons, see p. 667

FLUTICASONE PREPARATIONS
Fluticasone propionate: Flonase, Cutivate, Beser, Flovent Diskus, Flovent HFA, ArmonAir RespiClick, and generics
Fluticasone furoate: Flonase Sensimist, and Arnuity Ellipta
Corticosteroid

FLUTICASONE PROPIONATE

Nasal spray (Flonase and generics; OTC): 50 mCg/actuation (9.9 mL = 60 doses, 15.8 mL = 120 doses); contains benzalkonium chloride and polysorbate 80

Topical cream: 0.05% (15, 30, 60 g)

Topical ointment: 0.005% (15, 30, 60 g)

Topical lotion (Cutivate, Beser, and generics): 0.05% (60, 120 mL); contains parabens and propylene glycol

Aerosol inhaler (MDI) (Flovent HFA): 44 mCg/actuation (10.6 g), 110 mCg/actuation (12 g), 220 mCg/actuation (12 g); each inhaler provides 120 metered inhalations

Dry-powder inhalation (DPI) (Flovent Diskus): 50 mCg/dose, 100 mCg/dose, 250 mCg/dose; all strengths come in a package of 15 Rotadisks; each Rotadisk provides 4 doses for a total of 60 doses per package. Contains lactose.

Breath-activated aerosol powder inhaler (ArmonAir RespiClick): 55 mCg/inhalation, 113 mCg/inhalation, 232 mCg/inhalation; each inhaler contains 0.9 g of formulation and provides 60 doses.

FLUTICASONE FUROATE

Nasal spray (Flonase Sensimist [OTC]): 27.5 mCg/actuation (5.9 mL = 60 doses); contains benzalkonium chloride and polysorbate 80

Breath-activated aerosol powder inhaler (Arnuity Ellipta): 50 mCg/actuation, (30 doses), 100 mCg/actuation (14, 30 doses), 200 mCg/actuation dose (14, 30 doses)

Intranasal (allergic rhinitis):

Fluticasone propionate (Flonase and generics):

≥4 yr and adolescent: 1 spray (50 mCg) per nostril once daily. Dose may be increased to 2 sprays (100 mCg) per nostril once daily if inadequate response or severe symptoms. Reduce to 1 spray per nostril once daily when symptoms are controlled.

Adult: Initial 200 mCg/24 hr [2 sprays (100 mCg) per nostril once daily; OR 1 spray (50 mCg) per nostril BID]. Reduce to 1 spray per nostril once daily when symptoms are controlled.

Max. dose (4 yr–adult): 2 sprays (100 mCg) per nostril/24 hr

Fluticasone furoate (Veramyst):

2–11 yr: 1 spray (27.5 mCg) per nostril once daily. If needed, dose may be increased to 2 sprays each nostril once daily. Reduce to 1 spray per nostril once daily when symptoms are controlled.

≥11 yr and adult: 2 sprays (55 mCg) each nostril once daily. Reduce to 1 spray per nostril once daily when symptoms are controlled.

Max. dose (2 yr–adult): 2 sprays (55 mCg) per nostril/24 hr

Oral inhalation (asthma):

Fluticasone propionate (Flovent HFA and Diskus): Divide all 24 hr doses BID. If desired response is not seen after 2 wk of starting therapy, increase dosage. Then reduce to the lowest effective dose when asthma symptoms are controlled. Administration of MDI (HFA) with aerochamber enhances drug delivery.

FLUTICASONE PREPARATIONS *continued*

Recommended dosages for asthma (see following table).

Age	Previous Use of Bronchodilators Only: (Max. Dose)	Previous Use of Inhaled Corticosteroid: (Max. Dose)	Previous Use of Oral Corticosteroid: (Max. Dose)
Child (4–11 yr)	MDI: 88 mCg/24 hr (176 mCg/24 hr) DPI: 100 mCg/24 hr (200 mCg/24 hr)	MDI: 88 mCg/24 hr (176 mCg/24 hr) DPI: 100 mCg/24 hr (200 mCg/24 hr)	Dose not available
≥12 yr and adult	MDI: 176 mCg/24hr (880 mCg/24hr) DPI: 200 mCg/24 hr (1000 mCg/24 hr)	MDI: 176–440 mCg/24 hr (880 mCg/24 hr) DPI: 200–500 mCg/24 hr (1000 mCg/24 hr)	MDI: 880 mCg/24 hr (1760 mCg/24 hr) DPI: 1000–2000 mCg/24 hr (2000 mCg/24 hr)

DPI, Dry powder inhaler (breath activated); *MDI*, metered dose inhaler.

Breath-activated aerosol powder inhaler (ArmonAir RespiClick):

≥12 yr and adult:

No prior inhaled corticosteroids: Start with 55 mCg inhaled BID; **max. dose**: 232 mCg BID

Prior treatment with inhaled corticosteroids: Start with low (55 mCg), medium (113 mCg), or high (232 mCg) inhaled BID based on the strength of previous inhaled corticosteroid and disease severity; **max. dose**: 232 mCg BID

Fluticasone furoate (Arnuity Ellipta):

5–11 yr: Inhale 50 mCg once daily

≥12 yr and adult: Inhale 100–200 mCg once daily; **max. dose:** 200 mCg/24 hr.

Eosinophilic esophagitis (limited data; use oral fluticasone propionate HFA dosage form without spacer for PO administration as doses are swallowed):

Child (1–10 yr): 220 mCg QID × 4 wk, then 220 mCg TID × 3 wk, then 220 mCg BID × 3 wk, and 220 mCg once daily × 2 wk.

Child ≥11 yr and adolescent: 440 mCg QID × 4 wk, then 440 mCg TID × 3 wk, then 440 mCg BID × 3 wk, and 440 mCg once daily × 2 wk.

Topical (reassess diagnosis if no improvement in 2 wk):

Cream (see Chapter 8 for topical steroid comparisons):

≥3 mo and adult: Apply thin film to affected areas once daily–BID; then reduce to a less potent topical agent when symptoms are controlled.

Lotion (see remarks):

≥3 mo and adult: Apply thin film to affected areas once daily. Safety of use has not been evaluated longer than 4 wk.

Ointment:

Adult: Apply thin film to affected areas BID.

Fluticasone propionate and fluticasone furoate do not have equivalent potencies; follow specific dosing regimens for the respective products.

Concurrent administration with ritonavir and other CYP 450 3A4 inhibitors may increase fluticasone levels resulting in Cushing syndrome and adrenal suppression. **Use with caution** and monitor closely in hepatic impairment.

Intranasal: Clear nasal passages prior to use. May cause epistaxis and nasal irritation, which are usually transient. Taste and smell alterations, rare hypersensitivity reactions (angioedema, pruritis, urticaria, wheezing, dyspnea), and nasal septal perforation have been reported in postmarketing studies.

D

For explanation of icons, see p. 667

FLUTICASONE PREPARATIONS *continued*

Oral inhalation: Specific breath-activated dosage forms require the following minimum inspiratory flow rates for proper dose activation:

Arnuity Ellipta: 60 L/min

ArmonAir RespiClick: 30 L/min

Rinse mouth after each use. May cause dysphonia, oral thrush, and dermatitis. Esophageal candidiasis and hypersensitivity reactions have been reported. Compared to beclomethasone, has been shown to have less of an effect on suppressing linear growth in asthmatic children. Eosinophilic conditions may occur with the withdrawal or decrease of oral corticosteroids after the initiation of inhaled fluticasone.

FLUTICASONE PROPIONATE AND SALMETEROL

Advair Diskus, Advair HFA, AirDuo RespiClick, and generics

Corticosteroid and long acting β_2-adrenergic agonist

Aerosol inhaler (MDI) (Advair HFA):

45 mCg fluticasone propionate + 21 mCg salmeterol per inhalation (8 g delivers 60 doses, 12 g delivers 120 doses)

115 mCg fluticasone propionate + 21 mCg salmeterol per inhalation (8 g delivers 60 doses, 12 g delivers 120 doses)

230 mCg fluticasone propionate + 21 mCg salmeterol per inhalation (8 g delivers 60 doses, 12 g delivers 120 doses)

Breath-activated DPI (Advair Diskus; contains lactose):

100 mCg fluticasone propionate + 50 mCg salmeterol per inhalation (14, 60 doses)

250 mCg fluticasone propionate + 50 mCg salmeterol per inhalation (14, 60 doses)

500 mCg fluticasone propionate + 50 mCg salmeterol per inhalation (14, 60 doses)

Breath-activated aerosol powder inhaler (AirDuo RespiClick; contains lactose):

55 mCg fluticasone propionate + 14 mCg salmeterol per inhalation (0.45 g delivers 60 doses)

113 mCg fluticasone propionate + 14 mCg salmeterol per inhalation (0.45 g delivers 60 doses)

232 mCg fluticasone propionate + 14 mCg salmeterol per inhalation (0.45 g delivers 60 doses)

Asthma:

Without prior inhaled steroid use:

Breath-activated (DPI; Advair Diskus):

4–11 yr: Start with one inhalation BID of 100 mCg fluticasone propionate + 50 mCg salmeterol.

≥***12 yr and adult:*** Start with one inhalation BID of 100 mCg fluticasone propionate + 50 mCg salmeterol, OR 250 mCg fluticasone propionate + 50 mCg salmeterol; **max. dose**: one inhalation BID of 500 mCg fluticasone propionate + 50 mCg salmeterol.

Aerosol inhaler (MDI; Advair HFA):

≥***12 yr and adult:*** Start with 2 inhalations BID of 45 mCg fluticasone + 21 mCg salmeterol, OR 115 mCg fluticasone + 21 mCg salmeterol; **max. dose**: 2 inhalations BID of 230 mCg fluticasone + 21 mCg salmeterol.

Breath-activated aerosol powder inhaler (AirDuo RespiClick):

≥***12 yr and adult:*** Start with 1 inhalation BID of 55 mCg fluticasone + 14 mCg salmeterol; **max. dose**: one inhalation BID of 232 mCg fluticasone propionate + 14 mCg salmeterol.

FLUTICASONE PROPIONATE AND SALMETEROL *continued*

With prior inhaled steroid use (conversion from other inhaled steroids; see following table and below):

Inhaled Corticosteroid	Current Daily Dose	Recommended Strength of Fluticasone Propionate + Salmeterol Diskus (DPI) (Advair Diskus) Administered at One Inhalation BID	Recommended Strength of Fluticasone Propionate + Salmeterol Aerosol Inhaler (MDI) (Advair HFA) Administered at Two Inhalations BID
Beclomethasone dipropionate (Qvar Redihaler)	160 mCg	100 mCg + 50 mCg	45 mCg + 21 mCg
	320 mCg	250 mCg + 50 mCg	115 mCg + 21 mCg
	640 mCg	500 mCg + 50 mCg	230 mCg + 21 mCg
Budesonide	≤400 mCg	100 mCg + 50 mCg	45 mCg + 21 mCg
	800–1200 mCg	250 mCg + 50 mCg	115 mCg + 21 mCg
	1600 mCg	500 mCg + 50 mCg	230 mCg + 21 mCg
Flunisolide (Aerospan; HFA)	≤320 mCg	100 mCg + 50 mCg	45 mCg + 21 mCg
	640 mCg	250 mCg + 50 mCg	115 mCg + 21 mCg
Fluticasone propionate aerosol (HFA)	≤176 mCg	100 mCg + 50 mCg	45 mCg + 21 mCg
	440 mCg	250 mCg + 50 mCg	115 mCg + 21 mCg
	660–880 mCg	500 mCg + 50 mCg	230 mCg + 21 mCg
Fluticasone propionate dry powder (DPI)	≤200 mCg	100 mCg + 50 mCg	45 mCg + 21 mCg
	500 mCg	250 mCg + 50 mCg	115 mCg + 21 mCg
	1000 mCg	500 mCg + 50 mCg	230 mCg + 21 mCg
Mometasone furoate	220 mCg	100 mCg + 50 mCg	45 mCg + 21 mCg
	440 mCg	250 mCg + 50 mCg	115 mCg + 21 mCg
	880 mCg	500 mCg + 50 mCg	230 mCg + 21 mCg

DPI, Dry powder inhaler (breath activated); *MDI*, metered dose inhaler.

Breath-activated aerosol powder inhaler (AirDuo RespiClick): Select low (55 mCg fluticasone + 14 mCg salmeterol), medium (113 mCg fluticasone + 14 mCg salmeterol), or high (232 mCg fluticasone + 14 mCg salmeterol) dose strength based on the previous inhaled corticosteroid product or the strength of the inhaled corticosteroid from a combination product and disease severity. All dosage strengths are administered as one inhalation BID.

Max. doses:

Breath-activated (DPI; Advair Diskus): one inhalation BID of 500 mCg fluticasone propionate + 50 mCg salmeterol.

Aerosol inhaler (MDI; Advair HFA): two inhalations BID of 230 mCg fluticasone propionate + 21 mCg salmeterol.

Breath-activated aerosol powder inhaler (AirDuo RespiClick): one inhalation BID of 232 mCg fluticasone propionate + 14 mCg salmeterol.

Contraindicated with hypersensitivity to milk proteins. See Fluticasone Preparations and Salmeterol for remarks. Titrate to the lowest effective strength after asthma is adequately controlled.

For explanation of icons, see p. 667

FLUTICASONE PROPIONATE AND SALMETEROL *continued*

Specific breath-activated dosage forms require the following minimum inspiratory flow rates for proper dose activation:

Advair Diskus: 60 L/min

AirDuo RespiClick: 30 L/min

Proper patient education including dosage administration technique is essential; see patient package insert to specific dosage form for detailed instructions. Rinse mouth after each use.

FLUVOXAMINE

Generics; previously available as Luvox and Luvox CR

Antidepressant, selective serotonin reuptake inhibitor

Tabs: 25, 50, 100 mg

Extended-release capsules: 100, 150 mg

Obsessive compulsive disorder (use immediate-release tablets unless noted otherwise, see remarks):

8–17 yr: Start at 25 mg PO QHS. Dose may be increased by 25 mg/24 hr Q7–14 days (slower titration at Q2–4 wk may be used for minimizing behavioral side effects). Total daily doses >50 mg/24 hr should be divided BID. Female patients may require lower dosages compared to males.

Max. dose: Child: 8–11 yr: 200 mg/24 hr; and child ≥12–17 yr: 300 mg/24 hr

Adult: Start at 50 mg PO QHS. Dose may be increased by 50 mg/24 hr Q4–7 days up to a **max. dose** of 300 mg/24 hr. Total daily doses >100 mg/24 hr should be divided BID with larger dose at bedtime.

Extended-release capsule (adult): Start at 100 mg PO QHS. Dose may be increased by 50 mg/24 hr Q7 days up to a **max. dose** of 300 mg/24 hr.

Contraindicated with coadministration of cisapride, pimozide, thioridazine, tizanidine, or MAO inhibitors. **Use with caution** in hepatic disease (dosage reduction may be necessary as drug is extensively metabolized by the liver) and in combination with serotonergic drugs (e.g., TCAs, triptans, fentanyl, lithium, tramadol, amphetamines, tryptophan, and St. John's Wort). Monitor for clinical worsening of depression and suicidal ideation/behavior following the initiation of therapy or after dose changes.

Major substrate for CYP 450 1A2 and 2D6. Poor metabolizers of CYP 450 2D6 should consider an initial dose reduction of 25%–50% and titrate to response or use an alternative medication not metabolized by this enzyme.

Inhibits CYP 450 1A2, 2C19, 2C9, 2D6, and 3A3/4, which may increase the effects or toxicity of drugs metabolized by these enzymes. Dose-related use of thioridazine with fluvoxamine may cause prolongation of QT interval and serious arrhythmias. May increase warfarin plasma levels by 98% and prolong PT. May increase toxicity and/or levels of theophylline, caffeine, and tricyclic antidepressants. Side effects include: headache, insomnia, somnolence, nausea, diarrhea, dyspepsia, and dry mouth.

Titrate to lowest effective dose. Use a gradual taper when discontinuing therapy to prevent withdrawal symptoms.

Consider the benefits to potential risk for maternal use in breastfeeding. Maternal use during pregnancy and postpartum may result in breastfeeding difficulties.

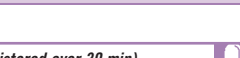
FOLIC ACID
FA-8 and many generics; previously available as Folvite
Water-soluble vitamin

Tabs [OTC]: 0.4, 0.8, 1 mg
Caps:
FA-8: 0.8 mg [OTC]
Generics: 5 mg, 20 mg
Oral solution: 0.05 mg/mL, 1 mg/mL
Injection: 5 mg/mL (10 mL); contains 1.5% benzyl alcohol

For U.S. RDA, see Chapter 21.
Folic acid deficiency PO, IM, IV, SC:
Infant: 0.1 mg/24 hr once daily
Child <4 yr: 0.1–0.3 mg/24 hr once daily
Child ≥4 yr and adolescent: 0.1–0.4 mg/24 hr once daily
Adult: 0.4 mg/24 hr once daily
Pregnant and lactating women: 0.8 mg/24 hr once daily

Normal levels: see Chapter 28. May mask hematologic effects of vitamin B_{12} deficiency, but will not prevent progression of neurologic abnormalities. High-dose folic acid may decrease the absorption of phenytoin.
Women of child-bearing age considering pregnancy should take at least 0.4 mg once daily before and during pregnancy to reduce risk of neural tube defects in the fetus. Pregnancy category changes to "C" if used in doses above the RDA.

FOMEPIZOLE
Antizol and generics
Antidote for ethylene glycol or methanol toxicity



Injection: 1 g/ mL (1.5 mL); preservative free

Child and adult not requiring hemodialysis (IV, all doses administered over 30 min):
Load: 15 mg/kg/dose × 1
Maintenance: 10 mg/kg/dose Q12 hr × 4 doses, then 15 mg/kg/dose Q12 hr until ethylene glycol or methanol level decreases to <20 mg/dL and the patient is asymptomatic with normal pH
Child and adult requiring hemodialysis (IV following the recommended doses at the intervals indicated here. Fomepizole is removed by dialysis. All doses administered IV over 30 min):
Dosing at the beginning of hemodialysis:
If <6 hr since last fomepizole dose: DO NOT administer dose.
If ≥6 hr since last fomepizole dose: Administer next scheduled dose.
Dosing during hemodialysis: Administer Q4 hr or, alternatively, 10–20 mg/kg loading dose, followed by a continuous infusion of 1–1.5 mg/kg/hr.
Dosing at the time hemodialysis is completed (based on the time between last dose and end of hemodialysis):
<1 hr: **DO NOT** administer dose at end of hemodialysis.
1–3 hr: Administer 1/2 of next scheduled dose.
>3 hr: Administer next scheduled dose.
Maintenance dose off hemodialysis: Give next scheduled dose 12 hr from last dose administered.

Continued

For explanation of icons, see p. 667

FOMEPIZOLE *continued*

Works by competitively inhibiting alcohol dehydrogenase. Safety and efficacy in pediatrics have not been established. **Contraindicated** in hypersensitivity to any components or other pyrazole compounds. Most frequent side effects include headache, nausea, and dizziness. Fomepizole is extensively eliminated by the kidneys (**use with caution** in renal failure) and removed by hemodialysis.

Drug product may solidify at temperatures <25°C (77°F); vial can be liquefied by running it under warm water (efficacy, safety, and stability are not affected). All doses must be diluted with at least 100 mL of D5W or NS to prevent vein irritation.

FOSCARNET
Foscavir and generics
Antiviral agent

Injection: 24 mg/mL (250 mL); preservative free
Contains 10 mEq Na/g drug

HIV positive or exposed with the following infection (IV):
CMV disease:
Infant, child, and adolescent:
Induction: 180 mg/kg/24 hr ÷ Q8–12 hr in combination with ganciclovir; continue until symptom improvement and convert to maintenance therapy
Maintenance: 90–120 mg/kg/dose Q24 hr
CMV retinitis (disseminated disease; IV):
Infant and child:
Induction: 180 mg/kg/24 hr ÷ Q8–12 hr × 14–21 days with or without ganciclovir
Maintenance: 90–120 mg/kg/24 hr once daily
Adolescent and adult:
Induction: 180 mg/kg/24 hr ÷ Q8–12 hr × 14–21 days
Maintenance: 90–120 mg/kg/24 hr once daily
Acyclovir-resistant herpes simplex (limited data; IV):
Infant and child: 40 mg/kg/dose Q8 hr or 60 mg/kg/dose Q12 hr for up to 3 wk or until lesions heal
Adolescent and adult: 40 mg/kg/dose Q8–12 hr × 14–21 days or until lesions heal
Varicella zoster unresponsive to acyclovir (IV):
Infant and child: 40–60 mg/kg/dose Q8 hr × 7–10 days
Adolescent: 90 mg/kg/dose Q12 hr
Varicella zoster, progressive outer retinal necrosis (IV):
Infant and child: 90 mg/kg/dose Q12 hr in combination with ganciclovir IV and intravitreal foscarnet with or without ganciclovir
Adolescent: 90 mg/kg/dose every 12 hr in combination with IV ganciclovir and intravitreal foscarnet and/or ganciclovir
Intravitreal route for progressive outer retinal necrosis (HIV positive or exposed):
Child and adolescent: 1.2 mg/0.05 mL or 2.4 mg/0.1 mL per dose 2–3 times weekly in combination with IV foscarnet and ganciclovir and/or intravitreal ganciclovir

Use with caution in patients with renal insufficiency and hypernatremia (large sodium content). **Discontinue** use in adults if serum Cr ≥ 2.9 mg/dL. **Adjust dose in renal failure (see Chapter 31).**

FOSCARNET *continued*

May cause peripheral neuropathy, seizures, neutropenia, esophageal ulceration, hallucinations, GI disturbance, increased LFTs, hypertension, chest pain, ECG abnormalities (QT interval prolongation has been reported), coughing, dyspnea, bronchospasm, and renal failure (adequate hydration and avoiding nephrotoxic medications may reduce risk). Hypocalcemia (increased risk if given with pentamidine), hypokalemia, and hypomagnesemia may also occur. Hypersensitivity reactions has been reported. Use with ciprofloxacin may increase risk for seizures.

Correction of dehydration and adequate hydration reduces the risk for nephrotoxicity. 10–20 mL/kg IV (**max. dose:** 1000 mL) of NS or D_5W should be administer prior to the first dose and concurrently with subsequent doses. For lower foscarnet dosage regimens of 40–60 mg/kg, use 50% of the aforementioned hydration recommendations. Actual hydration may need to be reduced when clinically indicated. Oral hydration methods may also be considered in patients who are able to tolerate.

For peripheral line IV administration, the concentration must be diluted to 12 mg/mL in NS or D_5W.

FOSPHENYTOIN
Cerebyx and generics
Anticonvulsant

Injection: 50 mg phenytoin equivalent (75 mg fosphenytoin)/1 mL (2, 10 mL)
1 mg phenytoin equivalent provides 0.0037 mmol phosphate

All doses are expressed as phenytoin sodium equivalents (PE) (see remarks for dose administration information):

Neonate, child, and adolescent: See Phenytoin and use the conversion of 1 mg phenytoin = 1 mg PE

Adult:

Loading dose:

Status epilepticus: 20 mg PE/kg IV (**max. dose:** 1500 mg PE/dose)

Nonemergent loading: 10–20 mg PE/kg IV/IM

Nonemergent initial maintenance dose (initiated 12 hr after loading dose): 4–6 mg PE/kg/24 hr IV/IM ÷ Q12–24 hr

All doses should be prescribed and dispensed in terms of mg phenytoin sodium equivalents (PE) to avoid medication errors. Safety in pediatrics has not been fully established.

Contraindicated in patients with history of phenytoin or other hydantoin hypersensitivity. **Use with caution** in patients with renal or hepatic impairment and porphyria (consider amount of phosphate delivered by fosphenytoin in patients with phosphate restrictions). Drug is also metabolized to liberate small amounts of formaldehyde, which is considered clinically insignificant with short-term use (e.g., 1 wk). Side effects: hypokalemia (with rapid IV administration), slurred speech, dizziness, ataxia, rash, exfoliative dermatitis (e.g., TEN, SJS; increased risk with patients with HLA-B*1502 allele), nystagmus, diplopia, and tinnitus. Angioedema has been reported. Increased unbound phenytoin concentrations may occur in patients with renal disease or hypoalbuminemia; measure "free" or "unbound" phenytoin levels in these patients.

Abrupt withdrawal may cause status epilepticus. BP and ECG monitoring should be present during IV loading dose administration. **Max. IV infusion rate:** 2 mg PE/kg/min up to a **max.** of 150 mg PE/min. Administer IM via 1 or 2 injection sites and IM route is not recommended in status epilepticus.

Therapeutic levels: 10–20 mg/L (free and bound phenytoin) OR 1–2 mg/L (free only). Recommended peak serum sampling times: 4 hr following an IM dose or 2 hr following an IV dose.

See Phenytoin remarks for drug interactions and additional side effects. Drug is more safely administered via peripheral IV than phenytoin.

D

For explanation of icons, see p. 667

FUROSEMIDE
Lasix and generics
Loop diuretic

Tabs: 20, 40, 80 mg
Injection: 10 mg/mL (2, 4, 10 mL)
Oral solution: 10 mg/mL (60, 120 mL), 40 mg/5 mL (500 mL)

IM, IV:

Neonate (see remarks): 0.5–1 mg/kg/dose Q8–24 hr; **max. dose**: 2 mg/kg/dose
Infant and child: 1–2 mg/kg/dose Q6–12 hr; **max. dose**: 6 mg/kg/dose not to exceed 200 mg/dose
Adult: 20–40 mg/24 hr ÷ Q6–12 hr; **max. dose**: 200 mg/dose

PO:

Neonate: Bioavailability by this route is poor; doses of 1–3 mg/kg/dose once daily to BID have been used.
Infant and child: Start at 2 mg/kg/dose; may increase by 1–2 mg/kg/dose no sooner than 6–8 hr following the previous dose. **Max. dose**: 6 mg/kg/dose. Dosages have ranged from 1–6 mg/kg/dose Q12–24 hr.
Adult: 20–80 mg/dose Q6–12 hr; **max. dose**: 600 mg/24 hr

Continuous IV infusion:

Infant and child: 0.1 mg/kg IV bolus followed by 0.05–0.4 mg/kg/hr infusion and titrate to effect
Adult: 40–100 mg IV bolus followed by 10–40 mg/hr infusion and titrate to effect

Contraindicated in anuria and hepatic coma. **Use with caution** in hepatic disease (hepatic encephalopathy has been reported); cirrhotic patients may require higher than usual doses. Ototoxicity may occur in presence of renal disease (especially when used with aminoglycosides and other nephrotoxic drugs), with rapid IV injection (do not infuse >4 mg/min in adults), or with hypoproteinemia. May cause hypokalemia, alkalosis, dehydration, hyperuricemia, and increased calcium excretion. Rash with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis have been reported. Prolonged use in premature infants and in children <4 yr may result in nephrocalcinosis. May increase risk for PDA in premature infants during the first week of life.

Furosemide-resistant edema in pediatric patients may benefit with the addition of metolazone. Some of these patients may have an exaggerated response leading to hypovolemia, tachycardia, and orthostatic hypotension requiring fluid replacement. Severe hypokalemia has been reported with a tendency for diuresis persisting for up to 24 hr after discontinuing metolazone, prolonged use of laxatives, or concomitant use of corticosteroids, ACTH, and large amounts of licorice.

High doses of furosemide may inhibit binding of thyroid hormones to carrier proteins and result in transient increase in free thyroid hormones followed by an overall decrease in total thyroid hormone levels.

Max. rate of intermittent IV dose: 0.5 mg/kg/min. For patients receiving ECMO, **do not** administer IV doses directly into the ECMO circuit as the medication is absorbed in the circuit, which may result in diminished effects and the need for higher doses.

Pregnancy category changes to "D" if used in pregnancy-induced hypertension.

G

GABAPENTIN

Neurontin, Gralise, Horizant and generics

Anticonvulsant

Caps: 100, 300, 400 mg

Tabs: 300, 600, 800 mg

Slow-release/extended-release tabs (these dosage forms are **not** interchangeable with other gabapentin products due to different pharmacokinetic profiles affecting the dosing interval; see specific product information for specific indications for use and dosage):

Gralise: 300, 600 mg

Horizant (Gabapentin Enacarbil): 300, 600 mg

Oral solution: 250 mg/5 mL (470 mL)

Seizures, *adjunctive therapy (maximum time between doses should not exceed 12 hr):*

3–<12 yr (PO, see remarks):

Day 1: 10–15 mg/kg/24 hr ÷ TID, then gradually titrate dose upward to the following dosages over a 3-day period:

3–4 yr: 40 mg/kg/24 hr ÷ TID

≥5–<12 yr: 25–35 mg/kg/24 hr ÷ TID

Dosages up to 50 mg/kg/24 hr have been well tolerated.

≥12 yr and adult (PO, see remarks): Start with 300 mg TID; if needed, increase dose up to 1800 mg/24 hr ÷ TID. Usual effective doses: 900–1800 mg/24 hr ÷ TID. Doses as high as 3.6 g/24 hr have been tolerated.

Neuropathic pain:

Child (PO; limited data):

Day 1: 5 mg/kg/dose (**max.** 300 mg/dose) at bedtime

Day 2: 5 mg/kg/dose (**max.** 300 mg/dose) BID

Day 3: 5 mg/kg/dose (**max.** 300 mg/dose) TID; then titrate dose to effect. Usual dosage range: 8–35 mg/kg/24 hr ÷ TID.

Maximum daily dose of 3600 mg/24 hr has been suggested but not formally evaluated.

Adult (PO):

Day 1: 300 mg at bedtime

Day 2: 300 mg BID

Day 3: 300 mg TID; then titrate dose to effect. Usual dosage range: 1800–2400 mg/24 hr; **max. dose:** 3600 mg/24 hr.

Post-herpetic neuralgia: the above dosage regimen may be titrated up PRN for pain relief to a daily dose of 1800 mg/24 hr ÷ TID (efficacy has been shown from 1800 to 3600 mg/24 hr, however no additional benefit has been shown for doses >1800 mg/24 hr). The Gralise dosage form is designed for once daily administration with the evening meals; whereas the Horizant dosage form is dosed once daily–BID. See specific product information for details.

Generally used as adjunctive therapy for partial and secondary generalized seizures, and neuropathic pain.

Somnolence, dizziness, ataxia, fatigue, and nystagmus were common when used for seizures (≥12 yr). Viral infections, fever, nausea and/or vomiting, somnolence, and hostility have been reported in patients 3–12 yr receiving other antiepileptics. Dizziness, somnolence, and peripheral edema are common side effects in adult with post-herpetic neuralgia. Suicidal behavior or ideation, agitation, and multi-organ hypersensitivity (e.g., anaphylaxis, angioedema, or drug reaction with eosinophilia and systemic symptoms [DRESS]) have been reported.

Continued

For explanation of icons, see p. 667

GABAPENTIN *continued*

Do not withdraw medication abruptly (gradually over a minimum of 1 wk). Drug is not metabolized by the liver and is primarily excreted in the urine unchanged. Higher doses may be required for children <5 yr because of faster clearance in this age group.

May be taken with or without food. In TID dosing schedule, **interval between doses should not exceed 12 hr. Adjust dose in renal impairment (see Chapter 31).**

GANCICLOVIR
Cytovene, Zirgan and generics
Antiviral agent

Injection (Cytovene and generics): 500 mg; contains 4 mEq Na per 1 g drug
Injection in solution: 500 mg/10 mL (10 mL)
Ophthalmic gel (drops):
Zirgan: 0.15% (5 g); contains benzalkonium chloride.

Cytomegalovirus (CMV) infections:
Neonate (congenital CMV): 12 mg/kg/24 hr ÷ Q12 hr IV × 6 wk or longer if HIV positive
Child >3 mo and adult:
Induction therapy (duration 14–21 days): 10 mg/kg/24 hr ÷ Q12 hr IV
IV maintenance therapy: 5 mg/kg/dose once daily IV for 7 days/wk or 6 mg/kg/dose once daily IV for 5 days/wk
Prevention of CMV in transplant recipients:
Child and adult:
Induction therapy (duration 7–14 days): 10 mg/kg/24 hr ÷ Q12 hr IV
IV maintenance therapy: 5 mg/kg/dose once daily IV for 7 days/wk or 6 mg/kg/dose once daily IV for 5 days/wk for 100–120 days post-transplant
Prevention of CMV in HIV-infected individuals (see www.aidsinfo.nih.gov for latest recommendations and guidelines for CMV treatment as well):
Recurrence prophylaxis:
Infant, child, adolescent, and adult: 5 mg/kg/dose IV once daily. Consider valganciclovir as an oral alternative.
Herpetic keratitis (ophthalmic gel/drops):
≥2 yr and adult: Apply 1 drop onto affected eye(s) 5 times a day (~Q3 hr while awake) until corneal ulcer is healed, then 1 drop TID × 7 days.

Limited experience with use in children <12 yr old. **Contraindicated** in severe neutropenia (ANC < 500/microliter) or severe thrombocytopenia (platelets < 25,000/microliter). **Use with extreme caution. Reduce dose in renal failure (see Chapter 31).** Has not been evaluated in hepatic impairment. For oral route of administration, see Valganciclovir.

Common side effects: neutropenia, thrombocytopenia, retinal detachment, and confusion. Drug reactions alleviated with dose reduction or temporary interruption. Ganciclovir may increase didanosine and zidovudine levels, whereas didanosine and zidovudine may decrease ganciclovir levels. Immunosuppressive agents may increase hematologic toxicities. Amphotericin B, cyclosporine and tacrolimus increases risk for nephrotoxicity. Imipenem/cilastatin may increase risk for seizures. May cause female and male infertility.

Minimum dilution is 10 mg/mL and should be infused IV over ≥1 hr. IM and SC administration are **contraindicated** because of high pH of 11.

GATIFLOXACIN
Zymaxid and generics
Antibiotic, quinolone

Ophthalmic solution: 0.5% (2.5 mL); may contain benzalkonium chloride
Previously available as a 0.3% ophthalmic solution (Zymar).

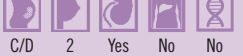
Conjunctivitis:
≥1 yr–adult: Instill 1 drop to affected eye(s) Q2 hr while awake (up to 8 times/24 hr) for the first day, then 1 drop BID–QID while awake on days 2–7.

Worsening of conjunctivitis, decreased visual acuity, excessive tear production, and keratitis are common side effects. Conjunctival hemorrhage has been reported.
Avoid touching the applicator tip to eye, fingers, or other surfaces, and **do not** wear contact lenses during treatment of ocular infections. Apply pressure to the lacrimal sac during and for 1–2 min after dose administration to reduce risk of systemic absorption.

GCSF

See Filgrastim

GENTAMICIN
Gentak and generics; previously available a Garamycin
Antibiotic, aminoglycoside



Injection: 10 mg/mL (2 mL, preservative free), 40 mg/mL (2, 20 mL); some products may contain sodium metabisulfite
Pre-mixed injection in NS: 40 mg (50 mL), 60 mg (50 mL), 80 mg (50, 100 mL), 100 mg (50, 100 mL), 120 mg (100 mL)
Ophthalmic ointment (Gentak and generics): 0.3% (3.5 g); may contain parabens
Ophthalmic drops: 0.3% (5 mL)
Topical ointment: 0.1% (15, 30 g)
Topical cream: 0.1% (15, 30 g)

Initial empiric dosage; patient-specific dosage defined by therapeutic drug monitoring (see remarks).
Parenteral (IM or IV):
Neonate/Infant (see table below):

Post-conceptional Age (wk)	Postnatal Age (days)	Dose (mg/kg/dose)	Interval (hr)
≤29[a]	0–7	5	48
	8–28	4	36
	>28	4	24
30–34	0–7	4.5	36
	>7	4	24
≥35	ALL	4	24[b]

[a]Or significant asphyxia, patent ductus arteriosus (PDA), indomethicin use, poor cardiac output, reduced renal function.
[b]Use Q36 hr interval for hypoxic-ischemic encephalopathy (HIE) patients receiving whole-body therapeutic cooling.

Continued

For explanation of icons, see p. 667

GENTAMICIN *continued*

Child: 7.5 mg/kg/24 hr ÷ Q8 hr
Adult: 3–6 mg/kg/24 hr ÷ Q8 hr
Cystic Fibrosis: 7.5–10.5 mg/kg/24 hr ÷ Q8 hr
Intrathecal/intraventricular (use preservative-free product only):
Newborn: 1 mg once daily
>3 mo: 1–2 mg once daily
Adult: 4–8 mg once daily
Ophthalmic ointment: Apply 0.5 inch ribbon to the conjunctival sac of the affected eye(s) Q8–12 hr
Ophthalmic drops: Instill 1–2 drops to affected eye(s) Q2–4 hr
Topical cream or ointment:
>1 yr and adult: Apply to affected area TID–QID

Use with caution in patients receiving anesthetics or neuromuscular blocking agents, and in patients with neuromuscular disorders. May cause nephrotoxicity and ototoxicity. Ototoxicity may be potentiated with the use of loop diuretics. Eliminated more quickly in patients with cystic fibrosis, neutropenia, and burns. **Adjust dose in renal failure (see Chapter 31).** Monitor peak and trough levels.

Therapeutic peak levels are 6–10 mg/L in general, and 8–10 mg/L in pulmonary infections, cystic fibrosis, neutropenia, osteomyelitis, and severe sepsis.

To maximize bactericidal effects, an individualized peak concentration to target a peak/minimal inhibitory concentration (MIC) ratio of 8–10:1 may be applied.

Therapeutic trough levels: <2 mg/L. Recommended serum sampling time at steady state: trough within 30 min prior to the 3rd consecutive dose and peak 30–60 min after the administration of the 3rd consecutive dose.

For initial dosing in obese patients, use an adjusted body weight (ABW). ABW = Ideal Body Weight + 0.4 (Total Body Weight − Ideal Body Weight).

Pregnancy category is a "C" for ophthalmic use, a "D" with IV use, and not classified for topical use.

GLUCAGON HCL
GlucaGen, Glucagon Emergency Kit, Baqsimi, and generics
Antihypoglycemic agent

Injection: 1 mg vial (requires reconstitution)
Nasal powder (Baqsimi): 3 mg/dose (1 or 2 pack); contains betadex and dodecylphosphocholine 1 unit = 1 mg

Hypoglycemia (see remarks):

Injectable route (IM, IV, SC):
Neonate, infant, and child <20 kg: 0.5 mg/dose (or 0.02–0.03 mg/kg/dose) Q20 min PRN
Child ≥20 kg and adult: 1 mg/dose Q20 min PRN
Intranasal route (see remarks):
≥4 yr and adult: Actuate 3 mg intranasally into one nostril × 1. If no response after 15 min, an additional 3 mg dose may be given.
β-blocker and calcium channel blocker overdose: Load with 0.05–0.15 mg/kg IV (usually about 10 mg in adults) over 1 min followed by an IV infusion of 0.05–0.1 mg/kg/hr.
Alternatively, 5 mg IV bolus Q5–10 min PRN up to 4 doses. If patient is responsive at a particular bolus dose, initiate an hourly IV infusion at that same responsive dose. For example, if the patent responded at 10 mg, then start an infusion of 10 mg/hr.

GLUCAGON HCL *continued*

Contraindicated in insulinoma, pheochromocytoma, and history of hypersensitivity to glucagon and components. Drug product is genetically engineered and identical to human glucagon. High doses have a cardiac stimulatory effect and have been used with some success in β-blocker and calcium channel blocker overdose. May cause nausea, vomiting, urticaria, and respiratory distress. Necrolytic migratory erythema (NME) has been reported with continuous IV infusion; assess benefit/risk for continued use.

Do not delay glucose infusion; dose for hypoglycemia is 2–4 mL/kg of dextrose 25%.

Glucagon may increase the effects/toxicity of warfarin. Indomethacin use may decrease the effects of glucagon.

Sufficient hepatic glycogen is necessary for effect; patients in states of starvation, with adrenal or chronic hypoglycemia, may not have adequate levels of glycogen. Onset of action: IM: 8–10 min; IV: 1 min. Duration of action: IM: 12–27 min; IV: 9–17 min.

INTRANASAL USE: See product information for dose administration instructions. Dose does not need to be inhaled and can be administered if the patient has nasal congestion or the common cold. Common side effects include nausea, vomiting, headache, rhinorrhea, nasal discomfort/congestion, cough, epistaxis, and irritation to the eyes, nose, and throat. In type-1 pediatric diabetes trials, the time to increase glucose ≥20 mg/dL from nadir was 11–15 min and peak plasma levels were achieved in 15–20 min with a median $T_{1/2}$: of 21–31 min.

GLYCERIN
Pedia-Lax, Sani-Supp, Fleet Liquid Glycerin Supp, and others including generics
Osmotic Laxative

Rectal solution (Fleet Liquid Glycerin Supp and generics; OTC): each dose contains 7.5 mL to deliver 5.4 mL of glycerin on average (box of 4)

Suppository (OTC):

Infant/pediatric:

Pedia-Lax and generics: 1 g (12s, 25s)

Sani-Supp Pediatric and generics: 1.2 g (12s, 25s)

Adult:

Sani-Supp Adult and generics: 2 g (12s, 24s, 25s, 50s)

Constipation:

Neonate: 0.5 mL/kg/dose rectal solution PR as an enema once daily PRN or sliver/chip of infant/pediatric suppository PR once daily PRN

Child <6 yr: 2–5 mL rectal solution PR as an enema or 1 infant/pediatric suppository PR once daily PRN

>6 yr—adult: 5–15 mL rectal solution PR as an enema or 1 adult suppository PR once daily PRN

Onset of action: 15–30 min. May cause rectal irritation, abdominal pain, bloating, and dizziness. Insert suppository high into rectum and retain for 15 min.

For explanation of icons, see p. 667

GLYCOPYRROLATE
Cuvposa and generics; previously available as Robinul
Anticholinergic agent

Tabs: 1, 1.5, 2 mg
Oral solution (Cuvposa): 1 mg/5 mL (473 mL); contains propylene glycol, and parabens
Injection: 0.2 mg/mL (1, 2, 5, 20 mL); some multidose vials contain 0.9% benzyl alcohol

Respiratory antisecretory:
IM/IV:
Child: 0.004–0.01 mg/kg/dose TID–QID
Adult: 0.1–0.2 mg/dose TID–QID
Max. dose: 0.2 mg/dose or 0.8 mg/24 hr
Oral:
Child: 0.04–0.1 mg/kg/dose TID–QID
Alternative dosage for 3–16 yr old with chronic severe drooling secondary to neurological conditions: Start with 0.02 mg/kg/dose PO TID and titrate in increments of 0.02 mg/kg/dose every 5–7 days as needed and tolerated up to a **max. dose** of 0.1 mg/kg/dose TID not exceed 1.5–3 mg/dose.
Adult: 1–2 mg/dose BID–TID
Reverse neuromuscular blockade:
Child and adult: 0.2 mg IV for every 1 mg neostigmine or 5 mg pyridostigmine

Use with caution in hepatic and renal disease, ulcerative colitis, asthma, glaucoma, ileus, or urinary retention. Atropine-like side effects: tachycardia, nausea, constipation, confusion, blurred vision, and dry mouth. These may be potentiated if given with other drugs with anticholinergic properties.
Onset of action: PO: within 1 hr; IM/SC: 15–30 min; IV: 1 min. Duration of antisialagogue effect: PO: 8–12 hr; IM/SC/IV: 7 hr. Oral doses should be administered 1 hr before and 2 hr after meals.
Pregnancy category is "B" for the injection and tablet dosage forms and "C" for the oral solution.

GRANISETRON
Sancuso, Sustol, and generics; previously available as Kytril
Antiemetic agent, 5-HT$_3$ antagonist

Injection: 1 mg/mL (1, 4 mL); 4 mL multi-dose vials contain benzyl alcohol
Prefilled syringe for subcutaneous extended-release injection (Sustol): 10 mg/0.4 mL (0.4 mL); contains propylene glycol
Tabs: 1 mg
Oral suspension: 0.2 mg/mL, 50 mCg/mL
Transdermal patch (Sancuso): 3.1 mg/24 hr

Chemotherapy-induced nausea and vomiting:
IV:
Child ≥2 yr and adult: 10–20 mCg/kg/dose 15–60 min before chemotherapy; the same dose may be repeated 2–3 times at ≥10-min intervals following chemotherapy (within 24 hr after chemotherapy) as a treatment regimen. **Max. dose**: 3 mg/dose or 9 mg/24 hr. Alternatively, a single 40 mCg/kg/dose 15–60 min before chemotherapy has been used.
SC (Sustol):
Adult: 10 mg at least 30 min prior to first dose of moderately emetogenic chemotherapy used in combination of dexamethasone. **Do not** administer more frequently than Q7 days.

GRANISETRON *continued*

PO:

Infant, child, and adolescent: 40 mCg/kg/dose BID is recommended for moderately emetogenic chemotherapy; initiate first dose 1 hr prior to chemotherapy

Adult: 2 mg/24 hr ÷ once daily–BID; initiate first dose 1 hr prior to chemotherapy

Post-operative nausea and vomiting prevention (dosed prior to anesthesia or immediately before anesthesia reversal) and treatment (IV; see remarks):

Adult: 1 mg × 1

Radiation-induced nausea and vomiting prevention:

Adult: 2 mg once daily PO administered within 1 hr of radiation

Transdermal patch (see remarks):

Prophylaxis for chemotherapy-induced nausea and vomiting (adult): Apply 1 patch 24–48 hr prior to chemotherapy. Patch removal at a minimum of 24 hr after completion of chemotherapy. Patch may be worn up to 7 days, depending on the chemotherapy regimen duration.

Use with caution in liver disease and preexisting cardiac conduction disorders and arrhythmias. May cause hypertension, hypotension, arrhythmias, agitation, and insomnia. Inducers or inhibitors of the CYP 450 3A3/4 drug metabolizing enzymes may increase or decrease, respectively, the drug's clearance. QT prolongation has been reported.

Safety and efficacy in pediatric patients for the prevention of postoperative nausea and vomiting has not been established due to lack of efficacy and QT prolongation in a prospective multicenter, randomized double blinded trial in 157 patients aged 2–16 yr.

Avoid external heat sources (e.g., heating pads) on and around the transdermal patch dosage form as heat may increase the rate of drug release. Application site reactions of pain, pruritus, rash, irritation, vesicles, and discoloration has been reported with transdermal patch use.

Onset of action: IV: 4–10 min. Duration of action: IV: ≤24 hr.

GRISEOFULVIN

Microsize: Generics; previously available as Grifulvin V, Griseofulvin Microsize

Ultramicrosize: Generics; previously available as Gris-PEG

Antifungal agent

Microsize:

Tabs: 125, 250, 500 mg

Oral suspension: 125 mg/5 mL (120 mL); contains 0.2% alcohol, parabens and propylene glycol

Ultramicrosize:

Tabs: 125, 250 mg

250 mg ultramicrosize is approximately 500 mg microsize

Microsize:

Child >2 yr and adolescent: 20–25 mg/kg/24 hr PO ÷ once daily–BID; give with milk, eggs, fatty foods

Adult: 500–1000 mg/24 hr PO ÷ once daily–BID

Max. dose (all ages): 1 g/24 hr

Ultramicrosize:

Child >2 yr and adolescent: 10–15 mg/kg/24 hr PO ÷ once daily–BID

Adult: 375 mg/dose PO once daily or BID

Max. dose (all ages): 750 mg/24 hr

Continued

For explanation of icons, see p. 667

GRISEOFULVIN *continued*

Contraindicated in porphyria, pregnancy, and hepatic disease. Monitor hematologic, renal, and hepatic function. May cause leukopenia, rash, headache, paresthesias, and GI symptoms. Severe skin reactions (e.g., Stevens-Johnson, TEN), erythema multiforme, LFT elevations (AST, ALT, bilirubin), and jaundice have been reported. Possible cross-reactivity in penicillin-allergic patients. Usual treatment period is 8 wk for tinea capitis and 4–6 mo for tinea unguium. Photosensitivity reactions may occur. May reduce effectiveness or decrease level of oral contraceptives, warfarin, and cyclosporine. Induces CYP 450 1A2 isoenzyme. Phenobarbital may enhance clearance of griseofulvin. Coadministration with fatty meals will increase the drug's absorption.

GUANFACINE
Intuniv and generics
α_2-adenergic agonist

Tabs: 1, 2 mg
Extended-release tabs: 1, 2, 3, 4 mg

Attention-deficit hyperactivity disorder (see remarks):
Immediate-release tab:
≥6 yr and adolescent:
≤45 kg: Start at 0.5 mg QHS, if needed and tolerated, increase dose every 3–4 days at 0.5 mg/24 hr increments by increasing the dosing frequency to BID, TID, QID. **Max. dose**: 27–40.5 kg: 2 mg/24 hr and 40.5–45 kg: 3 mg/24 hr.
>45 kg: Start at 1 mg QHS, if needed and tolerated, increase dose every 3–4 days at 1 mg/24 hr increments by increasing the dosing frequency to BID, TID, QID. **Max. dose**: 4 mg/24 hr.
Extended-release tab:
6–17 yr: Start at 1 mg Q24 hr, if needed and tolerated, increase dose no more than 1 mg per week up to the **max. dose** of 4 mg/24 hr for 6–12 yr and 7 mg/24 hr for 13–17 yr.
Use with strong CYP 450 3A4 inhibitors or inducers:

CYP 450 3A4 Characteristic	Adding Guanfacine With Respective CYP 450 3A4 Inducer/Inhibitor Already on Board	Adding Respective CYP 450 3A4 Inducer/Inhibitor With Guanfacine Already on Board
Strong inducer (e.g., carbamazepine, phenytoin, rifampin, St. John's Wort)	Guanfacine may be titrated up to double the recommended target dose.	Consider increasing guanfacine dose up to double the recommended target dose over 1–2 wk as tolerated. If the strong inducer is discontinued, decrease guanfacine dose to target dose over 1–2 wk.
Strong inhibitor (e.g., clarithromycin, azole antifungals)	Decrease guanfacine dose to 50% of recommended target dose.	Decrease guanfacine dose to 50% of recommended target dose. If the strong inhibitor is discontinued, increase guanficine dose to recommended target dose.

GUANFACINE *continued*

Use with caution in patients at risk for hypotension, bradycardia, heart block, and syncope. A dose-dependent hypotension and bradycardia may occur. Somnolence, fatigue, insomnia, dizziness, and abdominal pain are common side effects. Orthostatic hypotension, hallucinations, syncope, and erectile dysfunction have been reported.

Drug is a substrate for CYP 450 3A4. See dosing section for dosage adjustment with inhibitors and inducers.

Do not abruptly discontinue therapy (may cause rebound hypertension); taper of no more than 1 mg Q3–7 days has been recommended. Dose reductions may be required with clinically significant renal or hepatic impairment. When converting from an immediate-release tab to the extended-release tab, **do not** covert on a mg per mg basis (due to differences in pharmacokinetic profiles) but discontinue the immediate release and titrate with the extended-release product using the recommended dosing schedules.

H

HALOPERIDOL
Haldol, Haldol Decanoate, and generics
Antipsychotic agent

Injection (IM use only):
Lactate: 5 mg/mL (1, 10 mL); may contain parabens
Decanoate (long acting): 50, 100 mg/mL (1, 5 mL); in sesame oil with 1.2% benzyl alcohol
Tabs: 0.5, 1, 2, 5, 10, 20 mg
Oral solution: 2 mg/mL (15, 120 mL)

Child 3–12 yr (see remarks):
PO: Initial dose at 0.5 mg/24 hr ÷ BID–TID. If necessary, increase daily dosage by 0.25–0.5 mg/24 hr Q5–7 days PRN. Benefits are not to be expected for doses beyond 6 mg/24 hr. Usual maintenance doses for specific indications include the following:
Agitation: 0.01–0.03 mg/kg/24 hr once daily PO
Psychosis: 0.05–0.15 mg/kg/24 hr ÷ BID–TID PO
Tourette's syndrome: 0.05–0.075 mg/kg/24 hr ÷ BID–TID PO; may increase daily dose by 0.5 mg Q5–7 days
IM, as lactate, for 6–12 yr: 1–3 mg/dose Q4–8 hr; **max. dose**: 0.15 mg/kg/24 hr
>12 yr:
Acute agitation: 2–5 mg/dose IM as lactate or 1–15 mg/dose PO; repeat in 1 hr PRN
Psychosis: 2–5 mg/dose Q4–8 hr IM PRN or 1–15 mg/24 hr ÷ BID–TID PO
Tourette's syndrome: 0.5–2 mg/dose BID–TID PO; 3–5 mg/dose BID–TID PO may be used for severe symptoms

Contraindicated in severe toxic CNS depression, comas, Parkinson disease, and dementia Lewy bodies. **Use with caution** in patients with cardiac disease (risk of hypotension), renal or hepatic dysfunction, thyrotoxicosis, and in patients with epilepsy since the drug lowers the seizure threshold. Extrapyramidal symptoms, drowsiness, headache, tachycardia, ECG changes, nausea, and vomiting can occur. Higher than recommended doses are associated with a higher risk of QT-prolongation and torsades de pointes. Leukopenia/neutropenia, including agranulocytosis and rhabdomyolysis (IM route), and transient dyskinetic signs (following abrupt withdrawal from maintenance therapies) have been reported.

Continued

For explanation of icons, see p. 667

HALOPERIDOL *continued*

Drug is metabolized by CYP 450 1A2, 2D6, and 3A3/4 isoenzymes. May also inhibit CYP 450 2D6 and 3A3/4 isoenzymes. Serotonin-specific reuptake inhibitors (e.g., fluoxetine) may increase levels and effects of haloperidol. Carbamazepine and phenobarbital may decrease levels and effects of haloperidol. Monitor for encephalopathic syndrome when used in combination with lithium.

For poor metabolizers of CYP 450 2D6, consider a 50% reduction of initial dose and titrate to response, OR use an alternative medication not metabolized by this enzyme system.

Acutely aggravated patients may require doses as often as Q60 min. **Decanoate salt is given every 3–4 wk in doses that are 10–15 times the individual patient's stabilized oral dose.**

HEPARIN SODIUM

Various generics

Anticoagulant

Injection:

Porcine intestinal mucosa: 1000, 5000, 10,000, 20,000 U/mL (some products may be preservative-free; multidosed vials contain benzyl alcohol)

Lock flush solution (porcine based): 10, 100 U/mL (some products may be preservative-free or contain benzyl alcohol)

Injection for IV infusion (porcine based):

D_5W: 40 U/mL (500 mL), 50 U/mL (250, 500 mL), 100 U/mL (100, 250 mL); contains bisulfite

NS (0.9% NaCl): 2 U/mL (500, 1000 mL)

0.45% NaCl: 50 U/mL (250, 500 mL), 100 U/mL (250 mL); contains EDTA

120 U = approximately 1 mg

Anticoagulation empiric dosage:

Continuous IV infusion (initial doses for goal unfractionated heparin (UFH) anti-Xa level of 0.3–0.7 units/mL):

Age	Loading Dose (IV)[a]	Initial IV infusion Rate (units/kg/hr)
Neonate and infant <1 yr	75 U/kg IV	28
Child age 1–16 yr	75 U/kg IV (max. dose: 8000 U)	20 (max. initial rate: 1650 U/hr)
>16 yr	70 U/kg IV (max. dose: 8000 U)	16 (max. initial rate: 1650 U/hr)

[a]Do not give loading dose for patients with stroke or significant bleeding risk and obtain aPPT 4 hr after loading dose.

DVT or PE prophylaxis:

Adult: 5000 U/dose SC Q8–12 hr until ambulatory

Heparin flush (doses should be less than heparinizing dose):

Younger child: lower doses should be used to avoid systemic heparinization.

Older child and adult:

Peripheral IV: 1–2 mL of 10 U/mL solution Q4 hr

Central lines: 2–3 mL of 100 U/mL solution Q24 hr

TPN (central line) and arterial line: add heparin to make final concentration of 0.5–1 U/mL.

Contraindicated in active major bleeding, known or suspected HIT, and concurrent epidural therapy. **Use with caution** if platelets <50,000/mm^3. **Avoid** IM injections and other medications affecting platelet function (e.g., NSAIDs and ASA). Toxicities include bleeding, allergy, alopecia, and thrombocytopenia.

Adjust dose with one of the following laboratory goals:

Unfractionated heparin (UFH) anti-Xa level: 0.3–0.7 units/mL

aPTT level (reagent specific to reflect anti-Xa level of 0.3–0.7 units/mL): 50–80 sec.

D

HEPARIN SODIUM *continued*

These laboratory measurements are best measured 4–6 hr after initiation or changes in infusion rate. **Do not** collect blood levels from the heparinized line or same extremity as site of heparin infusion. If unfractionated heparin anti-Xa or aPTT levels are not available, a ratio of aPPT 1.5–2.5 times control value has been used in the past. Unfractionated heparin anti-Xa level is NOT THE SAME as low molecular weight heparin anti-Xa (used for monitoring low molecular weight heparin products such as enoxaparin).

Use with IV nitroglycerin may decrease the partial thromboplastin time (PTT) with subsequent rebound upon discontinuation of nitroglycerin. Antithrombin III (human) and NSAIDs may increase heparin's anticoagulant effects and bleeding risk.

Use preservative-free heparin in neonates. **Note:** heparin flush doses may alter aPTT in small patients; consider using more dilute heparin in these cases.

Use actual body weight when dosing obese patients. Due to recent regulatory changes to the manufacturing process, heparin products may exhibit decreased potency.

Antidote: Protamine sulfate (1 mg per 100 U heparin in previous 4 hr). For low molecular weight heparin (LMWH), see Enoxaparin.

HYALURONIDASE

Amphadase, Hylenex, and Vitrase

Antidote, extravasation

Injection:

Amphadase: 150 U/mL (1 mL); bovine source; contains edetate disodium and thimerosal

Hylenex: 150 U/mL (1 mL); recombinant human source; contains 1 mg albumin, 1.5 mg L-methionine, and 0.2 mg polysorbate 80 per 150 U

Vitrase: 200 U/mL (1.2 mL); ovine source containing lactose, preservative-free

Pharmacy can make a 15 U/mL dilution.

Extravasation:

Infant and child: Give 1 mL (150 U) by injecting 5 separate injections of 0.2 mL (30 U) at borders of extravasation site SC or intradermal using a 25- or 26-gauge needle. Alternatively, a diluted 15 U/mL concentration has been used with the same dosing instructions.

Contraindicated in dopamine and alpha-agonist extravasation and hypersensitivity to the respective product sources (bovine or ovine). May cause urticaria. Patients receiving large amounts of salicylates, cortisone, ACTH, estrogens, or antihistamines may decrease the effects of hyaluronidase (larger doses may be necessary). Administer as early as possible (minutes to 1 hr) after IV extravasation.

Hylenex product is chemically incompatible with sodium metabisulfite, furosemide, benzodiazepines, and phenytoin.

HYDRALAZINE HYDROCHLORIDE

Generics; previously available as Apresoline

Antihypertensive, vasodilator

Tabs: 10, 25, 50, 100 mg

Injection: 20 mg/mL (1 mL)

Oral liquid: 4 mg/mL

Some dosage forms may contain tartrazines or sulfites.

For explanation of icons, see p. 667

HYDRALAZINE HYDROCHLORIDE *continued*

Hypertensive crisis (may result in severe and prolonged hypotension; see Chapter 1, Table 1.7 for alternatives):

Child: 0.1–0.2 mg/kg/dose IM or IV Q4–6 hr PRN; **max. dose**: 20 mg/dose. Usual IV/IM dosage range is 1.7–3.5 mg/kg/24 hr.

Adult: 10–20 mg IM or IV Q4–6 hr PRN; may increase to **max. dose** of 40 mg/dose if needed

Chronic hypertension:

Infant and child: Start at 0.75–1 mg/kg/24 hr PO ÷ Q6–12 hr (**max. initial dose:** 10 mg/dose). If necessary, increase dose over 3–4 wk up to a **max. dose** of 5 mg/kg/24 hr for infants and 7.5 mg/kg/24 hr for children; or 200 mg/24 hr.

Adult: 10–50 mg/dose PO QID; **max. dose**: 300 mg/24 hr

Use with caution in severe renal and cardiac disease. Slow acetylators, patients receiving high-dose chronic therapy, and those with renal insufficiency are at highest risk of lupus-like syndrome (generally reversible). May cause reflex tachycardia, palpitations, dizziness, headaches, and GI discomfort. MAO inhibitors and beta-blockers may increase hypotensive effects. Indomethacin may decrease hypotensive effects.

Drug undergoes first pass metabolism. Onset of action: PO: 20–30 min; IV: 5–20 min. Duration of action: PO: 2–4 hr; IV: 2–6 hr. **Adjust dose in renal failure (see Chapter 31).**

HYDROCHLOROTHIAZIDE

Generics; previously available as HydroDiuril and Microzide

Diuretic, thiazide

Tabs: 12.5, 25, 50 mg

Caps: 12.5 mg

Oral suspension: 5 mg/mL, 10 mg/mL

Edema:

Neonate and infant <6 mo: 1–3 mg/kg/24 hr ÷ once daily–BID PO; **max. dose**: 37.5 mg/24 hr

≥6 mo, child and adolescent: 1–2 mg/kg/24 hr ÷ once daily–BID PO; **max. dose**: <2 yr: 37.5 mg/24 hr, child 2–12 yr: 100 mg/24 hr, and adolescent: 200 mg/24 hr

Adult: 25–100 mg/24 hr ÷ once daily–BID PO; **max. dose:** 200 mg/24 hr

Hypertension:

Infant and child: Start at 0.5–1 mg/kg/24 hr once daily PO; dose may be increased to a **max. dose** of 3 mg/kg/24 hr up to 50 mg/24 hr.

Adult: 12.5–25 mg/dose once daily–BID PO; doses >50 mg/24 hr often results in hypokalemia

See Chlorothiazide. May cause fluid and electrolyte imbalances, and hyperuricemia. Drug may not be effective when creatinine clearance is less than 25–50 mL/min. Use with carbamazepine may result in symptomatic hyponatremia.

Hydrochlorothiazide is also available in combination with potassium-sparing diuretics (e.g., spironolactone), ACE inhibitors, angiotensin II receptor antagonists, hydralazine, methyldopa, reserpine, and beta-blockers.

Pregnancy category is "D" if used in pregnancy-induced hypertension.

HYDROCORTISONE
Systemic dosage forms: Solu-Cortef, Cortef, and generics
Topical: Anusol HC, Cortifoam, Colocort, Cortenema, MiCort-HC, NuCort, Proctocort, and many others including generics
Corticosteroid

Hydrocortisone base:
Tabs (Cortef and generics): 5, 10, 20 mg
Oral suspension: 2 mg/mL
Rectal cream: 1% (30 g)
Anusol HC and generics: 2.5% (30 g)
Rectal suspension as an enema (Colocort, Cortenema): 100 mg/60 mL; may contain parabens
Topical ointment: 0.5% [OTC], 1% [OTC], 2.5%
Topical cream: 0.5% [OTC], 1% [OTC], 2.5%
Topical lotion: 1% [OTC], 2%, 2.5%
Na Succinate (Solu-Cortef):
Injection: 100, 250, 500, 1000 mg/vial; contains benzyl alcohol
Acetate:
Topical cream: 1% [OTC]
MiCort-HC: 2.5% (4, 28.4 g); contains parabens
Topical lotion (NuCort): 2% (60 g); contains benzyl alcohol
Suppository:
Anusol HC and generics: 25 mg
Proctocort and generics: 30 mg
Rectal foam aerosol (Cortifoam): 10% (90 mg/dose) (15 g); may contain parabens

Status asthmaticus:
Child:
Load (optional): 4–8 mg/kg/dose IV; **max. dose:** 250 mg
Maintenance: 8 mg/kg/24 hr ÷ Q6 hr IV
Adult: 100–500 mg/dose Q6 hr IV
Physiologic replacement: see Chapter 10 for dosing
Anti-inflammatory/immunosuppressive:
Child:
PO: 2.5–10 mg/kg/24 hr ÷ Q6–8 hr
IM/IV: 1–5 mg/kg/24 hr ÷ Q12–24 hr
Adolescent and adult:
PO/IM/IV: 15–240 mg/dose Q12 hr
Acute adrenal insufficiency: see Chapter 10 for dosing.
Topical use:
Child and adult: Apply to affected areas BID–QID, depending on severity
Ulcerative colitis, induction for mild/moderate case:
Child, adolescent and adult: Insert 1 application of 100 mg rectal enema once daily–BID × 2–3 weeks.
Hemorrhoids:
Adult:
Rectal cream: Apply sparingly up to BID with either 1% or 2.5% strength
Suppository: 25 or 30 mg PR BID × 2 weeks

Use with caution in immunocompromised patients, as they should avoid exposure to chicken pox or measles.
For potency comparisons of topical preparations, see Chapter 8. For doses based on body surface

For explanation of icons, see p. 667

HYDROMORPHONE HCL
Dilaudid and generics
Narcotic, analgesic

Tabs: 2, 4, 8 mg
Extended-release tabs: 8, 12, 16, 32 mg
Injection: 1, 2, 4 mg/mL (1 mL), 10 mg/mL (1, 5, 10 mL); may be preservative free
Prefilled injectable syringes: 10 mg/50 mL (50 mL), 15 mg/30 mL (30 mL)
Preservative-free: 12 mg/60 mL (60 mL)
Powder for injection (Dilaudid-HP): 250 mg
Suppository: 3 mg (6s)
Oral solution: 1 mg/mL; may contain parabens and metasulfite

Analgesia, initial doses with immediate-release dosage forms (titrate to effect):
Child (<50 kg):
IV: 0.015 mg/kg/dose Q3–6 hr PRN
PO: 0.03–0.08 mg/kg/dose Q3–4 hr PRN; **max. dose**: 5 mg/dose
Child and adolescent (≥50 kg; NOTE: doses are NOT weight-based):
IV: 0.2–0.6 mg/dose Q2–4 hr PRN
IM, SC: 0.8–1 mg/dose Q4–6 hr PRN
PO: 1–2 mg/dose Q3–4 hr PRN
PR: 3 mg Q4–8 hr PRN
Adult:
IV: 0.2–1 mg/dose Q2–3 hr PRN
IM, SC: 0.8–1 mg/dose Q3–4 hr PRN
PO: 2–4 mg/dose Q4–6 hr PRN
PR: 3 mg Q6–8 hr PRN

Refer to Chapter 6 for equianalgesic doses and for patient-controlled analgesia dosing.
Less pruritus than morphine. Similar profile of side effects to other narcotics. **Use with caution** in infants and young children, and **do not use** in neonates due to potential CNS effects. Dose reduction recommended in renal insufficiency or severe hepatic impairment. Pregnancy category changes to "D" if used for prolonged periods or in high doses at term.
The FDA has assigned a Risk Evaluation and Mitigation Strategy (REMS) for this medication, which involves an education program for provision of safety information. See www.opioidanalgesicrems.com.

HYDROXYCHLOROQUINE
Plaquenil and generics
Antimalarial, antirheumatic agent

Tabs: 200 mg (155 mg base)
Oral suspension: 25 mg/mL (19.375 mg/mL base)

All doses expressed in mg of hydroxychloroquine base.
Malaria prophylaxis (start 2 wk prior to exposure and continue for 4 wk after leaving endemic area):
Child: 5 mg/kg/dose PO once weekly; **max. dose**: 310 mg
Adult: 310 mg PO once weekly
Malaria treatment (acute uncomplicated cases):
For treatment of malaria, consult with ID specialist or see the latest edition of the AAP Red Book.
Child: 10 mg/kg/dose (**max. dose**: 620 mg) PO × 1 followed by 5 mg/kg/dose (**max. dose:** 310 mg) 6 hr later. Then 5 mg/kg/dose (**max. dose**: 310 mg) Q24 hr × 2 doses starting 24 hr after the first dose.
Adult: 620 mg PO × 1 followed by 310 mg 6 hr later. Then 310 mg Q24 hr × 2 doses starting 24 hr

HYDROXYCHLOROQUINE *continued*

Juvenile rheumatoid arthritis or systemic lupus erythematosus:

Child: 2.325–3.875 mg/kg/24 hr (base) PO ÷ once daily–BID; **max. dose**: 310 mg/24 hr not to exceed 5.425 mg/kg/24 hr

Contraindicated in psoriasis, porphyria, retinal or visual field changes, and 4-aminoquinoline hypersensitivity. **Use with caution** in liver disease, G6PD deficiency, concomitant hepatic toxic drugs, renal impairment, metabolic acidosis, or hematologic disorders. Long-term use in children is **not recommended.** May cause headaches, myopathy, GI disturbances, skin and mucosal pigmentation, agranulocytosis, visual disturbances, and increased digoxin serum levels. Hypoglycemia, proximal myopathy/neuropathy, and suicidal behavior have been reported. Baseline ocular exam is recommended within the first year of initiating long-term therapy, as retinal damage has been reported.

Use with aurothioglucose may increase risk for blood dyscrasias. When used in combination with other immunosuppressive agents for SLE and JRA, lower doses of hydroxychloroquine can be used.

Pregnancy category has not been formally assigned by the FDA. The only situation where use is recommended during pregnancy is during the suppression or treatment of malaria, when the benefits outweigh the risks.

HYDROXYZINE

Vistaril and generics

Antihistamine, anxiolytic, antiemetic

Tabs (HCl salt): 10, 25, 50 mg
Caps (pamoate salt): 25, 50, 100 mg
Oral syrup (HCl salt): 10 mg/5 mL (120, 473 mL); may contain alcohol and sodium benzoate
Oral solution: (HCl salt): 10 mg/5 mL (473 mL); may contain parabens, and propylene glycol
Injection for IM use (HCl salt): 25 mg/mL (1 mL), 50 mg/mL (1, 2 mL); may contain benzyl alcohol
NOTE: pamoate and HCL salts are equivalent in regards to mg of hydroxyzine.

Pruritus and anxiety:

Oral:

Child and adolescent: 2 mg/kg/24 hr ÷ Q6–8 hr PRN, **max. single dose**: <6 yr: 12.5 mg, 6–12 yr: 25 mg, and >12 yr: 100 mg

Alternative dosing by age:

<6 yr: 50 mg/24 hr ÷ Q6–8 hr PRN

≥6 yr: 50–100 mg/24 hr ÷ Q6–8 hr PRN

Adult: 25 mg/dose TID–QID PRN; **max. dose**: 600 mg/24 hr

IM:

Child and adolescent: 0.5–1 mg/kg/dose Q4–6 hr PRN; **max. single dose**: 100 mg

Adult: 25–100 mg/dose Q4–6 hr PRN; **max. dose**: 600 mg/24 hr

Antiemetic (excluding use during pregnancy):

Child and adolescent: 1.1 mg/kg/dose IM, **max. single dose:** 100 mg

Adult: 25–100 mg IM

Contraindicated in prolonged QT interval. May potentiate barbiturates, meperidine, and other CNS depressants. **Use with caution** with concomitant use of other medications known to prolong the QT interval. May cause dry mouth, drowsiness, tremor, convulsions, blurred vision, and hypotension. May cause pain at injection site. Fixed drug eruptions has been reported with use of the oral dosage form.

Increase dosage interval to Q24 hr or longer in the presence of liver disease (e.g., Primary biliary cirrhosis). action: 4–6 hr. IV administration is **NOT recommended**.

For explanation of icons, see p. 667

I

IBUPROFEN

PO: Motrin, Advil, Children's Advil, Children's Motrin, and generics
IV: NeoProfen, Caldolor
Nonsteroidal anti-inflammatory agent

Oral suspension [OTC]: 100 mg/5 mL (60, 120, 480 mL)
Oral drops [OTC]: 40 mg/mL (15, 30 mL)
Chewable tabs [OTC]: 100 mg
Caplets [OTC]: 100, 200 mg
Tabs: 200 [OTC], 400, 600, 800 mg
Capsules [OTC]: 200 mg
Injection:
NeoProfen and generic (lysine salt): 10 mg ibuprofen base/1 mL (2 mL)
Caldolor: 100 mg/mL (4, 8 mL); contains 78 mg/mL arginine

PO:

Infant and child (≥6 mo):
Analgesic/antipyretic: 5–10 mg/kg/dose Q6–8 hr PO; **max. dose**: 400 mg/dose or 40 mg/kg/24 hr
JRA (6 mo–12 yr): 30–50 mg/kg/24 hr ÷ Q6 hr PO; **max. dose**: 800 mg/dose or 2400 mg/24 hr

Adult:
Inflammatory disease: 400–800 mg/dose Q6–8 hr PO; **max. dose**: 800 mg/dose or 3.2 g/24 hr
Pain/fever/dysmenorrhea: 200–400 mg/dose Q4–6 hr PRN PO; **max. dose**: 3.2 g/24 hr

IV:

6 mo–<12 yr:
Analgesic and antipyretic: 10 mg/kg/dose up to 400 mg/dose Q4–6 hr PRN; **max. dose**: the lesser of 40 mg/kg/24 hr or 2400 mg/24 hr

12–17 yr:
Analgesic and antipyretic: 400 mg/dose Q4–6 hr PRN; **max. dose:** 2400 mg/24 hr

≥18 yr and adult:
Analgesic (see remarks): 400–800 mg/dose Q6 hr PRN; **max. dose:** 3200 mg/24 hr
Antipyretic (see remarks): 400 mg/dose Q4–6 hr or 100–200 mg/dose Q4 hr PRN; **max. dose:** 3200 mg/24 hr

Closure of ductus arteriosus:
<32 wk of gestation and 0.5–1.5 kg (use birth weight to calculate all doses and infuse all doses over 15 min; see remarks): 10 mg/kg/dose IV × 1 followed by two doses of 5 mg/kg/dose each, 24 and 48 hr after the initial dose. Hold second or third dose if urinary output is <0.6 mL/kg/hr; dosing should resume when laboratory studies indicate the return of normal renal function. If the ductus arteriosus fails to close or reopens, a second course of ibuprofen, the use of IV indomethacin, or surgery may be necessary.

Contraindicated with active GI bleeding and ulcer disease. **Use caution** with aspirin hypersensitivity, or hepatic/renal insufficiency, heart disease (risk for MI and stroke with prolonged use), dehydration, and in patients receiving anticoagulants. GI distress (lessened with milk), rashes, ocular problems, hypertension, granulocytopenia, and anemia may occur. Inhibits platelet aggregation. Consumption of more than three alcoholic beverages per day, use with corticosteroids or anticoagulants may increase risk for GI bleeding. False-positive test for urine cannabinoid and phencyclidine (PCP) screen may occur.

IBUPROFEN *continued*

May increase serum levels and effects of digoxin, methotrexate, and lithium. May decrease the effects of antihypertensives, aspirin (anti-platelet effects), furosemide, and thiazide diuretics. Pregnancy category changes to "D" if used in 3rd trimester or near delivery.

IV USE for analgesia/antipyretic: Hydrate patient well before use. Doses must be diluted to a concentration ≤4 mg/mL with NS, D5W, or LR and infused over ≥30 min for adults and ≥10 min for children. Most common reported side effects in clinical trials include nausea, flatulence, vomiting, and headache.

IV USE for PDA: Contraindicated in untreated infections, congenital heart diseases requiring a patent ductus arteriosus to facilitate satisfactory pulmonary and systemic blood flow, active intracranial or gastrointestinal bleeds, thrombocytopenia, coagulation defects, suspected/active NEC, and significant renal impairment. **Use with caution** in hyperbilirubinemia. Not indicated for IVH prophylaxis. Renal side effects are generally less frequent and severe when compared with IV indomethacin. NEC, GI perforation, and pulmonary hypertension have been reported. NeoProfen doses must be administered within 30 min of preparation and infused intravenously over 15 min.

ILOPROST
Ventavis, synthetic PGI_2
Prostaglandin I_2, vasodilator

Inhalation solution: 10 mCg/mL (1 mL), 20 mCg/mL (1 mL); contains ethanol and tromethamine

Pulmonary arterial hypertension (limited data):

Intermittent inhalation via nebulization: Start at 2.5 mCg/dose (some recommend 1.25 mCg/dose for infant and small child). If tolerated, increase dose to 5 mCg/dose at intervals of 6 to 9 times daily (Q2–3 hr while awake; Q3–4 hr may be considered for patients with moderate/severe hepatic impairment).

Use with caution in bleeding disorders, respiratory diseases, and hypotension.

Headache, nausea, cough, flu-like symptoms, and flushing are common side effects. Bronchospasm, hypotension, and AKI have been reported. May increase the effects/toxicity of anticoagulants, antiplatelet, antihypertensive, and vasodilating medications.

Administer by nebulization which may take 10–15 min. **Avoid** contact with skin or eyes and do not ingest by mouth.

IMIPENEM AND CILASTATIN
Primaxin IV and generics
Antibiotic, carbapenem

Injection: 250, 500 mg; each 1 mg drug contains 1 mg imipenem and 1 mg cilastatin
Contains 3.2 mEq Na/g drug

Dosages based on imipenem component.

Neonate (see remarks):

<1 kg:

≤***14 days old:*** 40 mg/kg/24 hr ÷ Q12 hr IV

15–28 days old: 50 mg/kg/24 hr ÷ Q12 hr IV

1–2 kg:

≤***7 days old:*** 40 mg/kg/24 hr ÷ Q12 hr IV

8–28 days old: 50 mg/kg/24 hr ÷ Q12 hr IV

For explanation of icons, see p. 667

IMIPENEM AND CILASTATIN *continued*

Neonate (cont., see remarks):
>2 kg:
≤7 days old: 50 mg/kg/24 hr ÷ Q12 hr IV
8–28 days old: 75 mg/kg/24 hr ÷ Q8 hr IV
Child (4 wk–3 mo): 100 mg/kg/24 hr ÷ Q6 hr IV
Child (>3 mo): 60–100 mg/kg/24 hr ÷ Q6 hr IV; **max. dose**: 4 g/24 hr
Cystic fibrosis:
Pulmonary exacerbation: 100 mg/kg/24 hr ÷ Q6 hr IV; **max. dose:** 4 g/24 hr
Non-tuberculosis mycobacterium: 30–40 mg/kg/24 hr ÷ Q12 hr IV; **max. dose:** 2 g/24 hr
Adult: 0.5–1 g/dose Q6–8 hr IV; **max. dose**: 4 g/24 hr or 50 mg/kg/24 hr, whichever is less

For IV use, give slowly over 30–60 min at a concentration ≤5 mg/mL to reduce risk for nausea (lowering the rate may reduce severity). Adverse effects: thrombophlebitis, pruritus, urticaria, GI symptoms, seizures, dizziness, hypotension, elevated LFTs, blood dyscrasias, and penicillin allergy. Greater risk for seizures may occur with CNS infections, concomitant use with ganciclovir, higher doses, and renal impairment. CSF penetration is variable but best with inflamed meninges. Not recommended in CNS infections for neonates due to cilastatin accumulation and seizure risk.

Do not administer with probenecid (increases imipenem/cilastatin levels) and ganciclovir (increased risk for seizures). May significantly reduce valproic acid levels.

Adjust dose in renal insufficiency (see Chapter 31).

IMIPRAMINE

Tofranil and generics

Antidepressant, tricyclic

Tabs (HCl): 10, 25, 50 mg
Caps (pamoate): 75, 100, 125, 150 mg; strengths are expressed as imipramine HCl equivalent

Antidepressant (see remarks):

Child (≥8 yr):
Initial: 1.5 mg/kg/24 hr ÷ BID–TID PO; increase 1 mg/kg/24 hr Q3–4 days to a **max. dose** of 5 mg/kg/24 hr
Adolescent:
Initial: 25–50 mg/24 hr ÷ once daily–TID PO; **max. dose**: 200 mg/24 hr. Dosages exceeding 100 mg/24 hr are generally not necessary.
Adult:
Initial: 75–100 mg/24 hr ÷ TID PO
Maintenance: 50–300 mg/24 hr QHS PO; **max. dose**: 300 mg/24 hr
Enuresis (≥6 yr):
Initial: 10–25 mg QHS PO
Increment if needed: 10–25 mg/dose at 1- to 2-wk intervals until **max. dose** for age or desired effect achieved. Continue × 2–3 mo, then taper slowly.
Max. dose:
6–12 yr: the lesser of 2.5 mg/kg/24 hr or 50 mg/24 hr
≥12 yr: 75 mg/24 hr
Augment analgesia for chronic pain:
Initial: 0.2–0.4 mg/kg/dose QHS PO; increase 50% every 2–3 days PRN to a **max. dose** of 1–3 mg/kg/dose QHS PO

IMIPRAMINE *continued*

Contraindicated in narrow-angle glaucoma and patients who used MAO inhibitors within 14 days. See Chapter 3 for management of toxic ingestion. Monitor for clinical worsening of depression and suicidal ideation/behavior following the initiation of therapy or after dose changes. **Use with caution** in renal or hepatic impairment. Side effects include sedation, urinary retention, constipation, dry mouth, dizziness, drowsiness, and arrhythmia. QHS dosing during first weeks of therapy will reduce sedation. Monitor ECG, BP, CBC at start of therapy and with dose changes. Tricyclics may cause mania. False-positive test for urine PCP screen may occur.

Therapeutic reference range for depression (sum of imipramine and desipramine) = 150–250 ng/mL. Levels >1000 ng/mL are toxic; however, toxicity may occur at >300 ng/mL.

Recommended serum sampling times at steady-state: Obtain trough level within 30 min prior to the next scheduled dose after 5–7 days of continuous therapy.

Imipramine is a major substrate for CYP 450 2C19 and 2D6. See the remarks in amitriptyline for pharmacogenomic dosing considerations. Carbamazepine may reduce imipramine levels, and cimetidine, fluoxetine, fluvoxamine, labetalol, quinidine may increase imipramine levels.

Onset of antidepressant effects: 1–3 wk. **Do not discontinue** abruptly in patients receiving long-term high-dose therapy.

Pregnancy category has not been officially assigned by the FDA as congenital abnormalities have been reported in humans with the causal relationship not being established.

IMMUNE GLOBULIN
Immune globulins

IM preparations:

GamaSTAN and GamaSTAN S/D: 150–180 mg/mL (2, 10 mL); GamaSTAN contains 0.16–0.26 M glycine and GamaSTAN contains 0.21–0.32 M glycine; both are preservative free

IV preparations in solution (preservative free):

Bivigam: 10% (100 mg/mL) (50, 100 mL); contains polysorbate 80 and 0.2–0.29 M glycine; sucrose free

Flebogamma DIF: 5% (50 mg/mL) (10, 50, 100, 200, 400 mL) 10% (100 mg/mL) (50, 100, 200 mL); contains 50 mg/mL sorbitol and ≤3 mg/mL polyethylene glycol; sucrose free

Gamunex-C: 10% (100 mg/mL) (10, 25, 50, 100, 200, 400 mL); contains 0.16–0.24 M glycine; sucrose free

Gammagard liquid: 10% (100 mg/mL) (10, 25, 50, 100, 200, 300 mL); contains 0.25 M glycine; sucrose free

Gammaked: 10% (100 mg/mL) (10, 25, 50, 100, 200 mL); contains 0.16–0.24 M glycine; sucrose free

Octagam: 5% (50 mg/mL) (20, 50, 100, 200, 500 mL), 10% (100 mg/mL) (20, 50, 100, 200, 300 mL); contains ~100 mg/mL maltose; sucrose free

Privigen 10% (100 mg/mL) (50, 100, 200, 400 mL); contains 210–290 mmol/L L-proline; sucrose free

Panzyga 10%: (100 mg/mL) (10, 25, 50, 100, 200, 300 mL); sucrose free

IV preparations in powder for reconstitution:

Carimune NF: 6, 12 g (contains 1.67 g sucrose and <20 mg NaCl per 1 g Ig); dilute to 3%, 6%, 9%, or 12%

Gammagard S/D: 5, 10 g (when diluted at 5% or 50 mg/mL, contains <1 mCg/mL of IgA, 3 mg/mL albumin, 22.5 mg/mL glycine, 20 mg/mL glucose, 2 mg/mL polyethylene glycol, 1 mCg/mL tri-n-butyl phosphate, 1 mCg/mL octoxynol 9, and 100 mCg/mL polysorbate 80); may be diluted to 5% or 10%

Continued

For explanation of icons, see p. 667

IMMUNE GLOBULIN *continued*

Subcutaneous (SC) preparations (sucrose and preservative free):

Hizentra: 20% (200 mg/mL) (5, 10, 20, 50 mL); contains 210–290 mmol/L L-proline, 8–30 mg/L polysorbate 80, and ≤50 mCg/mL IgA

Cutaquig: 16.9% (169 mg/mL) (6, 10, 12, 20, 24, 48 mL); contains 30 mEq/L sodium and ≤0.6 mg/mL IgA

Cuvitru: 20% (200 mg/mL) (5, 10, 20, 40, 50 mL); contains 0.25 M glycine and ~80 mCg/mL IgA

Intravenous (IV) preparations:

Kawasaki disease (should be initiated within first 10 days of symptoms): 2 g/kg × 1 dose over 8–12 hr infusion. If signs and symptoms persist, consider a second 2 g/kg dose. Some recommend using a different drug brand or lot number for the second dose.

Immune thrombocytopenia (ITP) (see RH$_o$[D] immune globulin intravenous for Rh-positive patients):

Acute therapy: 400–1000 mg/kg/dose once daily for 2–5 days for a total cumulative dose 2000 mg/kg

Maintenance therapy: 400–1000 mg/kg/dose Q3–6 wk based on clinical response

Replacement therapy for antibody-deficient disorders: Start at 400–500 mg/kg/dose Q4 wk and adjust dose based on clinical response and to maintain a trough IgG level ≥500 mg/dL. For severe hypogammaglobulinemia (<100 mg/dL), patients may benefit with a loading dose of 400 mg/kg/dose once daily × 2, followed by 400–500 mg/kg/dose Q4 wk.

Pediatric HIV with IgG <400 mg/dL: See replacement therapy for antibody-deficient disorder from above.

Bone marrow transplantation (may decrease risk for infection and death but not acute graft-versus-host disease): Start at 400–500 mg/kg/dose to maintain IgG levels ≥400 mg/dL resulting in dosage intervals ranging from once weekly to Q3–4 wk.

Measles, postexposure prophylaxis for individuals with primary humoral immunodeficiency or without evidence of measles immunity (6–16 yr): 400 mg/kg/dose as soon as possible and within 6 days after exposure.

General guidelines for administration (see package insert of specific products):

IV: Begin infusion at 0.01 mL/kg/min, double rate every 15–30 min, up to **max**. of 0.08 mL/kg/min. If adverse reactions occur, stop infusion until side effects subside and may restart at rate that was previously tolerated.

Subcutaneous (SC) preparations:

Converting to SC route from previous IV dosage for patients receiving IV immune globulin (IVIG) infusions at regular intervals for at least 3 mo (≥2 yr):

Initial weekly dose (start 1 wk after last IV dose):

SC Product	Dose Calculation (mg)	Dose Calculation (mL)
Hizentra	Dose (g) = 1.37 × Previous IVIG dose in grams (g) ÷ number of weeks between IVIG doses	mL = multiply dose (g) by 5
Cutaquig	Dose (g) = 1.40 × Previous IVIG dose in grams (g) ÷ number of weeks between IVIG doses	mL = multiply dose (g) by 6
Cuvitru	Dose (g) = 1.30 × Previous IVIG dose in grams (g) ÷ number of weeks between IVIG doses	mL = multiply dose (g) by 5

Adjust dose over time by clinical response and serum IgG trough levels. Obtain a previous trough level from IVIG therapy prior to SC conversion and repeat trough level 2–3 mo after initiating the SC route. A goal trough with the SC route of ~290 mg/dL higher than a trough with the IV route has been recommended.

Measles, postexposure prophylaxis for high-risk patients:

Hizentra: 0.2 g/kg/dose SC Q7 days × 2, or 0.4 g/kg/dose SC × 1

IMMUNE GLOBULIN *continued*

SC administration: Injection sites include the abdomen, thigh, upper arm, and/or lateral hip. Doses may be administered into multiple sites (spaced ≥2 inches apart) simultaneously. See following table.

SC Product	Max. Simultaneous Injection Sites	Max. Infusion Rate	Max. Infusion Volume
Hizentra	8	First infusion: 15 mL/hr per infusion site Subsequent infusions: 25 mL/hr per infusion site	First infusion: 15 mL per infusion site Subsequent infusions: 25 mL per infusion site
Cutaquig	6	First 6 infusions: 15–20 mL/hr per infusion site (max. rate for all sites combined: 30 mL/hr) Subsequent infusions: 25 mL/hr per infusion site (max. rate for all sites combined: gradually increase to 50 mL/hr, then 80 mL/hr and then if tolerated up to 100 mL/hr)	First 6 infusions: ≤25 mL per infusion site Subsequent infusions: gradual increase to 40 mL per infusion site
Cuvitru	4	First 2 infusions: 10–20 mL/hr per infusion site Subsequent infusions: ≤60 mL/hr per infusion site	First 2 infusions: <40 kg: ≤20 mL per infusion site ≥40 kg: ≤60 mL per infusion site Subsequent infusions (all weights): ≤60 mL per infusion site

Intramuscular (IM) preparations:

Measles, postexposure prophylaxis for high-risk patients: 0.5 mL/kg/dose (**max. dose**: 15 mL) IM × 1 within 6 days of exposure.

IM administration: Administer in the anterolateral aspects of the upper thigh or deltoid muscle of the upper arm. **Avoid** gluteal region due to risk of injury to sciatic nerve. Consider splitting doses for multiple injection sites to address age specific maximum IM injection volumes.

Use with caution in patients with increased risk of thrombosis (e.g., hypercoagulable states, prolonged immobilization, in-dwelling catheters, estrogen use, thrombosis history, cardiovascular risks, and hyperviscosity) or hemolysis (e.g., non-O blood type, associated inflammatory conditions, and receiving high cumulative doses of immune globulins over several days).

May cause flushing, chills, fever, headache, and hypotension. Hypersensitivity reaction may occur when IV form is administered rapidly. Maltose-containing products may cause an osmotic diuresis. May cause **anaphylaxis** in IgA-deficient patients due to varied amounts of IgA. Some products are IgA depleted; consult a pharmacist.

To decrease risk of renal dysfunction, including acute renal failure, IV preparations containing sucrose should not be infused at a rate such that the amount of sucrose exceeds 3 mg/kg/min.

SC route provides higher serum trough levels, lower rate of adverse reactions, and shorter administration time when compared with the IV route. Use of adjusted body weight [ABW = Ideal Body Weight + 0.5 (Actual Body Weight − Ideal Body Weight] for dosing in obese patients has been recommended.

Delay immunizations after immune globulin administration (see latest AAP Red Book for details).

For explanation of icons, see p. 667

INDOMETHACIN
Indocin, Tivorbex, and generics
Nonsteroidal antiinflammatory agent

Caps: 25, 50 mg
Tivorbex: 20, 40 mg
Sustained-release caps: 75 mg
Oral suspension: 25 mg/5 mL (237 mL); contains 1% alcohol
Suppositories: 50 mg (30s)
Injection: 1 mg

Anti-inflammatory/rheumatoid arthritis:
Child (≥2 yr): Start at 1–2 mg/kg/24 hr ÷ BID–QID PO; **max. dose**: the lesser of 4 mg/kg/24 hr or 200 mg/24 hr
Adult: 50–150 mg/24 hr ÷ BID–QID PO; **max. dose**: 200 mg/24 hr
Tivorbex: 20 mg TID PO or 40 mg BID–TID PO

Closure of ductus arteriosus:
Infuse intravenously over 20–30 min:

	Dose (mg/kg/dose Q12–24 hr)[a]		
Postnatal Age at Time of 1st Dose	**#1**	**#2**	**#3**
<48 hr	0.2	0.1	0.1
2–7 days	0.2	0.2	0.2
>7 days	0.2	0.25	0.25

[a]Do not administer if urine output is <0.6 mL/kg/hr or anuric.

For infants <1500 g, 0.1–0.2 mg/kg/dose IV Q24 hr may be given for an additional 3–5 days.
Intraventricular hemorrhage prophylaxis: 0.1 mg/kg/dose IV Q24 hr × 3 doses, initiated at 6–12 hr of age (give in consultation with a neonatologist).

Contraindicated in active bleeding, coagulation defects, necrotizing enterocolitis, and renal insufficiency (urine output <0.6 mL/kg/hr). **Use with caution** in cardiac dysfunction, hypertension, heart disease (risk for MI and stroke with prolonged use), and renal or hepatic impairment. May cause (especially in neonates) decreased urine output, thrombocytopenia, and decreased GI blood flow, and a reduction in the antihypertensive effects of β-blockers, hydralazine, and ACE inhibitors. **Fatal hepatitis reported in JRA treatment.** Pancreatitis has been reported. Thrombotic events have been observed in adults receiving high doses or prolonged duration of therapy. Monitor renal and hepatic function before and during use. False-positive test for urine cannabinoid screen may occur.
Reduction in cerebral blood flow associated with rapid IV infusion; infuse all IV doses over 20–30 min.
Sustained-release capsules are dosed once daily–BID. Pregnancy category changes to "D" if used for >48 hr or after 34 wk gestation or close to delivery.

INSULIN PREPARATIONS
Pancreatic hormone

Many preparations, at concentrations of 100, 500 Units/mL. See Chapter 10, Table 10.3.
Diluted concentrations of 1 Units/mL or 10 Units/mL may be necessary for smaller doses in neonates and infants.

D

INSULIN PREPARATIONS *continued*

Hyperkalemia: See Resuscitation Medications Table in the front matter of the book.
DKA: See Chapter 10, Figure 10.1.

When using insulin drip with new IV tubing, fill the tubing with the insulin infusion solution and wait for 30 min (before connecting tubing to the patient). Then flush the line and connect the IV line to the patient to start the infusion. This will ensure proper drug delivery. **Adjust dose in renal failure (see Chapter 31)). Use with caution** and monitor closely in hepatic impairment.

IODIDE

See Potassium Iodide

IODIXANOL
Visipaque
Radiopaque agent, contrast media

Injection: 270 mg/mL, 320 mg/mL (50, 100, 150, 200 mL); contains EDTA and tromethamine

Consult with your local radiologist for specific dosing and administration recommendations.
IV contrast for CT scans: Use Visipaque 320 mg/mL, check for contraindications, and all patients should be encouraged to drink extra fluids for 8 hrs after the exam as allowed.
eGFR ≥60 mL/min/1.73 m²: 2 mL/kg/dose
eGFR 30–60 mL/min/1.73 m²: Administered a reduced dose with IV fluids + acetylcysteine to reduce risk for nephropathy
eGFR <30 mL/min/1.73 m²: Avoid use unless life-threatening situation where benefits outweigh the risk
PO contrast for CT scans: see Iohexol

Contraindicated in children with prolonged fasting and the administration of a laxative before use. **Avoid use** via intrathecal route (serious life-threatening reactions may occur) and previous hypersensitivity reactions with contrast agents. **Use with caution** in asthma, hay fever, food allergy, congestive heart failure, severe liver or renal impairment, diabetic nephropathy, multiple myeloma, pheochromocytoma, hyperthyroidism, and sickle cell disease.
Common side effects include general discomfort, sensations of warmth, and pain. Cardiac arrest, dysrhythmia, heart failure, shock, severe dermatological reactions (e.g., SJS, TEN), sickle cell crisis, thromboembolic disorder, acute kidney injury, and hypersensitivity reactions have been reported.
Children at higher risk for adverse events with contrast medium administration may include those having asthma, sensitivity to medication and/or allergens, congestive heart failure, serum creatinine >1.5 mg/dL, or those aged <12 mo.
Avoid use with metformin as lactic acidosis and acute renal failure may occur. Postpone IV administration in patients who have recently received an oral cholecystographic contrast agent as renal toxicity may occur.
Visipaque 320 mg/mL has an osmolality of 290 mOsmol/kg than Omnipaque 350 mg/mL (884 mOsmol/kg) for a lower risk of contrast nephropathy. See product information for intravenous and intra-arterial administration guidelines.

For explanation of icons, see p. 667

IOHEXOL

Iohexol: Omnipaque 140, Omnipaque 180, Omnipaque 240, Omnipaque 300, Omnipaque 350, Omnipaque oral solution 9, Omnipaque oral solution 12, Oraltag
Iodixanol: Visipaque
Radiopaque agent, contrast media

Injection:

Omnipaque 140: 302 mg iohexol equivalent to 140 mg iodine/mL (50 mL)
Omnipaque 180: 388 mg iohexol equivalent to 180 mg iodine/mL (10, 20 mL)
Omnipaque 240: 518 mg iohexol equivalent to 240 mg iodine/mL (10, 20, 50, 100, 150, 200 mL)
Omnipaque 300: 647 mg iohexol equivalent to 300 mg iodine/mL (10, 30, 50, 75, 100, 125, 150, 200, 500 mL)
Omnipaque 350: 755 mg iohexol equivalent to 350 mg iodine/mL (50, 75, 100, 125, 150, 200, 250, 500 mL)

Oral solution:

Omnipaque, Oraltag: 9 mg iodine/mL (19 mg/mL iohexol equivalent; 500 mL)
Omnipaque: 12 mg iodine/mL (26 mg iohexol equivalent; 500 mL)
All preparations contain tromethamine and edetate calcium disodium.

Consult with your local radiologist for specific dosing and administration recommendations.

Oral contrast for CT scans: Use oral Omnipaque 9 mg iodine/mL solution. If oral solution not available, mix 13 mL of the Omnipaque 350 injection with 500 mL of non-carbonated beverage to make an Omnipaque 9 mg iodine/mL solution. Administer dose all at once or over a period of up to 45 min. The more contrast the patient consumes, the better the CT study.

1–7 kg: 40–60 mL
8–11 kg: 110–160 mL
12–15 kg: 165–240 mL
16–42 kg: 250–360 mL
>42 kg: ≥480 mL

IV contrast for CT scans: see Iodixanol

Avoid use with history of severe cutaneous reactions to iohexol. **Use with caution** in dehydration, previous allergic reaction to a contrast medium, iodine sensitivity, asthma, hay fever, food allergy, congestive heart failure, severe liver or renal impairment, diabetic nephropathy, multiple myeloma, pheochromocytoma, hyperthyroidism, and sickle cell disease. Allergic reactions, arrhythmias, hypothyroidism, transient thyroid suppression, and nephrotoxicity have been reported.

Children at higher risk for adverse events with contrast medium administration may include those having asthma, sensitivity to medication and/or allergens, congestive heart failure, serum creatinine >1.5 mg/dL, or those aged <12 mo.

Use **NOT** recommended with drugs that lower seizure threshold (e.g., phenothiazines), amiodarone (increased risk of cardiotoxicity), and metformin (lactic acidosis and acute renal failure).

Many other uses exist, see package insert for additional information. Iohexol is particularly useful when barium sulfate is **contraindicated** in patients with suspected bowel perforation or those where aspiration of contrast medium is of concern. Oral dose is poorly absorbed from the normal GI tract (0.1%–0.5%); absorption increases with bowel perforation or bowel obstruction. Concentrations 302–755 mg iohexol/mL have osmolalities from 1.1 to 3 times that of plasma (285 mOsm/kg) and CSF (301 mOsm/kg) and may be hypertonic.

IPRATROPIUM BROMIDE ± ALBUTEROL
Atrovent HFA and generics
In combination with albuterol: Combivent Respimat and generics; previously available as DuoNeb
Anticholinergic agent

Aerosol oral inhaler (Atrovent HFA): 17 mCg/dose (200 actuations per canister, 12.9 g); contains alcohol
Nebulized solution: 0.02% (500 mCg/2.5 mL) (25s, 30s, 60s, 120s, 360s)
Nasal spray: 0.03% (21 mCg per actuation, 30 mL provides 345 sprays); 0.06% (42 mCg per actuation, 15 mL provides 165 sprays)
In combination with albuterol:
Nebulized solution (generic; previously available as DuoNeb): 0.5 mg ipratropium bromide and 2.5 mg albuterol in 3 mL (30s, 60s)
Inhalation spray (Combivent Respimat): 20 mCg ipratropium and 100 mCg albuterol per actuation (120 actuations per canister, 4 g); contains benzalkonium chloride

Ipratropium:
Acute use in the ED or ICU:
Nebulizer treatments:
<12 yr: 250–500 mCg/dose Q20 min × 3, then Q2–4 hr PRN
≥12 yr: 500 mCg/dose Q20 min × 3, then Q2–4 hr PRN
Inhaler:
<12 yr: 4–8 puffs Q20 min PRN up to 3 hr
≥12 yr: 8 puffs Q20 min PRN up to 3 hr
Non-acute use:
Inhaler:
<12 yr: 1–2 puffs Q6 hr; **max. dose:** 12 puffs/24 hr
≥12 yr: 2–3 puffs Q6 hr; **max. dose:** 12 puffs/24 hr
Nebulized treatments:
Infant: 125–250 mCg/dose Q8 hr
Child ≤12 yr: 250–500 mCg/dose Q6–8 hr
>12 yr and adult: 250–500 mCg/dose Q6 hr
Nasal spray:
0.03% strength (21 mCg/spray):
Allergic and non-allergic rhinitis (≥6 yr and adult): 2 sprays (42 mCg) per nostril BID–TID
0.06% strength (42 mCg/spray):
Rhinitis associated with common cold (use up to a total of 4 days; safety and efficacy have not been evaluated >4 days):
2–<5 yr (limited data): 2 sprays (84 mCg) per nostril TID
5–11 yr: 2 sprays (84 mCg) per nostril TID
12 yr–adult: 2 sprays (84 mCg) per nostril TID–QID
Rhinitis associated with seasonal allergies:
2–<5 yr (limited data): 1 spray (42 mCg) per nostril TID × 14 days
≥5 yr– adult: 2 sprays (84 mCg) per nostril QID; use up to a total of 3 weeks (safety and efficacy have not been evaluated for >3 weeks)
Ipratropium in combination with albuterol:
Acute use in the ED or ICU:
Nebulizer treatments:
<12 yr: 1.5 or 3 mL (0.25 mg ipratropium and 1.25 mg albuterol or 0.5 mg ipratropium and 2.5 mg albuterol) Q 20 min × 3 then Q2–4 hr PRN
≥12 yr: 3 mL (0.5 mg ipratropium and 2.5 mg albuterol) Q 20 min × 3 then Q2–4 hr PRN

Continued

For explanation of icons, see p. 667

IPRATROPIUM BROMIDE ± ALBUTEROL *continued*

Inhalation spray (Combivent Respimat):

Ipratroprium in combination with albuterol (Acute use in the ED or ICU; cont.):

<12 yr: 4–8 sprays Q20 min × 3

≥12 yr: 8 sprays Q20 min × 3

Contraindicated in atropine hypersensitivity. **Use with caution** in narrow-angle glaucoma or bladder neck obstruction, though ipratropium has fewer anticholinergic systemic effects than atropine. May cause anxiety, dizziness, headache, GI discomfort, and cough with inhaler or nebulized use. Epistaxis, nasal congestion, and dry mouth/throat have been reported with the nasal spray. Reversible anisocoria may occur with unintentional aerosolization of drug to the eyes, particularly with mask nebulizers. Proven efficacy of nebulized solution in pediatrics is currently limited to reactive airway disease management in the emergency room and intensive care unit areas.

Current aerosol inhaler product does not contain soy products. Combination ipratropium and albuterol products are currently approved for use only in adults and has not been formally studied in children. See albuterol for additional remarks if using the combination product.

Bronchodilation onset of action is 1–3 min with peak effects within 1.5–2 hr and duration of action of 4–6 hr.

Shake inhaler well prior to use with spacer. Nebulized solution may be mixed with albuterol (or use the combination product).

Pregnancy category is "C" for Combivent Respimat. Breastfeeding safety **extrapolated** from safety of atropine.

IRON DEXTRAN

See Iron—Injectable Preparations

IRON SUCROSE

See Iron—Injectable Preparations

IRON—INJECTABLE PREPARATIONS

Ferric gluconate: Ferrlecit and generics
Iron dextran: INFeD
Iron sucrose: Venofer
Parenteral iron

Injection:

Ferric gluconate (Ferrlecit and generics): 62.5 mg/mL (12.5 mg elemental Fe/mL) (5 mL); contains 9 mg/mL benzyl alcohol and 20% sucrose

Iron dextran (INFeD): 50 mg/mL (50 mg elemental Fe/mL) (2 mL); products containing phenol 0.5% are only for IM administration; products containing sodium chloride 0.9% can be administered via the IM or IV route

Iron sucrose (Venofer): 20 mg/mL (20 mg elemental Fe/mL) (2.5, 5, 10 mL); contains 300 mg/mL sucrose; preservative free

IRON—NJECTABLE PREPARATIONS *continued*

FERRIC GLUCONATE (IV):

Iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy (most require 8 doses at 8 sequential dialysis treatments to achieve a favorable response):

Child ≥6 yr: 1.5 mg/kg elemental Fe (0.12 mL/kg) IV; **max. dose:** 125 mg elemental Fe/dose. Dilute dose in 25 mL NS and infuse over 1 hr.

Adult: 125 mg elemental Fe in 100 mL NS IV; infuse over 1 hr. Most require a minimum cumulative dose of 1 g elemental Fe administered over 8 sessions.

IRON DEXTRAN (IV or IM):

Iron deficiency anemia (≥4 mo, child, adolescent):

Test dose (IV over 5 min or IM; may initiate treatment dose 1 hr after test dose):

<10 kg: 10 mg

10–20 kg: 15 mg

≥20 kg: 25 mg

Total replacement dose of iron dextran (mL) = 0.0476 × lean body wt (kg) × (desired Hb [g/dL] − measured Hb [g/dL]) + 1 mL per 5 kg lean body weight (up to **max.** of 14 mL). Total replacement dose is divided into smaller daily doses if exceeds respective IV or IM daily **max. doses** (see below).

Acute blood loss: Total replacement dose of iron dextran (mL) = 0.02 × blood loss (mL) × hematocrit expressed as decimal fraction. Assumes 1 mL of RBC = 1 mg elemental iron.

If no reaction to test dose, give remainder of replacement dose ÷ over 2–3 daily doses.

Max. daily IV dose: 100 mg

Max. daily IM dose:

<5 kg: 0.5 mL (25 mg)

5–10 kg: 1 mL (50 mg)

>10 kg: 2 mL (100 mg)

IM administration: use "Z-track" technique.

IV administration: Dilute in NS at a **max. concentration** of 50 mg/mL and infuse over 1–6 hr at a **max. rate** of 50 mg/min.

IRON SUCROSE (IV):

Test dose (optional): Infuse 25% of first day dose up to a max. of 25 mg undiluted over 30 min.

Iron deficiency anemia in patients with chronic kidney disease:

Child:

ESRD on hemodialysis: (limited data from 14 children): 1 mg/kg/dialysis was adequate for correcting ferritin levels and 0.3 mg/kg/dialysis was successful in maintaining ferritin levels between 193 and 250 mCg/L. Doses were administered during the last hr of each dialysis and are recommended at a frequency of 3 times a week. A 10 mg test dose was administered.

Non-renal iron deficiency, refractory to PO therapy (limited data): Calculate total iron replacement dose (mg) = 0.6 × wt (kg) × (100 − [measured Hb ÷ desired Hb × 100]). Replacement dose is administered by giving an initial dose of 5–7 mg/kg (**max. dose**: 100 mg/24 hr) followed by a maintenance dose of 5–7 mg/kg/dose (**max. dose**: 300 mg/24 hr) Q3–7 days until total iron replacement dose is achieved.

Adult:

Hemodialysis-dependent: 100 mg elemental Fe 1–3 times a wk during dialysis up to a total cumulative dose of 1000 mg. May continue to administer at lowest dose to maintain target Hb, Hct, and iron levels.

Nonhemodialysis-dependent: 200 mg elemental Fe on 5 different days over a 2 wk period (total cumulative dose: 1000 mg).

IV administration: May administer undiluted over 2–5 min. For an infusion, dilute each 100 mg with a **max.** of 100 mL NS and infuse over at least 15 min.

For explanation of icons, see p. 667

IRON—INJECTABLE PREPARATIONS *continued*

Oral therapy with iron salts is preferred, injectable routes are painful. Gluconate and sucrose salts may be better tolerated than iron dextran. Adverse effects include hypotension, GI disturbances, fever, rash, myalgia, arthralgias, cramps, and headaches. Hypersensitivity reactions have been reported for iron dextran and sucrose products; use of test dose prior to first therapeutic dose is recommended.

IM administration is only possible with iron dextran salt. Follow infusion recommendations for specific product. Monitor vital signs during IV infusion. TIBC levels may not be meaningful within 3 wk after dosing.

Efficacy and safety of iron sucrose for maintenance therapy has been evaluated in children 2 yr and older with CKD and receiving erythropoietin therapy. Common side effects include headache, respiratory tract viral infection, peritonitis, vomiting, pyrexia, dizziness, and cough.

Pregnancy category is "B" for ferric gluconate and iron sucrose, and "C" for iron dextran.

IRON—ORAL PREPARATIONS

Ferrous sulfate: Fer-In-Sol, Slow FE, Slow Iron, and many generics
Ferrous gluconate: Ferate and generics
Ferrous fumarate: Ferretts, Ferrimin 150, Hemocyte, and generics
Polysaccharide-iron complex: Ferrex 150, EZFE, Myferon 150, Poly-Iron 150, NovaFerrum, NovaFerrum Pediatric Drops, and many other brands; previously available as Niferex
Oral iron supplements

Ferrous sulfate (20% elemental Fe):
- Drops and oral solution (Fer-In-Sol and generics; OTC): 75 mg (15 mg Fe)/1 mL (50 mL); contains 0.2% alcohol and sodium bisulfite
- Oral elixir and liquid (OTC): 220 mg (44 mg Fe)/5 mL; may contain 5% alcohol
- Oral syrup (OTC): 300 mg (60 mg Fe)/5 mL
- Tabs (OTC): 325 mg (65 mg Fe)
- Extended-release tabs (Slow FE, Slow Iron, and generics, OTC): 142 mg (45 mg Fe), 160 mg (50 mg Fe), 324 mg (65 mg Fe), and 325 mg (65 mg Fe)

Ferrous gluconate (12% elemental Fe):
- Tabs (Ferate and generics; OTC): 240 mg (27 mg Fe), 324 mg (37.5 mg Fe)

Ferrous fumarate (33% elemental Fe):
- Tabs (all OTC):
  - **Hemocyte and generics:** 90 mg (29.5 mg Fe), 324 mg (106 mg Fe)
  - **Ferretts:** 325 mg (106 mg Fe)
  - **Ferrimin 150:** 456 mg (150 mg Fe)

Polysaccharide-iron complex and ferrous bis-glycinate chelate (expressed in mg elemental Fe):
- Caps (OTC): 50 mg (NovaFerrum 50), 150 mg (Ferrex 150, Myferon 150, Poly-Iron 150, and others), 200 mg (EZFE); 150 mg strength may contain 50 mg vitamin C
- Oral liquid (NovaFerrum 125; OTC): 125 mg/5 mL (180 mL); contains sodium benzoate and 100 units cholecalciferol/5 mL
- Oral drops (NovaFerrum Pediatric Drops; OTC): 15 mg/mL (120 mL); contains sodium benzoate

Iron deficiency anemia:

Premature infant: 2–4 mg elemental Fe/kg/24 hr ÷ once daily–BID PO; **max. dose**: 15 mg elemental Fe/24 hr

Child: 3–6 mg elemental Fe/kg/24 hr ÷ BID–TID PO

Adult: 60–100 mg elemental Fe BID PO up to 60 mg elemental Fe QID

IRON—ORAL PREPARATIONS *continued*

Prophylaxis:

Child: Give dose below PO ÷ once daily–TID

Premature infant: 2 mg elemental Fe/kg/24 hr; **max. dose**: 15 mg elemental Fe/24 hr

Full-term infant: 1–2 mg elemental Fe/kg/24 hr; **max. dose**: 15 mg elemental Fe/24 hr

Child 2–12 yr: 2 mg elemental Fe/kg/24 hr; **max. dose**: 30 mg elemental Fe/24 hr

Adolescent and adult: 60 mg elemental Fe/24 hr PO once daily

Contraindicated in hemolytic anemia and hemochromatosis. **Avoid** use in GI tract inflammation. May produce constipation, dark stools (false positive guaiac is controversial), nausea, and epigastric pain. Iron and tetracycline inhibit each other's absorption. Antacids may decrease iron absorption.

Iron preparations are variably absorbed. Less GI irritation when given with or after meals. Vitamin C, 200 mg per 30 mg iron, may enhance absorption. Liquid iron preparations may stain teeth. Give with dropper or drink through straw.

Pregnancy category is "A" for ferrous sulfate and is unknown for the other salt forms.

ISONIAZID

Generics, INH; previously available as Nydrazid and Laniazid

In combination with rifampin: Rifamate and IsonaRif

In combination with rifampin and pyrazinamide: Rifater

Antituberculous agent

Tabs: 100, 300 mg

Syrup: 50 mg/5 mL (473 mL); contains parabens

Injection: 100 mg/mL (10 mL); contains 0.25% chlorobutanol

In combination with rifampin:

Caps (Rifamate, IsonaRif): 150 mg isoniazid + 300 mg rifampin

In combination with rifampin and pyrazinamide:

Caps (Rifater): 50 mg isoniazid + 120 mg rifampin + 300 mg pyrazinamide

See most recent edition of the AAP Red Book for details and length of therapy.

TB Treatment (see remarks):

Infant and child:

10–15 mg/kg (**max. dose**: 300 mg) PO once daily or 20–30 mg/kg (**max. dose**: 900 mg) per dose twice weekly with rifampin for uncomplicated pulmonary tuberculosis in compliant patients. Additional drugs are necessary in complicated disease.

Adult:

5mg/kg (**max. dose:** 300 mg) PO once daily or 15 mg/kg (**max. dose**: 900 mg) per dose twice weekly with rifampin. Additional drugs are necessary in complicated disease.

For INH-resistant TB: Discuss with Health Department or consult ID specialist.

Should not be used alone for treatment. Contraindicated in acute liver disease and previous isoniazid-associated hepatitis. Peripheral neuropathy, optic neuritis, seizures, encephalopathy, psychosis, and hepatic side effects may occur with higher doses, especially in combination with rifampin. Severe liver injury has been reported in children and adults treated for latent TB. Follow LFTs monthly. Pancreatitis, toxic epidermal necrolysis, and DRESS have been reported. May cause false-positive urine glucose test.

Supplemental pyridoxine (1–2 mg/kg/24 hr) is recommended for prevention of neurological side effects.

For explanation of icons, see p. 667

ISONIAZID *continued*

Inhibits CYP 450 1A2, 2C9, 2C19, and 3A3/4 microsomal enzymes; decrease dose of carbamazepine, diazepam, phenytoin, and prednisone. Prednisone may decrease isoniazid's effects. Also a substrate and inducer of CYP 450 2E1 and may potentiate acetaminophen hepatotoxicity. **Avoid** daily alcohol use to reduce risk for isoniazid-induced hepatitis.

May be given IM (same as oral doses) when oral therapy is not possible. Administer oral doses 1 hr prior to and 2 hr after meals. Aluminum salts may decrease absorption. **Adjust dose in renal failure (see Chapter 31)**.

ISOPROTERENOL

Isuprel and generics

Adrenergic agonist

Injection: 0.2 mg/mL (1, 5 mL); preparations may be preservative free or contain disodium EDTA

NOTE: The dosage units for adults are in mCg/min, compared to mCg/kg/min for children.

IV infusion:

Neonate–child: 0.05–2 mCg/kg/min; start at minimum dose and increase every 5–10 min by 0.1 mCg/kg/min until desired effect or onset of toxicity; **max. dose**: 2 mCg/kg/min.

Adult: 2–20 mCg/min; titrate to desired effect.

Use with caution in diabetes, hyperthyroidism, renal disease, CHF, ischemia, or aortic stenosis. May cause flushing, ventricular arrhythmias, profound hypotension, anxiety, and myocardial ischemia. Monitor heart rate, respiratory rate, and blood pressure. **Not** for treatment of asystole or for use in cardiac arrests, unless bradycardia is due to heart block.

Continuous infusion for bronchodilatation must be gradually tapered over a 24–48 hr period to prevent rebound bronchospasm. Tolerance may occur with prolonged use. Clinical deterioration, myocardial necrosis, congestive heart failure, and **death** have been reported with continuous infusion use in refractory asthmatic children.

ISOTRETINOIN

Absorica, Amnesteem, Claravis, Myorisan, Zenatane; previously available as Accutane

Retinoic acid, vitamin A derivative

Caps (all products contain soybean oil):

Absorica: 10, 20, 25, 30, 35, 40 mg

Amnesteem: 10, 20, 40 mg; contains EDTA

Claravis, Myorisan, Zenatane, and generics: 10, 20, 30, 40 mg; contains EDTA

Cystic acne/Severe Recalcitrant Nodular acne (see remarks):

Child (>12 yr) and adult: 0.5–2 mg/kg/24 hr ÷ BID PO × 15–20 wk or until the total cyst count decreases by 70%, whichever comes first. Dosages as low as 0.05 mg/kg/24 hr have been reported to be beneficial.

Contraindicated during pregnancy; known teratogen. Use with caution in females during childbearing years. May cause conjunctivitis, xerosis, pruritus, photosensitivity reactions (**avoid** exposure to sunlight and use sunscreen), epistaxis, anemia, hyperlipidemia, pseudotumor cerebri (especially in combination with tetracyclines; **avoid** this combination),

ISOTRETINOIN *continued*

cheilitis, bone pain, muscle aches, skeletal changes, lethargy, nausea, vomiting, elevated ESR, mental depression, aggressive/violent behavior, and psychosis. Serious skin reactions (e.g., Stevens Johnson syndrome, TEN) have been reported.

Elevation of liver enzymes may occur during treatment; a dosage reduction or continued treatment may result in normalization. Discontinue use if liver enzymes do not normalize or if hepatitis is suspected.

To avoid additive toxic effects, **do not** take vitamin A concomitantly. Increases clearance of carbamazepine. Hormonal birth control (oral, injectable, and implantable) failures have been reported with concurrent use. Monitor CBC, ESR, triglycerides, and LFTs.

Prescribers, site pharmacists, patients, and wholesalers must register with the iPLEDGE system (a risk minimization program) at www.ipledgeprogram.com or 1-866-495-0654 before doses are dispensed. Prescriptions may not be written for more than a 1-mo supply.

ITRACONAZOLE
Sporanox, Tolsura, and generics
Antifungal agent

Caps:
Sporanox and generics: 100 mg
Tolsura: 65 mg
Oral solution (Sporanox and generics): 10 mg/mL (150 mL); contains propylene glycol and saccharin

Neonate (limited data in full-term neonates treated for tinea capitis): 5 mg/kg/24 hr PO once daily × 6 wk

Child (limited data): 3–5 mg/kg/24 hr PO ÷ once daily–BID; dosages as high as 5–10 mg/kg/24 hr have been used for Aspergillus prophylaxis in chronic granulomatous disease. Population pharmacokinetic data in pediatric cystic fibrosis and bone marrow transplant patients suggest an oral liquid dosage of 10 mg/kg/24 hr PO ÷ BID or oral capsule dosage of 20 mg/kg/24 hr PO ÷ BID to be more reliable for achieving trough plasma levels between 500 and 2000 ng/mL.

Prophylaxis for recurrence of opportunistic disease in HIV:
Coccidioides spp.: 2–5 mg/kg/dose PO Q12 hr; **max. dose**: 400 mg/24 hr
Cryptococcus neoformans: 5 mg/kg/dose PO Q24 hr; **max. dose**: 200 mg/24 hr
Histoplasmosis: 5–10 mg/kg/dose PO once daily; **max. dose**: 200 mg/dose

Treatment of opportunistic disease in HIV:
Candidiasis: 5 mg/kg/24 hr PO ÷ Q12–24 hr; **max. dose**: 400 mg/24 hr
Coccidioides spp.: 2–5 mg/kg/dose (**max. dose**: 200 mg/dose) PO TID × 3 days, followed by 2–5 mg/kg/dose PO BID; **max. dose**: 400 mg/24 hr
Cryptococcus neoformans: 2.5–5 mg/kg/dose (**max. dose**: 200 mg/dose) PO TID × 3 days, followed by 5–10 mg/kg/24 hr (**max. dose**: 400 mg/24 hr) ÷ once to twice daily for a minimum of 8 wk
Histoplasmosis: 2–5 mg/kg/dose (**max. dose**: 200 mg/dose) PO TID × 3 days, followed by 2–5 mg/kg/dose (**max. dose**: 200 mg/dose) PO BID × 12 mo

Adult:
Blastomycosis and nonmeningeal histoplasmosis: 200 mg PO TID × 3 days, followed by 200 mg PO once daily or BID depending on severity
Aspergillosis and severe infections (use oral solution): 600 mg/24 hr PO ÷ TID × 3–4 days, followed by 200–400 mg/24 hr ÷ BID; **max. dose**: 600 mg/24 hr ÷ TID

Continued

For explanation of icons, see p. 667

ITRACONAZOLE *continued*

Oral solution and capsule dosage form should NOT be used interchangeably; oral solution is more bioavailable. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis. **Contraindicated** in CHF and certain interacting drugs (see below). **Use with caution** in hepatic and/or renal impairment, cardiac dysrhythmias, and azole hypersensitivity. May cause GI symptoms, headaches, rash, liver enzyme elevation, hepatitis, and hypokalemia. Double/blurred vision, dizziness, and tremor have been reported.

Like ketoconazole, it inhibits the activity of the CYP-450 3A4 drug metabolizing isoenzyme. Thus, the coadministration of cisapride, dofetilide, felodipine, methadone, nisoldipine, pimozide, quinidine, triazolam, lovastatin, simvastatin, ergot derivatives, and oral midazolam is contraindicated. May increase systemic hormone concentrations of oral contraceptives. See remarks in Ketoconazole for additional drug interaction information.

Steady-state serum concentrations of >0.25 mg/L itraconazole and >1 mg/L hydroxyitraconazole (metabolite) have been recommended. Recommended serum sampling time at steady state: any time after 2 wk after continuous dosing. Itraconazole has a 34–42-hour $T_{1/2}$.

Administer oral solution on an empty stomach but administer capsules with food. Oral capsule bioavailability has been shown to be reduced in immunocompromised patients. Achlorhydria reduces absorption of the drug. **Do not** use oral liquid dosage form in patients with GFR <30 mL/min because of hydroxypropyl-β-cyclodextrin excipient has reduced clearance with renal failure.

IVACAFTOR
Kalydeco
Cystic Fibrosis Transmembrane Conductance Regulator Potentiator

Oral granules: 50 mg (56 packets), 75 mg (56 packets)
Tabs: 150 mg (56 tabs)

Cystic Fibrosis (see remarks):
≥6 mo and child <6 yr (use oral granules):
5–<7 kg: 25 mg PO Q12 hr
7–<14 kg: 50 mg PO Q12 hr
≥14 kg: 75 mg PO Q12 hr
≥6 yr, adolescent and adult: 150 mg PO Q12 hr
Dosage modification with hepatic impairment:
Child-Pugh class B: Use above dosage with a once-daily dosage interval.
Child-Pugh class C: Studies have not been completed but exposure is expected to be higher than class B; use above dosage with caution once daily or with a less frequent dosage interval.
Dosage modification when used with CYP 450 3A inhibitors:

Age	Weight (kg)	Dosed With Strong CYP 450 3A Inhibitor (e.g., Ketoconazole, Itraconazole, Voriconazole, Posaconazole, Clarithromycin)	Dosed With Moderate CYP 450 3A Inhibitor (e.g., Erythromycin, Fluconazole)
≥6 mo and < 6 yr	5–<7 kg	25 mg PO twice weekly	25 mg PO once daily
	7–<14 kg	50 mg PO twice weekly	50 mg PO once daily
	≥14 kg	75 mg PO twice weekly	75 mg PO once daily
≥6 yr, adolescent, and adult	All	150 mg PO twice weekly	150 mg PO once daily

IVACAFTOR *continued*

Works as a CFTR potentiator on class 3 CFTR mutations. Originally indicated for G551D CFTR mutation but has since been approved for many other mutations; see product information for list of approved mutations.

Common side effects include rash, abdominal pain, diarrhea, nausea, dizziness, headache, nasal congestion, pharyngitis, and URIs. Increased liver enzymes and cataracts may occur; monitor baseline AST/ALT and ocular exam. Repeat AST/ALT every 3 months for the first year followed by annual assessments. Repeat ocular exams annually. May cause a false-positive urine drug screen test for cannabinoids. **Use with caution** in patients with CrCl ≤30 mL/min; has not been studied.

Ivacaftor is CYP 450 3A substrate; see dose modification table in the dosing section. Use with strong CYP 450 3A inducers (e.g., rifampin, rifabutin, carbamazepine, St. John's wort) is not recommended. Always evaluate potential drug-drug interactions; see https://www.kalydecohcp.com/drug-interactions. Avoid food or drink containing grapefruit or Seville oranges.

Administer all doses with high-fat foods to assure absorption. Oral granules can be mixed with 5 mL of soft foods or liquids such as puréed fruits or vegetables, yogurt, applesauce, water, breast milk, infant formula, milk, or juice. Once mixed, it should be consumed within an hour. If a dose (all dosage forms) is missed within 6 hr of a scheduled dose, administer a dose immediately. However, if the missed dose is >6 hr, skip that dose and resume therapy at the next scheduled dose. Never take a double dose for a missed dose.

IVERMECTIN
Stromectol, Sklice, Soolantra, and generics
Anthelmintic

Tab (Stromectol and generics): 3 mg
Topical lotion (Sklice): 0.5% (117 g); contains parabens
Topical cream (Soolantra): 1% (30, 45, 60 g); contains cetyl alcohol, EDTA, parabens, and propylene glycol

Systemic use:

Cutaneous lava migrans or strongyloidiasis: 0.2 mg/kg/dose PO once daily × 1–2 days for cutaneous lava migrans and × 2 days for strongyloidiasis; dosing by body weight (see first table)

Scabies: 0.2 mg/kg/dose PO × 1, may repeat dose in 7 or 10–14 days, dosing by body weight as follows:

Weight (kg)	Oral Dose
15–24	3 mg
25–35	6 mg
36–50	9 mg
51–65	12 mg
66–79	15 mg
≥80	0.2 mg/kg

Onchocerciasis: 0.15 mg/kg/dose PO × 1, may repeat dose every 6–12 mo until asymptomatic; dosing by body weight as follows:

Weight (kg)	Single Oral Dose
15–25	3 mg
26–44	6 mg
45–64	9 mg
65–84	12 mg
≥85	0.15 mg/kg

For explanation of icons, see p. 667

IVERMECTIN *continued*

Topical use:

Lotion:

Head lice infestation (≥6 mo to adult): Apply lotion to dry hair in sufficient amounts (up to one full tube) to thoroughly coat the hair and scalp for 10 min. Then rinse off with water.

Cream:

Rosacea (Adult): Apply cream to each affected area once daily.

Systemic Use: Rare fatal encephalopathy may occur in onchocerciasis with a concurrent heavy Loa loa infection. Reactions experienced with strongyloidiasis include diarrhea, nausea, vomiting, pruritus, rash, dizziness, and drowsiness. Adverse reactions experienced in onchocerciasis include cutaneous or systemic allergic/inflammatory reactions of varying severity (Mazzotti reaction) and ophthalmologic reactions. Specific reactions may include arthralgia/synovitis, lymph node enlargement and tenderness, pruritus, edema, fever, orthostatic hypotension, and tachycardia. Therapy for postural hypotension may include oral hydration, recumbency, IV normal saline, and/or IV steroids. Antihistamines or aspirin, or both, have been used for most mild-to-moderate cases. Ivermectin may increase the effects/toxicity of warfarin. Administer oral doses on an empty stomach with water.

Topical Use: Safety and efficacy have not been established for children <6 mo. Common side effects include conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin-burning. Contact dermatitis has been reported. Not for oral, ophthalmic, or intravaginal use. Use of lotion for children should be supervised by an adult to prevent oral ingestion.

K

KALYDECO

See Ivacaftor

KETAMINE

Ketalar and generics

General anesthetic

B | 3 | No | No | No

Injection: 10 mg/mL (20 mL), 50 mg/mL (10 mL), 100 mg/mL (5, 10 mL); contains benzethonium chloride

Child (see remarks):

Sedation:

PO: 5 mg/kg × 1

IV: 0.5–1 mg/kg; **max. dose**: 150 mg/dose

IM: 2–5 mg/kg × 1

Adult:

Analgesia with sedation:

IV (see remarks): 0.2–1 mg/kg

IM: 0.5–4 mg/kg

Contraindicated in significant hypertension and known hypersensitivity to the drug. **Use with caution** in elevated ICP, aneurysms, thyrotoxicosis, CHF, angina, and psychotic disorders. May cause hypertension, hypotension, emergence reactions, tachycardia, laryngospasm,

KETAMINE *continued*

respiratory depression, and stimulation of salivary secretions. Cystitis has been reported with chronic use/abuse. Intravenous use may induce general anesthesia. Diplopia and nystagmus have been noted following IV administration. False-positive test for urine phencyclidine (PCP) screen may occur.

Coadministration of an anticholinergic agent may be added in situations of clinically significant hypersalivation in patients with impaired ability to mobilize secretions. Benzodiazepine may be used in the presence of a ketamine-associated recovery reaction (prophylaxis use in adults may be beneficial). Ondansetron prophylaxis can slightly reduce vomiting. See *Ann Emerg Med.* 2001;57:449–461 for additional use information in the emergency department.

Drug is a substrate for CYP 450 2B6, 2C9 and 3A4 isoenzymes. Consider potential drug interactions with respective enzyme inhibitors and inducers, especially with prolonged use.

Rate of IV infusion should **not** exceed 0.5 mg/kg/min and **should not** be administered in less than 60 sec. For additional information including onset and duration of action, see Chapter 6.

KETOCONAZOLE
Nizoral, Nizoral A-D, Xolegel, Extina, Ketodan, and generics
Antifungal agent, imidazole

Tabs: 200 mg
Oral suspension: 100 mg/5 mL
Cream: 2% (15, 30, 60 g); contains sulfites
Gel: 2% [Xolegel] (45 g); contains 34% alcohol
Foam: 2% [Extina and generics] (50, 100 g); contains alcohol and propylene glycol
Shampoo: 1% [Nizoral A–D (OTC)] (125, 200 mL), 2% [Nizoral and generics] (120 mL)

Oral:
Child ≥2 yr and adolescent: 3.3–6.6 mg/kg/24 hr once daily
Adult: 200–400 mg/24 hr once daily
Max. dose (all ages): 400 mg/24 hr
Topical (≥12 yr; see remarks):
Cream: 1 application to affected area once daily × 2–6 wk. For seborrheic dermatitis, use BID × 4 wk.
Gel (Xolegel): 1 application to affected area once daily × 2 wk
Foam: 1 application to affected area BID × 4 wk
Shampoo:
1% (Dandruff): Apply to wet hair, generously lather, rinse thoroughly; use every 3–4 days for up to 8 wk PRN
2% (Tinea versicolor): Apply to wet hair and leave on for 5 minutes before rinsing × 1

The systemic dosage form should NOT be first-line treatment for any fungal infection due to concerns of hepatotoxicity and adrenal gland effects (per the FDA).

Monitor LFTs in long-term use and adrenal function for patients at risk. Drugs that decrease gastric acidity will decrease absorption. May cause nausea, vomiting, rash, headache, pruritus, and fever. Hepatotoxicity (including fatal cases) has been reported; use with hepatic impairment is **contraindicated.** High doses may decrease adrenocortical function and serum testosterone levels. Hypersensitivity reactions (including anaphylaxis), has been reported with all dosage forms.

Safety and efficacy with topical use in seborrheic dermatitis for patients >12 yr of age has been established. **Avoid** topical use on breast or nipples in nursing mothers.

Continued

For explanation of icons, see p. 667

KETAMINE *continued*

Inhibits CYP 450 3A4. **Contraindicated** when used with cisapride, disopyramide, methadone, mefloquine, quinidine, terfenadine, pimozide, or any drug that can prolong the QT interval (because of risk for cardiac arrhythmias), and HMG-CoA reductase inhibitors (e.g., simvastatin, and lovastatin). Excessive sedation and prolonged hypnotic effects with triazolam use (also **contraindicated**). May increase levels/effects of phenytoin, digoxin, cyclosporine, corticosteroids, nevirapine, protease inhibitors, and warfarin. Achlorhydria, phenobarbital, rifampin, isoniazid, H_2 blockers, antacids, and omeprazole can decrease levels of oral ketoconazole.

Administering oral doses with food or acidic beverages and 2 hr prior to antacids will increase absorption. For topical products, **avoid contact** with eyes and other mucous membranes.

To use shampoo, wet hair and scalp with water, apply sufficient amount to scalp and gently massage for about 1 min. Rinse hair thoroughly, reapply shampoo and leave on the scalp for an additional 3 min, and rinse.

KETOROLAC

Many generics (previously available as Toradol), Acular, Acular LS, Acuvail

Nonsteroidal anti-inflammatory agent

Injection: 15 mg/mL (1 mL), 30 mg/mL (1, 2 mL); contains 10% alcohol and tromethamine

Tabs: 10 mg; contains tromethamine

Ophthalmic solution (all containing tromethamine):

Acular and generic: 0.5% (3, 5, 10 mL); contains benzalkonium chloride and EDTA

Acular LS and generics: 0.4% (5 mL); contains benzalkonium chloride and EDTA

Acuvail: 0.45% (0.4 mL; 30s); preservative free

Systemic use is not to exceed 3–5 days, regardless of administration route (IM, IV, PO).

IM/IV:

Child: 0.5 mg/kg/dose IM/IV Q6–8 hr. **Max. dose**: 30 mg Q6 hr or 120 mg/24 hr.

Adult: 30 mg IM/IV Q6 hr. **Max. dose**: 120 mg/24 hr

PO:

Child >16 yr and adult: 10 mg PRN Q6 hr; max. dose: 40 mg/24 hr

Ophthalmic (see remarks):

Postoperative cataract surgery:

≥2 yr–adult (use 0.5%): 1 drop in each affected eye QID starting 24 hr after surgery × 2 wk

Postoperative corneal refractive surgery:

≥3 yr–adult (use 0.4%): 1 drop in each affected eye QID PRN for up to 4 days after surgery

Seasonal allergic conjunctivitis:

≥2 yr–adult (use 0.5%): 1 drop in each eye QID

May cause GI bleeding, nausea, dyspepsia, drowsiness, decreased platelet function, and interstitial nephritis. **Not recommended** in patients at increased risk of bleeding. **Do not use** in hepatic or renal failure. **Use with caution** in heart disease (risk for MI and stroke with prolonged use). False-positive test for urine cannabinoid screen may occur with systemic use.

Duration of therapy for ophthalmic use: 14 days after cataract surgery, and up to 4 days after corneal refractive surgery. Also indicated for ocular itching associated with seasonal allergic conjunctivitis. Bronchospasm or asthma exacerbations, corneal erosion/perforation/thinning/melt, and epithelial breakdown have been reported with ophthalmic use.

Pregnancy category changes to a "D" if used in the third trimester.

L

LABETALOL

Generics; previously available as Normodyne and Trandate

Adrenergic antagonist (α and β), antihypertensive

Tabs: 100, 200, 300 mg
Injection: 5 mg/mL (4, 20, 40 mL); contains parabens
Oral suspension: 10 mg/mL, 40 mg/mL

Child (see remarks):

PO: Initial: 1–3 mg/kg/24 hr ÷ BID. May increase up to a **maximum** of 12 mg/kg/24 hr up to 1200 mg/24 hr.

IV: Hypertensive emergency (start at lowest dose and titrate to effect; see Chapter 4 for additional information):

Intermittent dose: 0.2–1 mg/kg/dose Q10 min PRN; **max. dose**: 40 mg/dose

Infusion (hypertensive emergencies): 0.4–1 mg/kg/hr, to a **max. dose** of 3 mg/kg/hr; may initiate with a 0.2–1 mg/kg bolus; **max. bolus**: 40 mg.

Adult (see remarks):

PO: 100 mg BID, increase by 100 mg/dose Q2–3 days PRN to a **max. dose** of 2.4 g/24 hr. Usual range: 200–800 mg/24hr ÷ BID

IV: Hypertensive emergency (start at lowest dose and titrate to effect with a **max. total dose** of 300 mg for both methods of administration):

Intermittent dose: 10–20 mg/dose Q10 min PRN; **max. dose**: 80 mg/dose

Infusion: 0.5–2 mg/min, increase to titrate to response.

Contraindicated in asthma, pulmonary edema, cardiogenic shock, and heart block. May cause orthostatic hypotension, edema, CHF, bradycardia, AV conduction disturbances, bronchospasm, urinary retention, and skin tingling. **Use with caution** in hepatic disease (dose reduction may be necessary), diabetes, liver function test elevation, hepatic necrosis, and hepatitis. Cholestatic jaundice has been reported. Use with digitalis glycosides may increase risk for bradycardia. False-positive test for urine amphetamine screen may occur.

Patient should remain supine for up to 3 hr after IV administration. Pregnancy category changes to "D" if used in second or third trimesters.

Onset of action: PO: 1–4 hr; IV: 5–15 min.

LACOSAMIDE

Vimpat

Anticonvulsant

Oral solution: 10 mg/mL (200, 465 mL); contains aspartame, parabens, and propylene glycol
Tabs: 50, 100, 200 mg
Injection: 10 mg/mL (20 mL); preservative free

Continued

For explanation of icons, see p. 667

LACOSAMIDE *continued*

Partial-onset seizures as monotherapy or adjunctive therapy (PO):
Child (≥4–<17 yr):

Weight (kg)	Initial Dosage (PO)	Titration Regimen (PO)	Maintenance Dosage (PO)
11–<30	1 mg/kg/dose BID	Increase by 1 mg/kg/dose BID every 7 days	3–6 mg/kg/dose BID
30–<50	1 mg/kg/dose BID	Increase by 1 mg/kg/dose BID every 7 days	2–4 mg/kg/dose BID
≥50	50 mg BID	Increase by 50 mg BID every 7 days	Monotherapy: 150–200 mg BID Adjunctive therapy: 100–200 mg BID

17 yr and adult:

Initial Dosage (PO)	Titration Regimen (PO)	Maintenance Dosage (PO)
Monotherapy: 100 mg BID[a] Adjunctive therapy: 50 mg BID[a]	Increase by 50 mg BID every 7 days	Monotherapy: 150–200 mg BID Adjunctive therapy: 100–200 mg BID

[a]Alternative initial dosage (under medical supervision due to increased risk for CNS side effects): 200 mg × 1 and start 12 hr later, 100 mg BID × 7 days then titrate to the respective monotherapy or adjunctive therapy goal.

Converting from other single antiepileptic drug (AED) to lacosamide monotherapy: administer lacosamide in combination with the established single AED for at least 3 days before tapering. Gradually withdrawing the concomitant AED over 6 wk is recommended.

IV use: Use same dose when converting from PO to IV and vice versa. IV use should be considered for short-term use and has not been studied in pediatrics.

Use with caution with known cardiac conduction problems (e.g., second-degree AV block), severe cardiac disease (e.g., MI or heart failure), concomitant use with drugs known to prolong PR interval, and renal (see Chapter 31) and hepatic impairment. Lacosamide undergoes 95% renal excretion; a reduction of 25% of the **maximum** dosage is recommended for adult and pediatric patients with severe renal impairment (CrCl <30 mL/min and ESRD), or with mild/moderate hepatic impairment. Use is **not recommended** in severe hepatic impairment. Dose reduction may be also necessary with concurrent strong inhibitor of CYP 450 3A4 or 2C9 medication. Patients with mild/moderate hepatic impairment should be observed closely during dose titration. Oral bioavailability is approximately 100%.

Most common side effects in adults include diplopia, headache, dizziness, and nausea. Somnolence and irritability were frequently reported in pediatric studies. Patients should be advised of potential dizziness, ataxia, and syncope with use. Multiorgan hypersensitivity reactions (including DRESS, affecting the skin, kidney and liver), worsening of seizures, agranulocytosis, and euphoria (high doses) have been reported. As with other AEDs, monitor for suicidal behavior and ideation.

Oral doses may be administered with or without food. Swallow tablets whole; do not cut tablets. IV doses should be administered over 30–60 min. **Do not** abruptly withdraw therapy; gradually taper to prevent potential seizures.

LACTULOSE
Constulose, Enulose, Kristalose, and generics
Ammonium detoxicant, hyperosmotic laxative

Oral syrup: 10 g/15 mL (15, 30, 237, 473, 960, 1893 mL); contains galactose, lactose, and other sugars
Crystals for reconstitution (Kristalose): 10 g (30s), 20 g (30s)

Constipation:
Child: 1.5–3 mL/kg/24 hr PO ÷ BID; **max. dose:** 60 mL/24 hr
Adult: 15–30 mL/24 hr PO once daily to a **max. dose** of 60 mL/24 hr.
Portal systemic encephalopathy (adjust dose to produce 2–3 soft stools/day):
Infant: 2.5–10 mL/24 hr PO ÷ TID–QID
Child and adolescent: 40–90 mL/24 hr PO ÷ TID–QID
Adult: 30–45 mL/dose PO TID–QID; acute episodes 30–45 mL Q1–2 hr until 2–3 soft stools/day
Rectal (adult): 300 mL diluted in 700 mL water or NS in 30–60 min retention enema; may give Q4–6 hr.

Contraindicated in galactosemia. **Use with caution** in diabetes mellitus. GI discomfort and diarrhea may occur. For portal systemic encephalopathy, monitor serum ammonia, serum potassium, and fluid status.
Do not use with antacids. Dissolve crystal dosage form with 4 ounces of water or juice. All doses may be administered with juice, milk, or water.

LAMIVUDINE
Epivir, Epivir-HBV, 3TC, and generics
Antiviral agent, nucleoside analogue reverse transcriptase inhibitor

Tabs: 100 mg (Epivir-HBV and generics), 150, 300 mg (Epivir and generics)
Oral solution: 5 mg/mL (Epivir-HBV) (240 mL), 10 mg/mL (Epivir and generics) (240 mL); contains parabens

HIV: See www.aidsinfo.nih.gov/guidelines.
Prevention of maternal-fetal transmission to reduce nevirapine resistance (for infants born to mothers with no antiretroviral therapy before or during labor, infants born to mothers with only intrapartum antiretroviral therapy, infants born to mothers with suboptimal viral suppression at delivery, or infants born to mothers with known antiretroviral drug resistance):
Neonate ≥32 wk gestation (use in combination with zidovudine and either raltegravir or nevirapine): 2 mg/kg/dose PO BID within 6–12 hr after birth. Increase dose to 4 mg/kg/dose PO BID at 4 wk of age.
Chronic hepatitis B (see remarks):
2–17 yr: 3 mg/kg/dose PO once daily up to a **max. dose** of 100 mg/dose
18 and adult: 100 mg/dose PO once daily

See aidsinfo.nih.gov/guidelines for remarks for use in HIV. Oral tablet dosage form is preferred over oral solution for children ≥14 kg treated for HIV because subjects in the ARROW clinical trial receiving oral solution had lower rates of HIV viral suppression, lower plasma lamivudine exposure, and developed viral resistance more frequently.
May cause headache, fatigue, GI disturbances, rash, and myalgia/arthralgia. Lactic acidosis, severe hepatomegaly with steatosis, post-treatment exacerbations of hepatitis B and ALT elevations, pancreatitis, and emergence of resistant viral strains have been reported. Treatment should be suspended in any patient developing clinical or laboratory signs of lactic acidosis or hepatotoxicity.

For explanation of icons, see p. 667

LAMIVUDINE *continued*

Avoid use with sorbitol-containing medicines, as sorbitol reduces lamivudine exposure. Concomitant use with co-trimoxazole (TMP/SMX) may result in increased lamivudine levels.

Use Epivir-HBV product for chronic hepatitis B indication only. Safety and effectiveness beyond 1 yr have not been determined. If serum HBV DNA remains detectable after 24 wk of lamivudine monotherapy, consider switching to an alternative therapy. Patients with both HIV and hepatitis B should use the higher HIV doses along with an appropriate combination regimen.

May be administered with food. **Adjust dose in renal impairment (see Chapter 31).**

LAMOTRIGINE

Lamictal, Subvenite, Lamictal ODT, Lamictal XR, and generics

Anticonvulsant

Tabs (Lamictal, Subvenite, and generics): 25, 100, 150, 200 mg
Extended release tabs (Lamictal XR and generics): 25, 50, 100, 200, 250, 300 mg
Chewable tabs: 5, 25 mg
Orally disintegrated tabs (Lamictal ODT and generics): 25, 50, 100, 200 mg
Oral suspension: 1 mg/mL

Child 2–12 yr adjunctive seizure therapy (maintenance doses for patients <30 kg may need to be increased as much as 50%; see remarks):

WITH AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid (use immediate-release dosage forms):

Wk 1 and 2: 0.3 mg/kg/24 hr PO ÷ once daily–BID; rounded down to the nearest whole tablet.

Wk 3 and 4: 0.6 mg/kg/24 hr PO ÷ BID; rounded down to the nearest whole tablet.

Usual maintenance dose: 4.5–7.5 mg/kg/24 hr PO ÷ BID titrate to effect. To achieve the usual maintenance dose, increase doses Q 1–2 wk by 0.6 mg/kg/24 hr (rounded down to the nearest whole tablet) as needed.

Max. dose: 300 mg/24 hr ÷ BID.

WITH enzyme-inducing AEDs WITHOUT valproic acid (use immediate-release dosage forms):

Wk 1 and 2: 0.6 mg/kg/24 hr PO ÷ BID; rounded down to the nearest whole tablet.

Wk 3 and 4: 1.2 mg/kg/24 hr PO ÷ BID; rounded down to the nearest whole tablet.

Usual maintenance dose: 5–15 mg/kg/24 hr PO ÷ BID titrate to effect. To achieve the usual maintenance dose, increase doses Q 1–2 wk by 1.2 mg/kg/24 hr (rounded down to the nearest whole tablet) as needed.

Max. dose: 400 mg/24 hr ÷ BID.

WITH AEDs WITH valproic acid (use immediate-release dosage forms):

Wk 1 and 2: 0.15 mg/kg/24 hr PO ÷ once daily–BID; rounded down to the nearest whole tablet (see following table)

Wk 3 and 4: 0.3 mg/kg/24 hr PO ÷ once daily–BID; rounded down to the nearest whole tablet (see following table)

Weight (kg)	Weeks 1 and 2	Weeks 3 and 4
6.7–14	2 mg every other day	2 mg once daily
14.1–27	2 mg once daily	4 mg/24 hr ÷ once daily—BID
27.1–34	4 mg/24 hr ÷ once daily—BID	8 mg/24 hr ÷ once daily—BID
34.1–40	5 mg once daily	10 mg/24 hr ÷ once daily—BID

LAMOTRIGINE *continued*

Usual maintenance dose: 1–5 mg/kg/24 hr PO ÷ once daily–BID, titrate to effect. To achieve the usual maintenance dose, increase doses Q 1–2 wk by 0.3 mg/kg/24 hr (rounded down to the nearest whole tablet) as needed. If adding lamotrigine with valproic acid alone, usual maintenance dose is 1–3 mg/kg/24 hr.

Max. dose: 200 mg/24 hr.

>12 yr and adult adjunctive therapy:

WITH AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid (use immediate-release dosage forms):

Wk 1 and 2: 25 mg once daily PO

Wk 3 and 4: 50 mg once daily PO

Usual maintenance dose: 225–375 mg/24 hr ÷ BID PO, titrate to effect. To achieve the usual maintenance dose, increase doses Q 1–2 wk by 50 mg/24 hr as needed.

WITH enzyme-inducing AEDs WITHOUT valproic acid (use immediate-release dosage forms):

Wk 1 and 2: 50 mg once daily PO

Wk 3 and 4: 50 mg BID PO

Usual maintenance dose: 300–500 mg/24 hr ÷ BID PO, titrate to effect. To achieve the usual maintenance dose, increase doses Q 1–2 wk by 100 mg/24 hr as needed. Doses as high as 700 mg/24 hr ÷ BID have been used.

WITH AEDs WITH valproic acid: (use immediate-release dosage forms)

Wk 1 and 2: 25 mg every other day PO

Wk 3 and 4: 25 mg once daily PO

Usual maintenance dose: 100–400 mg/24 hr ÷ once daily–BID PO, titrate to effect. To achieve the usual maintenance dose, increase doses Q 1–2 wk by 25–50 mg/24 hr as needed. If adding lamotrigene to valproic acid alone, usual maintenance dose is 100–200 mg/24 hr.

Extended-release dosage form (Lamictal XR):

≥13 yr and adult adjunctive therapy (dose increases at wk 8 or later should not exceed 100 mg/24 hr at weekly intervals; see remarks):

	Weeks 1 and 2	Weeks 3 and 4	Week 5	Week 6	Week 7	Maintenance Dose
Patient NOT receiving enzyme-inducing drugs (e.g., carbamazepine) OR valproic acid	25 mg once daily	50 mg once daily	100 mg once daily	150 mg once daily	200 mg once daily	300–400 mg once daily
Patients receiving enzyme-inducing drugs (e.g., carbamazepine) WITHOUT valproic acid	50 mg once daily	100 mg once daily	200 mg once daily	300 mg once daily	400 mg once daily	400–600 mg once daily
Patients receiving valproic acid	25 mg every other day	25 mg once daily	50 mg once daily	100 mg once daily	150 mg once daily	200–250 mg once daily

Continued

For explanation of icons, see p. 667

LAMOTRIGINE *continued*

Converting Adjunctive Therapy to Lamotrigine Monotherapy:

	Immediate-Release Lamotrigine Dosage Form Regimen (≥16 Yr and Adult)	**Extended-Release Tabs (≥13 Yr and Adult)**
Patient NOT receiving enzyme-inducing drugs (e.g., carbamazepine) OR valproic acid	No specific dosing guidelines provided	After achieving a maintenance dose of 250–300 mg/24 hr with the above recommendations, withdraw the concomitant AED by 20% decrements each week over a 4-wk period
Patients receiving enzyme-inducing drugs (e.g., carbamazepine) WITHOUT valproic acid	After achieving a maintenance dose of 500 mg/24 hr with the above recommendations, withdraw the concomitant enzyme-inducing AED by 20% decrements each week over a 4-wk period	After achieving a maintenance dose of 500 mg/24 hr with the above recommendations, withdraw the concomitant enzyme-inducing AED by 20% decrements each week over a 4-wk period. After 2 wks of the complete withdrawal of enzyme-inducing AED, lamotrigine may be decreased no faster than 100 mg/24 hr each week to the maintenance dose of 250–300 mg/24 hr.
Patients receiving valproic acid	*Step 1*: Achieve maintenance dose of 200 mg/24 hr with the above recommendations. *Step 2*: Decrease valproic acid by decrements no greater than 500 mg/24 hr per week to reach 500 mg/24 hr and maintain for 1 wk *Step 3*: Increase lamotrigine to 300 mg/24 hr and decrease valproic acid to 250 mg/24 hr; maintain both for 1 wk *Step 4*: Increase lamotrigine by 100 mg/24 hr Q7 days until reaching maintenance dose of 500 mg/24 hr and discontinue valproic acid	*Step 1*: Achieve maintenance dose of 150 mg/24 hr with the above recommendations. *Step 2*: Decrease valproic acid by decrements no greater than 500 mg/24 hr per week to reach 500 mg/24 hr and maintain for 1 wk *Step 3*: Increase lamotrigine to 200 mg/24 hr and decrease valproic acid to 250 mg/24 hr; maintain both for 1 wk *Step 4*: Increase lamotrigine to 250–300 mg/24 hr and discontinue valproic acid

Bipolar disease (use immediate-release dosage forms; see remarks):
≥18 yr and adult (PO; see table below):

	Weeks 1 and 2	**Weeks 3 and 4**	**Week 5**	**Weeks 6 and Thereafter**
Patient NOT receiving enzyme-inducing drugs (e.g., carbamazepine) OR valproic acid	25 mg/24 hr	50 mg/24 hr	100 mg/24 hr	200 mg/24 hr (target dose)

LAMOTRIGINE *continued*

	Weeks 1 and 2	Weeks 3 and 4	Week 5	Weeks 6 and Thereafter
Patents receiving enzyme-inducing drugs (e.g., carbamazepine) WITHOUT valproic acid	50 mg/24 hr	100 mg/24 hr ÷ once daily—BID	200 mg/24 hr ÷ once daily—BID	Week 6: 300 mg/24 hr ÷ once daily—BID Week 7 and thereafter: may increase to 400 mg/24 hr ÷ once daily—BID (target dose)[a]
Patients receiving valproic acid	25 mg every other day	25 mg/24 hr	50 mg/24 hr	100 mg/24 hr (target dose)[b]

[a]If carbamazepine or other enzyme-inducing drug is discontinued, maintain current lamotrigine dose for 1 wk, then decrease daily lamotrigine dose in 100 mg increments at weekly intervals until 200 mg/24 hr.
[b]If valproic acid is discontinued, increase by 50 mg at weekly intervals, up to 200 mg/24 hr.

Enzyme-inducing AEDs include carbamazepine, phenytoin, and phenobarbital. Stevens-Johnson syndrome, toxic epidermal necrolysis, and other potentially life-threatening rashes have been reported in children (0.3%–0.8%) and adults (0.08%–0.3%) for adjunctive therapy in seizures. Reported rates for adults treated for bipolar/mood disorders as monotherapy and adjunctive therapy are 0.08% and 0.13%, respectively. May cause fatigue, drowsiness, ataxia, rash (especially with valproic acid), headache, nausea, vomiting, and abdominal pain. Diplopia, nystagmus, aseptic meningitis, hemophagocytic lymphohistiocytosis, aggression, and alopecia have also been reported. False-positive test for urine phencyclidine (PCP) screen may occur.

Use during the first 3 mo of pregnancy may result in a higher chance for cleft lip or cleft palate in the newborn. Suicidal behavior or ideation have been reported.

If converting from immediate-release to extended-release dosage form, initial dose of extended-release should match the total daily dose of the immediate-release dosage and be administered once daily. Adjust dose as needed with the recommended dosage guidelines.

Reduce maintenance dose in renal failure. Reduce all doses (initial, escalation, and maintenance) in liver dysfunction defined by the Child-Pugh grading system as follows:
Grade B: moderate dysfunction, decrease dose by ~50%
Grade C: severe dysfunction, decrease dose by ~75%

Withdrawal symptoms may occur if discontinued suddenly. A stepwise dose reduction over ≥2 wk (~50% per week) is recommended unless safety concerns require a more rapid withdrawal.

Lamotrigine is metabolized by uridine 5′- diphospho-glucuronyl transferases (UGT). Strong and moderate inducers of CYP 450 3A4 are known to induce UGT to increase lamotrigine clearance. Acetaminophen, carbamazepine, oral contraceptives (ethinylestradiol), phenobarbital, primidone, phenytoin, and rifampin may decrease levels of lamotrigine. Valproic acid may increase levels. False positive urine drug screen for phencyclidine (PCP) has been reported.

Safety and efficacy for maintenance therapy for bipolar disorder in 10–17 yr olds were not established in a RCT in 301 subjects.

Continued

For explanation of icons, see p. 667

LANSOPRAZOLE
Prevacid, Prevacid SoluTab, First-Lansoprazole, and generics
Gastric acid pump inhibitor

Caps, delayed-release: 15, 30 mg
Tabs, disintegrating delayed-release (Prevacid SoluTab): 15, 30 mg; contains aspartame
Oral suspension (First-Lansoprazole): 3 mg/mL (90, 150, 300 mL); contains benzyl alcohol

Neonate: 0.5–1.5 mg/kg/24 hr PO ÷ once daily–BID
Short-term treatment of GERD and erosive esophagitis, for up to 12 wk (see remarks):
infant ≥3 mo: 15 mg/24 hr ÷ once daily–BID
Child 1–11 yr (initial dose using fixed dosing):
≤30 kg: 15 mg PO once daily
>30 kg: 30 mg PO once daily
Subequent dosage increase (if needed): may be increased up to 30 mg PO BID after ≥2 wk of therapy without response at initial dose level.
Alternative weight based dosing:
Infant: 1–2 mg/kg/24 hr PO once daily
Child and adolescent: 0.7–3 mg/kg/24 hr PO ÷ once daily–BID; **max. dose:** 30 mg/24 hr
12 yr–adult:
GERD: 15 mg PO once daily for up to 8 wk
Erosive esophagitis: 30 mg PO once daily × 8–16 wk; maintenance dose: 15 mg PO once daily
Duodenal ulcer: 15 mg PO once daily × 4 wk; maintenance dose: 15 mg PO once daily
Gastric ulcer and NSAID induced ulcer: 30 mg PO once daily for up to 8 wk
Hypersecretory conditions: 60 mg PO once daily; dosage may be increased up to 90 mg PO BID, where doses >120 mg/24 hr are divided BID.

Common side effects include GI discomfort, headache, fatigue, rash, and taste perversion. Hypersensitivity reactions may result in anaphylaxis, angioedema, bronchospasm, interstitial nephritis, and urticaria. Prolonged use may result in vitamin $B_{(12)}$ deficiency (≥2 yr) or hypomagnesemia (>1 yr). Microscopic colitis resulting in watery diarrhea has been reported, and switching to an alternative proton-pump inhibitor may be beneficial in resolving diarrhea. Increased risk for fundic gland polys has been associated with long-term use >1 yr.

Drug is a substrate for CYP 450 2C19 and 3A3/4. Ultrarapid metabolizers of CYP 450 2C19 may experience reduced efficacy and may require a 4-fold higher dosage. Lansoprazole may decrease levels of itraconazole, ketoconazole, iron salts, mycophenolate, nelfinavir, and ampicillin esters; and increase the levels/effects of methotrexate, tacrolimus and warfarin. Theophylline clearance may be enhanced. **Reduce dose in severe hepatic impairment.** May be used in combination with clarithromycin and amoxicillin for *H. pylori* infections.

A multicenter, double blind, parallel-group study in infants (1 mo–1 yr) with GERD was no more effective than placebo.

Administer all oral doses before meals and 30 min prior to sucralfate. **Do not** crush or chew the granules (all dosage forms). Capsule may be opened and intact granules may be administered in an acidic beverage or food (e.g., apple or cranberry juice, apple sauce). **Do not** break or cut the orally disintegrating tablets. Use of oral disintegrating tablets dissolved in water has been reported to clog and block oral syringes and feeding tubes (gastric and jejunostomy). For IV use, use a 1.2 micron in-line filter.

LEVALBUTEROL
Xopenex, Xopenex HFA, and generics
Beta-2 adrenergic agonist

Prediluted nebulized solution: 0.31 mg in 3 mL, 0.63 mg in 3 mL, 1.25 mg in 3 mL (30s)
Concentrated nebulized solution: 1.25 mg/0.5 mL (0.5 mL) (30s)
Aerosol inhaler (MDI; Xopenex HFA and generics): 45 mCg/actuation (15 g delivers 200 doses)

Nebulizer:
≤4 yr: Start at 0.31 mg inhaled Q4–6 hr PRN; dose may be increased up to 1.25 mg Q4–6 hr PRN
5–11 yr: Start at 0.31 mg inhaled Q8 hr PRN; dose may be increased to 0.63 mg Q8 hr PRN
≥12 yr and adult: Start at 0.63 mg inhaled Q6–8 hr PRN; dose may be increased to 1.25 mg inhaled Q8 hr PRN
Aerosol inhaler (MDI):
≥4 yr and adult: 2 puffs Q4–6 hr PRN.
For use in acute exacerbations, more aggressive dosing may be employed.

R-isomer of racemic albuterol. Side effects include tachycardia, palpitations, tremor, insomnia, nervousness, nausea, and headache.
Clinical data in children demonstrate levalbuterol is as effective as albuterol with fewer cardiac side effects at equipotent doses (0.31–0.63 mg levalbuterol ~2.5 mg albuterol). However, when higher doses of levalbuerol (1.25 mg) were compared to 2.5 mg albuterol, changes in heart rate were similar.
More frequent dosing may be necessary in asthma exacerbation.

LEVETIRACETAM
Keppra, Keppra XR, Roweepra, Spritam, and generics
Anticonvulsant

Tabs: 250, 500, 750, 1000 mg
Extended release tabs (Keprra XR, Roweepra XR, and generics; see remarks): 500, 750 mg
Tabs, disintegrating (Spritam; see remarks): 250, 500, 750, 1000 mg
Oral solution: 100 mg/mL (480 mL); dye free and contains parabens
Injection: 100 mg/mL (5 mL); contains 45 mg sodium chloride and 8.2 mg sodium acetate trihydrate per 100 mg drug
Pre-mixed injection: 500 mg/100 mL in 0.82% sodium chloride, 1000 mg/100 mL in 0.75% sodium chloride, 1500 mg/100 mL in 0.54% sodium chloride

Partial seizures (adjunctive therapy; using immediate-release dosage forms and IV):
Infant (1–5 mo): Start at 7 mg/kg/dose PO/IV BID; increase by 7 mg/kg/dose BID every 2 wk as tolerated to the recommended dose of 21 mg/kg/dose BID. An average daily dose of 35 mg/kg/24 hr was reported in clinical trials.
Infant ≥6 mo–child 3 yr (>20 kg): Start at 10 mg/kg/dose PO/IV BID; increase by 10 mg/kg/dose BID every 2 wk as tolerated to the recommended dose of 25 mg/kg/dose BID. An average daily dose of 47 mg/kg/24 hr was reported in clinical trials.
Child 4–15 yr: Start at 10 mg/kg/dose PO/IV BID; increase by 10 mg/kg/dose BID every 2 wk as tolerated up to a **max. dose** of 30 mg/kg/dose BID or 3000 mg/24 hr. An average daily dose of 44 mg/kg/24 hr was reported in clinical trials.

Continued

For explanation of icons, see p. 667

LEVETIRACETAM *continued*

Partial seizures (adjunctive therapy; using immediate release dosage forms and IV, cont.):

Alternative dosing with oral tablets:

20–40 kg: Start at 250 mg PO BID; increase by 250 mg BID every 2 wk as tolerated up to a **maximum** of 750 mg BID.

>40 kg: Start at 500 mg PO BID; increase by 500 mg BID every 2 wk as tolerated up to a **maximum** of 1500 mg BID.

16 yr– adult: Start at 500 mg PO/IV BID; may increase by 500 mg/dose BID every 2 wk as tolerated up to a **max. dose** of 1500 mg BID.

Myoclonic seizure (adjunctive therapy; using immediate-release dosage forms and IV):

≥12 yr and adult: Start at 500 mg PO/IV BID; then increase dosage by 500 mg/dose BID every 2 wk as tolerated to reach the target dosage of 1500 mg BID.

Tonic-clonic seizure (primary generalized, adjunctive therapy; use immediate-release dosage forms and IV):

Child 6–15 yr: Start at 10 mg/kg/dose PO/IV BID; increase by 10 mg/kg/dose BID every 2 wk as tolerated to reach the target dosage of 30 mg/kg/dose BID.

Alternative fixed dosing with oral disintegrating tabs (Spritam):

20–40 kg: Start at 250 mg PO BID; increase by 250 mg BID every 2 wk as tolerated up to a **maximum** of 750 mg BID.

>40 kg: Start at 500 mg PO BID; increase by 500 mg BID every 2 wk as tolerated up to a **maximum** of 1500 mg BID.

16 yr– adult: Start at 500 mg PO/IV BID; then increase dosage by 500 mg/dose BID every 2 wk as tolerated to reach the target dosage of 1500 mg BID.

Refractory status epilepticus: (limited data):

Infant, child, and adolescent: 20 mg/kg (**max. dose**: 1500 mg/dose) IV over 15 min × 1, then start maintenance therapy based on clinical response and seizure type.

Do not abruptly withdraw therapy, to reduce risk for seizures. **Use with caution** in renal impairment **(reduce dose; see Chapter 31)** , hemodialysis, and neuropsychiatric conditions.

May cause loss of appetite, vomiting, dizziness, headaches, somnolence, agitation, depression, and mood swings. Drowsiness, fatigue, nervousness, and aggressive behavior have been reported in children. Nonpsychotic behavioral symptoms reported in children are approximately 3 times greater than in adults (37.6% vs. 13.3%). Suicidal behavior or ideation, serious dermatological reactions (e.g., Stevens Johnson and TEN), hematologic abnormalities (e.g., anemia, leukopenia), hyponatremia, and hypertension have been reported. Levetiracetam may decrease carbamazepine's effects. Ginkgo may decrease levetiracetam's effects.

Drug has excellent PO absorption. For IV use, use similar immediate-release PO dosages only when the oral route of administration is not feasible. Extended-release tablet is designed for once-daily administration at similar daily dosage of the immediate-release forms (e.g., 1000 mg once daily of the extended release tablet is equivalent to 500 mg BID of the immediate release tablet). Disintegrating tabs (Spritam) may be administered by allowing the tablet to disintegrate in the mouth when taken with a sip of liquid or made into a suspension (see package insert); **do not** swallow this dosage form whole.

LEVOCARNITINE

See Carnitine

LEVOFLOXACIN
Levaquin and generics
Antibiotic, quinolone

Tabs: 250, 500, 750 mg
Oral solution: 25 mg/mL (100, 200, 480 mL)
Injection: 25 mg/mL (20, 30 mL)
Pre-mixed injection in D_5W: 250 mg/50 mL, 500 mg/100 mL, 750 mg/150 mL
Ophthalmic drops (genericis previously available as Quixin): 0.5% (5 mL)

Child:
6 mo–<5 yr: 10 mg/kg/dose IV/PO Q12 hr; **max. dose:** 500 mg/24 hr
≥5 yr: 10 mg/kg/dose IV/PO Q24 hr; **max. dose:** 750 mg/24 hr
Recurrent or persistent acute otitis media (6 mo–<5 yr): 10 mg/kg/dose PO Q12 hr ×10 days; **max. dose:** 500 mg/24 hr
Community acquired pneumonia (IDSA/Pediatric Infectious Disease Society):
6 mo–<5 yr: 8–10 mg/kg/dose PO/IV Q12 hr; **max. dose:** 750 mg/24 hr
5–16 yr: 8–10 mg/kg/dose PO/IV Q24 hr; **max. dose:** 750 mg/24 hr
Inhalational anthrax (postexposure) and plague:
≥6 mo and <50 kg: 8 mg/kg/dose PO/IV Q12 hr; **max. dose**: 500 mg/24 hr
>50 kg: 500 mg PO/IV once daily
Duration of therapy:
Inhalational anthrax (postexposure): 60 days
Plague: 10–14 days
Adult:
Community acquired pneumonia: 500 mg PO/IV Q24 hr × 7–14 days; OR 750 mg PO/IV Q24 hr × 5 days
Complicated UTI/acute pyelonephritis: 750 mg PO/IV Q24 hr × 5–7 days
Acute bacterial sinusitis: 500 mg PO/IV Q24 hr × 10–14 days; OR 750 mg PO/IV Q24 hr × 5 days
Inhalational anthrax (post-exposure): 750 mg PO/IV Q24 hr × 60 days
Plague: 500 mg PO/IV Q24 hr × 10–14 days
Conjunctivitis:
≥1 yr and adult: Instill 1–2 drops of the 0.5% solution to affected eye(s) Q2 hr up to 8 times/24 hr while awake for the first 2 days, then Q4 hr up to 4 times/24 hr while awake for the next 5 days.

Contraindicated in hypersensitivity to other quinolones. **Avoid** in patients with history of QTc prolongation or taking QTc prolonging drugs, and excessive sunlight exposure. **Use with caution** in diabetes, seizures, myasthenia gravis, children <18 yr, and renal impairment **(adjust dose, see Chapter 31).** May cause GI disturbances, headache, and blurred vision with the ophthalmic solution. Musculoskeletal disorders (e.g., arthralgia, arthritis, tendinopathy, and gait abnormality) may occur. Peripheral neuropathy and uveitis have been reported. Safety in pediatric patients treated more than 14 days has not been evaluated. Like other quinolones, tendon rupture can occur during or after therapy (risk increases with concurrent corticosteroids). Psychiatric adverse events, increased intracranial pressure, seizures, and blood glucose disturbances have been reported. Use with NSAIDs may increase risk of CNS stimulation and seizures.

Infuse IV over 1–1.5 hr; **avoid** IV push or rapid infusion because of risk of hypotension. **Do not** administer antacids or other divalent salts with or within 2 hr of oral levofloxacin dose; otherwise may be administer with or without food.

For explanation of icons, see p. 667

LEVOTHYROXINE (T_4)
Synthroid, Levoxyl, Tirosint, Tirosint-Sol, Unithroid, Unithroid Direct, and generics
Thyroid product

Tabs: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mCg
Caps (Tirosint): 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 mCg
Injection: 100, 200, 500 mCg; preservative free
Oral solution (Tirosint-Sol): 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 mCg/1 mL (30 ampules per box)
Oral suspension: 25 mCg/mL

Hypothyroidism:
Child PO dosing (see remarks):
1–3 mo: 10–15 mCg/kg/dose once daily. If patient is at risk for developing cardiac failure start with lower dose of 25 mCg/24 hr; and if patient has very low T_4 (<5 mCg/dL) use higher 12–17 mCg/kg/24 hr dose.
3–6 mo: 8–10 mCg/kg/dose once daily
6–12 mo: 6–8 mCg/kg/dose once daily
1–5 yr: 5–6 mCg/kg/dose once daily
6–12 yr: 4–5 mCg/kg/dose once daily
>12 yr:
Incomplete growth and pre-puberty: 2–3 mCg/kg/dose once daily
Complete growth and puberty: 1.7 mCg/kg/dose once daily
Child IM/IV dose: 50%–75% of oral dose once daily
Adult:
PO: Start with 12.5–25 mCg/dose once daily. Increase by 25–50 mCg/24 hr at intervals of Q2–4 wk until euthyroid. Usual adult dose: 100–200 mCg/24 hr.
IM/IV dose: 50% of oral dose once daily
Myxedema coma or stupor:
Adult: 200–400 mCg IV × 1, then 50–100 mCg IV once daily; convert to oral therapy once patient is stabilized.

Contraindications include acute MI, thyrotoxicosis, and uncorrected adrenal insufficiency. May cause hyperthyroidism, rash, growth disturbances, hypertension, worsening of diabetic control, decreased bone mineral density (primarily in post-menopausal females), arrhythmias, diarrhea, and weight loss. Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children. Overtreatment may cause craniosynostosis in infants and premature closure of the epiphyses in children.

Total replacement dose may be used in children unless there is evidence of cardiac disease; in that case, begin with one-fourth of maintenance and increase weekly. Titrate dosage with clinical status and serum T_4 and TSH.

Increases the effects of warfarin. Phenytoin, rifampin, carbamazepine, iron and calcium supplements, antacids, grapefruit juice, and orlistat may decrease levothyroxine levels. Tricyclic antidepressants and SSRIs may enhance toxic effects. Use with ketamine may cause hypertension and tachycardia. High doses of propranolol or dexamethasone, and amiodarone may decrease the conversion of T_4 to T_3.

100 mCg levothyroxine = 65 mg thyroid USP. Administer oral doses on an empty stomach and tablets with a full glass of water. Iron and calcium supplements and antacids may decrease absorption; **do not** administer within 4 hr of these agents. Excreted in low levels in breast milk; preponderance of evidence suggests no clinically significant effect in infants.

LIDOCAINE
Xylocaine, L-M-X, Lidoderm, and generics
Anti-arrhythmic class Ib, local anesthetic

Injection: 0.5%, 1%, 1.5%, 2%, 4% (1% sol = 10 mg/mL)
IV infusion (in D_5W): 0.4% (4 mg/mL) (250, 500 mL); 0.8% (8 mg/mL) (250 mL)
Injection with epinephrine (some preparations may contain metasulfite and parabens or are preservative free):
Injection with 1:100,000 epinephrine: 1%, 2% lidocaine
Injection with 1:200,000 epinephrine: 0.5%, 1%, 1.5%, 2% lidocaine
Ointment: 5% (30, 50 g)
Cream, topical: 3% (30, 85 g), 4% (L-M-X-4 and generics)[OTC] (5, 15, 30, 45 g), 5% (L-M-X-5 and generics) (15, 30 g); may contain benzyl alcohol
Cream, rectal: 5% (L-M-X-5 and others; 15, 30 g); contains benzyl alcohol
Gel (external): 2% (5, 10, 20, 30 mL), 3% (10, 30 mL), 4% (10, 30 , 113 g), 5% (10, 30, 113 g); may contain benzyl alcohol, EDTA
Lotion: 3% (118, 177 mL), 4% (88 mL)
Solution (external): 4% (50 mL); may contain parabens
Transdermal patch:
Lidocaine Pain Relief and generics [OTC]: 4% (5s, 10s); may contain menthol, capsaicin, and methyl salicylate
Lidoderm and generics: 5% (1s, 15s, 30s)
Oral solution (mouth/throat): 2% (15, 100 mL), 4% (4 mL)
Topical cream or gel 2.5% with 2.5% prilocaine: See Lidocaine and Prilocaine

Anesthetic:
Injection (local): Use <2% concentration. Dosage varies with procedure, degree and duration of analgesia, tissue vascularity, and patient condition.
Without epinephrine: **max. dose** of 4.5 mg/kg/dose (up to 300 mg); do not repeat within 2 hr.
With epinephrine: **max. dose** of 7 mg/kg/dose (up to 500 mg); do not repeat within 2 hr.
Topical:
Cream (child ≥2 yr and adult): Apply to affected intact skin areas BID–QID; **max. dose**: 4.5 mg/kg/dose up to 300 mg
Gel, lotion, or ointment (child ≥2 yr and adult): Apply to affected intact skin areas once daily–QID (BID–TID for lotion); **max. dose**: 4.5 mg/kg up to 300 mg
Patch:
4% (≥12 yr and adult): Apply patch to painful area and leave in place for up to 12 hr. **Max. dose**: one patch/24 hr.
5% (adult): Apply to most painful area with up to 3 patches at a time. Patch(es) may be left in place for up to 12 hr in any 24 hr period.
Antiarrhythmic (infant, child, adolescent):
Bolus: 1 mg/kg/dose (**max. dose**: 100 mg) slowly IV; may repeat in 10–15 min × 2; **max. total dose** 3–5 mg/kg within the first hr. ETT dose = 2–3 × IV dose.
Continuous infusion: 20–50 mCg/kg/min IV/IO (**do not exceed** 20 mCg/kg/min for patients with shock, CHF, hepatic disease, or cardiac arrest); see inside cover for infusion preparation. Administer a 1 mg/kg bolus when infusion is initiated if bolus has not been given within previous 15 min.
Oral use (viscous liquid):
Child (≥3 yr): up to the lesser of 4.5 mg/kg/dose or 300 mg/dose, swish and spit Q3 hr PRN up to a **max. dose** of 4 doses per 12 hr period
Adult: 15 mL, swish and spit Q3 hr PRN up to a **max. dose** of 8 doses/24 hr

Continued

For explanation of icons, see p. 667

LIDOCAINE *continued*

For cardiac arrest, amiodarone is the preferred agent over lidocaine; lidocaine may used only when amiodarone is not available.

Contraindicated in Stokes-Adams or Wolff-Parkinson-White syndromes and SA, AV, or intraventricular heart block without a pacemaker. Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products. Side effects include hypotension, asystole, seizures, and respiratory arrest. Anaphylaxic reactions have been reported. Local anesthetic use has been associated with methemoglobinemia.

CYP 450 2D6 and 3A3/4 substrate. **Use with caution** in severe liver or renal disease. Decrease dose in hepatic failure or decreased cardiac output. **Do not use** topically for teething. Prolonged infusion may result in toxic accumulation of lidocaine, especially in infants. **Do not use** epinephrine-containing solutions for treatment of arrhythmias.

Therapeutic levels 1.5–5 mg/L. Toxicity occurs at >7 mg/L. Toxicity in neonates may occur at >5 mg/L due to reduced protein binding of drug. Elimination $T_{1/2}$: premature infant: 3.2 hr, adult: 1.5–2 hr.

When using the topical patch, **avoid** exposing the application site to external heat sources as this may increase the risk for toxicity.

LIDOCAINE AND PRILOCAINE

Many brand names, Oraqix, Eutectic mixture of lidocaine and prilocaine; previously available as EMLA

Topical analgesic

Cream: Lidocaine 2.5% + prilocaine 2.5% (5, 30 g)

Peridontal gel (Oraqix): Lidocaine 2.5% + prilocaine 2.5% (1.7 g in dental cartridges; 20s)

See Chapter 6, for general use information.

Neonate:

<37 wk gestation (limited data):

Painful procedures (e.g., IM injections): 0.5 g/site for 60 min.

≥37 wk gestation and <5 kg:

Painful procedures (e.g., IM injections): 1 g/site for 60 min. **Max. dose**: 1 g for all sites combined with a **max.** application area of 10 cm^2 and **max.** application time of 1 hr.

Circumcision: 1–2 g and cover with occlusive dressing for 60–90 min.

Infant and child: The following are the recommended **maximum doses** based on the child's age and weight.

Age and Weight	Maximum Total EMLA Dose (g)	Maximum Application Area (cm^2)	Maximum Application Time
Birth–<3 mo or <5 kg	1	10	1 hr
3–12 mo and >5 kg[a]	2	20	4 hr
1–6 yr and >10 kg	10	100	4 hr
7–12 yr and >20 kg	20	200	4 hr

[a]If patient is >3 mo and is not >5 kg, use the **maximum** total dose which corresponds to the patient's weight.
EMLA, Eutectic mixture of local anesthetics.

Adolescent and adult:

Minor procedures: 2.5 g/site over 20–25 cm^2 of skin for at least 60 min.

Painful procedures: 2 g/10 cm^2 of skin for at least 2 hr.

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LIDOCAINE AND PRILOCAINE *continued*

Should not be used in neonates <37 wk of gestation or in infants <12 mo old receiving treatment with methoglobin-inducing agents (e.g., sulfa drugs, acetaminophen, nitrofurantoin, nitroglycerin, nitroprusside, phenobarbital, phenytoin). **Use with caution** in patients with G6PD deficiency, patients treated with class I or III anti-arrhythmic drugs (additive or toxic cardiac effects), and in patients with renal and hepatic impairment. Prilocaine has been associated with methemoglobinemia. Long duration of application, large treatment area, small patients, or impaired elimination may result in high blood levels.

Apply topically to intact skin and cover with occlusive dressing; **avoid** mucous membranes or the eyes. Wipe cream off before procedure.

LINDANE

Gamma benzene hexachloride, and various generics

Scabicidal agent, pediculocide

Shampoo: 1% (60 mL)

Lotion: 1% (60 mL)

Child and adult (see remarks):

Scabies: Apply thin layer of lotion to skin from the neck to toes. Most patients will require 30 mL and larger patient may require the **maximum** dose of 60 mL. Bathe and rinse off medication in adults after 8–12 hr; children 6–8 hr. Do not re-treat.

Pediculosis capitis: Apply ≤30 mL (amount depends on length and density of hair; **max. dose:** 60 mL) shampoo to dry hair without adding water. Work shampoo thoroughly into hair and allow to remain in place for 4 min. Then add small amounts of water to the hair until a good lather forms. Immediately rinse all the lather away and **avoid** contact of lather to other body surfaces. Towel dry and comb hair with fine-tooth comb to remove nits. Do not re-treat.

Pediculosis pubis: May use lotion or shampoo (applied locally) as for scabies and pediculosis capitis (see above).

Contraindicated in premature infants and seizure disorders. **Use with caution** with drugs that lower seizure threshold. Systemically absorbed. Risk of toxic effects is greater in young children; use other agents (permethrin) in infants, young children (<2 yr), and during pregnancy. Lindane is considered second-line therapy owing to side-effect risk and reports of resistance.

May cause a rash; rarely may cause seizures or aplastic anemia. For scabies, change clothing and bed sheets after starting treatment and treat family members. For pediculosis pubis, treat sexual contacts.

Avoid contact with face, urethral meatus, damaged skin, or mucous membranes. **Do not use** any covering that does not breathe (e.g., plastic lining or clothing) over the applied lindane.

LINEZOLID

Zyvox and generics

Antibiotic, oxazolidinone

Tabs: 600 mg; contains ~0.45 mEq Na per 200 mg drug

Oral suspension: 100 mg/5 mL (150 mL); contains phenylalanine and sodium benzoate and 0.8 mEq Na per 200 mg drug

Injection, premixed: 200 mg in 100 mL, 600 mg in 300 mL; contains 1.7 mEq Na per 200 mg drug

Continued

For explanation of icons, see p. 667

LINEZOLID *continued*

Neonate:

<1 kg:

<14 days old: 10 mg/kg/dose IV Q12 hr

≥14 days old: 10 mg/kg/dose IV Q8 hr

≥1–2 kg:

<7 days old: 10 mg/kg/dose IV/PO Q12 hr

≥7–28 days old: 10 mg/kg/dose IV/PO Q8 hr

>2 kg: 10 mg/kg/dose IV/PO Q8 hr

Alternate dosing by gestational age:

<34 wk gestation:

<7 days old: 10 mg/kg/dose IV/PO Q12 hr

≥7–28 days old: 10 mg/kg/dose IV/PO Q8 hr

≥34 wk gestation and 0–28 days old: 10 mg/kg/dose IV/PO Q8 hr

Infant and child <12 yr old:

Pneumonia, bacteremia, bone/joint infections, septic thrombosis (MRSA), complicated skin/skin structure infections, vancomycin-resistant* E. faecium *(VRE) infections (including endocarditis): 10 mg/kg/dose IV/PO Q8 hr.

Uncomplicated skin/skin structure infections:

<5 yr: 10 mg/kg/dose IV/PO Q8 hr

5–11 yr: 10 mg/kg/dose IV/PO Q12 hr

Max. dose for all indications <12 yr: 600 mg/dose

≥12 yr and adult: 600 mg Q12 hr IV/PO; 400 mg Q12 hr IV/PO may be used for adults with uncomplicated infection.

Duration of therapy:

MRSA infections: variable based on response

Pneumonia: 10–14 days for non-MRSA and 7–21 days (per clinical response) for MRSA

Bacteremia: 10–28 days

Bone/joint infections: 3–6 wk

Skin/skin structure infections: 10–14 days; longer for complicated cases

Septic thrombosis (MRSA): 4–6 wk

VRE infections: 14–28 days, minimum of 8 wk for endocarditis

Most common side effects include diarrhea, headache, and nausea. Anemia, leukopenia, pancytopenia, thrombocytopenia may occur in patients who are at risk for myelosuppression and who receive regimens >2 wk. Complete blood count monitoring is recommended in these individuals. Pseudomembranous colitis, neuropathy (peripheral and optic), and severe cutaneous adverse reactions (e.g., TEN and SJS) have also been reported. CSF penetration is variable in patients with VP shunts.

Do not use with SSRIs (e.g., fluoxetine, paroxetine), tricyclic antidepressants, venlafaxine, and trazodone; may cause serotonin syndrome. **Avoid** use with monoamine oxidase inhibitors (e.g., phenelzine); and in patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis, and taking sympathomimetics or vasopressive agents (may elevate blood pressure). **Use caution** when consuming large amounts of foods and beverages containing tyramine; may increase blood pressure. Dosing information in severe hepatic failure and renal impairment with multi-doses have not been completed.

Protect all dosage forms from light and moisture. Oral suspension product must be gently mixed by inverting the bottle 3–5 times prior to each use **(do not shake).** All oral doses may be administered with or without food.

LISDEXAMFETAMINE
Vyvanse
CNS stimulant

Capsules: 10, 20, 30, 40, 50, 60, 70 mg
Chewable tabs: 10, 20, 30, 40, 50, 60 mg; contains mannitol and sucralose

Attention deficit hyperactivity disorder:
Child ≥6 yr and adult: Start with 20–30 mg PO QAM (adult start at 30 mg). May increase dose by 10–20 mg/24 hr at weekly intervals if needed, up to a **max. dose** of 70 mg/24 hr. Lower maximum dosages for renal insufficiency include the following:
GFR ≥30 mL/min/1.73 m²: 70 mg/24 hr
GFR 15–<30 mL/min/1.73 m²: 50 mg/24 hr
GFR <15 mL/min/1.73 m² or ESRD on hemodialysis: 30 mg/24 hr

Lisdexamfetamine is a pro-drug of dextroamphetamine which requires activation by intestinal/hepatic metabolism.
Contraindicated in amphetamine or sympathomimetic hypersensitivity, symptomatic cardiovascular disease, moderate/severe hypertension, hyperthyroidism, glaucoma, agitated states, drug/alcohol abuse history, and MAO inhibitors (concurrent or use within 14 days). As with other CNS simulant medications, serious cardiovascular events, including **death**, have been reported in patients with preexisting structural cardiac abnormalities or other serious heart problems. **Use with caution** in patients with hypertension, psychiatric conditions, and epilepsy. May cause insomnia, irritability, rash, appetite suppression/weight loss, dizziness, xerostomia, and GI disturbances. Dermatillomania, bruxism, Stevens-Johnson syndrome, and TEN have been reported.
Urinary acidifying agents may reduce levels of amphetamines and urinary alkalinizing agent may increase levels. May increase the effects of TCAs; increase or decrease the effects of guanfacine and phenytoin, and phenobarbital; and decrease the effects of adrenergic blockers, antihistamines, and antihypertensives. Norepinephrine may increase the effects of amphetamines.
Chewable tablets must be completely chewed before swallowing. Chewable tablet and capsule dosage forms can be converted on an equal mg-per-mg basis.
See Dextroamphetamine ± Amphetamine for additional remarks.

LISINOPRIL
Prinivil, Qbrelis, Zestril, and generics
Angiotensin converting enzyme inhibitor, antihypertensive

Tabs: 2.5, 5, 10, 20, 30, 40 mg
Oral solution (Qbrelis): 1 mg/mL (150 mL); contains sodium benzoate
Oral suspension: 1 mg/mL, 2 mg/mL

Hypertension (see remarks):
Child (<6 yr; limited data): use 6–16 yr dosing below.
6–16 yr: Start with 0.07–0.1 mg/kg/dose PO once daily; **max. initial dose:** 5 mg/dose. If needed, titrate dose upward at 1–2 wk intervals to doses up to 0.61 mg/kg/24 hr or 40 mg/24 hr (higher doses have not been evaluated).
Adult: Start with 10 mg PO once daily (use 5 mg if using a diuretic). If needed, increase dose by 5–10 mg/24 hr at 1–2 wk intervals. Usual dosage range: 10–40 mg/24 hr. **Max. dose:** 80 mg/24 hr.

Continued

For explanation of icons, see p. 667

LISINOPRIL *continued*

Use lower initial dose (50% of recommended dose) if using with a diuretic or with the presence of hyponatremia, hypovolemia, severe CHF, or decreased renal function.

Contraindicated in hypersensitivity and history of angioedema with other ACE inhibitors, and in combination with a neprilysin inhibitor (e.g., sacubitril). **Do not use** with aliskiren in patients with diabetes. **Avoid** use with dialysis with high-flux membranes because anaphylactoid reactions have been reported. **Use with caution** in aortic or bilateral renal artery stenosis, and hepatic impairment. Side effects include cough, dizziness, headache, hyperkalemia, hypotension (especially with concurrent diuretic or antihypertensive agent use), rash, and GI disturbances. Mood alterations, including depressive symptoms, have been reported.

Dual blockade of the renin-angiotensin system with lisinopril and angiotensin receptor antagonists (e.g., losartin) or aliskiren is associated with increased risk for hypotension, syncope, hyperkalemia, and renal impairment. Diabetic patients on lisinopril treated with oral antidiabetic agents should be monitored for hypoglycemia, especially during the first month of use. NSAIDs (e.g., indomethacin) may decrease linsinopril's effects. Use with mTOR inhibitors (e.g., sirolimus, everolimus) may increase risk for angioedema. **Adjust dose in renal impairment (see Chapter 31).**

Onset of action: 1 hr with maximal effect in 6–8 hr. Long-term blood pressure monitoring is recommended at Q2–4 wk until good control is achieved, followed by Q3–4 mo.

Additional indications with limited data in children include proteinuria associated with mild IgA nephropathy, and renal protection for diabetes or renal parenchymal disease.

Lisinopril should be discontinued as soon as possible when pregnancy is detected.

LITHIUM

Lithobid and many generics; previously available as Eskalith

Antimanic agent

Carbonate salt:

300 mg carbonate = 8.12 mEq lithium

Caps: 150, 300, 600 mg

Tabs: 300 mg

Extended-release tabs: 300 mg (Lithobid and generics), 450 mg

Citrate salt:

Syrup: 8 mEq/5 mL (500 mL); 5 mL is equivalent to 300 mg lithium carbonate

Child (see remarks):

Initial (immediate release dosage forms): 15–60 mg/kg/24 hr ÷ TID–QID PO. Adjust as needed (weekly) to achieve therapeutic levels.

Adolescent: 600–1800 mg/24 hr ÷ TID–QID PO (divided BID–TID using extended-release tablets).

Adult:

Initial: 300 mg TID PO. Adjust as needed to achieve therapeutic levels. Usual dose is about 300 mg TID–QID with immediate release dosage form. For extended-release tablets, 900–1800 mg/24 hr PO ÷ BID–TID.

Contraindicated in severe cardiovascular disease (including Brugada syndrome) or renal disease. Decreased sodium intake or increased sodium wasting, significant renal or cardiovascular disease, may increase lithium levels, resulting in toxicity. May cause goiter, nephrogenic diabetes insipidus, hypothyroidism, arrhythmias, or sedation at therapeutic doses. Nephrotic syndrome has been reported.

Co-administration with diuretics, metronidazole, ACE inhibitors, angiotensin receptor antagonists (e.g., losartan), or NSAIDs may increase risk for lithium toxicity. Use with iodine may increase risk for hypothyroidism. If used in combination with haloperidol, closely monitor neurologic toxicities by irreversible brain damage has been reported.

LITHIUM *continued*

Safety and efficacy for monotherapy for acute mania or mixed episodes of bipolar I disorder and maintenance monotherapy of bipolar I disorder in children 7–17 yr have been established from a clinical trial. Common adverse effects observed in this study included nausea/vomiting, polyuria, thyroid abnormalities, tremor, polydipsia, dizziness, rash/dermatitis, ataxia/gait disturbance, anorexia, and blurry vision.

Therapeutic levels: 0.6–1.5 mEq/L. In either acute or chronic toxicity, confusion and somnolence may be seen at levels of 2–2.5 mEq/L. **Seizures or death** may occur at levels >2.5 mEq/L. Recommended serum sampling: trough level within 30 min prior to the next scheduled dose. Steady-state is achieved within 4–6 days of continuous dosing. **Adjust dose in renal failure (see Chapter 31).**

LODOXAMIDE
Alomide
Antiallergic agent, mast cell stabilizer

Ophthalmic solution: 0.1% (10 mL); contains benzalkonium chloride

≥2 yr and adult: Instill 1–2 drops to affected eye(s) QID for up to 3 mo.

Transient burning, stinging or discomfort of the eye and headache are common side effects. Itching/pruritus, blurred vision, dry eye, tearing, hyperemia, crystalline deposits, and foreign body sensation may also occur.

Do not wear soft contact lenses during treatment because medication contains benzalkonium chloride.

LOPERAMIDE
Imodium, Imodium A–D, and generics
Antidiarrheal

Caps (OTC): 2 mg
Tabs (OTC): 2 mg
Oral suspension (OTC): 1 mg/7.5 mL (120 mL); each 30 mL contains 16 mg of sodium

Acute diarrhea (see remarks):
Child (initial doses within the first 24 hr):
2–5 yr (13–<21 kg): 1 mg PO TID
6–8 yr (21–27 kg): 2 mg PO BID
9–11 yr (>27–43 kg): 2 mg PO TID
Max. single dose 2 mg
Follow initial day's dose with 0.1 mg/kg/dose after each loose stool (not to exceed the aforementioned initial doses).
≥12 yr and adult: 4 mg/dose × 1, followed by 2 mg/dose after each stool up to **max. dose** of 8 mg/24 hr for 12–<18 yr and 16 mg/24 hr for adult.
Chronic diarrhea (see remarks):
Infant–child (limited data): 0.08–0.24 mg/kg/24 hr PO ÷ BID–TID; **max. dose**: 2 mg/dose

Continued

For explanation of icons, see p. 667

LOPERAMIDE *continued*

Contraindicated in acute dysentery; acute ulcerative colitis; bacterial enterocolitis caused by *Salmonella, Shigella, Campylobacter and Clostidium difficile;* and abdominal pain in the absence of diarrhea. **Avoid** use in children <2 yr due to reports of paralytic ileus associated with abdominal distention. Rare hypersensitivity reactions including anaphylactic shock have been reported. May cause nausea, rash, vomiting, constipation, cramps, dry mouth, and CNS depression. Use of higher than recommended dosages via abuse or misuse can cause serious cardiac events (e.g., Torsades de Pointes, arrhythmias, cardiac arrest, and QT prolongation).

Discontinue use if no clinical improvement is observed within 48 hr. Naloxone may be administered for CNS depression.

LORATADINE ± PSEUDOEPHEDRINE

Alavert, Claritin, Claritin Children's Allergy, Claritin RediTabs
In combination with pseudoephedrine:
Claritin-D 12 Hour, Claritin-D 24 Hour, Alavert Allergy and Sinus, Loratadine-D 12 Hour, Loratadine-D 24 Hour, Allergy Relief-D, and generics
Antihistamine, less sedating ± decongestant

Tabs [OTC]: 10 mg
Chewable tabs (Claritin Children's Allergy) [OTC]: 5 mg; contains aspartame
Disintegrating tabs (Claritin RediTabs and others) [OTC]: 5, 10 mg; contains aspartame
Oral solution or syrup [OTC]: 1 mg/mL (120 mL); contains propylene glycol and sodium benzoate; some preparations may contain metasulfite
Time-release tabs in combination with pseudoephedrine (PE):
Claritin-D 12 Hour, Alavert Allergy and Sinus, Loratadine-D 12 Hour, and generics [OTC]: 5 mg loratadine + 120 mg PE
Claritin-D 24 Hour, Loratadine-D 24 Hour, Allergy Relief-D and generics [OTC]: 10 mg loratadine + 240 mg PE

Loratadine:
2–5 yr: 5 mg PO once daily
≥6 yr and adult: 10 mg PO once daily. Disintegrating tablet may be dosed at 5 mg PO BID or 10 mg PO once daily.
Time-release tabs of loratidine and pseudoephedrine:
≥12 yr and adult (see remarks):
Claritin-D 12 Hour and generics: 1 tablet PO BID
Claritin-D 24 Hour and generics: 1 tablet PO once daily

May cause drowsiness, fatigue, dry mouth, headache, bronchospasams, palpitations, dermatitis, and dizziness. Has not been implicated in causing cardiac arrhythmias when used with other drugs that are metabolized by hepatic microsomal enzymes (e.g., ketoconazole, erythromycin). May be administered safely in patients who have allergic rhinitis and asthma.

In hepatic and renal function impairment (GFR <30 mL/min), prolong loratadine (single agent) dosage interval to every other day. **Adjust dose in renal failure (see Chapter 31).**

For time-release tablets of the combination product (loratadine and pseudoephedrine), prolong dosage interval in renal impairment (GFR <30 mL/min) as follows: Claritin-D 12 Hour: 1 tablet PO once daily; Claritin-D 24 Hour: 1 tablet PO every other day. **Do not** use the combination product in hepatic impairment because drugs cannot be individually titrated.

Administer doses on an empty stomach. For use of RediTabs, place tablet on tongue and allow it to disintegrate in the mouth with or without water. For Claritin-D products, also see remarks in Pseudoephedrine.

D

LORAZEPAM
Ativan and generics
Benzodiazepine anticonvulsant

Tabs: 0.5, 1, 2 mg
Injection: 2, 4 mg/mL (1, 10 mL); each contains 2% benzyl alcohol and propylene glycol
Oral solution: 2 mg/mL (30 mL); some dosage forms may be alcohol and dye free

Status epilepticus (IV route is preferred but may use IM route if IV is not available):
Neonate, infant, child, and adolescent: 0.05–0.1 mg/kg/dose IV over 2–5 min. May repeat dose in 10–15 min. **Max. dose**: 4 mg/dose. If IV access not available, 0.1 mg/kg/dose (**max.** 4 mg/dose) may be administered intranasally.
Adult: 4 mg/dose IV given slowly over 2–5 min. May repeat in 10–15 min. Usual total **max. dose** in 12-hr period is 8 mg.
Antiemetic adjunct therapy:
Child: 0.02–0.05 mg/kg/dose IV Q6 hr PRN; **max. single dose**: 2 mg.
Anxiolytic/sedation:
Infant and child: 0.05 mg/kg/dose Q4–8 hr PO/IV; **max. dose**: 2 mg/dose
May also give IM for preprocedure sedation.
Adult: 1–10 mg/24 hr PO ÷ BID–TID

Contraindicated in narrow-angle glaucoma and severe hypotension. **Use with caution** in renal insufficiency (glucoronide metabolite clearance is reduced), hepatic insufficiency (may worsen hepatic encephalopathy; decrease dose with severe hepatic impairment), compromised pulmonary function, and use of CNS depressant medications. May cause respiratory depression, especially in combination with opioids and other sedatives. May also cause sedation, dizziness, mild ataxia, mood changes, rash, and GI symptoms. Paradoxical excitation has been reported in children (10%–30% of patients <8 yr old).
When compared to diazepam for status epilepticus (3 mo–17 yr), lorazepam was found to be more sedating with a longer time to return to baseline mental status.
Significant respiratory depression and/or hypotension has been reported when used in combination with loxapine. Probenecid and valproic acid may increase the effects/toxicity of lorazepam and oral contraceptive steroids may decrease lorazepam's effects.
Injectable product may be given rectally. Benzyl alcohol and propylene glycol may be toxic to newborns at higher doses.
Onset of action for sedation: PO, 20–30 min; IM, 30–60 min; IV, 1–5 min. Duration of action: 6–8 hr.
Flumazenil is the antidote.

LOSARTAN
Cozaar and generics
Angiotensin II receptor antagonist

Tabs: 25, 50, 100 mg
Oral suspension: 2.5 mg/mL
Contains 2.12 mg potassium per 25 mg drug

Hypertension (see remarks):
6–16 yr: Start with 0.7 mg/kg/dose (**max. dose**: 50 mg/dose) PO once daily. Adjust dose to desired blood pressure response. **Max. dose** (higher doses have not been evaluated): 1.4 mg/kg/24 hr or 100 mg/24 hr.

For explanation of icons, see p. 667

LOSARTAN *continued*

Hypertension (see remarks; cont.):

≥17 yr and adult: Start with 50 mg PO once daily (use lower initial dose of 25 mg PO once daily if patient receiving diuretics, experiencing intravascular volume depletion, or has hepatic impairment). Usual maintenance dose is 25–100 mg/24 hr PO ÷ once daily–BID

Use with caution in angioedema (current or past), excessive hypotension (volume depletion), hepatic (use lower starting dose) or renal (contains potassium) impairment, hyperkalemia (including use with medications that can cause hyperkalemia), renal artery stenosis and severe CHF. Not recommended in patients <6 yr or in children with GFR <30 mL/min/1.73 m^2, owing to lack of data.

Discontinue use as soon as possible when pregnancy is detected because injury and death to developing fetus may occur. Pregnancy category is "C" during the first trimester but changes to "D" for the second and third trimesters.

Diarrhea, asthenia, dizziness, fatigue, and hypotension are common. Thrombocytopenia, rhabdomyolysis, hallucinations, and angioedema have been rarely reported.

Losartan is a substrate for CYP 450 2C9 (major) and 3A4. Fluconazole and cimetidine may increase losartan effects/toxicity. Rifampin, phenobarbital, and indomethacin may decrease its effects. Losartan may increase the risk of lithium toxicity. **Do not use** with aliskiren in patients with diabetes or with renal impairment (GFR <60 mL/min). Dual blockade of the renin-angiotensin system with losartin and ACE inhibitors (e.g., captopril) or aliskiren is associated with increased risk for hypotension, syncope, hyperkalemia, and renal impairment.

LOW MOLECULAR WEIGHT HEPARIN

See Enoxaparin

LUCINACTANT

See Surfactant, pulmonary

LUMACAFTOR AND IVACAFTOR

Orkambi

Cystic Fibrosis Transmembrane Conductance Regulator Corrector and Potentiator

Oral granules (Lumacaftor: Ivacaftor): 100 mg:125 mg (56 packets), 150 mg: 188 mg (56 packets)
Tabs (Lumacaftor:Ivacaftor): 100 mg:125 mg (112 tabs), 200 mg:125 mg (112 tabs)

Child ≥2–5 yr:

<14 kg: one lumacaftor 100 mg/ivacaftor 125 mg granule packet PO Q12 hr

≥14 kg: one lumacaftor 150 mg/ivacaftor 188 mg granule packet PO Q12 hr

Child ≥6–11 yr: two lumacaftor 100 mg/ivacaftor 125 mg tablets PO Q12 hr

Child ≥12, adolescent and adult: two lumacaftor 200 mg/ivacaftor 125 mg tablets PO Q12 hr

LUMACAFTOR AND IVACAFTOR *continued*

Dosage modification for hepatic impairment:

Level of Hepatic Impairment (Child-Pugh Class)	Age Group	Morning Dose	Evening Dose
A: Mild	2–5 yr	No dose adjustment; use usual dose	No dose adjustment; use usual dose
	≥6 yr	No dose adjustment; use usual dose	No dose adjustment; use usual dose
B: Moderate	2–5 yr	1 packet of granules	1 packet of granules every other day
	≥6 yr	2 tablets	1 tablet
C: Severe	2–5 yr	1 packet of granules[a]	No dose
	≥6 yr	1 tablet[a]	1 tablet[a]

[a]or less frequently as studies have not been conducted in severe hepatic impairment.

Dosage modification when used with CYP 450 3A inhibitors:

Already taking Orkambi and initiating a strong CYP 450 3A inhibitor (e.g., itraconazole): no dosage adjustment

Already taking a strong CYP 450 3A inhibitor and initiating Orkambi: Reduce Orkambi dosage to 1 tablet or 1 packet of granules every other day × the first week followed by the recommended daily dose. If Orkambi is interrupted for >1 wk and re-initiated while taking strong CYP 450 3A inhibitors, Orkambi should be reintroduced with the reduced dosage of 1 tablet or 1 packet of granules every other day × 1 wk followed by the recommended daily dose.

Works on CFTR trafficking defect by acting as a CFTR corrector (lumecaftor) and in combination with a CFTR potentiator (ivacaftor). Indicated for individuals with homozygous F508del CFTR mutation.

Respiratory events, such as chest discomfort, dyspnea and abnormal respiration, may occur during the initiation of therapy and may vary from transient to severe (requiring discontinuation). Common side effects include rash, diarrhea, nausea, flatulence, fatigue, nasal discharge, and URIs. Increased liver enzymes and cataracts may occur; monitor AST/ALT and ocular exam at baseline. Repeat AST/ALT every 3 mo for the first year followed by annual assessments. Repeat ocular exams annually. Hypertension has been reported. May cause a false positive urine drug screen for cannabinoids.

Use with **caution** with CrCl ≤30 mL/min and ESRD. Reduce dose with moderate/severe hepatic impairment (see dosage section) or when initiating therapy while taking a strong CYP 450 3A4 inhibitor.

Lumecaftor is a strong inducer of CYP 450 3A and ivacaftor is a CYP 450 3A substrate; see dose modification table in the dosing section. Use with strong CYP 450 3A inducers (e.g., rifampin, rifabutin, carbamazepine, St. John's wort) are not recommended. Lumecaftor/ivacaftor may reduce the efficacy of hormonal contraceptives and increase the incidence of menstruation-associated side effects (e.g., amenorrhea, dysmenorrhea, and irregular menses). Always evaluate potential drug-drug interactions; see https://www.orkambihcp.com/drug-interactionsddi–tool. Avoid food or drink containing grapefruit or Seville oranges.

Administer all doses with high-fat foods to assure absorption. Oral granules can be mixed with 5 mL of soft foods or liquids such as puréed fruits or vegetables, yogurt, applesauce, water, breast milk, infant formula, milk, or juice. Once mixed, it should be consumed within an hour. If a dose (all dosage forms) is missed within 6 hr of a scheduled dose, administer a dose immediately. However, if the missed dose is >6 hr, skip that dose and resume therapy at the next scheduled dose. Never take a double dose for a missed dose.

D

For explanation of icons, see p. 667

M

MAGNESIUM CITRATE
Various generics
16.17% Elemental Magnesium
Laxative/cathartic

Oral solution (OTC): 1.75 g/30 mL (300 mL); 5 mL = 3.9–4.7 mEq Mg
Tabs: 100 mg

Cathartic:
2–<6 yr: 2–4 mL/kg/24 hr PO ÷ once daily–BID; ***OR*** 60–90 mL/ 24 hr PO ÷ once daily–BID
6–12 yr: 100–150 mL/24 hr PO ÷ once daily–BID
>12 yr and adult: 150–300 mL/24 hr PO ÷ once daily–BID
Bowel prep:
Child >6 yr and adolescent: 4–6 mL/kg/24 hr (max. 300 mL/24 hr) PO ×1 as a single or divided dose the day prior to surgery.

Use with caution in renal insufficiency (monitor magnesium level) and patients receiving digoxin. May cause hypermagnesemia, diarrhea, muscle weakness, hypotension, and respiratory depression. Up to approximately 30% of dose is absorbed. May decrease absorption of H_2 antagonists, phenytoin, iron salts, tetracyclines, steroids, benzodiazepines, and quinolone antibiotics.

MAGNESIUM HYDROXIDE
Milk of Magnesia, Pedia-Lax, and various generics
41.69% Elemental Magnesium
Antacid, laxative

Oral liquid (OTC): 400 Mg/5 mL (Milk of Magnesia and others) (355, 473 mL)
Concentrated oral liquid (OTC): 2400 mg/10 mL (Milk of Magnesia concentrate) (100, 400 mL)
Chewable tabs (Pedia-Lax, see remarks [OTC]): 400 mg
400 mg magnesium hydroxide is equivalent to 166.76 mg elemental magnesium
Combination product with aluminum hydroxide: See Aluminum Hydroxide.

Laxative (all liquid mL doses based on 400 mg/5 mL magnesium hydroxide, unless noted otherwise):
Dose/24 hr ÷ once daily–QID PO
<2 yr: 0.5 mL/kg
2–5 yr: 5–15 mL ***OR*** 400–1200 mg (1–3 chewable tabs)
6–11 yr: 15–30 mL ***OR*** 1200–2400 mg (3–6 chewable tabs)
≥12 yr and adult: 30–60 mL ***OR*** 2400–4800 mg (6–12 chewable tabs)
Antacid:
Child:
Liquid: 2.5–5 mL/dose once daily–QID PO
Tabs: 400 mg once daily–QID PO
Adult:
Liquid: 5–15 mL/dose once daily–QID PO
Concentrated liquid (800 mg/5 mL): 2.5–7.5 mL/dose once daily–QID PO
Tabs: 400–1200 mg/dose once daily–QID PO

MAGNESIUM HYDROXIDE *continued*

See Magnesium Citrate. **Use with caution** in renal insufficiency (monitor magnesium level) and patients receiving digoxin. Drink a full 8 oz. of liquid with each dose of the chewable tablets.

Pedia-Lax chewable tablet is magnesium hydroxide. However, other dosage forms bearing the Pedia-Lax name in other dosage forms (e.g., oral liquid, suppository, and enema) contains different active ingredients.

MAGNESIUM OXIDE

Mag-200, Mag-Ox 400, Uro-Mag, and other generics
60.32% Elemental Magnesium
Oral magnesium salt

Tabs (OTC): 200, 400, 420, 500 mg
Caps (Uro-Mag; OTC): 140 mg
400 mg magnesium oxide is equivalent to 241.3 mg elemental Mg or 20 mEq Mg

Doses expressed in magnesium oxide salt.
Magnesium supplementation:
Child: 5–10 mg/kg/24 hr ÷ TID–QID PO
Adult: 400–800 mg/24 hr ÷ BID–QID PO
Hypomagnesemia:
Child: 65–130 mg/kg/24 hr ÷ QID PO
Adult: 2000 mg/24 hr ÷ QID PO

See Magnesium Citrate. **Use with caution** in renal insufficiency (monitor magnesium level) and patients receiving digoxin. **For dietary recommended intake (U.S. recommended daily allowance [RDA]) for magnesium, see Chapter 21.**

Pregnancy category is an "A" for doses up to 400 mg/24 hr.

MAGNESIUM SULFATE

Epsom salts, many others, and generics
9.9% Elemental Magnesium
Magnesium salt

Injection: 500 mg/mL (4 mEq/mL) (2, 10, 20, 50 mL)
Injection, prediluted in sterile water for injection; ready to use: 40 mg/mL (0.325 mEq/mL) (50, 100, 500, 1000 mL); 80 mg/mL (0.65 mEq/mL) (50 mL)
Injection, prediluted in D_5W; ready to use: 10 mg/mL (0.081 mEq/mL) (100 mL)
Granules (Epsom salts and generics): Approx. 40 mEq Mg per 5 g (454, 1810 g)
500 mg magnesium sulfate is equivalent to 49.3 mg elemental Mg or 4.1 mEq Mg

All doses expressed in magnesium sulfate salt.
Cathartic:
Child: 0.25 g/kg/dose PO Q4–6 hr
Adult: 10–30 g/dose PO Q4–6 hr
Hypomagnesemia or hypocalcemia:
IV/IM: 25–50 mg/kg/dose Q4–6 hr × 3–4 doses; repeat PRN. **Max. single dose:** 2 g
PO: 100–200 mg/kg/dose QID PO
Daily maintenance for parenteral nutrition:
30–60 mg/kg/24 hr or 0.25–0.5 mEq/kg/24 hr IV; max. dose: 1 g/24 hr

Continued

For explanation of icons, see p. 667

MAGNESIUM SULFATE *continued*

Adjunctive therapy for moderate to severe reactive airway disease exacerbation (bronchodilation); some recommend an IV saline bolus prior to magnesium administration to prevent hypotension:
Child: 25–75 mg/kg/dose (**max. dose**: 2 g) × 1 IV over 20 min.
Adult: 2 g/dose × 1 IV over 20 min.

When given IV, **beware** of hypotension, bradycardia, respiratory depression, complete heart block, and/or hypermagnesemia. Calcium gluconate (IV) should be available as **antidote.** **Use with caution** in patients with renal insufficiency (monitor magnesium levels) and with patients on digoxin. **Serum level dependent toxicity** includes the following: >3 mg/dL: CNS depression; >5 mg/dL: decreased deep tendon reflexes, flushing, somnolence; and >12 mg/dL: respiratory paralysis, heart block.
Max. IV intermittent infusion rate: 1 mEq/kg/hr or 125 mg $MgSO_4$ salt/kg/hr.
Pregnancy category is "D" because hypocalcemia, osteopenia, and fractures in the developing baby or fetus have been reported in pregnant women receiving magnesium >5–7 days for preterm labor.

MANNITOL

Osmitrol, Resectisol, and generics
Osmotic diuretic

Injection: 50, 100, 150, 200, 250 mg/mL (5%, 10%, 15%, 20%, 25%, respectively)
Irrigation solution (Resectisol): 50 mg/mL (5%) (2000 mL)

Oliguria (Child and adult):
Test dose to assess renal function: 0.2 g/kg/dose (**max. dose:** 12.5 g) IV over 3–5 min. If there is no diuresis within 2 hr, discontinue mannitol.
Initial: 0.5–1 g/kg/dose IV over 2–6 hr
Maintenance: 0.25–2 g/kg/dose Q4–6 hr IV over 2–6 hr
Intracranial pressure reduction (see remarks): 0.25–1 g/kg/dose IV/IO over 20–30 min; may repeat dose if needed

Contraindicated in severe renal disease, active intracranial bleed, dehydration (especially severe hypovolemia), prior hypersensitivity to mannitol, and pulmonary edema. May cause circulatory overload and electrolyte disturbances. For hyperosmolar therapy, keep serum osmolality at 310–320 mOsm/kg. **Do not use** with aminoglycosides as this may enhance nephrotoxicity risk.
Larger doses may require fluid bolus to prevent hypotension. May cause hypovolemia, headache, acute kidney injury, and polydipsia. Reduction in ICP occurs in 15 min and lasts 3–6 hr.
Caution: drug may crystallize at low temperatures with concentrations ≥15%; redissolve crystals by warming solution up to 70°C with agitation. Use an in-line filter (≤5 micron).

MEBENDAZOLE

Emverm; previously available as Vermox
Anthelmintic

Chewable tabs: 100 mg (may be swallowed whole or chewed) (boxes of 12s)

Child (>2 yr) and adult:
***Pinworms* (Enterobius):** 100 mg PO ×1, repeat in 2 wk if not cured.
***Hookworms, roundworms* (Ascaris), *and whipworm* (Trichuris):** 100 mg PO BID ×3 days. Repeat in 3–4 wk if not cured. Alternatively, may administer 500 mg PO ×1 and repeat in 3–4 wk if not cured.

MEBENDAZOLE *continued*

Capillariasis: 200 mg PO BID ×20–30 days
Visceral larva migrans (Toxocariasis): 100–200 mg PO BID ×5 days
***Trichinellosis* (Trichinella spiralis):** 200–400 mg PO TID ×3 days, then 400–500 mg PO TID ×10 days; use with steroids for severe symptoms
Ancylostoma caninum *(Eosinophilic enterocolitis):* 100 mg PO BID ×3 days.
See latest edition of the AAP Red Book for additional information.

Experience in children <2 yr and pregnancy is limited. May cause rash, headache, diarrhea, and abdominal cramping in cases of massive infection. Liver function test elevations and hepatitis have been reported with prolonged courses; monitor hepatic function with prolonged therapy.

Family may need to be treated as a group. Therapeutic effect may be decreased if administered to patients receiving aminoquinolones, carbamazepine, or phenytoin. Cimetidine may increase the effects/toxicity of mebendazole. Administer with food. Tablets may be crushed and mixed with food, swallowed whole, or chewed.

MEDROXYPROGESTERONE
Depo-Provera, Provera, Depo-Sub Q Provera 104, and generics
Contraceptive, progestin

Tabs (Provera and generics): 2.5, 5, 10 mg
Injection, suspension as acetate:
Depo-Provera and generics, for IM use only: 150 mg/mL (1 mL and 1 mL prefilled syringe), 400 mg/mL (2.5 mL); may contain parabens and polyethylene glycol
Injection, prefilled syringe as acetate:
Depo-Sub Q Provera 104, for SC use only: 104 mg (0.65 mL of 160 mg/mL); contains parabens and polyethylene glycol

Adolescent and adult:
Contraception: Initiate therapy during the first 5 days after onset of a normal menstrual period; within 5 days postpartum if not breastfeeding; or if breastfeeding, at 6 wk postpartum. When converting contraceptive method to Depo-Sub Q Provera, dose should be administered within 7 days after the last day of using the previous method (pill, ring, patch).
IM (Depo-Provera and generics): 150 mg Q3 mo (every 13 wk)
SC (Depo-Sub Q Provera 104): 104 mg Q3 mo (every 12–14 wk)
Amenorrhea: 5–10 mg PO once daily ×5–10 days
Abnormal uterine bleeding: 5–10 mg PO once daily ×5–10 days initiated on the 16th or 21st day of the menstrual cycle.
Endometriosis-associated pain (Depo-Sub Q Provera 104): 104 mg SC Q 3 mo. Do not use longer than 2 yr due to impact on bone mineral density.

Consider patient's risk for osteoporosis because of the potential for decrease in bone mineral density with long-term use. **Contraindicated** in pregnancy, breast or genital cancer, liver disease, missed abortion, thrombophlebitis, thromboembolic disorders, cerebral vascular disease, and undiagnosed vaginal bleeding. **Use with caution** in patients with family history of breast cancer, depression, diabetes, and fluid retention. May cause dizziness, headache, insomnia, fatigue, nausea, weight increase, appetite changes, amenorrhea, and breakthrough bleeding. Cholestatic jaundice, adrenal suppression, anaphylaxis, and increased intracranial pressure have been reported. Injection site reactions may include pain/tenderness, persistent atrophy/indentation/dimpling, lipodystrophy, sterile abscess, skin color change, and node/lump.

For explanation of icons, see p. 667

MEDROXYPROGESTERONE *continued*

Drug is a substrate to CYP 450 3A4 isoenzyme. Aminoglutethimide may decrease medroxyprogesterone levels. May alter thyroid and liver function tests, prothrombin time, factors VII, VIII, IX, and X, and metyrapone test.

Do not inject IM or SC product intravenously. Shake IM injection vial well before use, and administer in the upper arm or buttock. Administer SC injection product into the anterior thigh or abdomen. Administer oral doses with food.

MEFLOQUINE HCL

Generics; previously available as Lariam

Antimalarial

Tabs: 250 mg (228 mg base)

Doses expressed in mg mefloquine HCl salt

Malaria prophylaxis (start 2 wk prior to exposure and continue for 4 wk after leaving endemic area; see remarks):

Child (PO, administered Q7 days):

<10 kg: 5 mg/kg

10–19 kg: 62.5 mg (1/4 tablet)

20–30 kg: 125 mg (1/2 tablet)

31–45 kg: 187.5 mg (3/4 tablet)

>45 kg: 250 mg (1 tablet)

Adult: 250 mg PO Q7 days

Malaria treatment (uncomplicated/mild infection, chloroquine-resistant* Plasmodium vivax*):

Child ≥6 mo and >5 kg: 15 mg/kg (**max. dose:** 750 mg) ×1 PO followed by 10 mg/kg (**max. dose:** 500 mg) ×1 PO 6–12 hr later

Adult: 750 mg ×1 PO followed by 500 mg ×1 PO 6–12 hr later

See latest edition of the Red Book for additional information.

Contraindicated in active or recent history of depression, anxiety disorders, psychosis or schizophrenia, seizures, or hypersensitivity to quinine or quinidine. **Use with caution** in cardiac dysrhythmias and neurologic disease. May cause dizziness, ringing of the ears, headache, syncope, psychiatric symptoms (e.g., anxiety, paranoia, depression, hallucinations, and psychotic behavior), seizures, ocular abnormalities, GI symptoms, leukopenia, and thrombocytopenia. If neurologic or psychiatric side effects occur, discontinue therapy and use an alternative medication. Most adverse events occur within 3 doses with prophylaxis use. Monitor liver enzymes and ocular exams for therapies >1 yr.

Mefloquine is a substrate and inhibitor of P-glycoprotein and may reduce valproic acid levels. ECG abnormalities may occur when used in combination with quinine, quinidine, chloroquine, halofantrine, and β-blockers. If any of the aforementioned antimalarial drugs is used in the initial treatment of severe malaria, initiate mefloquine at least 12 hr after the last dose of any of these drugs. **Do not** initiate halofantrine or ketoconazole within 15 days of the last dose of mefloquine. Use with chloroquine may increase risk for seizures. Rifampin may decrease mefloquine levels.

Do not take on an empty stomach. Administer with at least 240 mL (8 oz) water. Treatment failures in children may be related to vomiting of administered dose. If vomiting occurs less than 30 min after the dose, administer a second full dose. If vomiting occurs 30–60 min after the dose, administer an additional half-dose. If vomiting continues, monitor patient closely and consider alternative therapy.

MEROPENEM
Merrem and generics
Carbapenem antibiotic

Injection: 0.5, 1 g
Contains 3.92 mEq Na/g drug

Neonate and infant <3 mo (IV):
Non-CNS general dosing (meropenem MIC <4):
≤2 kg:
≤14 days old: 20 mg/kg/dose Q12 hr
15–28 days old: 20 mg/kg/dose Q8 hr
29–60 days old: 30 mg/kg/dose Q8 hr
>2 kg:
≤14 days old: 20 mg/kg/dose Q8 hr
15–60 days old: 30 mg/kg/dose Q8 hr
Non-CNS infection with moderately resistant meropenem isolate (MIC 4–8 mCg/mL; from a single-dose PK simulation study):
>30 wk gestation and >7 days old: 40 mg/kg/dose IV Q8 hr
Intra-abdominal infection (meropenem MIC <4 mCg/mL):
<32-wk gestation:
<14 days old: 20 mg/kg/dose Q12 hr
≥14 days old: 20 mg/kg/dose Q8 hr
≥32-wk gestation:
<14 days old: 20 mg/kg/dose Q8 hr
≥14 days old: 30 mg/kg/dose Q8 hr
Meningitis (1–3 mo, IV; recommendation from 2004 IDSA meningitis practice guidelines): 40 mg/kg/dose Q8 hr
Infant (≥3 mo), child and adolescent (IV):
Meningitis, severe infections, cystic fibrosis pulmonary exacerbations: 40 mg/kg/dose (**max.** 2 g/dose) Q8 hr
Complicated skin and skin structure infection: 10 mg/kg/dose (**max. dose:** 500 mg/dose) Q8 hr. For severe or necrotizing infections or *Pseudomonas aeruginosa* infection (suspected or confirmed), use 20 mg/kg/dose (**max. dose:** 1 g/dose) Q8 hr.
Intra-abdominal and mild/moderate infections, and fever/neutropenia empiric therapy: 20 mg/kg/dose (**max. dose:** 1 g/dose) Q8 hr
Adult (IV):
Skin and subcutaneous tissue infections: 500 mg Q8 hr; use 1 g Q8 hr for suspected or confirmed Pseudomonas aeruginosa
Intra-abdominal and mild/moderate infections; and fever/neutropenia empiric therapy: 1 g Q8 hr
Meningitis and severe infections: 2 g Q8 hr

Contraindicated in patients sensitive to carbapenems, or with a history of anaphylaxis to β-lactam antibiotics. **Use with caution** in meningitis and CNS disorders (may cause seizures) and renal impairment **(adjust dose; see Chapter 31).** Drug penetrates well into the CSF.

May cause diarrhea, rash, nausea, vomiting, oral moniliasis, glossitis, pain and irritation at the IV injection site, and headache. Hepatic enzyme and bilirubin elevation, dermatologic reactions (including Stevens-Johnson, DRESS, and TEN), leukopenia, thrombocytopenia (in renal dysfunction), and neutropenia have been reported. Probenecid may increase serum meropenem levels. May reduce valproic acid levels.

Lengthening the IV drug administration time to 4 hr will improve the meropenem concentration time above the MIC and may be useful in situations of resistant organisms.

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For explanation of icons, see p. 667

MESALAMINE
Apriso, Asacol, Asacol HD, Canasa, Delzicol, Lialda, Pentasa, Rowasa, SfRowasa, and generics;
5-aminosalicylic acid, 5-ASA
Salicylate, GI antiinflammatory agent

Caps, controlled release:
Pentasa: 250, 500 mg
Delzicol and generics: 400 mg
Apriso (for Q24 hr dosing): 375 mg; contains aspartame
Tabs, delayed release:
Asacol: 400 mg
Asacol HD and generics: 800 mg
Lialda and generics: 1200 mg
Suppository (Canasa and generics): 1000 mg (30s, 42s)
Rectal suspension enema (Rowasa, SfRowasa, and generics): 4 g/60 mL; contains sulfites (SfRowasa is sulfite free) and sodium benzoate

Child and adolescent (ulcerative colitis):
Caps (controlled release) and tabs (delayed release): 50–100 mg/kg/24 hr ÷ Q6–12 hr PO;
max. dose: 1 g/dose
Delzicol (mild/moderate ulcerative colitis; ≥5–18 yr; see remarks):
17–32 kg: 800 mg QAM and 400 mg Q afternoon PO
33–53 kg: 1200 mg QAM and 800 mg Q afternoon PO
54–90 kg: 1200 mg QAM and Q afternoon PO
Older child and adolescent (ulcerative colitis):
Enema (Rowasa): 4 g QHS
Suppository (Canasa): 500 mg QHS–BID
Adult (ulcerative colitis):
Caps, controlled release:
Initial therapy: 1 g QID PO ×3–8 wk
Maintenance therapy for remission:
Apriso: 1.5 g QAM PO
Pentasa: 1 g QID PO
Tabs, delayed release:
Initial therapy:
Asacol: 800 mg TID PO ×6 wk
Asacol HD: 1.6 g TID PO ×6 wk
Delzicol: 800 mg TID PO\6 wk
Lialda: 2.4–4.8 g once daily PO up to 8 wk
Maintenance therapy for remission:
Asacol: 1.6 g/24 hr PO in divided doses
Delzicol: 1.6 g/24 hr PO divided BID–QID
Lialda: 2.4 g PO once daily
Suppository: 1000 mg QHS PR ×3–6 wk; retain each dose in the rectum for 1–3 hr or longer, if possible.
Rectal suspension: 60 mL (4 g) QHS ×3–6 wk, retaining each dose for about 8 hr; lie on left side during administration to improve delivery to the sigmoid colon.

Generally **not recommended** in children <16 yr with chicken pox or flu-like symptoms (risk of Reye syndrome). **Contraindicated** in active peptic ulcer disease, severe renal failure, and salicylate hypersensitivity. Rectal suspension should not be used in patients with history of ine hypersensitivity, impaired hepatic or

MESALAMINE *continued*

renal function, pyloric stenosis, and concurrent thrombolytics. May cause headache, GI discomfort, pancreatitis, pericarditis, and rash. Angioedema, Stevens-Johnson syndrome, DRESS, fatal infections (e.g., sepsis and pneumonia; discontinue use), and photosensitivity have been reported. May cause a false-positive urinary normetanephrine test.

Safety and efficacy of Asacol in children 5–17 yr for mild/moderate acute ulcerative colitis have been established over a 6 wk period. However, efficacy for maintenance of remission was not established in a 26 wk RCT (potential factors affecting outcome included improper dosage used and premature termination of trial). Safety and efficacy of Canasa suppositories have not been demonstrated for mild/moderate active ulcerative proctitis in a 6-wk open-label study in 49 patients 5–17 yr old.

Do not administer with lactulose or other medications that can lower intestinal pH. Use with myelosuppressive drugs (e.g., azathioprine, 6-mercaptopurine may increase risk for blood disorders, bone marrow failure and associated complications.

Two Delzicol 400-mg capsules have not been shown to be interchangeable or substitutable with one mesalamine 800-mg delayed-release tablet. Oral capsules are designed to release medication throughout the GI tract and oral tablets release medication at the terminal ileus and beyond. 400 mg PO mesalamine is equivalent to 1 g sulfasalazine PO. Tablets should be swallowed whole.

METFORMIN
Glucophage, Glucophage XR, Glumetza, Fortamet, Riomet, and generics
Antidiabetic, biguanide

Tabs: 500, 850, 1000 mg
Tabs, extended release:
Glucophage XR and generics: 500, 750 mg
Fortamet, Glumetza, and generics: 500, 1000 mg
Oral suspension (Riomet and generics): 100 mg/mL (120, 480 mL); may contain saccharin and propylene glycol

Type 2 Diabetes: Administer all doses with meals (e.g., BID: morning and evening meals).

Child (10–16 yr; PO) (see remarks):

Immediate-release dosage forms: Start with 500 mg BID; may increase dose every 1–2 wk as tolerated by 500 mg/24 hr in 2 divided doses up to a **max. dose** of 2000 mg/24 hr.

Extended-release tabs: Start with 500–1000 mg once daily ×7–14 days; may increase dose every 1–2 wk as tolerated by 500–1000 mg/24 hr as once daily or divided doses up to a **max. dose** of 2000 mg/24 hr.

Child ≥17 yr and adult (see remarks):

500-mg tabs: Start with 500 mg PO BID; may increase dose weekly by 500 mg/24 hr in 2 divided doses up to a **max. dose** of 2500 mg/24 hr. Administer 2500 mg/24 hr doses by dividing daily dose TID with meals.

850-mg tabs: Start with 850 mg PO once daily with morning meal; may increase by 850 mg every 2 wk up to a **max. dose** of 2550 mg/24 hr (first dosage increment: 850 mg PO BID; second dosage increment: 850 mg PO TID).

Extended-release tabs: Start with 500 mg PO once daily with evening meal; may increase by 500 mg every week up to a **max. dose** of 2000 mg/24 hr (if glycemic control is not achieved at **max. dose**, divide dose to 1000 mg PO BID). If using Fortamet, **max. dose** is 2500 mg/24 hr. If a dose >2000 mg is needed, consider switching to non–extended-release tablets in divided doses and increase dose to a **max. dose** of 2550 mg/24 hr.

Continued

For explanation of icons, see p. 667

METFORMIN *continued*

Assess patient's eGFR prior to initiating therapy. **Contraindicated** in severe renal impairment (<30 mL/min/1.73 m^2), hepatic impairment (increased risk for lactic acidosis), CHF, and metabolic acidosis and during radiology studies using iodinated contrast media. **Use with caution** when transferring patients from chlorpropamide therapy (potential hypoglycemia risk), excessive alcohol intake, hypoxemia, dehydration, surgical procedures, mild/moderate renal impairment, hepatic disease, anemia, and thyroid disease.

Fatal lactic acidosis (diarrhea; severe muscle pain, cramping; shallow and fast breathing; unusual weakness and sleepiness) and decrease in vitamin B_{12} levels have been reported. May cause GI discomfort (~50% incidence), anorexia, and vomiting. Transient abdominal discomfort or diarrhea have been reported in 40% of pediatric patients. Organic cationic transporter-2 (OCT2)and multidrug and toxin extrusion (MATE)inhibitors (e.g., cimetidine), furosemide, and nifedipine may increase the effects/toxicity of metformin. In addition to monitoring serum glucose and glycosylated hemoglobin, monitor renal function and hematologic parameters (baseline and annual).

Adult patients initiated on 500 mg PO BID may also have their dose increased to 850 mg PO BID after 2 wk.

COMBINATION THERAPY WITH SULFONYLUREAS: If patient has not responded to 4 wk of **maximum** doses of metformin monotherapy, consider gradual addition of an oral sulfonylurea with continued **maximum** metformin dosing (even if failure with sulfonylurea has occurred). Attempt to identify the minimum effective dosage for each drug (metformin and sulfonylurea) because the combination can increase risk for sulfonylurea-induced hypoglycemia. If patient does not respond to 1–3 mo of combination therapy with maximum metformin doses, consider discontinuing combination therapy and initiating insulin therapy.

Administer all doses with food.

METHADONE HCL
Dolophine, Methadose, and generics
Narcotic, analgesic

Tabs: 5, 10 mg
Tabs (dispersible): 40 mg
Oral solution: 5 mg/5 mL, 10 mg/5 mL; contains 8% alcohol
Concentrated solution: 10 mg/mL
Injection: 10 mg/mL (20 mL), contains 0.5% chlorobutanol

Analgesia (see remarks):
Child: 0.7 mg/kg/24 hr ÷ Q4–6 hr PO, SC, IM, or IV PRN pain; **max. dose:** 10 mg/dose.
Adult: 2.5–10 mg/dose Q3–4 hr PO, SC, IM, or IV PRN pain.
Detoxification or maintenance: See package insert.

Unintentional overdoses have resulted in fatalities and severe adverse events such as respiratory depression and cardiac arrhythmias. **Use with caution** in hepatic (**avoid** in severe cases) and biliary tract impairment. May cause respiratory depression, sedation, increased intracranial pressure, hypotension, and bradycardia. Cardiac QT interval prolongation and serious arrhythmias have occurred mostly with higher doses; **avoid use** with other medications which may prolong QT interval.

Average $T_{½}$: children 19 hr, and adults 35 hr. Duration of action PO is 6–8 hr initially and 22–48 hr after repeated doses. Respiratory effects last longer than analgesia. Accumulation may occur with continuous use making it necessary to adjust dose.

METHADONE HCL *continued*

Nevirapine may decrease serum levels of methadone. Fatalities have been reported with abuse in combination with benzodiazepines. Serotonin syndrome has been reported with use with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitor (SNRIs), TCAs, 5-HT3 antagonists, MAO inhibitors, and drugs that affect the serotonergic neurotransmitter system (e.g., trazodone, tramadol). Methadone is a substrate for CYP 450 3A3/4, 2D6, and 1A2 and inhibitor of 2D6.

See Chapter 6 for equianalgesic dosing and onset of action. **Adjust dose in renal failure (see Chapter 31).**

A Risk Evaluation and Mitigation Strategy (REMS)is required for healthcare providers to ensure the benefits outweigh the risks of addiction, abuse, and misuse. See www.fda.gov/OpioidAnalgesicREMSBlueprint or call 1-800-503-0784.

METHIMAZOLE

Tapazole and generics

Antithyroid agent

Tabs: 5, 10 mg

Hyperthyroidism:

Child:

Initial: 0.4–0.7 mg/kg/24 hr or 15–20 mg/m²/24 hr PO ÷ Q8 hr

Maintenance: 1/3–2/3 of initial dose PO ÷ Q8 hr

Max. dose: 30 mg/24 hr

Adult:

Initial: 15–60 mg/24 hr PO ÷ once daily or BID (for doses >30 mg)

Maintenance: 5–15 mg/24 hr PO once daily

Readily crosses placental membranes and distributes into breast milk (maternal doses ≤20 mg/24 hr is considered safe but there is insufficient data to support safe use with maternal doses >20 mg/24 hr). Blood dyscrasias, dermatitis, hepatitis, arthralgia, CNS reactions, pruritis, nephritis, hypoprothrombinemia, agranulocytosis, headache, fever, and hypothyroidism may occur.

May increase the effects of oral anticoagulants. When correcting hyperthyroidism, existing β-blocker, digoxin, and theophylline doses may need to be reduced to avoid potential toxicities.

Switch to maintenance dose when patient is euthyroid. Administer all doses with food.

METHYLDOPA

Generics

Central α-adrenergic blocker, antihypertensive

Tabs: 250, 500 mg

Oral suspension: 50 mg/mL

Hypertension:

Child: 10 mg/kg/24 hr ÷ Q6–12 hr PO; increase PRN Q2 days. **Max. dose**: 65 mg/kg/24 hr or 3 g/24 hr, whichever is less.

Adult: 250 mg/dose BID–TID PO. Increase PRN Q2 days to **max. dose** of 3 g/24 hr.

Continued

For explanation of icons, see p. 667

METHYLDOPA *continued*

Contraindicated in pheochromocytoma and active liver disease. **Use with caution** if patient is receiving haloperidol, propranolol, lithium, or sympathomimetics. Positive Coombs test rarely associated with hemolytic anemia. Fever, leukopenia, sedation, memory impairment, hepatitis, GI disturbances, orthostatic hypotension, black tongue, and gynecomastia may occur. May interfere with lab tests for creatinine, urinary catecholamines, uric acid, and AST.

May increase the AV blocking effects of β-blockers and antihypertensive effects of other antihypertensives. α_2-antagonist antidepressants, serotonin/norepinephrine reuptake inhibitors and methylphenidate may reduce the antihypertensive effects of methyldopa. **Do not use** in combination with MAO inhibitors (may enhance adverse effects of methyldopa). **Do not coadminister** oral doses with iron; decreases methyldopa absorption. **Adjust dose in renal failure (see Chapter 31).**

METHYLENE BLUE
ProvayBlue and generics
Antidote, drug-induced methemoglobinemia, and cyanide toxicity

Injection: 10 mg/mL (1%) (1, 10 mL)
Intravenous solution (ProvayBlue): 50 mg/10 mL (10 mL)

Methemoglobinemia:
Child and adult: 1–2 mg/kg/dose or 25–50 mg/m²/dose IV over 5 min. May repeat in 30–60 min if needed.

At high doses, may cause methemoglobinemia. **Avoid** subcutaneous or intrathecal routes of administration. **Use with caution** in G6PD deficiency or renal insufficiency. May cause nausea, vomiting, dizziness, headache, diaphoresis, stained skin, and abdominal pain. Causes blue-green discoloration of urine and feces.

Serotonin syndrome has been reported with the co-administration of SSRI, SNRI, or clomipramine. Use with bupropion, paroxetine, sertraline, duloxetine, vilazodone, venlafaxine, fluoxetine, or desipramine is considered **contraindicated**.

METHYLPHENIDATE HCL
Ritalin, Adhansia XR, Aptensio XR, Jornay PM, Methylin, Metadate CD, Metadate ER, Methylin ER, Concerta, Relexxii, QuilliChew ER, Quillivant XR, Ritalin LA, Cotempla XR-ODT, Daytrana, and generics
CNS stimulant

Tabs (Ritalin and generics): 5, 10, 20 mg
Chewable tabs (Methylin and generics): 2.5, 5, 10 mg; contains phenylalanine
Extended-release chewable tabs (dosed once daily in the morning):
QuilliChew ER: 20, 30, 40 mg; contains phenylalanine
Oral solution (Methylin and generics): 1 mg/mL, 2 mg/mL; may contain propylene glycol
Oral suspension, extended release (dosed once daily in the morning):
Quillivant XR: 25 mg/5 mL (60, 120, 150, 180 mL); contains sodium benzoate
Extended-release tabs:
8-hr duration (Metadate ER): 20 mg; dosed BID–TID
24-hr duration:
Concerta and generics: 18, 27, 36, 54 mg

METHYLPHENIDATE HCL *continued*

Extended-release oral disintegrating tabs:
Cotempla XR-ODT (dosed once daily in the morning): 8.6, 17.3, 25.9 mg; contains polyethylene glycol
Extended-release caps
24-hr duration:
Ritalin LA, Medatate CD, and generics: 10, 20, 30, 40, 50, 60 mg
Adhansia XR: 25, 35, 45, 55, 70, 85 mg
Aptensio XR: 10, 15, 20, 30, 40, 50, 60 mg
Jornay PM: 20, 40, 60, 80, 100 mg (dosed only in the evening)
Transdermal patch (Daytrana): 10 mg/9 hr (each 12.5 cm^2 patch contains 27.5 mg), 15 mg/9 hr (each 18.75 cm^2 patch contains 41.3 mg), 20 mg/9 hr (each 25 cm^2 patch contains 55 mg), 30 mg/9 hr (each 37.5 cm^2 patch contains 82.5 mg) (30s)

Attention-deficit/hyperactivity disorder (ADHD):

Immediate-release oral-dosage forms (Methylin, Ritalin; ≥6 yr):
Initial: 0.3 mg/kg/dose (or 2.5–5 mg/dose) given before breakfast and lunch. May increase by 0.1 mg/kg/dose PO (or 5–10 mg/24 hr) weekly until maintenance dose achieved. May give extra afternoon dose if needed.
Maintenance dose range: 0.3–1 mg/kg/24 hr
Max. dose: 2 mg/kg/24 hr or 60 mg/24 hr for those weighing ≤50 kg and 100 mg/24 hr >50 kg.
Extended-release once-daily oral-dosage form (Concerta; ≥6 yr):
Methylphenidate naive patients: Start with 18 mg PO QAM for children and adolescents and 18–36 mg PO QAM for adults; dosage may be increased at weekly intervals at 18 mg increments up to the following **max. dose**:
6–12 yr: 54 mg/24 hr
13–17 yr: 72 mg/24 hr **not to exceed** 2 mg/kg/24 hr
Patients weighing >50 kg: higher **max. dose** of 108 mg/24 hr may be used.
Patients currently receiving methylphenidate: See following table.

RECOMMENDED DOSE CONVERSION FROM METHYLPHENIDATE REGIMENS TO CONCERTA

Previous Methylphenidate Daily Dose	Recommended Concerta Dose
5 mg PO BID–TID or 20 mg SR PO once daily	18 mg PO QAM
10 mg PO BID–TID or 40 mg SR PO once daily	36 mg PO QAM
15 mg PO BID–TID or 60 mg SR PO once daily	54 mg PO QAM
20 mg PO BID–TID	72 mg PO QAM

After a week of receiving the above-recommended Concerta dose, dose may be increased in 18 mg increments at weekly intervals PRN up to a **maximum** of 54 mg/24 hr for 6–12 yr and 72 mg/24 hr (not to exceed 2 mg/kg/24 hr) for 13–17 yr.

Other extended-release oral-dosage forms (see specific product information if converting from another product or dosage form):

Product (Dosage Form)	Initial Dose (≥6 yr)[a]	Dosage Adjustment	Max. Dose
Adhansia XR (extended-release caps)	25 mg PO once daily in the AM	Increase at 10–15 mg increments at intervals ≥5 days PRN	85 mg/24 hr but doses ≥70 mg/24 hr were associated with higher rate of side effects in children
Aptensio XR (extended-release caps)	10 mg PO once daily in the AM	Increase at 10 mg increments Q7 days PRN	60 mg/24 hr

For explanation of icons, see p. 667

METHYLPHENIDATE HCL *continued*

Product (Dosage Form)	Initial Dose (≥6 yr)[a]	Dosage Adjustment	Max. Dose
Cotempia XR-ODT (extended-release oral disintegrating tabs)[b]	17.3 mg PO once daily in the AM	Increase at 8.6 or 17.3 mg increments Q7 days PRN	51.8 mg/24 hr
Jornay PM (extended-release caps)	20 mg PO QHS (between 6:30 and 9:30 PM; 8:00 PM was the most optimal time for 6–12 yr in clinical trials)	Increase at 20 mg increments Q7 days PRN; administered QHS	100 mg/24 hr
Metadate CD (extended-release caps)	20 mg PO once daily	Increase at 10–20 mg increments Q7 days PRN	≤50 kg: 60 mg/24 hr >50 kg: 100 mg/24 hr
Quillivant XR (extended-release oral suspension)[a]	20 mg PO once daily	Increase at 10–20 mg increments Q7 days PRN	60 mg/24 hr
QuilliChew (extended-release chewable tabs)	20 mg PO once daily	Increase by 10, 15, or 20 mg Q7 days PRN	Doses >60 mg/24 hr have not been studied
Ritalin LA (extended-release caps)	20 mg PO once daily	Increase at 10 mg increments Q7 days PRN	≤50 kg: 60 mg/24 hr >50 kg: 100 mg/24 hr

[a]Quillivant XR dosing recommendations for children 6–12 yr.
[b]Cotempia XR ODT dosing recommendations for children 6–17 yr.

Metadate ER (8-hr duration of action): Convert immediate-release tabs when the 8-hr dosage corresponds to the available extended-release tablet size. Usual **max. dose**: 60 mg/24 hr for children but some patients >50 kg may tolerate doses up to 100 mg/24 hr with increased monitoring.

Transdermal patch (Daytrana; see remarks): Apply to the hip 2 hr before the effect is needed and remove 9 hr later. Patch may be removed before 9 hr if shorter duration of effect is desired or if late day adverse effects appear.

6–17 yr: Start with 10 mg/9 hr patch once daily. Increase dose PRN Q7 days by increasing to the next dosage strength. Higher starting doses have been reported in patients converting from oral-dosage forms >20 mg/24 hr.

Contraindicated in glaucoma, anxiety disorders, motor tics, and Tourette syndrome. Medication should generally not be used in children <5 yr old; diagnosis of ADHD in this age group is extremely difficult and should be only done in consultation with a specialist. Sudden death (children, adolescents, and adults), stroke (adults), and MI (adults) have been reported in patients with preexisting structural cardiac abnormalities or other serious heart problems.

Use with caution in patients with hypertension, psychiatric conditions, and epilepsy. Insomnia, weight loss, anorexia, rash, nausea, emesis, abdominal pain, hypertension or hypotension, tachycardia, arrhythmias, palpitations, restlessness, headaches, fever, tremor, visual disturbances, and thrombocytopenia may occur. Abnormal liver function (ranging from transaminase elevation to severe hepatic injury), cerebral arteritis and/or occlusion, peripheral vasculopathy (including Raynaud phenomenon), leukopenia and/or anemia, hypersensitivity reactions, transient depressed mood, paranoia, mania, auditory hallucination, priapism, and scalp hair loss have been reported. Skin irritation, chemical leukoderma, and contact dermatitis have been reported with transdermal route. High doses

METHYLPHENIDATE HCL *continued*

May increase serum concentrations/effects of tricyclic antidepressants, dopamine agonists (e.g., haloperidol), phenytoin, phenobarbital, and warfarin. May decrease the effects of antihypertensive drugs. Effect of methylphenidate may be potentiated by MAO inhibitors; hypertensive crisis may also occur if used within 14 days of discontinuance of the MAO inhibitor.

Extended/sustained-release dosage forms have either an 8- or 24-hr dosage interval (as stipulated previously). Concerta dosage form delivers 22.2% of its dose as an immediate-release product with the remaining amounts as an extended-release product (e.g., 18-mg strength: 4 mg as immediate release and 14 mg as extended release). Jornay PM is dosed only in the evening and should **NOT** be taken in the morning. **Do not** consume alcohol with Ritalin LA dosage form, because it may result in a more rapid release of the drug. **Do not** expose transdermal application site to external heat sources (e.g., electric blankets, heating pads); this may increase drug release.

METHYLPREDNISOLONE

Medrol, Medrol Dosepack, Solu-Medrol, Depo-Medrol, and generics

Corticosteroid

Tabs: 2, 4, 8, 16, 32 mg

Tabs, dose pack (Medrol Dosepack and generics): 4 mg (21s)

Injection, Na succinate (Solu-Medrol and generics): 40, 125, 500, 1000 mg (IV or IM use); may contain benzyl alcohol

Injection, Acetate (Depo-Medrol and generics): 20, 40, 80 mg/mL (IM repository); may contain polyethylene glycol (1, 5 mL)

Antiinflammatory/immunosuppressive:

PO/IM/IV (use succinate salt for IM/IV): 0.5–1.7 mg/kg/24 hr ÷ Q6–12 hr.

Asthma exacerbations (2007 National Heart, Lung, and Blood Institute Guideline Recommendations; dose until peak expiratory flow reaches 70% of predicted or personal best):

Child ≤12 yr (IV/IM/PO; use succinate salt for IV/IM): 1–2 mg/kg/24 hr ÷ Q12 hr (**max. dose**: 60 mg/24 hr). Higher alternative regimen of 1 mg/kg/dose Q6 hr ×48 hr followed by 1–2 mg/kg/24 hr (**max. dose**: 60 mg/24 hr) ÷ Q12 hr has been suggested.

Child >12 yr and adult (IV/IM/PO; use succinate salt for IV/IM): 40–80 mg/24 hr ÷ Q12–24 hr.

Outpatient asthma exacerbation burst therapy (longer durations may be necessary):

PO:

Child ≤12 yr: 1–2 mg/kg/24 hr ÷ Q12–24 hr (**max. dose**: 60 mg/24 hr) ×3–10 days.

Child >12 yr and adult: 40–60 mg/24 hr ÷ Q12–24 hr ×3–10 days.

IM (use methylprednisolone acetate product) for patients vomiting or with adherence issues:

Child ≤4 yr: 7.5 mg/kg (**max. dose**: 240 mg) IM ×1

Child >4 yr, adolescent, and adult: 240 mg IM ×1.

Acute spinal cord injury:

30 mg/kg IV over 15 min followed in 45 min by a continuous infusion of 5.4 mg/kg/hr ×23 hr.

See Chapter 10 for relative steroid potencies. Acetate form may also be used for intra-articular and intralesional injection and has longer times to max. effect and duration of action; it should **NOT** be given IV. **Use with caution** with systemic sclerosis. Like all steroids, may cause hypertension, leukocytosis, pseudotumor cerebri, acne, Cushing syndrome, adrenal axis suppression, GI bleeding, hyperglycemia, and osteoporosis.

Barbiturates, phenytoin, and rifampin may enhance methylprednisolone clearance. Erythromycin, itraconazole, and ketoconazole may increase methylprednisolone levels. Methylprednisolone may increase cyclosporine and tacrolimus levels.

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For explanation of icons, see p. 667

METOCLOPRAMIDE
Reglan and generics
Antiemetic, prokinetic agent

Tabs: 5, 10 mg
Tabs, orally disintegrating (ODT): 5, 10 mg
Injection: 5 mg/mL (2 mL)
Oral solution: 5 mg/5 mL (473 mL)

Gastroesophageal reflux (GER) or GI dysmotility:
Infant and child: 0.1–0.2 mg/kg/dose up to QID IV/IM/PO; **max. dose**: 0.8 mg/kg/24 hr or 10 mg/dose
Adult: 10 mg/dose QAC and QHS IV/IM/PO
Antiemetic (child and adolescent): Premedicate with diphenhydramine to reduce extrapyramidal symptoms (EPS)
1–2 mg/kg/dose Q2–6 hr IV/IM/PO up to 5 doses/24 hr
Postoperative nausea and vomiting:
Child: 0.1–0.2 mg/kg/dose Q6–8 hr PRN IV; **max. dose:** 10 mg/dose
>14 yr and adult: 10 mg Q6–8 hr PRN IV

Contraindicated in GI obstruction, seizure disorder, tardive dyskinesia, pheochromocytoma, or in patients receiving drugs likely to cause EPS. May cause EPS, especially at higher doses. Sedation, headache, anxiety, depression, leukopenia, and diarrhea may occur. Neuroleptic malignant syndrome and tardive dyskinesia (increase risk with prolong duration of therapy; **avoid use** >12 wk) have been reported.
Metoclopramide is a substrate for CYP 450 2D6; inhibitors to this enzyme may increase risk metoclopramide toxicity. G6PD deficiency may increase risk for methemoglobinemia; **DO NOT** use methylene blue as it may cause a fatal hemolytic anemia.
For GER, give 30 min before meals and at bedtime. **Reduce dose in renal impairment (see Chapter 31).**

METOLAZONE
Generics; previously available as Zaroxolyn
Diuretic, thiazide-like

Tabs: 2.5, 5, 10 mg
Oral suspension: 0.25 mg/mL, 1 mg/mL

Dosage based on Zaroxolyn (for oral suspension, see remarks):
Child:
Edema: 0.2–0.4 mg/kg/24 hr ÷ once daily–BID PO
Adult:
Hypertension: 2.5–5 mg once daily PO
Edema: 2.5–20 mg once daily PO

Contraindicated in patients with anuria, hepatic coma, or hypersensitivity to sulfonamides or thiazides. **Use with caution** in severe renal disease, impaired hepatic function, gout, lupus erythematosus, diabetes mellitus, and elevated cholesterol and triglycerides. Electrolyte imbalance, GI disturbance, hyperglycemia, marrow suppression, chills, hyperuricemia, chest pain, hepatitis, and rash may occur.
Oral suspensions have increased bioavailability; therefore lower doses may be necessary when using these dosage forms. More effective than thiazide diuretics in impaired renal function; may be effective in GFRs as low as 20 mL/min. Furosemide-resistant edema in pediatric patients may

METOPROLOL
Lopressor, Toprol-XL, Kapspargo Sprinkle, and generics
Adrenergic blocking agent (β_1 selective), class II antiarrhythmic

Tabs: 25, 37.5, 50, 75, 100 mg
Extended-release tabs (Toprol-XL and generics): 25, 50, 100, 200 mg
Extended-release caps as sprinkles (Kapspargo Sprinkle): 25, 50, 100, 200 mg; contains corn starch
Oral liquid: 10 mg/mL
Injection: 1 mg/mL (5 mL)

Hypertension:

Child ≥1 yr and adolescent

Non–extended-release oral-dosage forms: Start at 1–2 mg/kg/24 hr PO ÷ BID (**max. initial dose:** 25 mg/dose); if needed, adjust dose up to a **max. dose** of 6 mg/kg/24 hr **up to** 200 mg/24 hr.

Extended-release tabs (≥6 yr and adolescent): Start at 1 mg/kg/dose (**max. dose:** 50 mg) PO once daily; if needed, adjust dose **up to** a **max. dose** of 2 mg/kg/24 hr or 200 mg/24 hr once daily (higher doses have not been evaluated).

Adult:

Non–extended-release tabs: Start at 50–100 mg/24 hr PO ÷ once daily–BID; if needed, increase dosage at weekly intervals to desired blood pressure. Usual effective dosage range is 100–200 mg/24 hr. Doses >450 mg/24 hr have not been studied. Patients with bronchospastic diseases should receive the lowest possible daily dose divided TID.

Extended-release tabs: Start at 25–100 mg/24 hr PO once daily; if needed, increase dosage at weekly intervals to desired blood pressure. Usual dosage range is 50–200 mg/24 hr. Doses >400 mg/24 hr have not been studied.

Contraindicated in sinus bradycardia, heart block >1st degree, sick sinus syndrome (except with functioning pacemaker), cardiogenic shock, and uncompensated CHF. **Use with caution** in hepatic dysfunction, peripheral vascular disease, history of severe anaphylactic hypersensitivity drug reactions, pheochromocytoma, and concurrent use with verapamil, diltiazem, or anesthetic agents that may decrease myocardial function. Should not be used with bronchospastic diseases. Reserpine and other drugs that deplete catecholamines (e.g., MAO inhibitors) may increase the effects of metoprolol. Metoprolol is a CYP 450 2D6 substrate. Poor metabolizers and extensive metabolizers who concomitantly use CYP 2D6 inhibitors will have significant increases in metoprolol blood levels to decrease its cardioselectivity.

Avoid abrupt cessation of therapy in ischemic heart disease; angina, ventricular arrhythmias, and MI have occurred. Common side effects include bradyarrhythmia, heart block, heart failure, pruritus, rash, GI disturbances, dizziness, fatigue, and depression. Bronchospasm, dyspnea, and elevations in transaminase, alkaline phosphatase, and LDH have all been reported.

METRONIDAZOLE
Flagyl, First-Metronidazole, MetroGel, MetroLotion, MetroCream, Rosadan, Noritate, Vandazole, Nuvessa, and generics
Antibiotic, antiprotozoal

Tabs: 250, 500 mg
Caps: 375 mg
Oral suspension: 50 mg/mL
First-Metronidazole: 50 mg/mL (150 mL), 100 mg/mL (150 mL); contains sodium benzoate and saccharin

For explanation of icons, see p. 667

METRONIDAZOLE *continued*

Ready-to-use injection: 5 mg/mL (100 mL); contains 28 mEq Na/g drug
Gel, topical:
Rosadan and generics: 0.75% (45 g)
MetroGel and generics: 1% (55, 60 g)
Lotion (MetroLotion and generics): 0.75% (59 mL); contains benzyl alcohol
Cream, topical:
MetroCream, Rosadan and generics: 0.75% (45 g); contains benzyl alcohol
Noritate: 1% (60 g); contains parabens
Gel, vaginal:
Vandazole, and generics: 0.75% (each applicator delivers ~5 g of gel containing ~37.5 mg metronidazole); contains parabens (70 g with 5 applicators)
Nuvessa: 1.3%: (each applicator delivers ~5 g containing ~65 mg metronidazole); contains parabens and benzyl alcohol (1 prefilled applicator)

Amebiasis:
Child: 35–50 mg/kg/24 hr PO ÷ Q8 hr ×10 days; **max. dose**: 750 mg/dose
Adult: 500–750 mg/dose PO Q8 hr ×10 days
Anaerobic infection (see remarks):
Neonate: PO/IV:
Loading dose (all ages): 15 mg/kg ×1
Maintenance dose based on postmenstural age (PMA):
PMA 24–25 wk: 7.5 mg/kg/dose Q24 hr
PMA 26–27 wk: 10 mg/kg/dose Q24 hr
PMA 28–33 wk: 7.5 mg/kg/dose Q12 hr
PMA 34–40 wk: 7.5 mg/kg/dose Q8 hr
PMA >40 wk: 7.5 mg/kg/dose Q6 hr
Infant/child/adolescent:
PO: 30–50 mg/kg/24 hr ÷ Q8 hr; **max. dose**: 2250 mg/24 hr
IV: 22.5–40 mg/kg/24 hr ÷ Q6–8 hr; **max. dose**: 4 g/24 hr
Adult:
PO/IV: 30 mg/kg/24 hr ÷ Q6–8 hr; **max. dose**: 4 g/24 hr. A 15 mg/kg/dose IV loading dose over 1 hr is administered 6 hr prior to the aforementioned maintenance dose for IV route.
Bacterial vaginosis:
Adolescent and adult:
PO:
Immediate-release tabs: 500 mg BID ×7 days
Vaginal:
Vaginal gel 0.75% (Adolescent and adult): ~37.5 mg (1 applicator full) QHS ×5 days
Vaginal gel 1.3% (≥12 yr and adult): ~65 mg (1 applicator full) at bedtime ×1
Giardiasis:
Child: 15–30 mg/kg/24 hr PO ÷ TID ×5–7 days; **max. dose**: 750 mg/24 hr
Adult: 250 mg PO TID ×5 days
Trichomoniasis: Treat sexual contacts.
Child <45 kg: 45 mg/kg/24 hr PO ÷ TID ×7 days; **max. dose**: 2000 mg/24 hr
Child ≥45 kg, adolescent/adult: 2 g PO ×1, or 500 mg PO BID ×7 days.
Clostridium difficile infection (IV may be less efficacious):
Child: 30 mg/kg/24 hr ÷ Q6 hr PO/IV ×10–14 days; **max. dose:** 2000 mg/24 hr
Severe fulminant infection (with oral or rectal vancomycin): 30 mg/kg/24 hr ÷ Q8 hr IV ×10 days
Adult: 500 mg TID PO/IV ×10–14 days
Severe fulminant infection (with oral or rectal vancomycin): 500 mg IV Q8 hr.

METRONIDAZOLE *continued*

Helicobacter pylori ***infection (use in combination with amoxicillin and acid-suppressing agent with/without clarithromycin):***
Child: 20 mg/kg/24 hr (**max. dose:** 1000 mg/24 hr) ÷ BID PO ×10–14 days
Adult: 250–500 mg TID–QID (QAC and QHS) PO ×10–14 days

Topical use: Apply and rub a thin film to affected areas at the following frequencies specific to product concentration.
0.75% cream: BID
1% cream: once daily

Avoid use in first-trimester pregnancy. **Use with caution** in patients with CNS disease, blood dyscrasias, severe liver (reduce dose by 50% with Child-Pugh C), or **renal disease (GFR <10 mL/min; see Chapter 31).** If using single 2-g dose in a breast-feeding mother, discontinue breastfeeding for 12–24 hr to allow excretion of the drug.

Nausea, diarrhea, urticaria, dry mouth, leukopenia, vertigo, metallic taste, and peripheral neuropathy may occur. Candidiasis may worsen. May discolor urine. Patients **should not** ingest alcohol for 24–48 hr after dose (disulfiram-type reaction). Fatal hepatotoxicity has been reported with individuals with Cockayne syndrome.

Single-dose oral regimen no longer recommended in bacterial vaginosis due to poor efficacy. May increase levels or toxicity of phenytoin, lithium, and warfarin. Phenobarbital and rifampin may increase metronidazole metabolism.

IV infusion must be given slowly over 1 hr. For intravenous use in all ages, some references recommend a 15-mg/kg loading dose.

MICAFUNGIN SODIUM
Mycamine
Antifungal, echinocandin

Injection: 50, 100 mg; contains lactose

Invasive candidiasis (see remarks):
Neonate and infant (based on a multidose pharmacokinetic and safety trial in 13 neonates/infants >48 hr and <120 days old with suspected or invasive candidiasis; minimum of 4–5 days of therapy):
<1 kg: 10 mg/kg/dose IV once daily; additional data from another multidose trial in 12 preterm neonates (median birth weight: 775 g, 27 wk gestation) suggest 15 mg/kg/dose IV once daily will provide similar AUC drug exposure of approximately 5 mg/kg/dose in adults.
≥1 kg: 7–10 mg/kg/dose IV once daily; 10–12 mg/kg/dose IV once daily may be needed for HIV-exposed/infected neonates.
Child and adolescent: 3–4 mg/kg/dose IV once daily; **max. dose**: 100 mg/dose
Adult: 100–150 mg IV once daily
Esophageal candidiasis, invasive aspergillosis, candidal endocarditis (see remarks):
Infant (≥1 mo), child and adult: 4 mg/kg/dose IV once daily; **max. dose:** 150 mg/24 hr
Adult: 150 mg IV once daily
Candida prophylaxis in hematopoietic stem cell transplant:
Infant (1 mo), child and adult: 1 mg/kg/dose IV once daily; **max. dose**: 50 mg/dose

Prior hypersensitivity to other echinocandins (anidulafungin, casopofungin) increases risk; anaphylaxis with shock has been reported. **Use with caution** in hepatic and renal impairment.

Continued

For explanation of icons, see p. 667

MICAFUNGIN SODIUM *continued*

No dosing adjustments are required based on race or gender, or in patients with severe renal dysfunction or mild to moderate hepatic function impairment. Effect of severe hepatic function impairment on micafungin pharmacokinetics has not been evaluated. Higher dosage requirements in premature and young infants may be attributed to the faster drug clearance due to lower protein binding. Higher treatment doses in infants and children have been reported at 8.6–12 mg/kg/dose IV once daily.

May cause GI disturbances, phlebitis, rash, hyperbilirubinemia, liver function test elevation, headache, fever, and rigor. Anemia, leukopenia, neutropenia, thrombocytopenia, TEN, Stevens-Johnson syndrome, and hemolysis have been reported. Micafungin is CYP450 3A isoenzyme substrate and weak inhibitor. May increase the effects/toxicity of nifedipine and sirolimus.

Safety and efficacy in children ≥4 mo have been demonstrated based on well-controlled studies and pharmacokinetic/safety studies.

MICONAZOLE

Topical products: Micatin, Desenex, Lotrimin AF, and other brands including generics
Vaginal products: Miconazole 7, Miconazole 3, Monistat, Vagistat-3, and other brands including generics
Antifungal agent

Cream (OTC): 2% (15, 30, 57, 118, 141 g); may contain benzoic acid
Ointment (OTC): 2% (43, 71, 85, 90 g)
Solution (OTC): 2% with alcohol (29.57 mL)
Topical solution (OTC): 2% with alcohol (30 mL)
Powder (OTC): 2% (43, 71, 85, 90 g)
Spray, liquid (OTC): 2% (150 g); contains alcohol
Spray, powder (OTC): 2% (85, 113, 133, 150 g); contains alcohol
Vaginal cream (OTC): 2% (45 g); contains benzoic acid
Vaginal suppository (OTC): 100 mg (7s), 200 mg (3s)
Vaginal combination packs:
Monistat 1 Combination Pack (OTC): 1200 mg suppository (1) and 2% cream (9 g)
Miconazole 3 Combo Pack, Monistat 3 Combo Pack, Vagistat-3 (OTC): 200 mg suppository (3s) and 2% cream (9 g)
Monistat 7 Combo Pack (OTC): 100 mg suppository (7s) and 2% cream (9 g)

Topical (≥2 yr and adolescent): Apply BID ×2–4 wk
Vaginal (≥12 yr and adult):
7-day regimen: 1 applicator full of 2% cream or 100 mg suppository QHS ×7 days
3-day regimen: 1 applicator full of 4% cream or 200 mg suppository QHS ×3 days
1-day regimen (Monistat 1): 1200 mg suppository ×1 at bedtime or during the day.

Use with caution in hypersensitivity to other imidazole antifungal agents (e.g., clotrimazole, ketoconazole). Side effects include pruritis, rash, burning, phlebitis, headaches, and pelvic cramps.

Drug is a substrate and inhibitor of the CYP 450 3A3/4 isoenzymes. Vaginal use with concomitant warfarin use has also been reported to increase warfarin's effect. Vegetable oil base in vaginal suppositories may interact with latex products (e.g., condoms and diaphragms); consider switching to the vaginal cream.

Avoid contact with eyes.

MIDAZOLAM
Nayzilam and various generics; previously available as Versed
Benzodiazepine

Injection: 1 mg/mL (2, 5, 10 mL), 5 mg/mL (1, 2, 5, 10 mL); some preparations may contain 1% benzyl alcohol
Oral syrup: 2 mg/mL (118 mL); contains sodium benzoate
Nasal solution (Nayzilam): 5 mg per 0.1 mL (2s); contains propylene glycol

Titrate to effect under controlled conditions (see remarks).
See Chapter 6 for additional routes of administration.

Sedation for procedures:

Infant, child, and adolescent:

IM: 0.1–0.15 mg/kg/dose 30–60 min prior to procedure. Higher dose of 0.5 mg/kg/dose has been used for anxious patients. **Max. dose**: 10 mg.

IV:

6 mo–5 yr: 0.05–0.1 mg/kg/dose over 2–3 min. May repeat dose PRN in 2–3 min intervals up to a **max. total dose** of 6 mg. A total dose up to 0.6 mg/kg may be necessary for desired effect.

6–12 yr: 0.025–0.05 mg/kg/dose over 2–3 min. May repeat dose PRN in 2–3 min intervals up to a **max. total dose** of 10 mg. A total dose up to 0.4 mg/kg may be necessary for desired effect.

>12–16 yr: Use adult dose; up to **max. total dose** of 10 mg.

PO:

≥6 mo, child, and adolescent <16 yr: 0.25–0.5 mg/kg/dose ×1; **max. dose**: 20 mg. Younger patients (6 mo–5 yr) may require higher doses of 1 mg/kg/dose, whereas older patients (6–15 yr) may require only 0.25 mg/kg/dose. Use 0.25 mg/kg/dose for patients with cardiac or respiratory compromise, concurrent CNS depressive drug, or high-risk surgery.

Intranasal (limited data; using IV dosage form):

Infant, child, and adolescent: 0.2–0.3 mg/kg/dose (**max.** 10 mg/dose) intranasally via an atomizer ×1. Higher doses of 0.4–0.5 mg/kg/dose (**max.** 10 mg/dose) have also been reported.

Adult:

IM: 0.07–0.08 mg/kg/dose 30–60 min prior to procedure; usual dose is 5 mg.

IV: 0.5–2 mg/dose over 2 min. May repeat PRN in 2–3 min intervals until desired effect. Usual total dose: 2.5–5 mg. **Max. total dose**: 10 mg.

Sedation with mechanical ventilation:

Intermittent:

Infant and child: 0.05–0.15 mg/kg/dose IV Q1–2 hr PRN

Continuous IV infusion (initial doses, titrate to effect):

Neonate:

<32-wk gestation: 0.5 mCg/kg/min

≥32-wk gestation: 1 mCg/kg/min

Infant and child: 1–2 mCg/kg/min

Refractory status epilepticus:

≥2 mo and child: Load with 0.15 mg/kg IV ×1 followed by a continuous infusion of 1 mCg/kg/min; titrate dose upward Q5 min to effect (mean dose of 2.3 mCg/kg/min with a range of 1–18 mCg/kg/min has been reported).

Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy:

≥12 yr and adult (Nayzilam intranasal; see remarks): Administer one spray (5 mg) intranasally into one nostril. If no response in 10 min, administer an additional 5 mg spray into the alternative nostril. **Do not** administer the second dose if patient has trouble breathing or if there is excessive

Continued

For explanation of icons, see p. 667

MIDAZOLAM *continued*

sedation that is uncharacteristic of the patient during a seizure episode. **Max. dose**: 10 mg/dose per episode; **not to exceed** one episode every 3 days and 5 episodes per month.

Contraindicated in patients with narrow-angle glaucoma and shock. **Use with caution** in CHF, renal impairment **(adjust dose; see Chapter 31)**, pulmonary disease, hepatic dysfunction, and neonates. Causes respiratory depression, hypotension, and bradycardia. Cardiovascular monitoring is recommended. Use lower doses or reduce dose when given in combination with narcotics or in patients with respiratory compromise.

Higher recommended dosage for younger patients (6 mo–5 yr) is attributed to the water-soluble properties of midazolam and the higher percent body water for younger patients.

Drug is a substrate for CYP 450 3A4. Serum concentrations may be increased by cimetidine, clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ranitidine, and protease inhibitors (**use contraindicated**). Sedative effects may be antagonized by theophylline. **Effects can be reversed by flumazenil.** For pharmacodynamic information, see Chapter 6.

Do not prime Nayzilam intranasal dosage form, because this will promote drug loss.

MILRINONE
Generics; previously available as Primacor
Inotrope, phosphodiesterase inhibitor

Injection: 1 mg/mL (10, 20, 50 mL)
Premixed injection in D_5W: 200 mCg/mL (100, 200 mL)

Child (limited data): 50 mCg/kg IV bolus over 15 min, followed by a continuous infusion of 0.25–0.75 mCg/kg/min and titrate to effect.
Adult: 50 mCg/kg IV bolus over 10 min, followed by a continuous infusion of 0.375–0.75 mCg/kg/min and titrate to effect. **Max. dose:** 1.13 mg/kg/24 hr.

Contraindicated in severe aortic stenosis, severe pulmonic stenosis, and acute MI. May cause headache, dysrhythmias, hypotension, hypokalemia, nausea, vomiting, anorexia, abdominal pain, hepatotoxicity, and thrombocytopenia. Pediatric patients may require higher mCg/kg/min doses because of a faster elimination $T_{½}$ and larger volume of distribution, when compared with adults. Hemodynamic effects can last up to 3–5 hr after discontinuation of infusion in children. **Reduce dose in renal impairment.**

MINERAL OIL
GoodSense Mineral Oil, Kondremul, Fleet Mineral Oil, and generics
Laxative, lubricant

Liquid, oral (GoodSense Mineral Oil and generics; OTC): 30, 472, 500, 1000 mL
Emulsion, oral (Kondremul; OTC): 480 mL; each 5 mL Kondremul contains 2.5 mL mineral oil
Rectal liquid (Fleet Mineral Oil and generics; OTC): 133 mL bottle delivers approximately 120 mL

Constipation:
Child 6–11 yr (see remarks):
Oral liquid: 5–15 mL/24 hr ÷ once daily–TID PO
Oral emulsion (Kondremul): 10–30 mL/24 hr ÷ once daily–TID PO
Rectal (2–11 yr): 66.5 mL as single dose
Child ≥12 yr and adult (see remarks):

MINERAL OIL *continued*

Oral emulsion (Kondremul): 30–90 mL/24 hr ÷ once daily–TID PO
Rectal:
2–<12 yr: ~60 mL (half-bottle) as a single dose
≥12 yr and adult: ~120 mL as single dose

May cause diarrhea, cramps, and lipid pneumonitis via aspiration. Use as a laxative **should not exceed** >1 wk. Onset of action is approximately 6–8 hr. Higher doses may be necessary to achieve desired effect. **DO NOT** give QHS dose and use with **caution** in children <5 yr to minimize risk of aspiration. May impair the absorption of fat-soluble vitamins, calcium, phosphorus, oral contraceptives, and warfarin. Emulsified preparations are more palatable and are dosed differently than the oral liquid preparation.

For disimpaction, doses up to 1 ounce (30 mL) per year of age (**max. dose** of 240 mL) BID can be given.

MINOCYCLINE
Minocin, Solodyn, Minolira, Ximino, Amzeeq, and generics
Antibiotic, tetracycline derivative

D X Yes Yes No

Tabs: 50, 75, 100 mg
Caps: 50, 75, 100 mg
Extended-release tabs (Q24 hr dosing):
Solodyn and generics: 55, 65, 80, 105, 115 mg
Minolira: 105, 135 mg
Other generics: 45, 90, 135 mg
Extended-release caps (Q24 hr dosing):
Ximino: 45, 90, 135 mg
Injection (Minocin): 100 mg; may contain 2.2 mEq magnesium/100 mg drug
Topical foam (Amzeeq): 4% (30 g); contains alcohols and dispensed in a pressurized container with butane, isobutane, and propane propellants

General infections:
Child (8–12 yr): 4 mg/kg/dose (**max. dose**: 200 mg/dose) ×1 IV/PO, then 2 mg/kg/dose Q12 hr IV/PO; **max. dose**: 200 mg/24 hr
Adolescent and adult: 200 mg/dose ×1 IV/PO, then 100 mg Q12 hr IV/PO
Chlamydia trachomatis/Ureaplasma urealyticum:
Adolescent and adult: 100 mg IV/PO Q12 hr ×7 days
Acne (≥12 yr–adult):
Immediate-release dosage forms: 50–100 mg PO once daily–BID
Extended-release tabs:
Solodyn and generics:
45–49 kg: 45 mg PO once daily
50–59 kg: 55 mg PO once daily
60–71 kg: 65 mg PO once daily
72–84 kg: 80 mg PO once daily
85–96 kg: 90 mg PO once daily
97–110 kg: 105 PO once daily
111–125 kg: 115 mg PO once daily
126–136 kg: 135 mg PO once daily

Continued

For explanation of icons, see p. 667

MINOCYCLINE *continued*

Acne (≥12 yr–adult, cont.):

Minolira:

45–59 kg: 52.5 mg (half of 105 mg tab)

60–89 kg: 67.5 mg (half of 135 mg tab) PO once daily

90–125 kg: 105 mg PO once daily

126–136 kg: 135 mg PO once daily

Extended-release caps:

Ximino:

45–59 kg: 45 mg PO once daily

60–90 kg: 90 mg PO once daily

91–136 kg: 135 mg PO once daily

Topical foam (Amzeeq; moderate-to-severe acne vulgaris):

≥9 yr and adult (see remarks): Apply to affected areas QHS until all areas are treated

Not recommended for children <8 yr and during the last half of pregnancy due to risk of permanent tooth discoloration. **Use with caution** in renal failure, lower dosage may be necessary. High incidence of vestibular dysfunction (30%–90%). Nausea, vomiting, allergy, increased intracranial pressure (e.g., pseudotumor cerebri), photophobia, and injury to developing teeth may occur. Hepatitis, including autoimmune hepatitis, liver failure, hypersensitivity reactions (e.g., anaphylaxis, Stevens Johnson syndrome, erythema multiforme), serum sickness–like and lupus-like syndrome have been reported.

May increase effects/toxicity of warfarin and decrease the efficacy of live attenuated oral typhoid vaccine. May be administered with food but **NOT** with milk or dairy products. See Tetracycline for additional drug/food interactions and comments.

TOPICAL USE: Dosage form is flammable; **avoid** smoking during and immediately after application. Not for oral, ophthalmic, or intravaginal use. Headache is the most common side effect. Hyperpigmentation, erythema, dryness, itching, and headache have also been reported.

MINOXIDIL

Tabs: Generics; previously available as Loniten

Topical: Rogaine Men's/Women's, Minoxidil for Men/Women, Hair Regrowth Treatment Men, Men's Rogaine Extra Strength

Antihypertensive agent, hair growth stimulant

C 2 Yes Yes No

Tabs: 2.5, 10 mg

Topical solution:

Minoxidil for Men, Minoxidil for Women, Rogaine, and generics (OTC): 2% (60 mL)

Hair Regrowth Treatment for Men, Men's Rogaine Extra Strength, Minoxidil Extra Strength for Men, and generics (OTC): 5% (60, 120 mL); contains 30% alcohol

Topical foam:

Rogaine Men's, Rogaine Women's, Rogaine Extra Strength (OTC): 5% (60 g); contains cetyl alcohol

Hypertension:

Child <12 yr: Start with 0.1–0.2 mg/kg/24 hr PO once daily; **max. dose**: 5 mg/24 hr. Dose may be increased in increments of 0.1–0.2 mg/kg/24 hr at 3-day intervals. Usual effective range: 0.25–1 mg/kg/24 hr PO ÷ once daily–TID; **max. dose**: 50 mg/24 hr.

≥12 yr and adult: Start with 5 mg PO once daily. Dose may be gradually increased at 3-day intervals. Usual effective range: 10–40 mg/24 hr ÷ once daily–TID; **max. dose**: 100 mg/24 hr.

MINOXIDIL continued

Topical (alopecia; see remarks):

Adult:

Solution (2% or 5%): Apply 1 mL to affected areas of the scalp BID (QAM and QHS)

Foam:

Female: Apply ½ capful to affected areas of the scalp once daily

Male: Apply ½ capful to affected areas of the scalp BID

Contraindicated in acute MI, dissecting aortic aneurysm, and pheochromocytoma. Concurrent use with a β-blocker and diuretic is recommended to prevent reflex tachycardia and reduce water retention, respectively. Use with **caution** in hepatic impairment as decrease in drug clearance has been reported in mild cirrhosis for adults. May cause drowsiness, dizziness, CHF, pulmonary edema, pericardial effusion, pericarditis, thrombocytopenia, leukopenia, Stevens-Johnson syndrome, TEN, and hypertrichosis (reversible) with systemic use. Neonatal hypertrichosis has been reported following use during pregnancy.

Concurrent use of guanethidine may cause profound orthostatic hypotension; use with other antihypertensive agents may cause additive hypotension. Patients with renal failure or receiving dialysis may require a dosage reduction. Antihypertensive onset of action within 30 min and peak effects within 2–8 hr.

TOPICAL USE: Local irritation, contact dermatitis may occur. **Do not use** in conjunction with other topical agents including topical corticosteroids, retinoids or petrolatum, or agents that are known to enhance cutaneous drug absorption. Onset of hair growth is 4 mo. Wash hands thoroughly after each application. The 5% solution is flammable.

MOMETASONE FUROATE ± FOMOTEROL FUMARATE

Asmanex, Nasonex, Elocon, and other generic nasal and topical products

In combination with fomoterol: Dulera

Corticosteroid

Nasal spray (Nasonex and generics): 0.05%, 50 mCg per actuation (17 g, provides 120 doses)

Aerosol for inhalation (Asmanex HFA): 50 mCg per actuation (13 g, provides 120 actuations), 100 mCg per actuation (13 g, provides 120 actuations), 200 mCg per actuation (13 g; provides 120 actuations)

Powder for inhalation, breath activated (Asmanex Twisthaler; see remarks): 110 mCg per actuation (7, 30 doses), 220 mCg per actuation (14, 60, 120 doses); contains lactose and milk proteins

Topical cream and ointment (Elocon and generics): 0.1% (15, 45 g)

Topical lotion (Elocon and generics): 0.1% (30, 60 mL); contains isopropyl alcohol

In combination with fomoterol:

Aerosol inhaler (Dulera):

50 mCg mometasone furoate + 5 mCg fomoterol fumarate dihydrate per inhalation (13 g delivers 120 inhalations)

100 mCg mometasone furoate + 5 mCg fomoterol fumarate dihydrate per inhalation (8.8 g delivers 60 inhalations, 13 g delivers 120 inhalations)

200 mCg mometasone furoate + 5 mCg fomoterol fumarate dihydrate per inhalation (8.8 g delivers 60 inhalations, 13 g delivers 120 inhalations)

Continued

For explanation of icons, see p. 667

MOMETASONE FUROATE ± FOMOTEROL FUMARATE *continued*

MOMETASONE FUROATE:

Intranasal (allergic rhinitis): Patients with known seasonal allergic rhinitis should initiate therapy 2–4 wk prior to anticipated pollen season.

Child 2–11 yr: 50 mCg (1 spray) each nostril once daily (100 mCg/24 hr)

Child ≥12 yr and adult: 100 mCg (2 sprays) each nostril once daily (200 mCg/24 hr).

Oral inhalation:

Asmanex HFA (aerosol for inhalation):

Child 5–<12 yr: 2 inhalations (100 mCg) BID of 50 mCg inhaler (200 mCg/24 hr)

Child ≥12 yr and adult: Max. effects may not be achieved until 2 wk. Titrate doses to lowest effective dose once asthma stabilized.

Previously treated with bronchodilators alone or medium-dose inhaled corticosteroids: 2 inhalations (200 mCg) BID of 100 mCg inhaler (400 mCg/24 hr)

Previously receiving high-dose inhaled or chronic oral corticosteroids: 2 inhalations (400 mCg) BID of 200 mCg inhaler (800 mCg/24 hr).

Max. dose (all ages): 800 mCg/24 hr.

Asmanex Twisthaler (breath activated powder for inhalation):

Child 4–11 yr: Start with 110 mCg (1 inhalation) QHS of the 110-mCg inhaler regardless of prior therapy. **Max. dose**: 110 mCg/24 hr.

Child ≥12 yr and adult: Max. effects may not be achieved until 1–2 wk or longer. Titrate doses to the lowest effective dose once asthma stabilized.

Previously treated with bronchodilators alone or with inhaled corticosteroids: Start with 220 mCg (1 inhalation) QHS. Dose may be increased up to a **max. dose** of 440 mCg/24 hr ÷ QHS or BID.

Previously treated with oral corticosteroids: Start with 440 mCg BID; **max. dose**: 880 mCg/24 hr.

Topical (see Chapter 8 for topical steroid comparisons):

Cream and ointment:

≥2 yr and adult: Apply a thin film to affected area once daily. Safety and efficacy for >3 wk has not been established for pediatric patients.

Lotion:

≥12 yr and adult: Apply a few drops to affected area and massage lightly into skin once daily until it disappears.

MOMETASONE FUROATE + FOMOTEROL FUMARATE (Dulera):

Child 5–<12 yr: Two inhalations BID of 50 mCg mometasone + 5 mCg fomoterol; **max. dose**: 2 inhalations BID

Child ≥12 yr and adult: Two inhalations BID of either 100 mCg mometasone + 5 mCg formoterol or 200 mCg mometasone + 5 mCg formoterol based on prior asthma therapy (see the following table). If using the lower strength (100 mCg mometasone + 5 mCg formoterol), allow for 2 wk of therapy before increasing to the higher strength if no adequate response. **Max. dose**: Two inhalations BID of 200 mCg mometasone + 5 mCg formoterol.

Previous Therapy	Recommended Starting Dose	Recommended Maximum Daily Dose
Medium-dose inhaled corticosteroids	100 mCg mometasone + 5 mCg formoterol: 2 inhalations BID	400 mCg mometasone + 20 mCg formoterol
High-dose inhaled corticosteroids	200 mCg mometasone + 5 mCg formoterol: 2 inhalations BID	800 mCg mometasone + 20 mCg formoterol

MOMETASONE FUROATE ± FOMOTEROL FUMARATE *continued*

Mometasone is a CYP 450 3A4 substrate; concurrent administration with ketoconazole and other CYP 450 3A4 inhibitors (e.g., protease inhibitors) may increase mometasone levels, resulting in Cushing syndrome and adrenal suppression. Blurred vision, cataracts, and glaucoma have been reported. Use with **caution** with hepatic impairment; increased drug exposure is possible.

INTRANASAL: Clear nasal passages and shake nasal spray well before each use. Onset of action for nasal symptoms of allergic rhinitis has been shown to occur within 11 hr after the first dose. Nasal burning and irritation may occur. Nasal septal perforation and taste and smell disturbances have been rarely reported. A clinical trial in children 6–17 yr old was not able to demonstrate effectiveness for treating nasal polyps.

ORAL INHALATION (all forms): Rinse mouth after each use. Fever, allergic rhinitis, URI, UTI, GI discomfort, and sore throat have been reported in children. Musculoskeletal pain, oral candidiasis, arthralgia, and fatigue may occur. May potentially worsen tuberculosis, fungal, bacterial, viral or parasitic infection, or ocular herpes simplex. **Do not use** Asmanex Twisthaler if allergic to milk proteins. The Twisthaler dosage form requires a minimum 30–60 L/min inspiratory flow rate to assure proper dose delivery. Breast-feeding information is currently unknown, but most experts consider use of inhaled corticosteroids acceptable.

MOMETASONE + FOMOTEROL (Dulera): Common side effects include nasopharyngitis, sinusitis, and headache. Angioedema, anaphylaxis, and arrhythmias have been reported. See Formoterol for additional remarks.

TOPICAL USE: HPA axis suppression and skin atrophy have been reported with cream and ointment use in infants 6–23 mo. **Avoid** application/contact to face, eyes, underarms, groin, and mucous membranes. Occlusive dressings and use in diaper dermatitis are not recommended.

MONTELUKAST

Singulair and generics

Antiasthmatic, antiallergy, leukotriene receptor antagonist

Chewable tabs: 4, 5 mg; contains phenylalanine
Tabs: 10 mg
Oral granules: 4 mg per packet (30s)

Asthma and allergic rhinitis:
Child (6 mo–5 yr): 4 mg (oral granules or chewable tablet) PO QHS; minimum age for use in asthma (per product label) is 12 mo.
Child (6–14 yr): 5 mg (chewable tablet) PO QHS
≥15 yr and adult: 10 mg PO QHS

Prevention of exercise-induced bronchospasm (administer dose at least 2 hr prior to exercise; additional doses should not be administered within 24 hr):
Child (6–14 yr): 5 mg (chewable tablet) PO
≥15 yr and adult: 10 mg PO

Chewable tablet dosage form is **contraindicated** in phenylketonuric patients. Side effects include: headache, abdominal pain, dyspepsia, fatigue, dizziness, cough, and elevated liver enzymes. Diarrhea, enuresis, epistaxis, pulmonary eosinophilia, thrombocytopenia, hypersensitivity reactions (including Stevens-Johnson and TEN), pharyngitis, nausea, otitis, sinusitis, and viral infections have been reported in children. Neuropsychiatric events, including aggression, anxiety, dream abnormalities, obsessive-compulsive symptoms, hallucinations, depression, suicidal behavior, and insomnia, have been reported.

Drug is a substrate for CYP 450 3A4 and 2C9. Phenobarbital and rifampin may induce hepatic metabolism to increase the clearance of montelukast.

Doses may be administered with or without food.

D

For explanation of icons, see p. 667

MORPHINE SULFATE
Roxanol, MS Contin, Avinza, Kadian, Arymo ER, MorphaBond ER, and many generics
Narcotic, analgesic

Oral solution: 10 mg/5 mL, 20 mg/5 mL
Concentrated oral solution: 100 mg/5 mL
Tabs: 15, 30 mg
Controlled-release tabs:
MS Contin and generics: 15, 30, 60, 100, 200 mg
Extended-release tabs:
MorphaBond ER: 15, 30, 60, 100 mg
Arymo ER: 15, 30, 60 mg
Extended-release caps:
Avinza (10% of dose as immediate release): 30, 60, 90, 120 mg
Kadian: 10, 20, 30, 40, 50, 60, 80, 100, 200 mg
Generics: 10, 20, 30, 40, 45, 50, 60, 75, 80, 90, 100, 120 mg
Rectal suppository: 5, 10, 20, 30 mg (12s)
Injection: 0.5, 1, 2, 4, 5, 8, 10, 15, 25, 50 mg/mL

Titrate to effect.
Neonate:
Analgesia/tetralogy (cyanotic) spells: 0.05–0.2 mg/kg/dose IM, slow IV, SC Q4 hr
Opiate withdrawal: 0.08–0.2 mg/kg/dose PO Q3–4 hr PRN
Infant 1–6 mo:
Analgesia:
PO: 0.08–0.1 mg/kg/dose Q3–4 hr PRN
IV: 0.025–0.03 mg/kg/dose Q2–4 hr PRN
Infant >6 mo and child:
Analgesia:
PO: 0.2–0.5 mg/kg/dose (**initial max. dose**: 15–20 mg/dose) Q4–6 hr PRN (immediate release) or 0.3–0.6 mg/kg/dose Q12 hr PRN (controlled release)
IM/IV/SC: 0.1–0.2 mg/kg/dose Q2–4 hr PRN; **max. initial dose**: infant: 2 mg/dose, 1–6 yr: 4 mg/dose, 7–12 yr: 8 mg/dose, and adolescent: 10 mg/dose.
Adult (analgesia):
PO: 10–30 mg Q4 hr PRN (immediate release) or 15–30 mg Q8–12 hr PRN (controlled release)
IM/IV/SC: 2–15 mg/dose Q2–6 hr PRN
Continuous IV infusion and SC infusion: Dosing ranges, titrate to effect.
Neonate (IV route only): 0.01–0.02 mg/kg/hr
Infant and child:
Postoperative pain: 0.01–0.04 mg/kg/hr
Sickle cell and cancer: 0.04–0.07 mg/kg/hr
Adult: 0.8–10 mg/hr
To prepare infusion for neonates, infants, and children, use the following formula:

$$50 \times \frac{\text{Desired dose (mg/kg/hr)}}{\text{Desired infusion rate (mL/hr)}} \times \text{Wt (kg)} = \frac{\text{mg morphine}}{\text{50 mL fluid}}$$

Dependence, CNS and respiratory depression, nausea, vomiting, urinary retention, constipation, hypotension, bradycardia, increased ICP, miosis, biliary spasm, and allergy may occur. Be aware of concomitant medications with similar side effect profiles.

D

MORPHINE SULFATE *continued*

Naloxone may be used to reverse effects, especially respiratory depression. Causes histamine release resulting in itching and possible bronchospasm. Low-dose naloxone infusion may be used for itching. Inflammatory masses (e.g., granulomas) have been reported with continuous infusions via indwelling intrathecal catheters.

Dosage reduction may be necessary with liver cirrhosis. See Chapter 6 for equianalgesic dosing. Pregnancy category changes to "D" if used for prolonged periods or in higher doses at term. Rectal dosing is same as oral dosing but is not recommended due to poor absorption. Controlled/sustained-release oral tablets must be administered whole. Controlled-release oral capsules may be opened and the entire contents sprinkled on applesauce immediately prior to ingestion. **Be aware** of the various oral solution concentrations; the concentrated oral solution (100 mg/5 mL) has been associated with accidental overdoses. **Adjust dose in renal failure (see Chapter 31).**

The FDA has assigned a REMS for Opioid Analgesia; see www.fda.gov/OpioidAnalgesicREMSPCG. The REMS strongly encourages the (1) completion of a REMS-compliant education program; (2) counsel patients/caregivers on prescription safe use, risks, storage, and disposal; (3) emphasize the importance of reading the Medication Guide provided by pharmacists at all times; and (4) consider other methods for improving patient, household, and community safety.

MUPIROCIN
Bactroban, Centany, Centany AT, Bactroban Nasal, and generics
Topical antibiotic

Ointment: 2% (15, 22, 30 g); contains propylene glycol
Cream: 2% (15, 30 g); may contain benzyl alcohol
Nasal ointment (Bactroban Nasal): 2% (1 g), as calcium salt

Topical (see remarks):
≥3 mo–adult: Apply small amount TID to affected area ×5–10 days. Topical ointment may be used in infants ≥2 mo for impetigo.

Intranasal for elimination of nasal colonization of* Staphylococcus aureus, *including MRSA:
Infant and child: Apply small amount intranasally BID ×5–10 days.
Child ≥12 yr and adult: Apply 500 mg (half of 1 g nasal ointment) intranasally BID ×5–10 days.

Avoid contact with the eyes. Topical cream is not intended for use in lesions >10 cm in length or 100 cm^2 in surface area. **Do not use** topical ointment preparation on open wounds because of concerns about systemic absorption of polyethylene glycol. May cause minor local irritation and dry skin. Intranasal route may cause nasal stinging, taste disorder, headache, rhinitis, and pharyngitis. Severe allergic reactions (e.g., anaphylaxis, urticaria, angioedema and rash) have been reported.

If clinical response is not apparent in 3–5 days with topical use, reevaluate infection.

MYCOPHENOLATE
Mycophenolate mofetil: CellCept and generics
Mycophenolic acid: Myfortic and generics
Immunosuppressant agent

Mycophenolate mofetil:
Caps: 250 mg
Tabs: 500 mg

For explanation of icons, see p. 667

MYCOPHENOLATE *continued*

Mycophenolate mofetil (cont.):
Oral suspension: 200 mg/mL (160 mL); contains phenylalanine (0.56 mg/mL) and methylparabens
Injection: 500 mg; may contain polysorbate 80
Mycophenolic acid:
Delayed-release tabs (Myfortic and generics): 180, 360 mg

Infant ≥3 mo, child, and adolescent (see remarks):
Renal transplant:
Caps, tabs, or suspension: 600 mg/m^2/dose PO/IV BID up to a **max. dose** of 2000 mg/24 hr; alternatively, patients with body surface areas (BSAs)**≥**1.25 m^2 may be dosed as follows:
1.25–1.5 m^2: 750 mg PO BID
>1.5 m^2: 1000 mg PO BID
Delayed-release tabs (Myfortic; ≥5 yr): 400 mg/m^2/dose PO BID; **max. dose**: 720 mg BID; this dosage form not recommended in patients with BSAs <1.19 m^2. Alternatively, patients with BSAs **≥**1.19 m^2 may be dosed as follows:
1.19–1.58 m^2: 540 mg PO BID
>1.58 m^2: 720 mg PO BID
Nephrotic syndrome:
Frequently relapsing: 12.5–18 mg/kg/dose or 600 mg/m^2/dose PO BID up to a **max. dose** of 2000 mg/24 hr for 1–2 yr and taper prednisone regimen.
Steroid dependent: 12–18 mg/kg/dose or 600 mg/m^2/dose PO BID up to a **max. dose** of 2000 mg/24 hr for at least 12 mo.
Adult (in combination with corticosteroids and cyclosporine; check specific transplantation protocol for specific dosage):
IV: 2000–3000 mg/24 hr ÷ BID
Oral:
Caps, tabs, or suspension: 2000–3000 mg/24 hr PO ÷ BID
Delayed-release tabs (Myfortic): 720–1080 mg PO BID

Check specific transplantation protocol for specific dosage. Mycophenolate mofetil is a prodrug for mycophenolic acid. Owing to differences in absorption, the delayed-release tablets should **not** be interchanged with other oral-dosage forms on an equivalent milligram-to-milligram basis. Increases risk of first trimester pregnancy loss and increased risk of congenital malformations (especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, and esophagus).

Common side effects may include headache, hypertension, diarrhea, vomiting, bone marrow suppression, anemia, fever, opportunistic infections, and sepsis. May cause drowsiness and increase the risk for bacterial, fungal, protozoal, and viral infections, and lymphomas or other malignancies. GI bleeds and increased risk for rejection in heart transplant patients switched from calcineurin inhibitors (e.g., cyclosporine and tacrolimus) and CellCept to sirolimus and CellCept have been reported. Cases of progressive multifocal leukoencephalopathy (PML), pure red cell aplasia (PRCA), posttransplant lymphoproliferative disorder (PTLD), and hypogammaglobulinemia have also been reported.

Use of mycophenolic acid (Myfortic) should be **avoided** in patients with hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency (e.g., Lesch-Nyhan and Kelley-Seegmiller syndrome) because it may exacerbate disease symptoms characterized by increased uric acid leading to acute arthritis, tophi, nephrolithiasis/urolithiasis, and renal failure.

Use with caution in patients with active GI disease or renal impairment (GFR <25 mL/min/1.73 m^2) outside of the immediate posttransplant period. In adults with renal impairment, **avoid** doses >2 g/24 hr and observe carefully. Dose should be interrupted or reduced in the presence of neutropenia (ANC <1.3 × 10^3/microliter). No dose adjustment is needed for patients experiencing delayed graft function postoperatively.

MYCOPHENOLATE *continued*

Drug interactions: (1) Displacement of phenytoin or theophylline from protein-binding sites will decrease total serum levels and increase free serum levels of these drugs. Salicylates displace mycophenolate to increase free levels of mycophenolate. (2) Competition for renal tubular secretion results in increased serum levels of acyclovir, ganciclovir, probenecid, and mycophenolate (when any of these are used together). (3) **Avoid** live and live attenuated vaccines (including influenza); decreases vaccine effectiveness. (4) Proton pump inhibitors, antacids, cholestyramine, cyclosporine, and telmisartan may reduce mycophenolate levels.

Administer oral doses on an empty stomach. Infuse intravenous doses over 2 hr. Oral suspension may be administered via NG tube with a minimum size of 8 Fr.

N

NAFCILLIN
Generics; previously available as Nallpen
Antibiotic, penicillin (penicillinase resistant)

Injection: 1, 2, 10 g; contains 2.9 mEq Na/g drug
Injection, premixed in iso-osmotic dextrose: 1 g in 50 mL, 2 g in 100 mL

Neonate (IM/IV):
<1 kg:
≤14 days old: 50 mg/kg/24 hr ÷ Q12 hr
15–28 days old: 75 mg/kg/24 hr ÷ Q8 hr
1–2 kg:
≤7 days old: 50 mg/kg/24 hr ÷ Q12 hr
8–28 days old: 75 mg/kg/24 hr ÷ Q8 hr
>2 kg:
≤7 days old: 75 mg/kg/24 hr ÷ Q8 hr
8–28 days old: 100 mg/kg/24 hr ÷ Q6 hr
Infant and child (IM/IV):
Mild to moderate infections: 100–150 mg/kg/24 hr ÷ Q6 hr
Severe infections: 150–200 mg/kg/24 hr ÷ Q4–6 hr; give 200 mg/kg/24 hr ÷ Q4–6 hr for Staphylococcal endocarditis or meningitis.
Max. dose: 12 g/24 hr
Adult:
IV: 1000–2000 mg Q4–6 hr
IM: 500–1000 mg Q4–6 hr
Max. dose: 12 g/24 hr

Allergic cross-sensitivity with penicillin. Solutions containing dextrose may be **contraindicated** in patients with known allergy to corn or corn products. High incidence of phlebitis with IV dosing. May cause rash, bone marrow suppression, and false-positive urinary and serum proteins. Hypokalemia has been reported. Acute interstitial nephritis is rare.

Cerebrospinal fluid (CSF) penetration is poor unless meninges are inflammed. **Use with caution** in patients with combined renal and hepatic impairment (reduce dose by 33%–50%). Nafcillin may increase elimination of cyclosporine and warfarin.

For explanation of icons, see p. 667

NALOXONE
Narcan, Evzio, and generics
Narcotic antagonist

Injection: 0.4 mg/mL (1, 10 mL); some preparations may contain parabens
Injection, in syringe: 2 mg/2 mL (2 mL)
Auto-injector (Evzio): 2 mg/0.4 mL (2 each with trainer device)
Nasal liquid (Narcan): 2 mg/0.1 mL (4 each), 4 mg/0.1 mL (2 each); contains benzalkonium chloride

Opiate intoxication (full reversal, IM/IV/SC, use 2–10 times IV dose for ETT route; see remarks):
Neonate, infant, child ≤20 kg or ≤5 yr: 0.1 mg/kg/dose. May repeat PRN Q2–3 min.
Child >20 kg or >5 yr: 2 mg/dose. May repeat PRN Q2–3 min.
Continuous infusion (child and adult): 0.005 mg/kg loading dose followed by infusion of 0.0025 mg/kg/hr has been recommended. A range of 0.0025–0.16 mg/kg/hr has been reported. Taper gradually to avoid relapse.
Adult: 0.4–2 mg/dose. May repeat PRN Q2–3 min. Use 0.1- to 0.2-mg increments in opiate-dependent patients.
Intranasal route for opiate intoxication (full reversal):
All ages: 4 mg (0.1 mL) of nasal liquid (Narcan) into one nostril Q2–3 min PRN in alternating nostrils.
Opioid-dependent patient at risk for opioid withdrawal: Use lower 2 mg (0.1 mL) nasal liquid (Narcan) into one nostril Q2–3 min PRN in alternating nostrils. Alternatively, the 2 mg/2 mL intravenous (IV) syringe dosage form with nasal adapter may be used by administering 1 mg (1 mL) per nostril.
Opiate-induced pruritus (limited data): 0.25–2 mCg/kg/hr IV; a dose-finding study in 59 children suggests a minimal dose of 1 mCg/kg/hr when used as prophylactic therapy. Doses ≥3 mCg/kg/hr increases the risk for reduced pain control.

Short duration of action may necessitate multiple doses. For severe intoxication, doses of 0.2 mg/kg may be required. If no response is achieved after a cumulative dose of 10 mg, reevaluate diagnosis. **In the nonarrest situation, use the lowest dose effective (may start at 0.001 mg/kg/dose). See Chapter 6 for additional information.**
Will produce narcotic withdrawal syndrome in patients with chronic dependence. Use with **caution** in patients with chronic cardiac disease. Abrupt reversal of narcotic depression may result in nausea, vomiting, diaphoresis, tachycardia, hypertension, and tremulousness. Aggressive behavior has been reported in abrupt reversal of an opioid overdose. False-positive test for urine opiates screen may occur.
IV administration is preferred. Onset of action may be delayed with other routes of administration.

NAPROXEN/NAPROXEN SODIUM
Naprosyn, EC-Naprosyn, Naprosyn DR, Naprelan, Aleve [OTC], and many others including generics
Nonsteroidal anti-inflammatory agent

Naproxen:
Tabs: 250, 375, 500 mg
Delayed release tabs (EC-Naprosyn, Naprosyn DR): 375, 500 mg
Oral suspension (Naprosyn and generics): 125 mg/5 mL; contains 0.34 mEq Na/1 mL and parabens

NAPROXEN/NAPROXEN SODIUM *continued*

Naproxen Sodium:

Tabs:

Aleve and generics (over the counter [OTC]): 220 mg (200 mg base); contains 0.87 mEq Na

Generics: 275 mg (250 mg base), 550 mg (500 mg base); contains, 1 mEq, 2 mEq Na, respectively

Controlled-release tabs (Naprelan and generics): 412.5 mg (375 mg base), 550 mg (500 mg base), 825 mg (750 mg base)

All doses based on naproxen base.

Child >2 yr:

Analgesia: 5–10 mg/kg/dose Q12 hr PO

JRA: 10–20 mg/kg/24 hr ÷ Q12 hr PO

Usual max. dose: 1000 mg/24 hr

Adolescent and adult:

Analgesia:

Over-the-counter dosage forms: 200 mg Q8–12 hr PRN PO (400 mg initial dose may be needed). **Max. dose**: 600 mg/24 hr.

Prescription-strength dosage forms: 250 mg Q8–12 hr PRN (500 mg initial dose may be needed) or 500 mg Q12 hr PRN PO. **Max. dose**: 1250 mg/24 hr for first day then 1000 mg/24 hr.

Rheumatoid arthritis, ankylosing spondylitis:

Immediate release forms: 250–500 mg BID PO

Delayed release tabs (EC-Naprosyn, Naprosyn DR): 375–500 mg BID PO

Controlled-release tabs (Naprelan): 750–1000 mg once daily PO. For patients converting from immediate and delayed release forms, calculate daily dose and administer Naprelan as a single daily dose.

Max. dose (all dosage forms): 1000–1500 mg/24 hr.

Dysmenorrhea:

500 mg × 1, then 250 mg Q6–8 hr PRN PO or 500 mg Q12 hr PRN PO; **max. dose**: 1250 mg/24 hr for first day then 1000 mg/24 hr.

Contraindicated in treating perioperative pain for coronary artery bypass graft surgery. May cause GI bleeding, thrombocytopenia, heartburn, headache, drowsiness, vertigo, and tinnitus. **Use with caution** in patients with GI disease, cardiac disease (risk for thrombotic events, myocardial infarction [MI], stroke), renal or hepatic impairment, and those receiving anticoagulants. False-positive test for urine cannabinoid screen may occur.

Use is **NOT** recommended for moderate/severe renal impairment (CrCl <30 mL/min). See ibuprofen for other side effects.

Pregnancy category changes to D if used in the third trimester or near delivery. Administer doses with food or milk to reduce GI discomfort.

NEO-POLYMYCIN OPHTHALMIC OINTMENT

See neomycin/polymyxin B ophthalmic products.

NEOSPORIN OPHTHALMIC SOLUTION

See neomycin/polymyxin B ophthalmic products.

NEO-POLYCIN HC

For explanation of icons, see p. 667

NEOMYCIN SULFATE
Generics
Antibiotic, aminoglycoside; ammonium detoxicant

Tabs: 500 mg
Oral solution: 25 mg/mL; contains parabens.
125 mg neomycin sulfate is equivalent to 87.5 mg neomycin base.

Enteric bacterial eradication:
Preterm (>1.2 kg) and newborn: 50 mg/kg/24 hr ÷ Q6 hr PO for up to 2 wk
Hepatic encephalopathy (limited data):
Infant and child: 50–100 mg/kg/24 hr ÷ Q6–8 hr PO × 5–6 days. **Max. dose:** 12 g/24 hr
Adult: 4–12 g/24 hr ÷ Q4–6 hr PO × 5–6 days
Bowel prep (in combination with erythromycin base; many other regimens exist):
Child: 90 mg/kg/24 hr PO ÷ Q4 hr × 2–3 days
Adult: 1 g Q1 hr PO × 4 doses, then 1 g Q4 hr PO × 5 doses

Contraindicated in ulcerative bowel disease, intestinal obstruction, or aminoglycoside hypersensitivity. Monitor for nephrotoxicity and ototoxicity. Oral absorption is limited, but levels may accumulate. Consider dosage reduction in the presence of renal failure. May cause itching, redness, edema, colitis, candidiasis, or poor wound healing if applied topically. Prevalence of neomycin hypersensitivity has increased. May decrease absorption of penicillin V, vitamin B_{12}, digoxin, and methotrexate. May potentiate oral anticoagulants and the adverse effects of other neurotoxic, ototoxic, or nephrotoxic drugs.

NEOMYCIN/POLYMYXIN B OPHTHALMIC PRODUCTS
Neomycin/Polymyxin B + Bacitracin:
Neo-Polycin and generics
Neomycin/Polymyxin B + Dexamethasone:
Maxitrol and generics
Neomycin/Polymyxin B + Gramicidin:
Generics
Neomycin/Polymyxin B + Hydrocortisone:
Generics
Neomycin/Polymyxin B + Bacitracin + Hydrocortisone:
Neo-Polycin HC and generics
Ophthalmic antibiotic ± corticosteroid

Neomycin/Polymyxin B + Bacitracin:
Ophthalmic ointment (Neo-Polycin Ophthalmic Ointment and generics): 3.5 g neomycin, 10,000 U polymyxin B, and 400 U bacitracin per g ointment (3.5 g)
Neomycin/Polymyxin B + Dexamethasone:
Ophthalmic ointment (Maxitrol and generics): 3.5 mg neomycin, 10,000 U polymyxin B, and 1 mg dexamethasone per 1 g (3.5 g);
Ophthalmic suspension (Maxitrol and generics): 3.5 mg neomycin, 10,000 U polymyxin B, and 1 mg dexamethasone per 1 mL (5 mL); contains benzalkonium chloride
Neomycin/Polymyxin B + Gramicidin:
Ophthalmic solution: 1.75 neomycin, 10,000 U polymyxin B, and 0.025 mg gramicidin per 1 mL (10 mL); contains propylene glycol, alcohol, and trimerosal

NEOMYCIN/POLYMYXIN B OPHTHALMIC PRODUCTS *continued*

Neomycin/Polymyxin B + Hydrocortisone:

Ophthalmic suspension: 3.5 mg neomycin, 10,000 U polymyxin B, and 10 mg hydrocortisone per 1 mL (7.5 mL)

Neomycin/Polymyxin B + Bacitracin + Hydrocortisone:

Ophthalmic ointment (Neo-Polycin HC and generics): 3.5 mg neomycin, 10,000 U polymyxin B, 400 U bacitracin, and 10 mg hydrocortisone per 1 g (3.5 g)

Neomycin/Polymyxin B + Bacitracin:

Child and adult: Apply 0.5-inch ribbon to affected eye(s) Q3–4 hr for acute infections or BID–TID for mild/moderate infections × 7–10 days.

Neomycin/Polymyxin B + Dexamethasone:

Child (≥2 yr)–adult:

Ophthalmic suspension: Instill 1–2 drops into the conjunctival sac of the affected eye(s) 4–6 times per day for mild/moderate infections. For severe infections, administered Q1 hr and taper to discontinuation as inflammation subsides. No more than 20 mL should be prescribed initially.

Ophthalmic ointment: Apply ~0.5-inch ribbon into the conjunctival sac of the affected eye(s) TID–QID. Reevaluate diagnosis if signs and symptoms do not improve in 48 hr. Do not dispense >8 g.

Neomycin/Polymyxin B + Gramicidin:

Child and adult: Instill 1–2 drops to affected eye(s) Q4 hr or 2 drops every hour for severe infections × 7–10 days.

Neomycin/Polymyxin B + Hydrocortisone:

Child and adult: Instill 1–2 drops to affected eye(s) Q3–4 hr. More frequent dosing has been used for severe infection in adults.

Neomycin/Polymyxin B + Bacitracin + Hydrocortisone:

Child and adult (limited data): Apply ointment sparingly to inside of lower lid of affected eye(s) Q3–4 hr. Reevaluate diagnosis if signs and symptoms do not improve in 48 hr. Monitor intraocular pressure if use is equal to or greater than 10 days.

Contraindicated if patient is hypersensitive to specific medications (e.g., neomycin, polymyxin B, gramicidin, bacitracin, or hydrocortisone) of respective product. **Use with caution** in glaucoma. Blurred vision, burning and stinging may occur. Increased intraocular pressure and mycosis may occur with prolonged use. **Avoid** prolonged use with products containing corticosteroids.

Ophthalmic solution/suspension: Shake well before use and **avoid** contamination of tip of eye dropper. Apply finger pressure to lacrimal sac during and 1–2 min after dose application.

Ophthalmic ointment: Do not touch tube tip to eyelids or other surfaces to prevent contamination.

NEOMYCIN/POLYMYXIN B/BACITRACIN
Neosporin, Neo to Go, Neo-Polycin, Triple Antibiotic, and generics
Topical antibiotic

Ointment, topical (OTC): 3.5 mg neomycin sulfate, 400 U bacitracin, 5000 U polymyxin B/g (1, 15, 30, 454 g)

For ophthalmic products, see Neomycin/Polymyxin B ophthalmic products

Child and adult: Apply to minor wounds and burns once daily–TID

Do not use for extended periods. May cause superinfection, delayed healing. See neomycin for additional remarks. Prevalence of neomycin hypersensitivity has increased.

For explanation of icons, see p. 667

NEOSTIGMINE
Bioxiverz and generics
Anticholinesterase (cholinergic) agent

Injection (Bioxiverz and generics): 0.5, 1 mg/mL (10 mL) (as methylsulfate); may contain parabens or phenol.
Prefilled syringe injection: 1 mg/mL (3 mL); contains phenol.

Myasthenia gravis diagnosis: Use with atropine (see remarks)
Child: 0.025–0.04 mg/kg IM × 1
Adult: 0.02 mg/kg IM × 1
Treatment:
Child: 0.01–0.04 mg/kg/dose IM/IV/SC Q2–4 hr PRN
Adult: 0.5–2.5 mg/dose IM/IV/SC Q1–3 hr PRN up to **max. dose** of 10 mg/24 hr
Reversal of nondepolarizing neuromuscular blocking agents: Administer with atropine or glycopyrrolate.
Neonate: 0.025–0.07 mg/kg/dose IV
Infant: 0.025–0.1 mg/kg/dose IV
Child: 0.025–0.08 mg/kg/dose IV
Adult: 0.5–2 mg/dose IV
Max. dose (all ages): 5 mg/dose

Contraindicated in GI and urinary obstruction. **Caution** in asthmatics. May cause cholinergic crisis, bronchospasm, salivation, nausea, vomiting, diarrhea, miosis, diaphoresis, lacrimation, bradycardia, hypotension, fatigue, confusion, respiratory depression, and seizures. Titrate for each patient, but **avoid** excessive cholinergic effects.
For reversal of neuromuscular blockade, infants and small children may be at greater risk of complications from incomplete reversal of neuromuscular blockade due to decreased respiratory reserve.
For diagnosis of myasthenia gravis (MG), administer atropine 0.011 mg/kg/dose IV immediately before or IM (0.011 mg/kg/dose) 30 min before neostigmine. For treatment of MG, patients may need higher doses of neostigmine at times of greatest fatigue.
Antidote: Atropine 0.01–0.04 mg/kg/dose. Atropine and epinephrine should be available in the event of a hypersensitivity reaction.
Adjust dose in renal failure (see Chapter 31).

NEVIRAPINE
Viramune, Viramune XR, NVP, and generics
Antiviral, nonnucleoside reverse transcriptase inhibitor

Tabs: 200 mg
Extended-release tabs:
Generics: 100, 400 mg
Viramune XR: 400 mg
Oral suspension: 10 mg/mL (240 mL); contains parabens

HIV: See www.aidsinfo.nih.gov/guidelines
Prevention of vertical transmission during high-risk situations (women who received no antepartum antiretroviral prophylaxis, women with suboptimal viral suppression at delivery, or women with known antiretroviral drug-resistant virus) and in combination with other antiretroviral medications (see Chapter 17 for additional information):
Newborn: 3 doses (based on birth weight) in the first week of life; dose 1: within 48 hr of birth; dose 2: 48 hr after dose 1; dose 3: 96 hr after dose 2

NEVIRAPINE *continued*

Birth weight: 1.5–2 kg: 8 mg/dose PO
Birth weight: >2 kg: 12 mg/dose PO

See www. aidsinfo.nih.gov/guidelines for additional remarks.

Use with caution in patients with hepatic or renal dysfunction. **Contraindicated** in moderate/severe hepatic impairment (Child-Pugh Class B or C) and postexposure (occupational or nonoccupational) prophylactic regimens. Most frequent side effects with continuous therapy include skin rash (may be life-threatening, including Stevens-Johnson syndrome and DRESS; permanently discontinue and never restart), fever, abnormal liver function tests, headache, and nausea. **Discontinue therapy** if any of the following occurs: severe rash; rash with fever, blistering, oral lesions, conjunctivitis or muscle aches. Permanently discontinue and do not restart therapy if symptomatic hepatitis, severe transaminase elevations or hypersensitivity reactions occur.

Life-threatening hepatotoxicity has been reported primarily during the first 12 wk of continuous therapy. Patients with increased serum transaminase or a history of hepatitis B or C infection prior to nevirapine are at greater risk for hepatotoxicity. Women, including pregnant women, with CD_4 cell counts >250/mm^3 or men with CD_4 cell counts >400/mm^3 are at risk for hepatotoxicity. Monitor liver function tests (obtain transaminases immediately after development of hepatitis signs/symptoms, hypersensitivity reactions, or rash) and complete blood counts. Hypophosphatemia has been reported.

Nevirapine induces the CYP 450 3A4 drug metabolizing isoenzyme to cause an autoinduction of its own metabolism within the first 2–4 wk of therapy and has the potential to interact with many drugs. **Carefully review the patient's drug profile for other drug interactions each time nevirapine is initiated or when a new drug is added to a regimen containing nevirapine.**

Doses can be administered with food and concurrently with didanosine.

NIACIN/VITAMIN B3
Niacor, Niaspan, Slo-Niacin, Nicotinic acid, Vitamin B_3, and many generics
Vitamin, water soluble

Tabs (OTC): 50, 100, 250, 500 mg
Timed or extended-release tabs: 250 (OTC), 500, 750, 1000 mg
Caps (OTC): 500, 1000 mg
Timed- or extended-release caps (OTC): 250, 500 mg
Powder (OTC): 500 g

US recommended dietary allowance (RDA): See Chapter 21.
Pellagra (PO): Usual treatment duration is 3–4 wk
Child: 50–100 mg/dose TID
Adult: 50–100 mg/dose TID–QID
Max. dose: 500 mg/24 hr

Contraindicated in hepatic dysfunction, active peptic ulcer, and severe hypotension. **Use with caution** in unstable angina, acute MI (especially if patient is receiving vasoactive drugs), renal dysfunction, and in patients with history of jaundice, hepatobiliary disease, or peptic ulcer. Adverse reactions of flushing, pruritus, or GI distress may occur with oral administration. May cause hyperglycemia, hyperuricemia, blurred vision, abnormal liver function tests, dizziness, and headaches. Burning sensation of the skin, skin discoloration, hepatitis, and elevated creatine kinase have been reported. May cause false-positive urine catecholamines (fluorometric methods) and urine glucose (Benedict reagent).

Pregnancy category changes to C if used in doses above the RDA or for typical doses used for lipid disorders. **See Chapter 21 for multivitamin preparations.**

For explanation of icons, see p. 667

NICARDIPINE
Cardene IV, Cardene SR, and generics
Calcium channel blocker, antihypertensive

Caps (immediate release): 20, 30 mg
Sustained-release caps (Cardene SR): 30, 45, 60 mg
Injection:
Cardene IV: 0.1 mg/mL (200 mL; premixed in isotonic dextrose or saline), 0.2 mg/mL (200 mL; premixed in isotonic saline)
Generic: 2.5 mg/mL (10 mL); contains sorbitol

Child (see remarks):
Hypertension:
Continuous IV infusion for severe hypertension: Start at 0.5–1 mCg/kg/min, dose may be increased as needed every 15–30 min up to a **max.** of 4–5 mCg/kg/min.

Adult (see remarks):
Hypertension:
Oral:
Immediate release: 20 mg PO TID, dose may be increased after 3 days to 40 mg PO TID if needed.
Sustained release: 30 mg PO BID, dose may be increased after 3 days to 60 mg PO BID if needed.
Continuous IV infusion: Start at 5 mg/hr, increase dose as needed by 2.5 mg/hr Q5–15 min up to a **max. dose** of 15 mg/hr. Following attainment of desired BP, decrease infusion to 3 mg/hr and adjust rate as needed to maintain desired response.

Reported use in children has been limited to a small number of preterm infants, infants, and children.

Contraindicated in advanced aortic stenosis. **Avoid** systemic hypotension in patients following an acute cerebral infarct or hemorrhage. Use with **caution** in hepatic or renal dysfunction by carefully titrating dose. The drug undergoes significant first-pass metabolism through the liver and is excreted in the urine (60%). Use **caution** when converting to another dosage form; they are NOT equivalent on a milligram-per-milligram basis.

May cause headache, dizziness, asthenia, peripheral edema, and GI symptoms. Nicardipine is a substrate for CYP 450 3A and inhibitor of CYP 450 2 C9/19. Cimetidine increases the effects/toxicity of nicardipine. Nicardipine may increase effect/toxicity of cyclosporine and tacrolimus. **See *Nifedipine* for additional drug and food interactions.**

Onset of action for orally administered drug is 20 min with peak effects in 0.5 to 2 hr. Onset of action of intravenously administered drug is 1 min. Duration of action following a single IV or PO dose is 3 hr. To reduce the risk for venous thrombosis, phlebitis, and vascular impairment with IV administration, do not use small veins (e.g., dorsum of hand or wrist). **Avoid** intra-arterial administration or extravasation. For additional information, **see Chapter 4.**

NIFEDIPINE
Procardia, Adalat CC, Nifedical XL, Procardia XL, and many generics
Calcium channel blocker, antihypertensive

Caps: (Procardia and generics): 10 mg (0.34 mL), 20 mg (0.45 mL)
Sustained-release tabs: (Adalat CC, Nifedical XL, Procardia XL and generics): 30, 60, 90 mg
Oral suspension: 4 mg/mL

D

NICARDIPINE *continued*

Child (see remarks for precautions):

Chronic hypertension:

Sustained release tabs: Start with 0.25–0.5 mg/kg/24 hr (initial **max. dose**: 30–60 mg/24 hr) ÷ Q12–24 hr. May increase to **max. dose**: 3 mg/kg/24 hr up to 120 mg/24 hr.

Adult:

Chronic hypertension or angina:

Sustained-release tabs: Start with 30 or 60 mg PO once daily. May increase to **max. dose** of 90 mg/24 hr for Adalat CC, Afeditab CR, and Nifediac CC, and 120 mg/24 hr for Procardia XL.

Use of immediate-release dosage form in children is controversial and has been abandoned by many. **Use with caution** in children with acute CNS injury due to increased risk for stroke, seizure, hepatic impairment, and altered level of consciousness. To prevent rapid decrease in blood pressure in children, an initial dose of ≤0.25 mg/kg is recommended.

Use with caution in patients with congestive heart failure (CHF), aortic stenosis, GI obstruction/narrowing (bezoar formation), and cirrhosis (reduced drug clearance). May cause severe hypotension, peripheral edema, flushing, tachycardia, headaches, dizziness, nausea, palpitations, and syncope. Acute generalized exanthematous pustulosis has been reported.

Although overall use in adults has been abandoned, the immediate-release dosage form is **contraindicated** in adults with severe obstructive coronary artery disease or recent MI and in hypertensive emergencies.

Nifedipine is a substrate for CYP 450 3A3/4, and 3A5-7. **Do not administer** with grapefruit juice; may increase bioavailability and effects. Itraconazole and ketoconazole may increase nifedipine levels and/or effects. CYP 3A inducers (e.g., rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine) may reduce nifedipine's effects. Nifedipine may increase phenytoin, cyclosporine, and digoxin levels. For hypertensive emergencies, **see Chapter 4**.

For sublingual (SL) administration, capsule must be punctured and liquid expressed into the patient's mouth. A small amount is absorbed via the SL route. Most effects are due to swallowing and oral absorption. **Do not** crush or chew sustained-release tablet dosage form.

NITROFURANTOIN

Furadantin, Macrodantin, Macrobid, and generics

Antibiotic

Caps (macrocrystals; Macrodantin and generics): 25, 50, 100 mg

Caps (dual release; Macrobid and generics): 100 mg (25 mg macrocrystal/75 mg monohydrate)

Oral suspension (Furadantin and generics): 25 mg/5 mL (230 mL); contains parabens and saccharin

Child (>1 mo; oral suspension or macrocrystals):

Treatment: 5–7 mg/kg/24 hr ÷ Q6 hr PO; **max. dose:** 400 mg/24 hr

UTI prophylaxis: 1–2 mg/kg/dose QHS PO; **max. dose:** 100 mg/24 hr

≥12 yr and adult:

Treatment:

Macrocrystals: 50–100 mg/dose Q6 hr PO

Dual-release (Macrobid): 100 mg/dose Q12 hr PO

UTI prophylaxis (macrocrystals): 50–100 mg/dose PO QHS

Continued

For explanation of icons, see p. 667

NITROFURANTOIN *continued*

Contraindicated in severe renal disease, infants below 1 mo of age, glomerular filtration rate (GFR) below 60 mL/min (reduced drug distribution the urine), active/previous cholestatic jaundice/hepatic dysfunction, and pregnant women at term. **Use with caution** in G6PD deficiency, anemia, lung disease, and peripheral neuropathy. May cause nausea, hypersensitivity reactions (including vasculitis), vomiting, cholestatic jaundice, headache, hepatotoxicity, polyneuropathy, and hemolytic anemia.

Anticholinergic drugs and high-dose probenecid may increase nitrofurantoin toxicity. Magnesium salts may decrease nitrofurantoin absorption. Causes false-positive urine glucose with Clinitest. Administer doses with food or milk.

Pregnancy category changes to X at term (38–42 wk gestation). Breastfeeding in mothers receiving nitrofurantoin is not recommended for infants below 1 mo and those with G6PD deficiency; use in infants 1 mo and without G6PD deficiency is compatible.

NITROGLYCERIN

Nitro-Bid, Nitrostat, Nitro-Time, Nitro-Dur, Nitrolingual, Nitromist, Minitran, Rectiv, and generics

Vasodilator, antihypertensive

Injection: 5 mg/mL (10 mL); contains alcohol or propylene glycol

Prediluted injection in D5W: 100 mcg/mL (250 mL), 200 mcg/mL (250 mL), 400 mcg/mL (250 mL); contains alcohol and propylene glycol

Sublingual tabs (Nitrostat and generics): 0.3, 0.4, 0.6 mg

Sustained-release caps (Nitro-Time and generics): 2.5, 6.5, 9 mg

Ointment, topical (Nitro-Bid): 2% (1, 30, 60 g)

Ointment, rectal (Rectiv): 0.4% (30 g); contains propylene glycol

Patch (Nitro-Dur, Minitran, and generics): 2.5 mg/24 hr (0.1 mg/hr), 5 mg/24 hr (0.2 mg/hr), 7.5 mg/24 hr (0.3 mg/hr), 10 mg/24 hr (0.4 mg/hr), 15 mg/24 hr (0.6 mg/hr), 20 mg/24 hr (0.8 mg/hr) (30s, 100s)

Spray, translingual (Nitrolingual and generics): 0.4 mg per metered spray (4.9, 12 g; delivers 60 and 200 doses, respectively); contains 20% alcohol (flammable)

Aerosol spray, translingual (Nitromist): 0.4 g per spray (4.1, 8.5 g; delivers 90 and 230 doses, respectively); contains peppermint oil and menthol

NOTE: The IV dosage units for children are in mCg/kg/min, compared with mCg/min for adults.

Infant/child:

Continuous IV infusion: Begin with 0.25–0.5 mCg/kg/min; may increase by 0.5–1 mCg/kg/min Q3–5 min PRN. Usual dose: 1–5 mCg/kg/min. **Max. dose**: 20 mCg/kg/min.

Adult:

Continuous IV infusion: 5 mCg/min IV, then increase Q3–5 min PRN by 5 mCg/min up to 20 mCg/min. If no response, increase by 10 mCg/min Q3–5 min PRN up to a **max.** of 400 mCg/min.

Sublingual: 0.3–0.4 mg Q5 min. **Max.** of three doses in 15 min.

Oral: 2.5–6.5 mg TID–QID; up to 26 mg QID

Ointment: Apply 1/2 inch upon rising in the morning and another 1/2 inch 6 hr later if needed, double the dose to 1 in with the same dosing schedule the next day and subsequently to 2 in if needed. Max. recommended dose: 2 doses/24 hr. Provide 10–12 hr/day of nitrate-free to minimize tolerance.

NITROGLYCERIN *continued*

Patch: 0.2–0.4 mg/hr initially, then titrate to 0.4–0.8 mg/hr; apply new patch daily (tolerance is minimized by removing patch for 10–12 hr/24 hr)

Contraindicated in glaucoma, with increased ICP, cerebral hemorrhage, traumatic brain injury, shock, severe anemia, concurrent phosphodiesterase-5 inhibitor (e.g., sildenafil), and concurrent guanylate cyclase stimulator (e.g., riociguat). In small doses (1–2 mCg/kg/min) acts mainly on systemic veins and decreases preload. At 3–5 mCg/kg/min acts on systemic arterioles to decrease resistance. May cause headache, flushing, hypersensitivity reactions, hypotension, GI upset, blurred vision, and methemoglobinemia. **Use with caution** in severe renal impairment, and hepatic failure. IV nitroglycerin may antagonize anticoagulant effect of heparin.

Decrease dose gradually in patients receiving drug for prolonged periods to avoid withdrawal reaction. Must use polypropylene infusion sets to avoid adsorption of drug to plastic tubing. Use in heparized patients may result in a decrease of PTT with subsequent rebound effect on discontinuation of nitroglycerin.

Onset (duration) of action: IV: 1–2 min (3–5 min); sublingual: 1–3 min (30–60 min); PO sustained release: 40 min (4–8 hr); topical ointment: 20–60 min (2–12 hr); and transdermal patch: 40–60 min (18–24 hr).

NITROPRUSSIDE
Nitropress, Nipride RTU, and generics
Vasodilator, antihypertensive

Injection:

Nitropress and generics: 25 mg/mL (2 mL)

Prediluted injection in 0.9% sodium chloride:

Nipride RTU: 0.2 mg/mL (100 mL), 0.5 mg/mL (100 mL)

Child, adolescent, and adult: IV, continuous infusion

Dose: Start at 0.3–0.5 mCg/kg/min, titrate to effect. Usual dose is 3–4 mCg/kg/min.

Max. dose: 10 mCg/kg/min.

Contraindicated in patients with decreased cerebral perfusion and in situations of compensatory hypertension (increased ICP). Monitor for hypotension and acidosis. Dilute with D_5W and protect from light.

Pediatric efficacy is supported by a dose-ranging trial, an open-label trial, and adult trials. No novel safety issues were found in the aforementioned pediatric trials.

Nitroprusside is nonenzymatically converted to cyanide, which is converted to thiocyanate. Cyanide may produce metabolic acidosis and methemoglobinemia; thiocyanate may produce psychosis and seizures. Monitor thiocyanate levels if used for more than 48 hr or in a dose equal to or greater than 4 mCg/kg/min. **Thiocyanate levels should be less than 50 mg/L. Monitor cyanide levels (toxic levels >2 mCg/mL)** in patients with hepatic dysfunction and thiocyanate levels in patients with renal dysfunction.

Onset of action is 2 min with a 1- to 10-min duration of effect.

For explanation of icons, see p. 667

NOREPINEPHRINE BITARTRATE
Levophed and generics
Adrenergic agonist

Injection: 1 mg/mL as norepinephrine base (4 mL); may contain sulfites

NOTE: The dosage units for children are in mCg/kg/min compared with mCg/min for adults.
Child: Continuous IV infusion doses as norepinephrine base. Start at 0.05–0.1 mCg/kg/min. Titrate to effect. **Max. dose:** 2.5 mCg/kg/min.
Adult: Continuous IV infusion **doses as norepinephrine base.** Start at 8–12 mCg/min and titrate to effect. Usual maintenance dosage range: 2–4 mCg/min.

May cause cardiac arrhythmias, hypertension, hypersensitivity, headaches, vomiting, uterine contractions, and organ ischemia. May cause decreased renal blood flow and urine output. **Avoid** extravasation into tissues; may cause severe tissue necrosis. If this occurs, treat locally with phentolamine.

NORTRIPTYLINE HYDROCHLORIDE
Pamelor and generics
Antidepressant, tricyclic

Caps: 10, 25, 50, 75 mg; may contain benzyl alcohol, EDTA
Oral solution: 10 mg/5 mL (473 mL); contains up to 4% alcohol, benzoic acid, and sorbitol

Depression (see remarks):
Child 6–12 yr: 1–3 mg/kg/24 hr ÷ TID–QID PO or 10–20 mg/24 hr ÷ TID–QID PO
Adolescent: 1–3 mg/kg/24 hr ÷ TID–QID PO or 30–50 mg/24 hr ÷ TID–QID PO
Adult: 75–100 mg/24 hr ÷ TID–QID PO
Max. dose (all ages): 150 mg/24 hr
Nocturnal enuresis (see remarks):
6–7 yr (20–25 kg): 10 mg PO QHS
8–11 yr (26–35 kg): 10–20 mg PO QHS
>11 yr (36–54 kg): 25–35 mg PO QHS

See imipramine for contraindications and common side effects. Also **contraindicated** with linezolid or IV methylene blue due to increased risk for serotonin syndrome. **Avoid** use in patients with Brugada syndrome. Fewer CNS and anticholinergic side effects than with amitriptyline. May cause mild pupillary dilation, which can lead to narrow angle glaucoma.
Lower doses and slower dose titration are recommended in hepatic impairment. Therapeutic antidepressant effects occur in 7–21 days. Monitor for clinical worsening of depression and suicidal ideation/behavior following the initiation of therapy or after dose changes. **Do not** discontinue abruptly. Nortriptyline is a substrate for the CYP 450 1A2 and 2D6 drug-metabolizing enzymes. Use and dosing considerations have been recommended based on the following CYP 450 2D6 phenotypes:
Ultrarapid metabolizer: Use of alternative drug not metabolized by CYP 2D6. If use warranted, titrate to the highest target dose and monitor serum levels.
Intermediate metabolizer: Reduce recommended initial dose by 25% and monitor serum levels.
Poor metabolizer: **Avoid use** to prevent potential side effect and use alternative drug not metabolized by CYP 2D6. If use is warranted, reduce recommended initial dose by 50% and monitor serum levels.
Rifampin may increase the metabolism of nortriptyline.
Therapeutic nortriptyline levels for depression: 50–150 ng/mL. Recommended serum sampling time: obtain a single level 8 or more hours after an oral dose (following 4 days of continuous dosing for children and after 9–10 days for adults).

NYSTATIN
Bio-Statin, Nyamyc, Nystop, and generics; previously available as Mycostatin and Nilstat
Antifungal agent

Tabs: 500,000 U
Oral suspension: 100,000 U/mL (5, 60, 480 mL)
Topical cream and ointment: 100,000 U/g (15, 30 g)
Topical powder (Nyamyc, Nystop, and generics): 100,000 U/g (15, 30, 60 g)

Oropharyngeal candidiasis:
Preterm infant: 0.5 mL (50,000 U) to each side of mouth QID
Term infant: 1–4 mL (100,000–400,000 U) to each side of mouth QID
Child, adolescent, and adult: 4–6 mL (400,000–600,000 U) swish and swallow QID
Non-esophageal mucous membrane GI Candidiasis:
Adult (oral tabs): 500,000–1,000,000 U PO Q8 hr until 48 hr after clinical cure
Topical (all topical dosage forms):
All ages: Apply to affected areas BID-QID.

May produce diarrhea and GI side effects. Local irritation, contact dermatitis, and Stevens-Johnson syndrome have been reported. Treat until 48–72 hr after resolution of symptoms. Drug is poorly absorbed through the GI tract. Oral suspension should be swished about the mouth and retained in the mouth as long as possible before swallowing.

O

OCTREOTIDE ACETATE
Sandostatin, Sandostatin LAR Depot, and generics
Somatostatin analog, antisecretory agent

Injection (amps): 0.05, 0.1, 0.5 mg/mL (1 mL)
Injection (multidose vials): 0.2, 1 mg/mL (5 mL); contains phenol
Injection, microspheres for suspension (Sandostatin LAR Depot; see remarks): 10, 20, 30 mg (in kits with 2 mL diluent and 1.5-inch 20-gauge needles)

Infant and child (limited data):
Intractable diarrhea:
IV/SC: 1–10 mCg/kg/24 hr ÷ Q12–24 hr. Dose may be increased within the recommended range by 0.3 mCg/kg/dose every 3 days as needed. **Max. dose**: 1500 mCg/24 hr.
IV continuous infusion: bolus of 1 mCg/kg/dose followed by 1 mCg/kg/hr; this has been used in diarrhea associated with graft-versus-host disease.

Cholelithiasis, hyperglycemia, hypoglycemia, hypothyroidism, nausea, diarrhea, abdominal discomfort, headache, dizziness, and pain at injection site may occur. Growth hormone suppression may occur with long-term use. Bradycardia, thrombocytopenia, and increased risk for pregnancy in patients with acromegaly and pancreatitis have been reported. Cyclosporine levels may be reduced in patients receiving this drug. May increase the effects/toxicity of bromocriptine.
Patients with severe renal failure requiring dialysis may require dosage adjustments due to an increase in half-life. Effects of hepatic dysfunction on octreotide have not been evaluated.
Sandostatin LAR Depot is administered once every 4 wk **only** by the IM route and is currently indicated for IV/SC therapy. See package insert for details.

For explanation of icons, see p. 667

OFLOXACIN (OTIC AND OPHTHALMIC)
Floxin Otic, Ocuflox, and generics; previously available as Floxin
Antibiotic, quinolone

Otic solution (Floxin Otic and generics): 0.3% (5, 10 mL); may contain benzalkonium chloride
Ophthalmic solution (Ocuflox and generics): 0.3% (5, 10 mL); may contain benzalkonium chloride

Otic use:
Otitis externa:
6 mo–12 yr: 5 drops to affected ear(s) once daily × 7 days
≥13 yr–adult: 10 drops to affected ear(s) once daily × 7 days
Chronic suppurative otitis media:
≥12 yr–adult: 10 drops to affected ear(s) BID × 14 days
Acute otitis media with tympanostomy tubes:
1–12 yr: 5 drops to affected ear(s) BID × 10 days
Ophthalmic use (>1 yr–adult):
Conjunctivitis: 1–2 drops to affected eye(s) 2–4 hr while awake × 2 days, then QID × 5 additional days
Corneal ulcer: 1–2 drops to affected eye(s) Q30 min while awake and Q4–6 hr while asleep at night × 2 days, followed by Q1 hr while awake × 5 days, and then QID until treatment has been completed.

Pruritus, local irritation, taste perversion, dizziness, earache have been reported with otic use. Ocular burning/discomfort is frequent with ophthalmic use. Consult with ophthalmology in corneal ulcers.

When otic solution is being used, the solution should be warmed by holding the bottle in the hand for 1–2 min. The use of cold solutions may result in dizziness. For otitis externa, the patient should lie with the affected ear upward before instillation and remain in the same position after dose administration for 5 min to enhance drug delivery. For acute otitis media with tympanostomy tubes, the patient should lie in the same position prior to instillation and the tragus should be pumped 4 times after the dose to assist in drug delivery to the middle ear.

Systemic use of ofloxacin is typically replaced by levofloxacin, its S-isomer, which has a more favorable side effect profile than ofloxacin. See **levofloxacin.**

OLANZAPINE
Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and generics
Antipsychotic, atypical second generation

Tabs: 2.5, 5, 7.5, 10, 15, 20 mg
Orally disintegrating tabs (Zyprexa Zydis and generics): 5, 10, 15, 20 mg; contains phenylalanine
IM injection:
Short-acting: 10 mg; contains tartaric acid
Long-acting pamoate salt (Zyprexa Relprevv):
Every 2 week dosing: 210, 300 mg; contains mannitol, polysorbate 80
Every 4 week dosing: 405 mg; contains mannitol, polysorbate 80

PO DOSING:
Bipolar I disorder (manic or mixed episodes):
Child 4–6 yr of age (limited data, based on an open-label trial in 15 subjects): Start at 1.25 mg PO once daily × 7 days, then increase dose Q7 days PRN as tolerated to a target dose of 10 mg once daily.
Child 6–12 yr of age (limited data): Start at 2.5 mg PO once daily × 7 days, then increase dose in 2.5 or 5 mg increments Q7 days to a target dose of 10 mg once daily. Suggested **max. dose**: 20 mg/24 hr.

OLANZAPINE *continued*

Adolescent (see remarks): Start at 2.5 or 5 mg PO once daily × 7 days, then increase dose in 2.5 or 5 mg increments Q7 days to a target dose of 10 mg once daily. Suggested **max. dose**: 20 mg/24 hr (doses >20 mg/24 hr have not been evaluated).

Adult: Start at 10 or 15 mg PO once daily (use 10 mg if used with lithium or valproate). If needed, increase or decrease dose by 5 mg daily at intervals not <24 hr. Maintenance dosage range: 5–20 mg/24 hr. Suggested **max. dose**: 20 mg/24 hr (doses >20 mg/24 hr have not been evaluated).

Schizophrenia:

Child ≥8 yr of age and adolescent (see remarks): Start with 2.5 or 5 mg PO once daily, increase dose in 2.5 or 5 mg increments Q7 days to the target dose of 10 mg once daily (doses >20 mg/24 hr have not been evaluated).

Adult: Start with 5 or 10 mg PO once daily (use 5 mg for individuals who are debilitated, predisposed to hypotension, pharmacodynamically sensitive to olanzapine, or nonsmoking females ≥65 yr old) with a target dose of 10 mg once daily within 5–7 days. If needed, increase or decrease dose by 5 mg daily at weekly intervals. Usual dosage range: 10–15 mg once daily. Additional clinical assessment is recommended for doses >10 mg/24 hr (doses >20 mg/24 hr have not been evaluated).

IM DOSING:

Short acting for acute agitation associated with bipolar I or schizophrenia:

Child and adolescent (limited retrospective data in 15 children and 35 adolescents): ≤12 yr: 5 mg and adolescent (13–17 yr): 10 mg. Dosing frequencies and max. doses were not reported.

Adult: 10 mg (5 mg for geriatric patients and 2.5 mg for individuals who are debilitated, predisposed to hypotension, or pharmacodynamically sensitive to olanzapine). If needed, additional doses × 2 may be given; second dose 2 hr after the first dose and third dose 4 hr after the second dose. Recommended **max. dose** is 30 mg/24 hr (10 mg × 3 given 2–4 hr apart); safety of doses >30 mg /24 hr has not been evaluated.

Long-acting pamoate salt (Zyprexa Relprevv) for schizophrenia (adult): see remarks and package insert for specific dosage based on established oral dosage.

Use with caution in cardiovascular or cerebrovascular disease, hypotensive conditions, diabetes/hyperglycemia, elevated serum lipids and cholesterol, paralytic ileus, hepatic impairment, seizure disorders, narrow angle glaucoma, and prostatic hypertrophy. Medication exhibits anticholinergic effects.

Common side effects include orthostatic hypotension, peripheral edema, hypercholesterolemia, hyperprolactinemia, appetite simulation, weight gain (greater in adolescents than adults; monitoring is recommended), hypertriglyceridemia, constipation, xerostomia, akathisia, asthenia, dizziness, somnolence, tremor, and personality disorder. Neuroleptic malignant syndrome, dystonia, cognitive and motor impairment, tardive dyskinesia (irreversible with cumulative high doses), neutropenia, leukopenia, agranulocytosis, suicidal intent, acute pancreatitis, pulmonary embolism, increases in liver function tests (ALT, AST, GGT), DRESS, and hyperthermia have been reported.

Olanzapine is a major substate for CYP 450 1A2 and minor substrate for 2D6. It also is a weak inhibitor to CYP 450 1A2, 2C9/19. Do not use in combination with alcohol, benzodiazepines, or opiates due to increased risk for sedation and cardiopulmonary depression. Caution is also indicated with anticholinergic agents (e.g., azelastine, glycopyrrolate), as olanzapine may enhance the anticholinergic effects. Use with QTc-prolonging medications may further increase the risk for QTc prolongation. Metoclopramide may enhance neurological side effects of olanzapine. Do not use oral disintegrating tablets in phenylketonuria.

$T_{½}$: 37 hr for children and 21–54 hr for adults via PO route. Short-acting IM $T_{½}$ in adults is similar to PO route but long-acting IM $T_{½}$ is ~30 days in adults.

Maintenance treatment for bipolar I disorder and schizophrenia has not been systematically evaluated in adolescents. Therefore it is recommended to utilize the lowest dose to maintain efficacy and to reassess the need for maintenance treatment periodically for this age group.

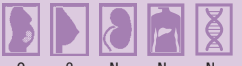
For explanation of icons, see p. 667

OLANZAPINE *continued*

All oral dosages may be taken either with or without food. For orally disintegrating tabs, tablet must be placed in patient's mouth immediately after removing it from the foil pack (by peeling off the foil, not by pushing the tablet through the foil) and allowed to dissolve in saliva; then swallowed with or without liquids.

Zyprexa Relprevv (long-acting IM injection): post injection delirium and sedation syndrome have been reported with this dosage form. Patients must be observed by a health care provider at a health care facility for at least 3 hr after administration. The FDA REMS program requires prescribers, healthcare facilities, and pharmacies to register with the Zyprexa Relprevv Patient Care Program at 1-877-772-9390 for use of this product.

OLOPATADINE
Patanol, Pataday, Pazeo, Patanase, and generics
Antihistamine



Ophthalmic solution (products may contain benzalkonium chloride):
Patanol and generics: 0.1% (5 mL)
Pataday and generics: 0.2% (2.5 mL)
Pazeo: 0.7% (2.5 mL)
Nasal spray (Patanase and generics): 0.6% (30.5 g provides 240 metered spray doses); contains benzalkonium chloride.

Ophthalmic use for allergic conjunctivitis:
0.1% solution (Patanol and generics):
Patients ≥3 yr old and adults: 1 drop in affected eye(s) BID (spaced 6–8 hr apart).
0.2% solution (Pataday) or 0.7% (Pazeo):
Patients ≥2 yr old and adults: 1 drop in affected eye(s) once daily
Intranasal use of allergic rhinitis:
Patients 6–11 yr old: Inhale 1 spray into each nostril BID
Patients ≥12 yr old and adults: Inhale 2 sprays into each nostril BID.

Ocular use: DO NOT use while wearing contact lenses; wait at least 10 min after instilling drops before inserting lenses. Ocular side effects include burning or stinging, dry eye, foreign body sensation, hyperemia, keratitis, lid edema, and pruritus. May also cause headaches, asthenia, pharyngitis, rhinitis, and taste perversion.
Nasal use: Common side effects include bitter taste and headaches. Nasal ulceration, epistaxis, nasal septal perforation, throat pain and postnasal drip have been reported.
To reduce the risk of drug being systemically absorbed with ophthalmic use, place pressure on the tear duct by the corner of the eye for ≥1 min, then remove the excess solution with an absorbent tissue.

OMEPRAZOLE
Prilosec, Prilosec OTC, First-Omeprazole, Omeprazole and Syrpend SF Alka, and generics
In combination with sodium bicarbonate: Zegerid, Zegerid OTC, and generics
Gastric acid pump inhibitor

Caps, sustained release: 10, 20, 40 mg; may contain magnesium
Tabs, delayed release (Prilosec OTC and generics; OTC): 20 mg; may contain magnesium

OMEPRAZOLE *continued*

Oral suspension:

First-Omeprazole: 2 mg/mL (90, 150, 300 mL); contains benzyl alcohol.

Omeprazole and Syrpend SF Alka: 2 mg/mL (100 mL); sugar free and preservative free.

Compounded formulation: 2 mg/mL; contains ~0.5 mEq sodium bicarbonate per 1 mg drug.

Granules for oral suspension (Prilosec): 2.5 and 10 mg packets (30s); contains magnesium.

In combination with sodium bicarbonate:

Powder for oral suspension (Zegerid and generics): 20, 40 mg packets (30s); each packet (regardless of strength) contains 1680 mg (20 mEq) sodium bicarbonate.

Caps, immediate-release (Zegerid, Zegerid OTC, and generics): 20 (OTC), 40 mg; each capsule (regardless of strength) contains 1100 mg (13.1 mEq) sodium bicarbonate.

Chewable tabs (Zegerid): 20 and 40 mg; each tab (regardless of strength) contains 600 mg (7.1 mEq) sodium bicarbonate and 700 mg magnesium hydroxide.

Infant and child:

Esophagitis, GERD, or ulcers: Start at 1 mg/kg/24 hr PO ÷ once daily–BID (**max. dose:** 20 mg/24 hr). Reported effective range: 0.2–3.5 mg/kg/24 hr. Children 1–6 yr may require higher doses due to enhanced drug clearance. Alternative dosing by weight category:

3–<5 kg: 2.5 mg PO once daily

5–<10 kg: 5 mg PO once daily

10–<20 kg: 10 mg PO once daily

20 kg and above: 20 mg PO once daily

Adult:

Duodenal ulcer or GERD: 20 mg/dose PO once daily × 4–8 wk; may give up to 12 wk for erosive esophagitis

Gastric ulcer: 40 mg/24 hr PO ÷ once daily–BID × 4–8 wk

Pathologic hypersecretory conditions: Start with 60 mg/24 hr PO once daily. If needed, dose may be increased up to 120 mg/24 hr PO ÷ TID. Daily doses >80 mg should be administered in divided doses.

Common side effects: headache, diarrhea, nausea, and vomiting. Allergic reactions including anaphylaxis, acute interstitial nephritis, and vitamin B_{12} deficiency (with prolonged use) have been reported. Fundic gland polyps has been associated with long-term use of PPIs. Has been associated with increased risk for *Clostridium difficile*–associated diarrhea.

Drug induces CYP 450 1A2 (decreases theophylline levels) and is also a substrate and inhibitor of CYP 2C19. Recommended dosage modification for ultrarapid metabolizers of CYP 2C19 is to increase the usual dose by threefold. Increases $T_{½}$ of citalopram, diazepam, phenytoin, and warfarin. May decrease the effects of itraconazole, ketoconazole, clopidogrel, iron salts, and ampicillin esters. St. John's wort and rifampin may decrease omeprazole effects. May be used in combination with clarithromycin and amoxicillin for *Helicobacter pylori* infections. Omeprazole may interfere with serum chromogranin A (CgA) diagnostic test for neuroendocrine tumors; discontinue use at least 14 days prior to testing.

Bioavailability may be increased with hepatic dysfunction or in patients of Asian descent. Safety and efficacy for GERD in children <1 mo have not been established.

Administer all doses before meals. Administer 30 min prior to sucralfate. Capsules contain enteric-coated granules to ensure bioavailability. Do not chew or crush capsule. For doses unable to be divided by 10 mg, capsule may be opened and intact pellets may be administered in an acidic beverage (e.g., apple juice, cranberry juice) or applesauce. The extemporaneously compounded oral suspension product may be less bioavailable due to the loss of the enteric coating.

OMNIPAQUE

See iohexol

For explanation of icons, see p. 667

ONDANSETRON
Zofran, Zofran ODT, Zuplenz, and generics
Antiemetic agent, 5-HT3 antagonist

Injection: 2 mg/mL (2, 20 mL); may contain parabens and some preparations are preservative free
Tabs: 4, 8. 24 mg
Tabs, orally disintegrating (ODT): 4, 8 mg; contains aspartame
Oral solution: 4 mg/5 mL (50 mL); contains sodium benzoate
Oral film (Zuplenz): 4, 8 mg (30s)

Preventing nausea and vomiting associated with chemotherapy:
Oral (give initial dose 30 min before chemotherapy):
Child (≥2 yr of age and adolescent), dose based on body surface area:
<0.3 m²: 1 mg TID PRN nausea
0.3–0.6 m²: 2 mg TID PRN nausea
0.6–1 m²: 3 mg TID PRN nausea
>1 m²: 4–8 mg TID PRN nausea
Dose based on age:
<4 yr of age: Use dose based on body surface area from preceding dosages.
4–11 yr of age: 4 mg TID PRN nausea
>11 yr of age and adult: 8 mg TID or 24 mg once daily PRN nausea
IV (child and adult):
Moderately emetogenic drugs: 0.15 mg/kg/dose (**max. dose**: 8 mg/dose for child and 16 mg/dose adult) at 30 min before and 4 and 8 hr after emetogenic drugs. Then same dose Q4 hr PRN.
Highly emetogenic drugs: 0.15 mg/kg/dose (**max. dose**: 16 mg/dose) 30 min before 4 and 8 hr after emetogenic drugs. Then 0.15 mg/kg/dose (**max. dose**: 16 mg/dose) Q4 hr PRN.
Preventing nausea and vomiting associated with surgery (additional doses for controlling nausea and vomiting may not provide any benefits):
IV/IM (administered prior to anesthesia over 2–5 min):
Child (1 mo12 yr of age):
<40 kg: 0.1 mg/kg/dose ×1
≥40 kg: 4 mg × 1
Adult: 4 mg × 1
Oral:
Adult: 16 mg × 1, 1 hr prior to induction of anesthesia
Preventing nausea and vomiting associated with radiation therapy:
Child: use above dosage for preventing nausea and vomiting associated with chemotherapy and give initial dose 1–2 hr prior to radiation.
Adult:
Total body irradiation: 8 mg PO 1–2 hr prior to radiation once daily-BID
Single high-dose fraction radiation to abdomen: 8 mg PO 1–2 hr prior to radiation with subsequent doses Q8 hr after first dose × 1–2 days after completion of radiation.
Daily fractionated radiation to abdomen: 8 mg PO 1–2 hr prior to radiation with subsequent doses Q8 hr after first dose for each day radiation is given.
Vomiting in acute gastroenteritis (oral route is preferred, use IV route when oral administration is not possible):
Oral (child 6 mo-10 yr old and weighing ≥8 kg; use oral disintegrating tablet):
8–15 kg: 2 mg × 1
>15 and ≤30 kg: 4 mg × 1
>30 kg: 8 mg × 1
IV (≥1 mo): 0.15–0.3 mg/kg/dose × 1; **max. dose**: 4 mg/dose

ONDANSETRON *continued*

Avoid use in congenital long-QTc syndrome. Bronchospasm, tachycardia, hypokalemia, seizures, headaches, lightheadedness, constipation, diarrhea and transient increases in AST, ALT, and bilirubin may occur. Transient blindness (resolution within a few min up to 48 hr), arthralgia, Stevens-Johnson syndrome, TEN, hepatic dysfunction, and rare/transient ECG changes (including QTc-interval prolongation) have been reported. Data limited for use in children below 3 yr of age.

ECG monitoring is recommended in patients with electrolyte abnormalities, CHF, or bradyarrhythmias. Drug clearance is higher for surgical and cancer patients <18 yr as compared with adults. Clearance is slower for children 1–4 mo old compared with children >4–24 mo old.

Ondansetron is a substrate for CYP 450 1A2, 2D6, 2E1, and 3A3/4 drug metabolizing enzymes. It is likely that the inhibition/loss of one of the previously listed enzymes will be compensated by others and may result in insignificant changes to the elimination of ondansetron, which may be affected by CYP 450 enzyme inducers. Ultrarapid metabolizers of CYP 450 2D6 is associated with decreased response and use of an alternative drug not predominantly metabolized by CYP 2D6 (e.g., granisetron) is recommended. Follow theophylline, phenytoin, or warfarin levels closely, if used in combination. Use with apomorphine may result in profound hypotension and loss of consciousness and is **contraindicated.**

To administer the oral film dosage form (Zuplenz), film must be placed on top of patient's tongue, allowed to dissolve completely in 4–20 sec, and swallowed with or without liquid.

OSELTAMIVIR PHOSPHATE
Tamiflu and generics
Antiviral, neurominidase inhibitor

Caps: 30, 45, 75 mg
Oral suspension: 6 mg/mL (60 mL,); may contain saccharin and sodium benzoate
May also be extemporaneously compounded from capsules (6 mg/mL)

Treatment of influenza (initiate therapy within 2 days of onset of symptoms):
Preterm neonate (limited data): Usual duration of therapy for 5 days.
Post–menstrual age (PMA) neonate <38 wk: 1 mg/kg/dose PO BID
PMA 38–40 wk: 1.5 mg/kg/dose PO BID
Full-term neonate (PMA >40 wk): 3 mg/kg/dose PO BID × 5 days
Child <1 yr: see following table.

Age (mo)	Dosage for 5 days	Volume of Oral Suspension (6 mg/mL)
<3	12 mg PO BID	2 mL
3–5	20 mg PO BID	3.33 mL
6–11	25 mg PO BID	4.2 mL

Child ≥1–12 yr: see following table.

Weight (kg)	Dosage for 5 days	Volume of Oral Suspension (6 mg/mL)
≤15	30 mg PO BID	5 mL
>15–23	45 mg PO BID	7.5 mL
>23–40	60 mg PO BID	10 mL
>40	75 mg PO BID	12.5 mL

≥13 yr old and adult: 75 mg PO BID × 5 days.

Continued

For explanation of icons, see p. 667

OSELTAMIVIR PHOSPHATE *continued*

Prophylaxis of influenza (initiate therapy within 2 days of exposure; see remarks):

Child 3 mo–<1 yr: 3 mg/kg/dose PO once daily; alternative dosage based on age:

3–5 mo: 20 mg PO once daily

6–11 mo: 25 mg PO once daily

Child 1–12 yr:

≤15 kg: 30 mg PO once daily

16–23 kg: 45 mg PO once daily

24–40 kg: 60 mg PO once daily

>40 kg: 75 mg PO once daily

≥13 yr old and adult: 75 mg PO once daily for a minimum of 7 days and up to 6 wk; initiate therapy within 2 days of exposure.

Currently indicated for the treatment of influenza A and B strains. Use in children <1 yr of age has not been recommended due to concerns of excessive CNS penetration and fatalities in 7-day-old rats.

Nausea and vomiting generally occur within the first 2 days and are the most common adverse effects. Insomnia, vertigo, seizures, hypothermia, neuropsychiatric events (may result in fatal outcomes), arrhythmias, rash, and toxic epidermal necrolysis have also been reported. If the glomerular filtration rate (GFR) is 10–30 mL/min, reduce treatment dose to 75 mg PO once daily × 5 days for adults. (See Chapter 31.)

PROPHYLACTIC USE: Oseltamivir is not a substitute for annual flu vaccination. Safety and efficacy have been demonstrated for ≤6 wk of therapy; duration of protection lasts for as long as dosing is continued. Adjust prophylaxis dose if GFR is 10–30 mL/min by extending the dosage interval to once every other day.

Probenecid increases oseltamivir levels. Oseltamivir decreases the efficacy of the nasal influenza vaccine (live attenuated influenza vaccine, FluMist); **avoid** administration of vaccine within 2 wk before or 48 hr after oseltamivir administration unless medically indicated.

Dosage adjustments in hepatic impairment, severe renal disease, and dialysis have not been established for either treatment or prophylactic use. The safety and efficacy of repeated treatment or prophylaxis courses have not been evaluated. Doses may be administered with or without food.

OXACILLIN

Various generics

Antibiotic, penicillin (penicillinase resistant)

Injection: 1, 2, 10 g

Injection, premixed in iso-osmotic dextrose: 1 g/50 mL, 2 g/50 mL

Injectable products contain 2.8–3.1 mEq Na per 1 g drug

Neonate (IM/IV):

≤7 days old:

<2 kg: 50 mg/kg/24 hr ÷ Q12 hr

≥2 kg: 75 mg/kg/24 hr ÷ Q8 hr

8–28 days old:

<1 kg:

8–14 days old: 50 mg/kg/24 hr ÷ Q12 hr

15–28 days old: 75 mg/kg/24 hr ÷ Q8 hr

1–2 kg: 75 mg/kg/24 hr ÷ Q8 hr

≥2 kg: 100 mg/kg/24 hr ÷ Q6 hr

OXACILLIN *continued*

Meningitis (IV):
≤7 days old: 75 mg/kg/24 hr ÷ Q8–12 hr
8–28 days old: 150–200 mg/kg/24 hr ÷ Q6–8 hr

Infant and child (IM/IV): 100–200 mg/kg/24 hr ÷ Q4–6 hr (**max. dose**: 12 g/24 hr); use 200 mg/kg/24 hr for endocarditis and severe infections.

Adult (IM/IV): 250–2000 mg/dose Q4–6 hr; use higher dosage range for endocarditis or severe infections

Max. dose (all ages): 12 g/24 hr.

Rash and GI disturbances are common. Leukopenia, reversible hepatotoxicity, and acute interstitial nephritis has been reported. Hematuria and azotemia have occurred in neonates and infants with high doses. May cause false-positive urinary and serum proteins.

Probenecid increases serum oxacillin levels. Tetracyclines may antagonize the bactericidal effects of oxacillin.

CSF penetration is poor unless meninges are inflamed. Use the lower end of the usual dosage range for patients with creatinine clearances <10 mL/min. **Adjust dose in renal failure (see Chapter 31).**

OXCARBAZEPINE
Trileptal, Oxtellar XR, and generics
Anticonvulsant

Tabs: 150, 300, 600 mg
Extended release tabs (Oxtellar XR): 150, 300, 600 mg
Oral suspension: 300 mg/5 mL (250 mL); contains saccharin, ethanol, and propylene glycol

IMMEDIATE RELEASE PRODUCT:

Child (2–<4 yr old):

Adjunctive therapy for partial-onset seizures: Start with 8–10 mg/kg/24 hr PO ÷ BID up to a **max. dose** of 600 mg/24 hr. For children <20 kg, may consider using a starting dose of 16–20 mg/kg/24 hr PO ÷ BID; gradually increase the dose over a 2–4 wk period and do not exceed 60 mg/kg/24 hr ÷ BID.

Child (4–16 yr old, see remarks):

Adjunctive therapy for partial-onset seizures: Start with 8–10 mg/kg/24 hr PO ÷ BID up to a **max. dose** of 600 mg/24 hr. Then gradually increase the dose over a 2-wk period to the following maintenance doses:
20–29 kg: 900 mg/24 hr PO ÷ BID
29.1–39 kg: 1200 mg/24 hr PO ÷ BID
>39 kg: 1800 mg/24 hr PO ÷ BID

Conversion to monotherapy for partial-onset seizures: Start with 8–10 mg/kg/24 hr PO ÷ BID and simultaneously initiate dosage reduction of concomitant AEDs and withdrawal completely over 3–6 wk. Dose may be increased at weekly intervals, as clinically indicated, by a **maximum** of 10 mg/kg/24 hr to achieve the recommended monotherapy maintenance dose as described in the following table.

Initiation of monotherapy for partial-onset seizures (with no concomitant AEDs): Start with 8–10 mg/kg/24 hr PO ÷ BID. Then increase by 5 mg/kg/24 hr Q3 days up to the recommended monotherapy maintenance dose as described in the following table:

Continued

For explanation of icons, see p. 667

OXCARBAZEPINE *continued*

IMMEDIATE-RELEASE PRODUCT:

Child (4-16 yr, see remarks, cont.)

RECOMMENDED MONOTHERAPY MAINTENANCE DOSES FOR CHILDREN BY WEIGHT

Weight (kg)	Daily Oral Maintenance Dose (mg/24 hr) Divided BID
20–<25	600–900
25–<35	900–1200
35–<45	900–1500
45–<50	1200–1500
50–<60	1200–1800
60–<70	1200–2100
≥70	1500–2100

Adult:

Adjunctive therapy for partial-onset seizures: Start with 600 mg/24 hr PO ÷ BID. Dose may be increased at weekly intervals, as clinically indicated, by a **maximum** of 600 mg/24 hr. Usual maintenance dose is 1200 mg/24 hr PO ÷ BID. Doses ≥2400 mg/24 hr are generally not well tolerated due to CNS side effects.

Conversion to monotherapy for partial-onset seizures: Start with 600 mg/24 hr PO ÷ BID and simultaneously initiate dosage reduction of concomitant AEDs. Dose may be increased at weekly intervals as clinically indicated, by a **max** of 600 mg/24 hr to achieve a dose of 2400 mg/24 hr PO ÷ BID. Concomitant AEDs should be terminated gradually over approximately 3–6 wk.

Initiation of monotherapy for partial-onset seizures: Start with 600 mg/24 hr PO ÷ BID. Then increase by 300 mg/24 hr every 3 days up to 1200 mg/24 hr PO ÷ BID.

EXTENDED RELEASE TABS (Oxtellar XR; see remarks):

Child 6–17 yr of age:

Adjunctive therapy for partial-onset seizures: Start with 8–10 mg/kg/24 hr PO once daily up to a **max. dose** of 600 mg/24 hr. Then gradually increase at weekly intervals in increments of 8–10 mg/kg/24 hr (**max. dosage** increment: 600 mg) to the following maintenance doses:

20–29 kg: 900 mg PO once daily

29.1–39 kg: 1200 mg PO once daily

≥39.1 kg: 1800 mg PO once daily

Adult:

Adjunctive therapy for partial-onset seizures: Start with 600 mg PO once daily (consider using 900 mg if patient is receiving concomitant enzyme-inducing AEDs). Then gradually increase at weekly intervals in 600 mg/24 hr increments to the maintenance dose of 1200–2400 mg once daily.

Clinically significant hyponatremia may occur; generally seen within the first 3 mo of therapy. May also cause headache, dizziness, drowsiness, ataxia, fatigue, nystagmus, urticaria, diplopia, abnormal gait, and GI discomfort. About 25%–30% of patients with carbamazepine hypersensitivity will experience a cross reaction with oxcarbazepine. Serious dermatologic reactions (Stevens-Johnson syndrome [SJS] and TEN), multiorgan hypersensitivity reactions (e.g., DRESS), bone marrow depression, osteoporosis, pancreatitis, folic acid deficiency, hypothyroidism, rare cases of anaphylaxis and angioedema, and suicidal behavior or ideation have been reported. Increased risk for severe dermatologic reactions (e.g., SJS and TEN) has been associated with the HLA-B*1502 (prevalent among persons of Asian descent) alleles.

OXCARBAZEPINE *continued*

Inhibits CYP 450 2C19 and induces CYP 450 3A4/5 drug metabolizing enzymes. Carbamazepine, cyclosporine, phenobarbital, phenytoin, rifampin, valproic acid and verapamil may decrease oxcarbazepine levels. Oxcarbazepine may increase phenobarbital and phenytoin levels. Oxcarbazepine can decrease the effects of oral contraceptives, cyclosporine, felodipine, and lamotrigine.

If GFR <30 mL/min, adjust dosage by administering 50% of the normal starting dose (max. dose: 300 mg/24 hr) followed by a slower than normal increase in dose if necessary **(see Chapter 31).** No dosage adjustment is required in mild/moderate hepatic impairment. Use is **not recommended** in severe hepatic impairment due to lack of information.

Extended release and immediate release products are not bioequivalent, as higher doses of the extended release product may be necessary. Doses may be administered with or without food.

OXYBUTYNIN CHLORIDE

Ditropan XL, Oxytrol, Oxtgrol for Women, and generics; previously available as Ditropan

Anticholinergic agent, antispasmodic

Tabs: 5 mg

Tabs, extended-release (Ditropan XL and generics): 5, 10, 15 mg

Syrup: 1 mg/mL (473 mL); contains parabens

Transdermal system (Oxytrol, Oxytrol for Women): delivers 3.9 mg/24 hr (1, 8s); contains 36 mg per system

Child ≤5 yr:

Immediate release: 0.2 mg/kg/dose BID–TID PO; **max. dose**: 15 mg/24 hr

Child >5 yr:

Immediate release: 5 mg/dose BID–TID PO; **max. dose**: 20 mg/24 hr

Extended release (≥6 yr): Start with 5 mg/dose once daily PO; if needed, increase as tolerated by 5-mg increments up to a **maximum** of 20 mg/24 hr.

Adult:

Immediate release: 5 mg/dose BID–TID PO; **max. dose**: 5 mg QID

Extended release (Ditropan XL): 5–10 mg/dose once daily PO, adjust in 5-mg weekly increments if needed, up to a **max. dose** of 30 mg/dose once daily PO

Transdermal system:

Female: 1 patch (3.9 mg/24 hr) every 4 days

Male: 1 patch (3.9 mg/24 hr) every 3–4 days (twice weekly)

Use with caution in hepatic or renal disease, hyperthyroidism, GE reflux, IBD, concurrent use of bisphosphonates, or cardiovascular disease. Anticholinergic side effects may occur, including drowsiness, confusion, and hallucinations. **Contraindicated** in glaucoma, GI obstruction, megacolon, myasthenia gravis, severe colitis, hypovolemia, and GU obstruction. Memory impairment, angioedema, and QT-interval prolongation have been reported. Oxybutynin is a CYP 450 3A4 substrate; inhibitors and inducers of CYP 450 3A4 may increase and decrease the effects of oxybutynin, respectively. May antagonize the effects of metoclopramide.

Dosage adjustments for the extended-release dosage form are at weekly intervals. The extended-release tablets **should not** be crushed, chewed, or divided. Apply transdermal system on dry intact skin on the abdomen, hip, or buttock; rotate the site and avoiding same-site application within 7 days.

For explanation of icons, see p. 667

OXYCODONE
OxyContin, Roxicodone, Xtampza ER, and many others including generics
Narcotic, analgesic

Expressed as hydrochloride salt unless indicated otherwise.
Oral solution: 1 mg/mL (5, 15, 473 mL); contains alcohol
Concentrated oral solution: 20 mg/mL (30 mL); may contain saccharin
Tabs: 5, 10, 15, 20, 30 mg
Controlled-release tabs (OxyContin and generics): 10, 15, 20, 30, 40, 60, 80 mg (80 mg strength for opioid-tolerant patients only)
Caps: 5 mg
Extended-release caps (Xtampza ER): 9, 13.5, 18, 27, 36 mg oxycodone base; equivalent to 10, 15, 20, 30, and 40 mg oxycodone hydrochloride salt, respectively

Opioid naïve doses based upon oxycodone hydrochloride salt:
Child: 0.05–0.15 mg/kg/dose Q4–6 hr PRN up to 5 mg/dose PO
Adolescent (≥50 kg) and adult: 5–10 mg Q4–6 hr PRN PO; see remarks for use of controlled-release tablets.

There is a potential for abuse; CNS and respiratory depression, increased ICP, histamine release, constipation, and GI distress may occur. **Use with caution** in severe renal impairment (increases $T_{½}$) and mild/moderate hepatic dysfunction (use of one-third to one-half of usual dose has been recommended). **Naloxone is the antidote.** See Chapter 6 for equianalgesic dosing. Check dosages of acetaminophen or aspirin when using combination products (e.g., Percocet, Percodan). Oxycodone is metabolized by the CYP 450 3A4 (major) and 2D6 (minor) isoenzyme.

When controlled-released tablets (e.g., Oxycontin) are being used, determine patient's total 24-hr requirement should be determined and divided by 2 to administer on a Q12 hr dosing interval. Oxycontin 80-mg tablet is **USED ONLY** for opioid-tolerant patients; this strength can cause fatal respiratory depression in opioid-naive patients. Controlled-release dosage form should not be used as a PRN analgesic and must be swallowed whole.

Pregnancy category changes to D if used for prolonged periods or in high doses at term.

The FDA has assigned a Risk Evaluation and Mitigation Strategy (REMS) for opioid analgesia; see www.fda.gov/OpioidAnalgesicREMSPCG. The REMS strongly encourages the (1) completion of a REMS-compliant education program; (2) counsel patients/caregivers on prescription safe use, risks, storage, and disposal; (3) emphasize the importance of reading the medication guide provided by pharmacists at all times; and (4) consider other methods for improving patient, household, and community safety.

OXYCODONE AND ACETAMINOPHEN
Endocet, Percocet, Roxicet, and many others including generics
Combination analgesic with a narcotic

Tabs (Percocet, Endocet, and others including generics):
Most common strength: oxycodone HCl 5 mg + acetaminophen 325 mg
Other strengths:
Oxycodone HCl 2.5 mg + acetaminophen 325 mg
Oxycodone HCl 7.5 mg + acetaminophen 325 mg
Oxycodone HCl 10 mg + acetaminophen 325 mg

OXYCODONE AND ACETAMINOPHEN *continued*

Oral solution: Oxycondone HCl 5 mg + acetaminophen 325 mg/5 mL (500 mL); may contain 0.4% alcohol and saccharin

Dose based on amount of oxycodone and acetaminophen. Do not exceed 4 g/24 hr of acetaminophen.

See oxycodone and acetaminophen. Check dosages of acetaminophen and oxycodone when using these combination products.

The FDA has assigned a Risk Evaluation and Mitigation Strategy (REMS) for Opioid Analgesia; see www.fda.gov/OpioidAnalgesicREMSPCG. The REMS strongly encourages the (1) completion of a REMS-compliant education program; (2) counsel patients/caregivers on prescription safe use, risks, storage and disposal; (3) emphasize the importance of reading the Medication Guide provided by pharmacists at all times; and (4) consider other methods for improving patient, household and community safety.

OXYCODONE AND ASPIRIN

Various generics; previously available as Percodan and Endodan,

Combination analgesic (narcotic and salicylate)

Tabs: Oxycodone 4.8355 mg and aspirin 325 mg

Dose based on amount of oxycodone and aspirin. Do not exceed 4 g/24 hr of aspirin.

See oxycodone and aspirin. **Must not be used** in children <16 yr of age because of risk for Reye syndrome. Check dosages of aspirin and oxycodone when using these combination products.

The FDA has assigned a Risk Evaluation and Mitigation Strategy (REMS) for Opioid Analgesia; see www.fda.gov/OpioidAnalgesicREMSPCG. The REMS strongly encourages the (1) completion of a REMS-compliant education program; (2) counsel patients/caregivers on prescription safe use, risks, storage and disposal; (3) emphasize the importance of reading the Medication Guide provided by pharmacists at all times; and (4) consider other methods for improving patient, household and community safety.

OXYMETAZOLINE

Afrin 12 Hour, Neo-Synephrine 12-Hour Nasal, Nostrilla and many others including generics

Nasal decongestant, vasoconstrictor

Nasal spray (OTC): 0.05% (15, 30 mL); may contain benalkonium chloride and propylene glycol

Nasal decongestant (not to exceed 3 days in duration):

≥6 yr of age to adult: 2–3 sprays or 2–3 drops in each nostril BID. **Do not exceed** 2 doses/24 hr.

Contraindicated in patients on MAO inhibitor therapy. Rebound nasal congestion may occur with excessive use (>3 days) via the nasal route. Systemic absorption may occur. Headache, insomnia, hypertension, transient burning, stinging, dryness, nasal mucosal ulceration, and sneezing have occurred.

Accidental ingestion in children <5 yr of age has been reported and required hospitalization for adverse events (nausea, vomiting, lethargy, tachycardia, respiratory depression, bradycardia, hypotension, hypertension, sedation, mydriasis, stupor, hypothermia, drooling and coma).

For explanation of icons, see p. 667

P

PALIVIZUMAB
Synagis
Monoclonal antibody

Injection, solution: 100 mg/mL (0.5, 1 mL; single use); contains glycine and histidine.

RSV prophylaxis during RSV season for the following age and clinical criteria (see latest edition of Red Book for most recent indications).

Following recommendations are from *Pediatrics* 2014;134(2):415–420.

Candidates for recommended use:

<12 mo of age (one of the following):

Born at ≤28-wk gestation; OR
With chronic lung disease (CLD) of prematurity (<32-wk gestation requiring >21% oxygen for at least 28 days after birth); OR
With hemodynamically significant congenital heart disease

<24 mo of age:

Born at ≤32-wk gestation with CLD requiring medical therapy (e.g., ≥28 days of supplemental oxygen, bronchodilator, diuretics, or chronic steroids) within 6 mo prior to start of RSV season.

Candidates for consideration:

<12 mo of age (one of the following):

With congenital airway abnormalities or neuromuscular disorders that decrease ability to manage airway secretions; OR
With cystic fibrosis with clinical evidence of CLD and/or nutritional compromise

≤24 mo of age (one of the following):

With cystic fibrosis with severe lung disease (previous pulmonary exacerbation in first year of life or abnormal chest x-ray) or weight for length less than the 10th percentile; OR
Profoundly immunocompromised; OR
Undergoing cardiac transplantation during RSV season

DOSE:

≤24 mo old: 15 mg/kg/dose IM Q monthly just prior to and during the RSV season. **Maximum** of five doses per RSV season is recommended by the AAP. Therapy should be discontinued if child experiences breakthrough RSV hospitalization.

RSV season typically November through April in the northern hemisphere but may begin earlier or persist later in certain communities. **IM** is currently the only route of administration, so **use with caution** in patients with thrombocytopenia or any coagulation disorder. The following adverse effects have been reported at slightly higher incidences when compared with placebo: rhinitis, rash, pain, increased liver enzymes, pharyngitis, cough, wheeze, diarrhea, vomiting, conjunctivitis, and anemia. Rare acute hypersensitivity reactions have been reported (first or subsequent doses).

Does not interfere with the response to routine childhood vaccines. May interfere with immunologic-based RSV diagnostic tests (some antigen detection–based assays and viral culture assays) but not with reverse transcriptase-polymerase chain reaction (PCR)-based assays.

Palivizumab is currently indicated for RSV prophylaxis in high-risk infants only. Efficacy and safety have not been demonstrated for treatment of RSV.

Cardiopulmonary bypass and ECMO will significantly reduce serum concentrations; administer a dose immediately after the bypass procedure or ECMO even if it is <1 mo from the previous dose.

Each dose should be administered IM in the anterolateral aspect of the thigh. It is recommended to divide doses with total injection volumes >1 mL. **Avoid** injection in the gluteal muscle because of risk for damage to the sciatic nerve.

D

PANCRELIPASE/PANCREATIC ENZYMES
Creon, Pancreaze, Pertzye, Ultresa, Viokace, and Zenpep
Pancreatic enzyme

Delayed-release enterically coated beads, microspheres, or minitabs in capsules (porcine derived):

Product	Lipase (USP) Units	Amylase (USP) Units	Protease (USP) Units
Creon[a]			
3	3,000	15,000	9,500
6	6,000	30,000	19,000
12	12,000	60,000	38,000
24	24,000	120,000	76,000
36	36,000	180,000	114,000
Pancreaze[b]			
MT 2	2,600	10,850	6,200
MT 4	4,200	24,600	14,200
MT 10	10,500	61,500	35,500
MT 16	16,800	98,400	56,800
MT 20	21,000	83,900	54,700
Pertzye[a,c]			
4	4,000	15,125	14,375
8	8,000	30,250	28,750
16	16,000	60,500	57,500
24	24,000	90,750	86,250
Ultresa[b]			
4	4,000	8,000	8,000
13	13,800	27,600	27,600
20	20,700	41,400	41,400
23	23,000	46,000	46,000
Zenpep[d]			
3	3,000	14,000	10,000
5	5,000	24,000	17,000
10	10,000	42,000	32,000
15	15,000	63,000	47,000
20	20,000	84,000	63,000
25	25,000	105,000	79,000
40	40,000	168,000	126,000

[a]Enteric coated microspheres.
[b]Enteric coated minitabs.
[c]Contains bicarbonate.
[d]Enteric coated beads.

Tabs (porcine derived):

Product	Lipase (USP) Units	Amylase (USP) Units	Protease (USP) Units
Viokace			
10	10,440	39,150	39,150
20	20,880	78,300	78,300

Continued

For explanation of icons, see p. 667

PANCRELIPASE/PANCREATIC ENZYMES *continued*

Initial doses (actual requirements are patient specific):
Enteric coated microspheres and microtabs:
Infant: 2000–4000 U lipase per 120 mL (formula or breast milk)
Child <4 yr: 1000 U lipase/kg/meal
Child ≥4 yr and adult: 500 U lipase/kg/meal
Max. dose (child–adult): 2500 U lipase/kg/meal, or 10,000 U lipase/kg/24 hr, or 4000 U lipase/g fat/24 hr.

Total daily dose should include approximately three meals and two to three snacks per day. Snack doses are approximately half of meal doses, depending on the amount of fat and food consumed.

May cause occult GI bleeding, allergic reactions to porcine proteins, hyperuricemia, and hyperuricosuria with high doses. Dose should be titrated to eliminate diarrhea and to minimize steatorrhea. **Do not** chew microspheres or microtabs. Concurrent administration with H_2 antagonists or gastric acid pump inhibitors may enhance enzyme efficacy. Doses higher than 6000 U lipase/kg/meal have been associated with colonic strictures in children <12 yr. Nonenteric coated dosage forms (e.g., powder and tablet) are not preferred, owing to potential GI mucosal ulceration. Patients who are unable to swallow capsules intact may mix the contents with small amount of acidic soft foods (pH ≤4.5; such as applesauce) and swallow immediately after mixing.

Avoid use of generic pancreatic enzyme products because they been associated with treatment failures. Products not approved by the FDA are no longer allowed to be distributed in the United States.

Patients requiring enzyme supplementation who receive enteral feeding via a feeding tube may alternatively use a digestive enzyme cartridge (RELiZORB).

PANCURONIUM BROMIDE

Generics

Nondepolarizing neuromuscular blocking agent

Injection: 1 mg/mL (10 mL); contains benzyl alcohol

Intermittent dosing (see remarks):
Neonate:
Initial: 0.02 mg/kg/dose IV
Maintenance: 0.05–0.1 mg/kg/dose IV Q0.5–4 hr PRN
1 mo–adult:
Initial: 0.04–0.1 mg/kg/dose IV
Maintenance: 0.015–0.1 mg/kg/dose IV Q30–60 min
***Continuous* IV infusion (see remarks):**
Neonate: 0.02–0.04 mg/kg/hr
Child: 0.03–1 mg/kg/hr
Adolescent and adult: 0.02–0.04 mg/kg/hr

Onset of action is 1–2 min. May cause tachycardia, salivation, and wheezing. Severe anaphylactic reactions have been reported; cross reactivity between neuromuscular blocking agents has been reported.

Drug effects may be accentuated by hypothermia, acidosis, neonatal age, decreased renal function, halothane, succinylcholine, hypokalemia, hyponatremia, hypocalcemia, clindamycin, tetracycline, and aminoglycoside antibiotics. Drug effects may be antagonized by alkalosis, hypercalcemia, peripheral neuropathies, diabetes mellitus, demyelinating lesions, carbamazepine, phenytoin,

PANCURONIUM BROMIDE *continued*

theophylline, anticholinesterases (e.g., neostigmine, pyridostigmine), and azathioprine. For obese patients, use of lean body weight for dose calculation has been recommended to prevent intense block of long duration and possible overdose.

Antidote is neostigmine (with atropine or glycopyrrolate). **Avoid** use in severe renal impairment (<10 mL/min). Patients with cirrhosis may require a high initial dose to achieve adequate relaxation, but muscle paralysis will be prolonged.

PANTOPRAZOLE
Protonix and generics
Gastric acid pump inhibitor

Tab, delayed release: 20, 40 mg
Injection: 40 mg; contains edetate sodium
Oral suspension: 2 mg/mL ✍; contains 0.25 mEq sodium bicarbonate per 1 mg drug
Enterically coated granules for delayed-release oral suspension (Protonix): 40 mg packets (30s); contains polysorbate 80

Child (see remarks):

GERD (limited data):

Infant and <5 yr: 1.2 mg/kg/24 hr PO once daily. **Note:** Pantoprazole did not significantly improve GERD symptoms scores in an open-label trial in 128 infants (1–11 mo) receiving 1.2 mg/kg/24 hr PO once daily ×4 wk, followed by a 4 wk double blinded placebo-controlled withdrawal phase.

≥5 yr and adolescent: 20 or 40 mg PO once daily

GERD with erosive esophagitis:

1–5 yr (limited data): 0.3, 0.6, or 1.2 mg/kg/24 hr PO once daily all improved GERD symptoms in an 8-wk multicenter, randomized placebo control trial for 60 subjects with GERD and histologic/erosive esophagitis.

≥5 yr (up to 8 wk of therapy):

15–<40 kg: 20 mg PO once daily

≥40 kg: 40 mg PO once daily

IV (data limited to pharmacokinetic trials): Some doses ranging from 0.32–1.88 mg/kg/dose have been reported from three separate trials (total *N* = 31; 0.01–16.4 yr). Patients with systemic inflammatory response syndrome (SIRS) cleared the drug more slowly, resulting in higher T½ and AUC, than patients without. Despite limited data, 1–2 mg/kg/24 hr ÷ Q12–24 hr have been used. Additional studies are needed.

Adult:

GERD with erosive esophagitis:

PO: 40 mg once daily ×8–16 wk

IV: 40 mg once daily ×7–10 days

Peptic ulcer: 40–80 mg PO once daily ×4–8 wk

Hypersecretory conditions:

PO: 40 mg BID; dose may be increased as needed up to a **max. dose** of 240 mg/24 hr.

IV: 80 mg Q12 hr; dose may be increased as needed to Q8 hr (**max. dose**: 240 mg/24 hr). Therapy >7 days at 240 mg/24 hr has not been evaluated.

Convert from IV to PO therapy as soon as patient is able to tolerate PO. Common side effects include diarrhea and headache. May cause transient elevation in LFTs. Like other PPIs, may increase risk for *Clostridium difficile*–associated diarrhea. Hypomagnesemia has been reported with long-term use. Hypersensitivity reactions (e.g., anaphylaxis, shock,

Continued

For explanation of icons, see p. 667

PANTOPRAZOLE *continued*

angioedema, bronchospasm, acute interstitial nephritis, and urticaria), agranulocytosis, pancytopenia, and taste disorders have been reported. Fundic gland polyps have been associated with long term use of PPIs.

May interfere with serum chromogranin A (CgA) diagnostic test for neuroendocrine tumors; discontinue use at least 14 days prior to testing. False-positive test for urine cannabinoid screen may occur.

Drug is a substrate for CYP 450 2C19 (major), 2D6 (minor), and 3A3/4 (minor) isoenzymes. Recommended dosage modification for ultrarapid metabolizers of CYP 2C19 is to increase the usual dose by fivefold. May decrease the absorption of itraconazole, ketoconazole, iron salts, and ampicillin esters. May increase the effect/toxicity of methotrexate.

Children 1–2 yr of age have demonstrated more rapid clearance of pantoprazole in pharmacokinetic studies; this age group may require higher doses. All oral doses may be taken with or without food. **Do not** crush or chew tablets. The extemporaneously compounded oral suspension may be less bioavailable owing to the loss of the enteric coating. Granules for delayed-release oral suspension product may be mixed with 5 mL apple juice (administer immediately followed by rinsing container with more apple juice), or sprinkled on 1 teaspoonful of apple sauce (administer within 10 min); see package insert for NG administration.

For IV infusion, doses may be administered over 15 min at a concentration of 0.4–0.8 mg/mL or over 2 min at a concentration of 4 mg/mL. Midazolam and zinc are **not compatible** with the IV dosage form. Parenteral routes other than IV are **not recommended.**

PAROMOMYCIN SULFATE
Generics; previously available as Humatin
Amebicide, antibiotic (aminoglycoside)

Caps: 250 mg

Intestinal amebiasis* (Entamoeba histolytica), Dientamoeba fragilis, *and* Giardia lamblia *infection:

Child and adult: 25–35 mg/kg/24 hr PO ÷ Q8 hr ×7 days

Tapeworm (Taenia saginata, Taenia solium, Diphyllobothrium latum, and Dipylidium caninum):

Child: 11 mg/kg/dose PO Q15 min ×4 doses

Adult: 1 g PO Q15 min ×4 doses

Tapeworm (Hymenolepis nana):

Child and adult: 45 mg/kg/dose PO once daily ×5–7 days

Cryptosporidial diarrhea:

Adult: 1.5–2.25 g/24 hr PO ÷3–6× daily. Duration varies from 10–14 days to 4–8 wk. Maintenance therapy has also been used. Alternatively, 1 g PO BID ×12 wk in conjunction with azithromycin 600 mg PO once daily ×4 wk has been used in patients with AIDS.

Contraindicated in intestinal obstruction. **Use with caution** in ulcerative bowel lesions to avoid renal toxicity via systemic absorption. Drug is generally poorly absorbed and therefore not indicated for sole treatment of extraintestinal amebiasis. Side effects include GI disturbance, hematuria, rash, ototoxicity, and hypocholesterolemia. Bacterial overgrowth of nonsusceptible organisms, including fungi, may occur. May decrease the effects of digoxin.

PAROXETINE
Paxil, Pexeva, Paxil CR, Brisdelle, and generics
Antidepressant, selective serotonin reuptake inhibitor

Tabs (Paxil, Pexeva, and generics): 10, 20, 30, 40 mg
Caps (Brisdelle and generics): 7.5 mg
Controlled-release tabs (Paxil CR and generics): 12.5, 25, 37.5 mg
Oral suspension (Paxil): 10 mg/5 mL (250 mL); contains saccharin and parabens

Child:

Depression: Well-controlled clinical trials have failed to demonstrate efficacy in children. The FDA recommends paroxetine not to be used for this indication.

Obsessive compulsive disorder (limited data, based on a 10-wk randomized controlled trial in 207 children 7–17 yr; mean age 11.1 + 3.03 yr): Start with 10 mg PO once daily. If needed, adjust upwards by increasing dose no more than 10 mg/24 hr no more frequently than Q7 days up to a **max. dose** of 50 mg/24 hr. Mean doses of 20.3 mg/24 hr (children) and 26.8 mg/24 hr (adolescents) were used.

Social anxiety disorder (limited data; 8–17 yr): Start with 10 mg PO once daily. If needed, increase dose by 10 mg/24 hr no more frequently than Q7 days up to a **max. dose** of 50 mg/24 hr.

Adult:

Depression:

Immediate release dosage forms: Start with 20 mg PO QAM ×4 wk. If no clinical improvement, increase dose by 10 mg/24 hr Q7 days PRN up to a **max. dose** of 50 mg/24 hr.

Controlled-release tabs (Paxil CR and generics): Start with 25 mg PO QAM ×4 wk. If no improvement, increase dose by 12.5 mg/24 hr Q7 days PRN up to a **max. dose** of 62.5 mg/24 hr.

Obsessive compulsive disorder (immediate release): Start with 20 mg PO once daily; increase dose by 10 mg/24 hr Q7 days PRN up to a **max. dose** of 60 mg/24 hr. Usual dose is 40 mg PO once daily.

Panic disorder:

Immediate release dosage forms: Start with 10 mg PO QAM; increase dose by 10 mg/24 hr Q7 days PRN up to a **max. dose** of 60 mg/24 hr.

Paxil CR: Start with 12.5 mg PO QAM; increase dose by 12.5 mg/24 hr Q7 days PRN up to a **max. dose** of 75 mg/24 hr.

Contraindicated in patients taking MAO inhibitors (within 14 days of discontinuing MAO inhibitors), linezolid, methylene blue, pimozide, or thioridazine. **Use with caution** in patients with history of seizures, renal or hepatic impairment, cardiac disease, suicidal concerns, mania/hypomania, concurrent use with other serotonergic drugs (e.g., triptans, fentanyl, lithium, tramadol, amphetamines, or St. John's Wort), and diuretic use. Patients with severe renal or hepatic impairment should initiate therapy at 10 mg/24 hr and increase dose as needed up to a **max.** of 40 mg/24 hr.

Common side effects include anxiety, nausea, anorexia, and decreased appetite. Monitor for clinical worsening of depression and suicidal ideation/behavior following the initiation of therapy or after dose changes. Stevens-Johnson syndrome has been reported.

Paroxetine is an inhibitor and substrate for CYP 450 2D6. Ultrametabolizers of CYP 2D6 should avoid use of paroxetine and use an alternative medication not metabolized by this enzyme system. A 50% initial dose reduction for poor CYP 2D6 metabolizers has been recommended. May increase the effects/toxicity of tricyclic antidepressants, theophylline, and warfarin. May decrease the effects of tamoxifen. Cimetidine, ritonavir, MAO inhibitors (fatal serotonin syndrome), dextromethorphan, phenothiazines, and type 1C antiarrhythmics may increase the effect/toxicity of paroxetine. Weakness, hyperreflexia, and poor coordination have been reported when taken with sumatriptan.

Do not discontinue therapy abruptly; may cause sweating, dizziness, confusion, and tremor. May be taken with or without food.

For explanation of icons, see p. 667

PENICILLIN G PREPARATIONS—AQUEOUS POTASSIUM AND SODIUM
Pfizerpen and generics
Antibiotic, aqueous penicillin

Injection (K^+): 5, 20 million units (contains 1.7 mEq K and 0.3 mEq Na/1 million units penicillin G)
Premixed frozen injection (K^+): 1 million units in 50 mL dextrose 4%; 2 million units in 50 mL dextrose 2.3%; 3 million units in 50 mL dextrose 0.7% (contains 1.7 mEq K and 0.3 mEq Na/1 million units penicillin G)
Injection (Na^+): 5 million units (contains 2 mEq Na/1 million units penicillin G)
Conversion: 250 mg = 400,000 units

Neonate (IM/IV; use higher end of dosage range for meningitis and severe infections):
≤7 days old: 50,000–100,000 units/kg/24 hr ÷ Q12 hr
8–28 days old:
<1 kg:
8–≤14 days old: 50,000–100,000 units/kg/24 hr ÷ Q12 hr
15–28 days old: 75,000–150,000 units/kg/24 hr ÷ Q8 hr
≥1 kg: 75,000–150,000 units/kg/24 hr ÷ Q8 hr
Group B streptococcal meningitis:
≤7 days: 250,000–450,000 units/kg/24 hr ÷ Q8 hr
8–28 days: 450,000–500,000 units/kg/24 hr ÷ Q4–6 hr
Congenital syphilis (total of 10 days of therapy; if >1 day of therapy is missed, restart the entire course):
≤7 days: 100,000 units/kg/24 hr ÷ Q12 hr IV; increase to the following dosage at day 8 of life.
8–28 days: 150,000 units/kg/24 hr ÷ Q8 hr IV
Infant, child, and adolescent:
IM/IV (use higher end of dosage range and Q4 hr interval for meningitis and severe infections): 100,000–400,000 units/kg/24 hr ÷ Q4–6 hr; **max. dose:** 24 million units/24 hr
Neurosyphilis:
Infant and child: 200,000–300,000 units/kg/24 hr ÷ Q4–6 hr IV ×10–14 days; **max. dose:** 24 million units/24 hr
Adolescent: 3–4 million units Q4 hr IV ×10–14 days; **max. dose:** 24 million units/24 hr
Adult:
IM/IV: 12–24 million units/24 hr ÷ Q4–6 hr
Neurosyphilis: 18–24 million units/24 hr ÷ Q4–6 hr IV ×10–14 days.

Use penicillin V potassium for oral use. Side effects: anaphylaxis, urticaria, hemolytic anemia, interstitial nephritis, Jarisch-Herxheimer reaction (syphilis). Preparations containing potassium and/or sodium salts may alter serum electrolytes. $T_{½}$ = 30 min; may be prolonged by concurrent use of probenecid. For meningitis, use higher daily dose at shorter dosing intervals. For the treatment of anthrax *(Bacillus anthracis),* see www.bt.cdc.gov for additional information. **Adjust dose in renal impairment (see Chapter 31).**

Tetracyclines, chloramphenicol, and erythromycin may antagonize penicillin's activity. Probenecid increases penicillin levels. May cause false-positive or false-negative urinary glucose (Clinitest method), false-positive direct Coombs test, and false-positive urinary and/or serum proteins.

PENICILLIN G PREPARATIONS—BENZATHINE
Bicillin L-A
Antibiotic, penicillin (very-long-acting IM)

Injection: 600,000 units/mL (1, 2, 4 mL); contains parabens and povidone
Injection should be IM only.

Group A streptococci:
Infant and child: 25,000–50,000 units/kg/dose IM ×1. **Max. dose:** 1.2 million units/dose **OR:**
>1 mo and <27 kg: 600,000 units/dose IM ×1
≥27 kg and adult: 1.2 million units/dose IM ×1
Rheumatic fever prophylaxis (Q3 wk administration is recommended for high-risk situations):
Infant and child (>1 mo and <27 kg): 600,000 units/dose IM Q3–4 wk.
Child ≥27 kg and adult: 1.2 million units/dose IM Q3–4 wk
Congenital Syphilis:
Neonate: 50,000 units/kg/dose IM ×1
Syphilis (if >1 day of therapy is missed, restart the entire course; divided total dose into two injection sites):
Infant and child:
Primary, secondary, and early latent syphilis (<1-yr duration): 50,000 units/kg/dose ×1
Late latent syphilis or latent syphilis of unknown duration: 50,000 units/kg/dose Q7 days ×3 doses.
Max. dose: 2.4 million units/dose
Adult:
Primary, secondary, and early latent syphilis: 2.4 million units/dose IM ×1
Late latent syphilis or latent syphilis of unknown duration: 2.4 million units/dose IM Q7 days ×3 doses.

Provides sustained levels for 2–4 wk. **Use with caution** in renal failure, asthma, G6PD deficiency (risk for methemoglobinemia), and cephalosporin hypersensitivity. Side effects and drug interactions same as for Penicillin G Preparations–Aqueous Potassium and Sodium. Injection site reactions are common.
Deep IM administration only. Do not administer intravenously (cardiac arrest and death may occur), and **do not inject** into or near an artery or nerve (may result in permanent neurologic damage).

PENICILLIN G PREPARATIONS—PENICILLIN G BENZATHINE AND PENICILLIN G PROCAINE
Bicillin C-R, Bicillin C-R 900/300
Antibiotic, penicillin (very-long-acting IM)

Bicillin CR: 300,000 units penicillin G procaine + 300,000 units penicillin G benzathine/mL to provide 600,000 units penicillin per 1 mL (2 mL Tubex syringe)
Bicillin CR (900/300): 150,000 units penicillin G procaine + 450,000 units penicillin G benzathine/mL (2 mL Tubex syringe)
All preparations contain parabens and povidone.
Injection should be for IM use only.

Dosage based on total amount of penicillin.
Group A streptococci (see remarks):
Infant and child (Bicillin CR):
<14 kg: 600,000 units/dose IM ×1
14–27 kg: 900,000–1,200,000 units/dose IM ×1

For explanation of icons, see p. 667

PENICILLIN G PREPARATIONS—PENICILLIN G BENZATHINE AND PENICILLIN G PROCAINE *continued*

Dosage based on total amount of penicillin.

Group A streptococci (see remarks; cont.):

Child >27 kg and adult

Bicillin C-R: 2,400,000 units/dose IM ×1

Bicillin C-R 900/300: 1,200,000 units/dose IM ×1

Pneumococcal infection (non-CNS): dosed Q2–3 days until afebrile for 48 hr (see remarks)

Child (Bicillin C-R): 600,000 units/dose IM

Adult (Bicillin C-R or Bicillin C-R 900/300): 1,200,000 units/dose IM

This preparation provides early peak levels in addition to prolonged levels of penicillin in the blood. **Do not use this product to treat syphilis; treatment failure can occur. Use with caution** in renal failure, asthma, significant allergies, G6PD deficiency (risk for methemoglobinemia), and cephalosporin hypersensitivity. The addition of procaine penicillin has not been shown to be more efficacious than benzathine alone. However, it may reduce injection discomfort.

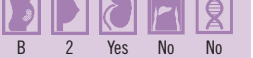
Deep IM administration only. Do not administer intravenously (cardiac arrest and death may occur), and **do not** inject into or near an artery or nerve (may result in permanent neurologic damage).

Side effects and drug interactions same as for Penicillin G Preparations–Aqueous Potassium and Sodium. Immune hypersensitivity reaction has been reported.

PENICILLIN G PREPARATIONS—PROCAINE

Generics; previously available as Wycillin

Antibiotic, penicillin (long-acting IM)



Injection: 600,000 units/mL (1, 2 mL); may contain parabens, phenol, povidone, and formaldehyde) Contains 120 mg procaine per 300,000 units penicillin.

Injection should be for IM use only.

Newborn (see remarks): 50,000 units/kg/24 hr IM once daily

Infant and child: 25,000–50,000 units/kg/24 hr ÷ Q12–24 hr IM. **Max. dose:** 4.8 million units/24 hr

Adult: 0.6–4.8 million units/24 hr ÷ Q12–24 hr IM

Congenital syphilis, syphilis (if >1 day of therapy is missed, restart the entire course; see remarks):

Neonate, infant, child: 50,000 units/kg/dose once daily IM ×10 days.

Neurosyphilis (see remarks):

Adolescent and adult: 2.4 million units IM once daily and probenecid 500 mg Q6 hr PO ×10–14 days (both medications).

Inhaled anthrax: Postexposure prophylaxis (total duration of therapy with all forms of therapy is 60 days; switch to an alternative form of therapy after 2 wk of procaine penicillin because of the risk for adverse effects; see remarks):

Child and adolescent: 25,000 units/kg/dose (**max. dose**: 1.2 million units/dose) IM Q12 hr

Adult: 1.2 million units IM Q12 hr

Provides sustained levels for 2–4 days. **Use with caution** in renal failure, asthma, significant allergies, cephalosporin hypersensitivity, G6PD deficiency (risk for methemoglobinemia), and neonates (higher incidence of sterile abscess at injection site and risk of procaine toxicity). Side effects and drug interactions similar to Penicillin G Preparations–Aqueous Potassium and Sodium. In addition, may cause CNS stimulation and seizures. Immune hypersensitivity reaction has been reported.

Deep IM administration only. Do not administer intravenously (cardiac arrest and death may occur), and **do not inject** into or near an artery or nerve (may result in permanent neurologic damage). Large doses may be administered in two injection sites. No longer recommended for empiric treatment of gonorrhea due to resistant strains.

PENICILLIN V POTASSIUM
Generics; previously available as Veetids
Antibiotic, penicillin

Tabs: 250, 500 mg
Oral solution: 125 mg/5 mL, 250 mg/5 mL (100, 200 mL); may contain saccharin
Contains 0.7 mEq potassium/ 250 mg drug
Conversion: 250 mg = 400,000 units

Infant and child: 25–75 mg/kg/24 hr ÷ Q6–8 hr PO; **max. dose:** 2 g/24 hr
Adolescent and adult: 125–500 mg/dose PO Q6–8 hr
Acute group A streptococcal pharyngitis (use BID dosing regimen ONLY if good compliance is expected):
Child <27 kg: 250 mg PO BID–TID ×10 days
Child ≥27 kg, adolescent and adult: 500 mg PO BID–TID ×10 days
Rheumatic fever prophylaxis, and pneumococcal prophylaxis for sickle cell disease and functional or anatomic asplenia (regardless of immunization status):
2 mo – <3 yr: 125 mg PO BID
3–5 yr: 250 mg PO BID; for sickle cell and asplenia, use may be discontinued after 5 yr of age if child received recommended pneumococcal immunizations and did not experience invasive pneumococcal infection.
Recurrent rheumatic fever prophylaxis:
Child and adult: 250 mg PO BID

See Penicillin G Preparations–Aqueous Potassium and Sodium for side effects and drug interactions. GI absorption is better than penicillin G. **Note**: Must be taken 1 hr before or 2 hr after meals. Penicillin will prevent rheumatic fever if started within 9 days of the acute illness. **Adjust dose in renal failure (see Chapter 31).**

PENTAMIDINE ISETHIONATE
Pentam 300, NebuPent, and generics
Antibiotic, antiprotozoal

Injection (Pentam 300 and generics): 300 mg
Inhalation (NebuPent): 300 mg

Treatment (child and adult):
Pneumocystis jiroveci (carinii): 4 mg/kg/24 hr IM/IV once daily ×14–21 days (IV is the preferred route)
Trypanosomiasis (Trypanosoma gambiense, Trypanosoma rhodesiense without CNS involvement): 4 mg/kg/24 hr IM/IV once daily ×7–10 days
Visceral leishmaniasis (Leishmania donovani, L. infantum, L. chagasi): 4 mg/kg/dose IM/IV once daily, or once every other day ×15–30 doses
Cutaneous leishmaniasis (Leishmania [Viannia] panamensis): 2–4 mg/kg/dose IM/IV once or twice a week until lesions healed
Prophylaxis (child and adult):
P. jiroveci (carinii):
IM/IV: 4 mg/kg/dose Q4 wk (Q2–4 wk for hematopoietic stem cell transplant); **max. single dose:** 300 mg
Inhalation (use with Respigard II nebulizer):
<5 yr: 9 mg/kg (**max. dose**: 300 mg/dose) Q month
≥5 yr: 300 mg Q month

For explanation of icons, see p. 667

PENTAMIDINE ISETHIONATE *continued*

Use with caution in ventricular tachycardia, Stevens-Johnson syndrome, and daily doses >21 days. May cause hypoglycemia, hyperglycemia, hypotension (both IV and IM administration), nausea, vomiting, fever, mild hepatotoxicity, pancreatitis, megaloblastic anemia, nephrotoxicity, hypocalcemia, and granulocytopenia. Additive nephrotoxicity with aminoglycosides, amphotericin B, cisplatin, and vancomycin may occur. Aerosol administration may also cause bronchospasm, cough, oxygen desaturation, dyspnea, and loss of appetite. Infuse IV over 1–2 hr to reduce the risk of hypotension. Sterile abscess may occur at IM injection site.

Adjust dose in renal impairment (see Chapter 31) with systemic use.

PENTOBARBITAL

Nembutal and generics

Barbiturate

Injection: 50 mg/mL (20, 50 mL); contains propylene glycol and 10% alcohol

Hypnotic

Child:

IM: 2–6 mg/kg/dose. **Max. dose:** 100 mg

Adult:

IM: 150–200 mg

Reduction in Elevated ICP (adjunct therapy; patient must to be intubated): Barbituate coma may be used if needed.

Child and adolescent:

IV/IO: 1–3 mg/kg/dose

IM/PR: 2–6 mg/kg/dose

Max. dose: 100 mg/dose

Barbiturate coma

Child and adult:

IV: loading dose: 10–15 mg/kg given slowly over 1–2 hr

Maintenance: Begin at 1 mg/kg/hr. Dose range: 1–3 mg/kg/hr as needed.

Contraindicated in liver failure and history of porphyria. Use in preprocedure sedation has been replaced by other agents. **Use with caution** in hypovolemic shock, CHF, hypotension, and hepatic impairment. No advantage over phenobarbital for control of seizures. May cause drug-related isoelectric EEG. **Do not administer** for >2 wk in treatment of insomnia. May cause hypotension, arrhythmias, hypothermia, respiratory depression, and dependence.

Onset of action: IM: 10–15 min; IV: 1 min. Duration of action: IV: 15 min.

Administer IV at a rate of <50 mg/min.

Therapeutic serum levels: sedation: 1–5 mg/L; hypnosis: 5–15 mg/L; coma: 20–40 mg/L (steady state is achieved after 4–5 days of continuous IV dosing).

PERMETHRIN

Elimite, Nix, and generics

Scabicidal agent

Cream (Elimite and generics): 5% (60 g); contains 0.1% formaldehyde

Liquid cream rinse/lotion (Nix Lice Killing Crème Rinse-OTC and generics) [OTC]: 1% (59 mL with comb); may contain 20% isopropyl alcohol

PERMETHRIN *continued*

Additional OTC permethrin products for use on bedding, furniture, and garments include the following:
Liquid spray (Nix Lice Control Spray): 0.25% (150 mL)
Spray (Rid Home Lice Bedbug and Dust Mite Spray): 0.5% (141.8 g)

Pediculus humanus capitis, Phthirus pubis *(> 2 mo, child, and adolescent):*
Head lice: Saturate hair and scalp with 1% cream rinse/lotion after shampooing, rinsing, and towel drying hair. Leave on for 10 min, then rinse. May repeat in 7 days. May be used for lice in other areas of the body (e.g., pubic lice) in same fashion. If the 1% cream rinse is resistant, the 5% cream may be used after shampooing, rinsing, and towel drying hair. Leave on for 8–14 hr overnight under a shower cap; then rinse off. May repeat in 7 days.
Scabies: Apply 5% cream from neck to toe (head to toe for infants and toddlers) wash off with water in 8–14 hr. May repeat in 14 days if mites appear. Use in full-term infants <1 mo is safe and effective when applied for a 6 hr period.

Ovicidal activity generally makes single-dose regimen adequate. However, resistance to permethrin has been reported. May cause pruritus, hypersensitivity, burning, stinging, erythema, and rash. For either lice or scabies, instruct patient to launder bedding and clothing. For lice, treat symptomatic contacts only. For scabies, treat all contacts even if asymptomatic.
Avoid contact with eyes during application. Shake well before using. **Do not use** near eyes, inside of nose, mouth, or vagina, or for lice in eyebrows/eyelashes. Topical cream dosage form contains formaldehyde. Dispense 60 g per one adult or two small children.

PHENAZOPYRIDINE HCL
Pyridium, Azo-Urinary Pain Relief [OTC], Azo-Urinary Pain Relief Maximum Strength [OTC], and generics
Urinary analgesic

Tabs: 95 mg [OTC] (12s, 30s), 97.5 mg [OTC] (12s, 24s), 99.7 mg [OTC] (6s, 12s, 48s), 100 mg, 200 mg
Oral suspension: 10 mg/mL

UTI (use with an appropriate antibacterial agent):
Child 6–<12 yr: 12 mg/kg/24 hr ÷ TID PO until symptoms of lower urinary tract irritation are controlled or for 2 days. **Max. dose**: 200 mg/dose.
≥12 yr and adult: 190–200 mg TID PO until symptoms are controlled or for 2 days.

May cause pruritus, rash, GI distress, vertigo, and headache. Anaphylactoid-like reaction, methemoglobinemia, hemolytic anemia, and renal and hepatic toxicity have been reported, usually at overdosage levels. Colors urine orange; stains clothing. May also stain contact lenses and interfere with urinalysis tests based on spectrometry or color reactions. Give doses with or after meals.
Avoid use in moderate/severe renal impairment; adjust dose in mild renal impairment (see Chapter 31).

For explanation of icons, see p. 667

PHENOBARBITAL
Generics; previously available as Luminal
Barbiturate

Tabs: 15, 16.2, 30, 32.4, 60, 64.8, 97.2, 100 mg
Elixir or oral solution: 20 mg/5 mL (473 mL); may contain alcohol
Injection: 65, 130 mg/mL (1 mL); may contain 10% alcohol and propylene glycol

Status epilepticus:
Loading dose, IV:
Neonate, infant, and child: 15–20 mg/kg/dose (max. loading dose: 1000 mg) in a single or divided dose. May give additional 5 mg/kg doses Q15–30 min to a **max. total** of 40 mg/kg.
Seizures maintenance therapy (PO/IV): Monitor levels.
Neonate: 3–5 mg/kg/24 hr ÷ once daily–BID
Infant: 5–6 mg/kg/24 hr ÷ once daily–BID
Child 1–5 yr: 6–8 mg/kg/24 hr ÷ once daily–BID
Child 6–12 yr: 4–6 mg/kg/24 hr ÷ once daily–BID
>12 yr: 1–3 mg/kg/24 hr ÷ once daily—BID
Hyperbilirubinemia (limited data; <12 yr): 3–8 mg/kg/24 hr PO ÷ BID–TID. Doses up to 12 mg/kg/24 hr have been used. Not recommended for biliary cirrhosis.
Preoperative sedation (child): 1–3 mg/kg/dose IM/IV/PO ×1. Give 60–90 min before procedure.

Contraindicated in porphyria, severe respiratory disease with dyspnea, or obstruction.
Use with caution in hepatic or renal disease (reduce dose). IV administration may cause respiratory arrest or hypotension. Side effects include drowsiness, cognitive impairment, ataxia, hypotension, hepatitis, rash, respiratory depression, apnea, megaloblastic anemia, and anticonvulsant hypersensitivity syndrome. Paradoxic reaction in children (not dose related) may cause hyperactivity, irritability, or insomnia. Induces several liver enzymes (CYP 450 1A2, 2A6, 2B6, 2C8/9, 3A4), P-glycoprotein, and glucoronidation (UGT1A1), thus decreases blood levels of many drugs (e.g., anticonvulsants). **IV push not to exceed 1 mg/kg/min.**
$T_{½}$ is variable with age: neonates, 45–100 hr; infants, 20–133 hr; children, 37–73 hr. Owing to long half-life, consider other agents for sedation for procedures.
Therapeutic levels: 15–40 mg/L. Recommended serum sampling time at steady state: trough level obtained within 30 min prior to the next scheduled dose after 10–14 days of continuous dosing.
Adjust dose in renal failure (see Chapter 31).

PHENTOLAMINE MESYLATE
OraVerse and generics; previously available as Regitine
Adrenergic blocking agent (α); antidote, extravasation

Injection: 5 mg vial; may contain mannitol
Injection in solution for submucosal use:
OraVerse: 0.4 mg/1.7 mL (1.7 mL in dental cartridges) (10s); contains edetate disodium

Treatment of α-adrenergic drug extravasation (most effective within 12 hr of extravasation):
All doses are five doses administered SC around the site of extravasation within 12 hr of extravasation. Monitor for hypotension (BP) Q15 min ×4 then Q1 hr ×2. See the following table for weight-based dosing and recommended drug concentration.

PHENTOLAMINE MESYLATE *continued*

Patient Weight	Drug Concentration (Diluted with Preservative-Free NS)	Dose for each syringe ×5 syringes	Total Dose from All 5 Syringes
<1 kg	0.2 mg/mL	0.05 mL	0.05 mg
1–<2.5 kg	0.2 mg/mL	0.1 mL	0.1 mg
2.5–<5 kg	1 mg/mL	0.05 mL	0.25 mg
5–<10 kg	1 mg/mL	0.1 mL	0.5 mg
10–<20 kg	1 mg/mL	0.2 mL	1 mg
20–<30 kg	1 mg/mL	0.4 mL	2 mg
30–<40 kg	1 mg/mL	0.6 mL	3 mg
40–<50 kg	1 mg/mL	0.8 mL	4 mg
≥50 kg	1 mg/mL	1 mL	5 mg

Max. total dose:

Neonate: 2.5 mg

Infant, child, adolescent, and adult: 0.1–0.2 mg/kg/dose or 5 mg

Diagnosis of pheochromocytoma, IM/IV:

Child: 0.05–0.1 mg/kg/dose up to a **max. dose** of 5 mg.

Adult: 5 mg/dose

Hypertension, prior to surgery for pheochromocytoma, IM/IV:

Child: 0.05–0.1 mg/kg/dose up to a **max. dose** of 5 mg 1–2 hr ***before*** to surgery, repeat Q2–4 hr PRN.

Adult: 5 mg/dose 1–2 hr ***before*** to surgery, repeat Q2–4 hr PRN.

Contraindicated in MI, coronary insufficiency and angina. **Use with caution** in hypotension, arrhythmias, and cerebral vascular spasm/occlusion.

For diagnosis of pheochromocytoma, patient should be resting in a supine position. A blood pressure reduction of more than 35 mm Hg systolic and 24 mm Hg diastolic is considered a positive test for pheochromocytoma. For treatment of extravasation, use 27- to 30-gauge needle with multiple small injections, and monitor site closely because repeat doses may be necessary.

PHENYLEPHRINE HCL

Vazculep, Neo-Synephrine, Biorphen, many others, and generics

Adrenergic agonist

Injection:

Vazculep and generics: 10 mg/mL (1%) (1, 5, 10 mL); may contain metasulfites

Ready to use injection:

Biorphen: 0.1 mg/mL (5 mL)

Nasal spray/drops [OTC; may contain benzalkonium chloride]:

0.125% (Little Remedies Decongestant Nose Drops): 0.125% (15 mL)

0.25% (Neo-Synephrine Mild Strength, Rhinall): 0.25% (15, 30, 40 mL)

0.5% (Neo-Synephrine Regular Strength): 0.5% (15 mL)

1% (4-Way, Nasal Four, Neo-Synephrine Extra Strength): 1% (15, 30 mL)

NOTE: For Neo-Synephrine 12-hr Nasal, see Oxymetazoline

Ophthalmic drops (Altafrin and generics): 2.5% (2, 15 mL), 10% (5 mL); contains benzalkonium chloride

Tabs (Sudafed PE and others) [OTC]: 10 mg

Oral solution (Sudafed PE Children's; OTC): 2.5 mg/5 mL (118 mL)

Continued

For explanation of icons, see p. 667

PHENYLEPHRINE HCL *continued*

Hypotension:

NOTE: the IV drip dosage units for children are in mCg/kg/min, compared with mCg/min for adults. To prepare infusion: See inside front cover.

Child:

IV bolus: 5–20 mCg/kg/dose (initial **max. dose**: 500 mCg/dose, subsequent max. dose: 1000 mCg/dose) Q10–15 min PRN

IV drip: 0.1–0.5 mCg/kg/min; titrate to effect

IM/SC: 0.1 mg/kg/dose Q1–2 hr PRN; **max. dose**: 5 mg

Adult:

IV bolus: 0.1–0.5 mg/dose Q10–15 min PRN; max. initial dose: 0.5 mg/dose

IV drip: Initial rate at 100–180 mCg/min; titrate to effect. Usual maintenance dose: 40–60 mCg/min.

Pupillary dilation (see remarks):

<1 yr: 2.5% solution; 1 drop in each eye 15–30 min before exam.

Child (≥1 yr) and adult: 2.5% or 10% solution; 1 drop in each eye 10–60 min before exam.

Nasal decongestant (in each nostril; give up to 3 days):

Child 2–<6 yr: 1–3 drops to each nostril of 0.125% solution Q4 hr PRN

Child 6–12 yr: 1–3 sprays/drops to each nostril of 0.25% solution Q4 hr PRN

>12 yr–adult: 1–3 sprays/drops to each nostril of 0.25%, 0.5% or 1% solution Q4 hr PRN

Oral decongestant (see remarks):

4–<6 yr: 2.5 mg (5 mL) PO Q4 hr PRN, up to 15 mg (30 mL)/24 hr

≥6–<12 yr: 5 mg (10 mL) PO Q4 hr PRN up to 30 mg (60 mL)/24 hr

≥12 yr and adult: 10 mg PO Q4 hr PRN up to 60 mg/24 hr

Use with caution in presence of arrhythmias, hyperthyroidism, or hyperglycemia. May cause tremor, insomnia, or palpitations. Metabolized by MAO. **Contraindicated** in pheochromocytoma and severe hypertension. Injectable product may contain sulfites.

Nasal decongestants may cause rebound congestion with excessive use (>3 days). The 1% nasal spray can be used in adults with extreme congestion.

Oral phenylephrine is found in a variety of combination cough and cold products and has replaced pseudoephedrine and phenylpropanolamine. Over-the-counter (OTC or nonprescription) use of this product is **not recommended** for children younger than age 6; reports of serious adverse effects (cardiac and respiratory distress, convulsions, and hallucinations) and fatalities (from unintentional overdosages, including combined use of other OTC products containing the same active ingredients) have been made.

Ophthalmic use: Apply pressure to the lacrimal sac during and 2 min after administering drops to minimize systemic absorption.

PHENYTOIN
Dilantin, Dilantin Infatab, Phenytoin Infatab, Phenytek, and generics
Anticonvulsant, class Ib antiarrhythmic

D 2 Yes Yes Yes

Chewable tabs (Dilantin Infatab and generics): 50 mg

Extended-release caps:

Dilantin: 30, 100 mg

Phenytek: 200, 300 mg

Generics: 100, 200, 300 mg

Oral suspension (Dilantin and generics): 125 mg/5 mL (240 mL); contains ≤0.6% alcohol

Injection: 50 mg/mL (2, 5 mL); contains alcohol and sodium benzoate

D

PHENYTOIN *continued*

Status epilepticus: See Chapter 1 and remarks.

Loading dose (all ages): 20 mg/kg IV; **max. dose:** 1500 mg/24 hr

Maintenance for seizure disorders (initiate 12 hr after administration of loading dose):

Neonate: start with 5 mg/kg/24 hr PO/IV ÷ Q12 hr; usual range 4–8 mg/kg/24 hr PO/IV ÷ Q8–12 hr.

Infant/child: start with 5 mg/kg/24 hr ÷ BID–TID PO/IV; usual dose range (doses divided BID–TID):

6 mo–3 yr: 8–10 mg/kg/24 hr

4–6 yr: 7.5–9 mg/kg/24 hr

7–9 yr: 7–8 mg/kg/24 hr

10–16 yr: 6–7 mg/kg/24 hr

Note: Use once daily–BID dosing with extended release caps.

Adult: Start with 100 mg/dose Q8 hr IV/PO and carefully titrate (if needed) by 100 mg increments Q2–4 wk to 300–600 mg/24 hr (or 6–7 mg/kg/24 hr) ÷ Q8–24 hr IV/PO.

Contraindicated in patients with heart block or sinus bradycardia; those who are receiving delavirdine (decrease virologic response); and history of hydantoin hypersensitivity. **Use with caution** in patients with pacemakers or cardiac dysrhythmias because of its class IB antiarrhythmic properties. IM administration is **not recommended** because of erratic absorption and pain at injection site; consider fosphenytoin. Side effects include gingival hyperplasia, hirsutism, dermatitis, blood dyscrasia, ataxia, lupus-like and Stevens-Johnson syndromes, lymphadenopathy, liver damage, and nystagmus. Suicidal behavior or ideation, bradycardia, cardiac arrest, and multiorgan hypersensitivity (DRESS) have been reported. An increased risk for serious skin reactions (e.g., TEN and Stevens-Johnson) may occur in patients with the HLA-B*1502 allele; do not use this medication in individuals who carry this genotype.

Many drug interactions: levels may be increased by cimetidine, chloramphenicol, INH, sulfonamides, trimethoprim, etc. Levels may be decreased by some antineoplastic agents. Phenytoin induces hepatic microsomal enzymes (CYP 450 1A2, 2C8/9/19, and 3A3/4), leading to decreased effectiveness of oral contraceptives, fosamprenavir (used without ritonavir), quinidine, valproic acid, theophylline, and other substrates to the previously listed CYP 450 hepatic enzymes. May increase levels of amprenavir when administered with fosamprenavir and ritonavir. May cause resistance to neuromuscular blocking action of nondepolarizing neuromuscular blocking agents (e.g., pancuronium, vecuronium, rocuronium, and cisatracurium) and decrease concentrations of T_4 and T_3 (typically without clinical hypothyroidism).

The following initial maintenance dose modifications for HLA-B*1502 allele noncarriers and CYP 450 2C9 phenotypes have been recommended:

CYP 2C9 intermediate metabolizer: 25% reduction with therapeutic drug monitoring

CYP 2C9 poor metabolizer: 50% reduction with therapeutic drug monitoring

Ideal body weight should be used for calculating dosages. Suggested dosing intervals for specific oral dosage forms: extended release caps (once daily–BID); chewable tablets, and oral suspension (TID). Oral absorption reduced in neonates. $T_{½}$ is variable (7–42 hr) and dose dependent. Drug is highly protein bound; free fraction of drug will be increased in patients with hypoalbuminemia.

For seizure disorders, therapeutic levels: 10–20 mg/L (free and bound phenytoin) ***OR*** 1–2 mg/L (free only). Monitor free phenytoin levels in hypoalbuminemia or renal insufficiency. Recommended serum sampling times: trough level (PO/IV) within 30 min prior to the next scheduled dose; peak or postload level (IV) 1 hr after the end of IV infusion. Steady state is usually achieved after 5–10 days of continuous dosing. For routine monitoring, measure trough.

IV push/infusion rate: **Not to exceed** 0.5 mg/kg/min in neonates, or 1 mg/kg/min infants, children, and adults with **maximum** of 50 mg/min; may cause cardiovascular collapse. Consider fosphenytoin in situations of tenuous IV access and risk for extravasation.

For explanation of icons, see p. 667

PHOSPHORUS SUPPLEMENTS
K-PHOS Neutral, Av-Phos 250 Neutral, Phospho-Trin 250 Neutral, Phospha 250 Neutral, Virt-Phos 250 Neutral, PHOS-NaK, Sodium Phosphate, Potassium Phosphate, and many generics for injections
Electrolyte supplement

Oral:

Na and K phosphate:

PHOS-NaK and generics; powder: 250 mg (8 mM) P, 6.96 mEq (160 mg) Na, 7.16 mEq (280 mg) K per packet of powder (100s); reconstitute with 75 mL water or juice per packet

K-PHOS Neutral, Av-Phos 250 Neutral, Phospho-Trin 250 Neutral, Phospha 250 Neutral, Virt-Phos 250 Neutral, and generics; tabs: 250 mg P (8 mM), 13 mEq Na, 1.1 mEq K; administer each dose with a full glass of water

K-PHOS No. 2; tabs: 250 mg P (8 mM), 5.8 mEq Na, 2.3 mEq K; administer each dose with a full glass of water

K phosphate:

K-Phos Original; tabs: 500 mg potassium acid phosphate (114 mg phosphorus and 3.7 mEq K); dissolve each tab in 3–4 oz water

Injection:

Na phosphate: 3 mM (93 mg) P, 4 mEq Na/mL (5 mL)

K phosphate: 3mM (93 mg) P, 4.4 mEq K/mL (5 mL)

Conversion: 31 mg P = 1 mM P

Acute hypophosphatemia: 0.16–0.32 mM/kg/dose (or 5–10 mg/kg/dose) IV over 6 hr

Maintenance/replacement:

Child:

IV: 0.5–1.5 mM/kg (or 15–45 mg/kg) over 24 hr

PO: 30–90 mg/kg/24 hr (or 1–3 mM/kg/24 hr) ÷ TID–QID

Adult:

IV: 50–65 mM (or 1.5–2 g) over 24 hr

PO: 3–4.5 g/24 hr (or 100–150 mM/24 hr) ÷ TID–QID

Recommended IV infusion rate: ≤0.1 mM/kg/hr (or 3.1 mg/kg/hr) of phosphate. When potassium salt is used, the rate will be limited by the **max.** potassium infusion rate. **Do not** co-infuse with calcium containing products.

May cause tetany, hyperphosphatemia, hyperkalemia, or hypocalcemia. **Use with caution** in patients with renal impairment. Be aware of sodium and/or potassium load when supplementing phosphate. IV administration may cause hypotension and renal failure, or arrhythmias, heart block, cardiac arrest with potassium salt. PO dosing may cause nausea, vomiting, abdominal pain, or diarrhea. See Chapter 21 for daily requirements and Chapter 11 for additional information on hypophosphatemia and hyperphosphatemia.

PHYSOSTIGMINE SALICYLATE
Generics; previously available as Antilirium
Cholinergic agent

Injection: 1 mg/mL (2 mL); contains 2% benzyl alcohol and 0.1% sodium bisulfite

Reversal of toxic anticholinergic effects from antihistamine or anticholinergic agents:

Child: 0.02 mg/kg/dose IM or IV (administered no >0.5 mg/min), dose may be repeated every 5–10 min if no response or return of anticholinergic symptoms up to a **max. total** of 2 mg

PHYSOSTIGMINE SALICYLATE *continued*

Adult: 0.5–2 mg IM or IV (administered no >1 mg/min), if needed repeat dose every 10–30 min until response is seen or when adverse effects occurs.

Physostigmine antidote: Atropine always should be available. **Contraindicated** in asthma, gangrene, diabetes, cardiovascular disease, GI or GU tract obstruction, any vagotonic state, and patients receiving choline esters or depolarizing neuromuscular blocking agents (e.g., decamethonium, succinylcholine). May cause seizures, arrhythmias, bradycardia, GI symptoms, and other cholinergic effects. Rapid IV administration can cause bradycardia and hypersalivation leading to respiratory distress and seizures.

PHYTONADIONE/VITAMIN K_1

Mephyton and generics

Vitamin, fat soluble

Tabs (Mephyton and generics): 5 mg

Oral suspension: 1 mg/mL

Injection, emulsion (contains no more than 110 mCg/L aluminum):
2 mg/mL (0.5 mL); preservative free but contains propylene glycol
10 mg/mL (1 mL); contains 0.9% benzyl alcohol

Vitamin K deficiency bleeding (Neonatal hemorrhagic disease): Preservative free dosage form is preferred.

Prophylaxis (IM, administered 1 hr within 1 hr after birth):
<1 kg: 0.5 mg/kg/dose ×1
1–1.5 kg: 0.5 mg ×1
>1.5 kg: 1 mg ×1

Treatment: 1–2 mg/24 hr IM/SC/IV

Oral anticoagulant (warfarin) overdose (see remarks):

No significant bleeding:

INR 4–4.5: Consider PO vitamin K at dosage indicated for INR >4.5–<10 below and monitor INR Q24 hr. Lower or hold warfarin dose.

INR >4.5–<10: Hold warfarin dose and monitor INR Q24 hr until INR <4. Give vitamin K for patients with high bleeding risk:
<40 kg: 0.03 mg/kg PO ×1
≥40 kg: 1–2.5 mg PO ×1

INR ≥10: Hold warfarin dose and monitor INR Q12 hr and give vitamin K (dose may be repeated Q12–24 hr PRN):
<40 kg: 0.06 mg/kg PO ×1
≥40 kg: 5–10 mg PO ×1

Minor bleeding (any elevated INR): Hold warfarin and monitor INR Q12–24 hr, repeat vitamin K dose in 24 hr if full correction not achieved and bleeding persists.

PO:
<40 kg: 0.03 mg/kg ×1
≥40 kg: 1–2.5 mg × 1

IV: 0.5–2.5 mg ×1

Significant or Life-threatening bleeding (any elevated INR): Hold warfarin and give vitamin K 5–10 mg IV ×1 in combination with FFP (10–15 mL/kg) or prothrombin complex concentrate (KCentra). Monitor INR Q4–6 hr, repeat vitamin K dose if full correction not achieved at 12–24 hr and bleeding persists.

Continued

For explanation of icons, see p. 667

PHYTONADIONE/VITAMIN K_1 *continued*

Vitamin K deficiency:

Infant and child:

PO: 2.5–5 mg/24 hr

IM/SC/IV: 1–2 mg/dose ×1

Adolescent and adult:

PO: 2.5–25 mg/24 hr

IM/SC/IV: 2.5–25 mg/dose ×1

IV or IM doses may cause flushing, dizziness, cardiac/respiratory arrest, hypotension, and anaphylaxis. IV or IM administration is indicated only when other routes of administration are not feasible (or in emergency situations).

Monitor PT/PTT. Large doses (10–20 mg) in newborns may cause hyperbilirubinemia and severe hemolytic anemia. Blood coagulation factors increase within 6–12 hr after oral doses and within 1–2 hr following parenteral administration. Use of higher doses for warfarin overdose may cause warfarin resistance for ≥1 wk. Concurrent administration of oral mineral oil may decrease GI absorption of oral vitamin K.

IV injection rate **not to exceed** 3 mg/m²/min or 1 mg/min. Protect product from light. **See Chapter 21 for multivitamin preparations.**

PILOCARPINE HCL

Isopto Carpine, Salagen, and generics

Cholinergic agent

C	3	No	Yes	No

Ophthalmic solution (Isopto Carpine and generics): 1% (15 mL), 2% (15 mL), 4% (15 mL); may contain benzalkonium chloride

Tab (Salagen and generics): 5, 7.5 mg

For elevated intraocular pressure:

Infant and child <2 yr: Instill 1 drop of the 1% solution into each affected eye(s) TID

Child ≥2 yr, adolescent, and adult: Instill 1–2 drop(s) in each affected eye up to 4 times a day; concentration and dosage frequency is dependent on the degree of elevated pressure and miotic response.

Xerostomia:

Adult: 5 mg/dose PO TID, dose may be titrated to 10 mg/dose PO TID in patients who do not respond to lower dose and who are able to tolerate the drug. 5 mg/dose PO QID has been used in Sjögren syndrome.

OPHTHALMIC USE: Contraindicated in acute iritis or anterior chamber inflammation and uncontrolled asthma. May cause stinging, burning, lacrimation, headache, and retinal detachment. **Use with caution** in patients with corneal abrasion or significant cardiovascular disease. Use with topical NSAIDs (e.g., ketorolac) may decrease topical pilocarpine effects.

ORAL USE: Sweating, nausea, rhinitis, chills, flushing, urinary frequency, dizziness, asthenia, and headaches have also been reported. Reduce oral dosing in the presence of mild hepatic insufficiency (Child-Pugh score of 5–6); **avoid use** in severe hepatic insufficiency.

PIMECROLIMUS
Elidel and generics
Topical immunosuppressant, calcineurin inhibitor

Cream: 1% (30, 60, 100 g); contains benzyl alcohol and propylene glycol

Atopic dermatitis (second line therapy):
Child ≥2 yr, adolescent, and adult (see remarks): Apply a thin layer to affected area BID and rub in gently and completely. Reevaluate patient in 6 wk if lesions are not healed.

Do not use in children <2 yr (higher rate of upper respiratory infections), in immunocompromised patients, or with occlusive dressings (promotes systemic absorption). **Avoid use** on malignant or premalignant skin conditions as rare cases of lymphoma and skin malignancy have been reported with topical calcineurin inhibitors. Approved as a second line therapy for atopic dermatitis for patients who fail to respond, or do not tolerate, other approved therapies. Use medication for short periods of time by using the minimum amounts to control symptoms; long-term safety is unknown. **Avoid** contact with eyes, nose, mouth, and cut, infected, or scraped skin. Minimize and **avoid** exposure to natural and artificial sunlight, respectively.

Most common side effects include burning at the application site, headache, viral infections, and pyrexia. Skin discoloration, skin flushing associated with alcohol use, anaphylactic reactions, ocular irritation after application to the eye lids or near the eyes, angioneurotic edema, and facial edema have been reported. Drug is a CYP 450 3A3/4 substrate.

PIPERACILLIN WITH TAZOBACTAM
Zosyn and generics
Antibiotic, penicillin (extended spectrum with β-lactamase inhibitor)

8:1 ratio of piperacillin to tazobactam:
Injection, powder: 2 g piperacillin and 0.25 g tazobactam; 3 g piperacillin and 0.375 g tazobactam; 4 g piperacillin and 0.5 g tazobactam; 12 g piperacillin and 1.5 g tazobactam; 36 g piperacillin and 4.5 g tazobactam
Injection, premixed in iso-osmotic dextrose: 2 g piperacillin and 0.25 g tazobactam in 50 mL; 3 g piperacillin and 0.375 g tazobactam in 50 mL; 4 g piperacillin and 0.5 g tazobactam in 100 mL
Contains 2.84 mEq Na/g piperacillin

All doses based on piperacillin component.
Neonate and infant (IV):
≤2 kg:
≤7 days old: 100 mg/kg/dose Q8 hr
8–28 days old:
≤30 wk post menstrual age: 100 mg/kg/dose Q8 hr
>30 wk post menstrual age: 80 mg/kg/dose Q6 hr
29–60 days old: 80 mg/kg/dose Q6 hr
>2 kg:
≤60 days old: 80 mg/kg/dose Q6 hr
NOTE: For patients with a post menstrual age of >35 wk, a pharmacokinetic study suggests using 80 mg/kg/dose IV Q4 hr to achieve targeted drug concentration time above the MIC.

Continued

For explanation of icons, see p. 667

PIPERACILLIN WITH TAZOBACTAM continued

All doses based on piperacillin component.

Child and adolescent (IV): Severe infections (shortening the dosing interval to Q6 hr and lengthening the dose administration time to 4 hr (see remarks) may enhance the pharmacodynamic properties):

2–9 mo: 80 mg/kg/dose Q6–8 hr

>9 mo, child, and adolescent: 100 mg/kg/dose Q6–8 hr

Max. dose (all ages): 16 g/24 hr

Appendicitis or peritonitis (IV route for 7–10 days; dosing interval may be shortened to Q6 hr to enhance pharmacodynamic properties):

2–9 mo: 80 mg/kg/dose Q6–8 hr

>9 mo–adolescent:

≤40 kg: 100 mg/kg/dose (max. 3000 mg/dose) Q6–8 hr

>40 kg: 3 g/dose Q6 hr

Max. dose (all ages): 16 g/24 hr.

Adult:

Intra-abdominal or soft tissue infections: 3 g IV Q6 hr

Nosocomial pneumonia: 4 g IV Q6 hr

Cystic fibrosis (antipseudomonal; see remarks):

All ages: 350–600 mg/kg/24 hr IV ÷ Q4–6 hr; **max. dose:** 24 g/24 hr.

Tazobactam is a β-lactamase inhibitor, thus extending the spectrum of piperacillin. Like other penicillins, CSF penetration occurs only with inflamed meninges. GI disturbances, pruritus, rash, and headaches are common. Abnormal platelet aggregation and prolonged bleeding, serious skin reactions (e.g., Stevens-Johnson, DRESS, acute generalized exanthematous pustulosis, and TEN) have been reported. Cystic fibrosis patients have an increased risk for fever and rash. Increases in renal failure risk (in critically ill adults) and incidence of acute kidney injury (in combination with IV vancomycin) have been reported.

Coagulation parameters should be tested more frequently and monitored regularly with high doses of heparin, warfarin, or other drugs affecting blood coagulation or thrombocyte function. May falsely decrease aminoglycoside serum levels if the drugs are infused close to one another; allow a minimum of 2 hr between infusions to prevent this interaction. May prolong the neuromuscular blockade effects of vecuronium.

Prolonging the dose administration time to 4 hr will maximize the pharmacokinetic/pharmacodynamic properties by prolonging the time of drug concentration above the MIC; especially for pathogens with piperacillin MICs of 8–16 mCg/mL. **Adjust dose in renal impairment, (see Chapter 31).**

POLYCITRA

See Citrate Mixtures

POLYETHYLENE GLYCOL—ELECTROLYTE SOLUTION

Bowel cleansing products: GoLYTELY, CoLyte, NuLYTELY, TriLyte, and many others including generics

Laxative products: MiraLax, GaviLAX, GlycoLax, HealthyLax, PegyLax, and many others including generics

Bowel evacuant, osmotic laxative

Powder for oral solution:

Bowel cleansing products:

GoLYTELY and others: Polyethylene glycol 3350 236 g; contains Na sulfate 22.74 g, Na bicarbonate 6.74 g, NaCl 5.86 g, KCl 2.97 g (mixed with water to 4 L). Contents vary somewhat. See products

POLYETHYLENE GLYCOL—ELECTROLYTE SOLUTION *continued*

Laxative products:

MiraLax [OTC], GaviLAX [OTC], Glycolax [OTC], HealtyLax [OTC], PegyLax [Rx], and generics [OTC and Rx]: Polyethylene glycol 3350 (17, 119, 238, 255, 510, 527, 765, 850 g)

Bowel cleansing (using products containing supplemental electrolytes for bowel cleansing such as GoLYTELY, CoLyte, NuLYTELY, TriLyte and others; and patients should be NPO 3–4 hr prior to dosing):

Child:

Oral/nasogastric: 25–40 mL/kg/hr until rectal effluent is clear (usually in 4–10 hr)

Adult:

Oral: 240 ml PO Q10 min up to 4 L or until rectal effluent is clear

Nasogastric: 20–30 mL/min (1.2–1.8 L/hr) up to 4 L or until rectal effluent is clear.

Bowel cleansing (using Miralax or equivalent products):

≥2 yr and adolescent: 1.5 g/kg/24 hr (**max. dose**: 100 g/24 hr) ×4 days.

Constipation (MiraLax and others):

Child (limited data in 20 children with chronic constipation, 18 mo–11 yr; see remarks): a mean effective dose of 0.84 g/kg/24 hr PO ÷ BID for 8 wk (range: 0.25–1.42 g/kg/24 hr) was used to yield 2 soft stools per day. Do not exceed 17 g/24 hr. If patient >20 kg, use adult dose.

Adult: 17 g (one heaping tablespoonful) mixed in 240 mL of water, juice, soda, coffee, or tea PO once daily

Fecal impaction:

GoLYTELY and others:

≥2 yr (PO/NG tube): 20 mL/kg/hr up to a **maximum** of 1 L/hr ×4 hr per 24 hr for 2 days.

Miralax and others:

>3 yr: 1–1.5 g/kg/24 hr (**max. dose:** 100 g/24 hr) PO ×3–6 days. Following disimpaction, give a maintenance dose of 0.4 g/24 hr for ≥2 mo.

Contraindicated in polyethylene glycol hypersensitivity. Monitor electrolytes, BUN, serum glucose, and urine osmolality with prolonged administration. Seizures resulting from electrolyte abnormalities have been reported.

BOWEL CLEANSING: Contraindicated in toxic megacolon, gastric retention, colitis, and bowel perforation. **Use with caution** in patients prone to aspiration or with impaired gag reflex. Effect should occur within 1–2 hr. Solution generally more palatable if chilled.

CONSTIPATION (MiraLax and others): Contraindicated in bowel obstruction.

Child: Dilute powder using the ratio of 17 g powder to 240 mL of water, juice, or milk. An onset of action within 1 wk in 12 of 20 patients, with the remaining 8 patients reporting improvement during the second week of therapy. Side effects reported in this trial included diarrhea, flatulence, and mild abdominal pain. (See *J Pediatr* 2001;139[3]:428–432 for additional information.)

Adult: 2–4 days may be required to produce a bowel movement. Most common side effects include nausea, abdominal bloating, cramping, and flatulence. Use beyond 2 wk has not been studied.

POLYMYXIN B SULFATE AND BACITRACIN

See Bacitracin ± Polymyxin B

For explanation of icons, see p. 667

POLYMYXIN B SULFATE AND TRIMETHOPRIM SULFATE
Polytrim Ophthalmic Solution and generics
Topical antibiotic (ophthalmic preparations listed)

Ophthalmic solution: Polymyxin B sulfate 10,000 U/mL, and trimethoprim sulfate 1 mg/mL (10 mL); some preparations may contain 0.04 mg/mL benzalkonium chloride

≥2 mo, child, adolescent, and adult: Instill 1 drop in the affected eye(s) Q3 hr (**max.** of 6 doses/24 hr) ×7–10 days.

Active against susceptible strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus viridans*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. **Not indicated** for the prophylaxis or treatment of ophthalmia neonatorum. Local irritation consisting of redness, burning, stinging, and/or itching is common. Hypersensitivity reactions consisting of lid edema, itching, increased redness, tearing, and/or circumocular rash have been reported.

Apply finger pressure to lacrimal sac during and for 1–2 min after dose application.

POLYMYXIN B SULFATE, NEOMYCIN SULFATE, HYDROCORTISONE OTIC
Generics; previously available as Cortisporin Otic
Topical otic antibiotic

Otic solution or suspension: Polymyxin B sulfate 10,000 U/mL, neomycin sulfate 5 mg/mL (3.5 mg/mL neomycin base), hydrocortisone 10 mg/mL (10 mL); some preparations may contain thimerosol and metabisulfite.

For ophthalmic suspension, see NEOMYCIN/POLYMYXIN B OPHTHALMIC PRODUCTS

Otitis externa:

≥2 yr, child, and adolescent: 3 drops TID–QID ×7–10 days. If preferred, a cotton wick may be saturated and inserted into ear canal. Moisten wick with antibiotic every 4 hr. Change wick Q24 hr.

Adult: 4 drops TID–QID ×7–10 days.

Contraindicated in patients with active varicella and herpes simplex and in cases with perforated eardrum (possible ototoxicity). **Use with caution** in chronic otitis media and when the integrity of the tympanic membrane is in question. Metabisulfite-containing products may cause allergic reactions to susceptible individuals. Hypersensitivity (itching, skin rash, redness, swelling, or other sign of irritation in or around the ear) may occur. Neomycin may cause sensitization. Prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi. May cause cutaneous sensitization.

Shake suspension well before use. Warm the medication to body temperature prior to use.

POLYSPORIN

See Bacitracin ± Polymyxin B

POLYTRIM OPHTHALMIC SOLUTION

See Polymyxin B Sulfate and Trimethoprim Sulfate

POSACONAZOLE
Noxafil
Antifungal agent

Delayed release tabs: 100 mg
Injection: 300 mg/16.7 mL (16.7 mL); contains EDTA and sulfobutyl ether-β-cyclodextrin (SBECD)
Oral suspension: 40 mg/mL (105 mL); contains polysorbate 80 and sodium benzoate

Child ≤12 yr (see remarks):

Oral suspension:

Antifungal prophylaxis for hematopoietic stem cell transplant recipients: 4 mg/kg/dose PO TID initiated 2–4 days prior to discharge. Duration of therapy: the longer of 100 days posttransplant or when CD_3 T cells is ≥200/mm^3 and CD^4 is ≥100/mm^3.

IV: Clinical trials with IV dosage form currently limited to a phase I study compared with the oral suspension dosage form; results pending.

Adolescent (≥13 yr) and adult (see remarks):

Prophylaxis for invasive Aspergillus and Candida: Duration based on neutropenia or immunosuppression recovery.

IV (≥18 yr) or delayed-release tablets: 300 mg Q12 hr IV/PO tab ×2 doses followed by 300 mg Q24 hr IV/PO tab the next day.

Oral suspension: 200 mg PO TID

Oropharyngeal Candidiasis:

Oral suspension: 100 mg PO Q12 hr ×2 doses followed by 100 mg PO Q24 hr ×13 days.

Refractory Oropharyngeal Candidiasis (to itraconazole/fluconazole): Duration based on severity and clinical response.

Oral suspension: 400 mg PO Q12 hr

Contraindicated with use of ergot alkaloids (e.g., ergotamine); major substrates for CYP 450 3A4 (e.g., atorvastatin, lovastatin, simvastatin, sirolimus); or CYP 450 3A4 medications that prolong the QTc interval (e.g., pimozide and quinidine). **Use with caution** electrolyte imbalances (correct prior to use), cardiac arrhythmias, and hepatic or renal impairment. Use of IV dosage form is not recommended for eGFR <50 mL/min due to the risk for accumulation of SBECD excipient.

Hypokalemia, diarrhea, nausea, vomiting, headache, and fever are common side effects. Serious reactions include hypersensitivity reactions, arrhythmias, QTc prolongation, and hepatotoxicity (consider discontinuing therapy). Pseudoaldosteronism and pancreatitis have been reported.

Posaconazole is a substrate of UDP-glucoronosyltransferase 1–4 (UGT1A4) and P-gp efflux and strong inhibitor of CYP 450 3A4 (see earlier for contraindicated substrates for concurrent use). Use with vincristine has been associated with neurotoxicity, seizures, peripheral neuropathy, SIADH, and paralytic ileus.

Oral suspension and tablets are **NOT** bioequivalent/interchangeable and their respective uses are indication specific. Administer delayed-release tablets with food to enhance absorption. **Do not** crush or chew delayed-release tablets. IV dosage information currently limited in adults.

PORACTANT ALFA

See Surfactant, pulmonary

For explanation of icons, see p. 667

POTASSIUM IODIDE
Iosat, SSKI, ThyroShield, ThyroSafe, and others
Antithyroid agent

Tabs:
Iosat [OTC]: 65 mg (50 mg iodine), 130 mg
ThyroSafe [OTC]: 65 mg
Oral solution:
ThyroShield [OTC]: 65 mg/mL (30 mL); contains parabens and saccharin
Saturated solution (SSKI): 1000 mg/mL (30, 240 mL); 10 drops = 500 mg potassium iodide
Potassium content is 6 mEq (234 mg) K^+/g potassium iodide

Neonatal Graves disease: 50–100 mg (about 1–2 drops of SSKI) PO once daily
Thyrotoxicosis:
Child: 50–250 mg (about 1–5 drops of SSKI) PO TID
Adult: 50–500 mg (1–10 drops of SSKI) PO TID
Cutaneous or lymphocutaneous sporotrichosis (treat for 4–6 wk after lesions have completely healed; increase dose until either max. dose is achieved or signs of intolerance appear):
Child and adolescent (limited data): 50 mg PO TID. Dose may be gradually increased as tolerated to the **max. dose** of the lesser of 50 mg/kg/dose or 2000–2500 mg PO TID.
Adult: Start with 250 mg PO TID. Doses may be gradually increased as tolerated to the **max. dose** of 2000–2500 mg PO TID.

Contraindicated in pregnancy, hyperkalemia, iodine-induced goiter, and hypothyroidism. **Use with caution** in cardiac disease and renal failure. GI disturbance, metallic taste, rash, salivary gland inflammation, headache, lacrimation, and rhinitis are symptoms of iodism. Give with milk or water after meals. Monitor thyroid function tests. Onset of antithyroid effects: 1–2 days.
Lithium carbonate and iodide-containing medications may have synergistic hypothyroid activity. Potassium-containing medications, potassium-sparing diuretics, and ACE inhibitors may increase serum potassium levels.
For use as a thyroid blocking agent in nuclear or radiation emergencies, see https://www.fda.gov/drugs/bioterrorism-and-drug-preparedness/radiation-emergencies

POTASSIUM SUPPLEMENTS
Many brand names and generics
Electrolyte

Potassium chloride (40 mEq K = 3 g KCl):
Sustained-release caps: 8, 10 mEq
Sustained-release tabs: 8, 10, 15, 20 mEq
Powder: 20 mEq/packet (30s, 100s)
Oral solution/liquid: 10% (6.7 mEq/5 mL), 20% (13.3 mEq/5 mL) (473 mL)
Concentrated injection: 2 mEq/mL
Potassium gluconate (40 mEq K = 9.4 g K gluconate):
Tabs: 465 mg (2 mEq), 581 mg (2.5 mEq)
Caps [OTC as K-99]: 595 mg (2.56 mEq)
Potassium acetate (40 mEq K = 3.9 g K acetate):
Concentrated injection: 2 mEq/mL
Potassium bicarbonate/citric acid (10 mEq K = 1 g K bicarbonate):
Effervescent tab for oral solution (Effer-K): 10, 20, 25 mEq; each 10 mEq K contains 0.84 g citric acid

POTASSIUM SUPPLEMENTS *continued*

Potassium phosphate:
See Phosphorus Supplements

Normal daily requirements: See Chapter 21.
Replacement: Determine based on maintenance requirements, deficit and ongoing losses. See Chapter 11.
Hypokalemia:
Oral:
Child: 1–4 mEq/kg/24 hr ÷ BID–QID. Monitor serum potassium.
Adult: 40–100 mEq/24 hr ÷ BID–QID; limit single doses by 20–25 mEq to minimize GI side effects
IV: MONITOR SERUM K CLOSELY.
Child: 0.5–1 mEq/kg/dose given as an infusion of 0.5 mEq/kg/hr ×1–2 hr.
Max. IV infusion rate: 1 mEq/kg/hr. This may be used in critical situations (i.e., hypokalemia with arrhythmia).
Adult:
Serum K ≥2.5 mEq/L: Replete at rates up to 10 mEq/hr. **Total dosage not to exceed** 200 mEq/24 hr.
Serum K <2.5 mEq/L: Replete at rates up to 40 mEq/hr. **Total dosage not to exceed** 400 mEq/24 hr.
Max. peripheral IV solution concentration: 40 mEq/L
Max. concentration for central line administration: 150–200 mEq/L

PO administration may cause GI disturbance and ulceration. Oral liquid supplements should be diluted in water or fruit juice prior to administration. Sustained-release tablets must be swallowed whole, and **NOT** dissolved in the mouth or chewed.
Do not administer IV potassium undiluted. IV administration may cause irritation, pain, and phlebitis at the infusion site. **Rapid or central IV infusion may cause cardiac arrhythmias.** Patients receiving infusion >0.5 mEq/kg/hr (>20 mEq/hr for adults) should be placed on an ECG monitor.

PRALIDOXIME CHLORIDE
Protopam, 2-PAM, and generics
In combination with atropine: Duodote, ATNAA
Antidote, organophosphate poisoning

Injection (Protopam): 1000 mg
Injection for intramuscular injection, in autoinjector device: 600 mg/2 mL (2 mL); dispenses 600 mg; contains benzyl alcohol
In combination with atropine (Duodote, ATNNA):
Injection for intramuscular injection in autoinjector device: 600 mg/2 mL of pralidoxime and 2.1 mg/0.7 mL of atropine; contains benzyl alcohol. Duodote or ATNNA must be administered by emergency medical services personnel who have had adequate training in the recognition and treatment of nerve agent or insecticide intoxication.

Organophosphate poisoning (use with atropine):
Child:
IV intermittent: 20–50 mg/kg/dose (**max. dose**: 2000 mg) ×1 IV. May repeat in 1–2 hr if muscle weakness is not relieved, then at Q10–12 hr PRN if cholinergic signs reappear.
IV continuous infusion: loading dose of 20–50 mg/kg/dose (**max. dose**: 2000 mg) IV over 15–30 min followed by 10–20 mg/kg/hr.

Continued

For explanation of icons, see p. 667

PRALIDOXIME CHLORIDE *continued*

Organophosphate poisoning (use with atropine):

Child (cont.):

IM:

<40 kg: 15 mg/kg/dose ×1 IM. May repeat Q15 min PRN up to a **maximum total dose** of 45 mg/kg for mild symptoms; may repeat twice in rapid succession for severe symptoms (**maximum total dose** of 45 mg/kg). For persistent symptoms, may repeat another maximum 45 mg/kg series (in 3 divided doses) approximately 1 hr after the last injection.

≥40 kg: 600 mg ×1 IM. May repeat Q15 min PRN up to a **max. total dose** of 1800 mg for mild symptoms; may repeat twice in rapid succession for severe symptoms (**max. total dose** of 1800 mg). For persistent symptoms, may repeat another **max.** 1800 mg series (in 3 divided doses) approximately 1 hr after the last injection.

Adult:

IV intermittent: 1–2 g/dose ×1 IV. May repeat in 1–2 hr if muscle weakness is not relieved, then at Q10–12 hr PRN if cholinergic signs reappear.

IM: Use aforementioned ≥40-kg child IM dosage.

In combination with atropine (Duodote, ATNNA; see remarks for description of symptoms):

Child and adult >41 kg:

Mild Symptoms of Nerve Agent or Insecticide Exposure: Inject one prefilled syringe IM ×1 and wait 10–15 min for effect. If severe symptoms emerge at any time after the first dose, inject 2 additional prefilled syringes IM in rapid succession.

Severe Symptoms of Nerve Agent or Insecticide Exposure: Inject three prefilled syringes IM in rapid succession.

Contraindicated in poisonings due to phosphorus, inorganic phosphates, or organic phosphates without anticholinesterase activity. **Do not use** as an antidote for carbamate classes of pesticides. Removal of secretions and maintaining a patent airway is critical. May cause muscle rigidity, laryngospasm, and tachycardia after rapid IV infusion. Drug is generally ineffective if administered 36–48 hr after exposure. Additional doses may be necessary.

For IV administration, dilute to 50 mg/mL or less and infuse over 15–30 min (**not to exceed** 200 mg/min). Reduce dosage in renal impairment since 80%–90% of the drug is excreted unchanged in the urine 12 hr after administration.

Pralidoxime and atropine combination (Duodote): Safety and efficacy data are only available for children and adults >41 kg (90 lbs). Duodote product information description of mild and severe symptoms:

Mild symptoms: increased airway secretions, blurred vision, bradycardia, breathing difficulties, chest tightness, drooling, miosis, nausea, vomiting, runny nose, salivation, stomach cramps (acute onset), tachycardia, teary eyes, tremors/muscular twitching, wheezing/coughing.

Severe symptoms: breathing difficulties (severe), confused/strange behavior, convulsions, copious secretions from lung or airways, involuntary urination/defecation, muscular twitching/generalized weakness (severe), unconsciousness.

IM injection is via the midlateral thigh.

PREDNISOLONE

C/D 2 No No No

Oral products:

Orapred ODT, Pediapred, Millipred, Veripred 20, and generics; previously available as Prelone

Ophthalmic products:

Pred Forte, Pred Mild, Omnipred, Econopred, and generics

Corticosteroid

Tabs: 5 mg

PREDNISOLONE *continued*

Tablets, orally disintegrating (as Na phosphate) (Orapred ODT and generics): 10, 15, 30 mg
Oral solution/syrup (as Na phosphate):
Pediapred and generics: 5 mg/5 mL (120 mL); alcohol and dye free
Generics: 10 mg/5 mL (237 mL), 15 mg/5 mL (237 mL), 20 mg/5 mL (237 mL), 25 mg/5 mL (237 mL); may contain parabens, alcohol and some preparations may be dye free
Ophthalmic suspension (as acetate; both strengths contain benzalkonium chloride and may contain bisulfites):
Pred Mild: 0.12% (5, 10 mL)
Econopred: 0.125% (5, 10 mL)
Omnipred, PredForte, Econopred Plus and generics: 1% (5, 10, 15 mL)
Ophthalmic solution (as Na phosphate): 1% (10 mL); may contain benzalkonium chloride

See Prednisone for systemic oral dosing (equivalent dosing).
Ophthalmic (consult ophthalmologist before use; see remarks):
Ophthalmic suspension:
Child (limited data) and adult: 1–2 drops to the conjunctival sac of the affected eye(s) BID–QID (dosage frequency may be increased during initial 24–48 hr if needed). Reevaluate patient if signs and symptoms do not improve after 2 days.
Ophthalmic solution:
Child and adult: Start with 1–2 drops Q1 hr during the day and Q2 hr during the night until favorable response, then reduce dose to 1 drop Q4 hr. Dose may be further reduced to 1 drop TID–QID.

See Prednisone for remarks. See Chapter 10 for relative steroid potencies. Pregnancy category changes to "D" if used in the first trimester.
OPHTHALMIC USE: Contraindicated in viral (e.g., herpes simplex, vaccinia, and varicella), fungal, and mycobacterial infections of the cornea and conjunctiva. Increase in intraocular pressure, cataract formation, eye pain, and delayed wound healing may occur.

PREDNISONE
Deltasone, Rayos, and generics
Corticosteroid

Tabs (Deltasone and generics): 1, 2.5, 5, 10, 20, 50 mg
Delayed release tabs (Rayos): 1, 2, 5 mg
Oral solution: 1 mg/mL (120, 500 mL); may contain 5% alcohol and saccharin
Concentrated solution (Prednisone Intensol): 5 mg/mL (30 mL); contains 30% alcohol

Antiinflammatory/immunosuppressive:
Child: 0.5–2 mg/kg/24 hr PO ÷ once daily–BID
Acute asthma:
Child: 2 mg/kg/24 hr PO ÷ once daily–BID ×5–7 days; **max. dose**: 80 mg/24 hr. Patients may benefit from tapering if therapy exceeds 5–7 days.
Asthma exacerbations (2007 National Heart, Lung, and Blood Institute [NHLBI] Guideline Recommendations; dose until peak expiratory flow reaches 70% of predicted or personal best):
Child ≤12 yr: 1–2 mg/kg/24 hr PO ÷ Q12 hr (**max. dose**: 60 mg/24 hr).
>12 yr and adult: 40–80 mg/24 hr PO ÷ Q12–24 hr.
Outpatient asthma exacerbation burst therapy (2007 NHLBI guidelines; longer durations may be necessary):
Child ≤12 yr: 1–2 mg/kg/24 hr PO ÷ Q12–24 hr **(max. dose:** 60 mg/24 hr) ×3–10 days.
Child >12 yr and adult: 40–60 mg/24 hr PO ÷ Q12–24 hr ×3–10 days

Continued

For explanation of icons, see p. 667

PREDNISONE *continued*

Nephrotic syndrome:

Child (use ideal body weight for obese patients): Starting dose of 2 mg/kg/24 hr PO (**max. dose:** 60 mg/24 hr) ÷ once daily–TID is recommended. Further treatment plans are individualized. Consult a nephrologist.

See Chapter 10 for physiologic replacement, relative steroid potencies, and doses based on body surface area. Methylprednisolone is preferable in hepatic disease because prednisone must be converted to methylprednisolone in the liver.

Side effects may include: mood changes, seizures, hyperglycemia, diarrhea, nausea, abdominal distension, GI bleeding, HPA axis suppression, osteopenia, cushingoid effects, and cataracts with prolonged use. Prednisone is a CYP 450 3A3/4 substrate and inducer. Barbiturates, carbamazepine, phenytoin, rifampin, and isoniazid may reduce the effects of prednisone, whereas estrogens may enhance the effects. Pregnancy category changes to "D" if used in the first trimester.

PRIMAQUINE PHOSPHATE
Various generics
Antimalarial

Tabs: 26.3 mg (15 mg base)
Oral suspension: 10.52 mg (6 mg base)/5 mL

Doses expressed in mg of primaquine base:

Malaria:

Prevention of relapses for Plasmodium vivax or Plasmodium ovale only (initiate therapy during the last 2 wk of, or following a course of, suppression with chloroquine or comparable drug):
Child: 0.5 mg/kg/dose (**max. dose**: 30 mg/dose) PO once daily ×14 days
Adult: 30 mg PO once daily ×14 days

Prevention of chloroquine-resistant strains (initiate 1 day prior to departure and continued until 3–7 days after leaving endemic area):
Child: 0.5 mg/kg/dose PO once daily; **max. dose:** 30 mg/24 hr.
Adult: 30 mg PO once daily

P jiroveci (carinii) pneumonia (in combination with clindamycin):
Child: 0.3 mg/kg/dose (**max. dose**: 30 mg/dose) PO once daily ×21 days.
Adult: 30 mg PO once daily ×21 days

Contraindicated in granulocytopenia (e.g., rheumatoid arthritis, lupus erythematosus) and bone marrow suppression. **Avoid use** with quinacrine and with other drugs that have a potential for causing hemolysis or bone marrow suppression. **Use with caution** in G6PD and NADH methemoglobin-reductase deficient patients due to increased risk for hemolytic anemia and leukopenia, respectively. Monitor ECG for QTc prolongation in patients with cardiac disease, history of arrhythmias, uncorrected hypokalemia and/or hypomagnesemia, bradycardia, and receiving concomitant QTc prolonging medications. Use in pregnancy is **not recommended** by the AAP Red Book. Cross sensitivity with iodoquinol.

May cause headache, visual disturbances, nausea, vomiting, and abdominal cramps. Hemolytic anemia, leukopenia, cardiac arrhythmia, QTc interval prolongation, and methemoglobinemia have been reported. Administer all doses with food to mask bitter taste.

PRIMIDONE
Mysoline and generics
Anticonvulsant, barbiturate

Tabs: 50, 250 mg

Neonate: 12–20 mg/kg/24 hr PO ÷ BID–QID; initiate therapy at the lower dosage range and titrate upwards.

Child, adolescent, and adult:

Day of Therapy	<8 Yr	≥8 Yr and Adult
Days 1–3	50 mg PO QHS	100–125 mg PO QHS
Days 4–6	50 mg PO BID	100–125 mg PO BID
Days 7–9	100 mg PO BID	100–125 mg PO TID
Day 10 and thereafter	125–250 mg PO TID or 10–25 mg/kg/ 24 hr ÷ TID—QID	250 mg PO TID-QID; **max. dose:** 2 g/24 hr

Use with caution in renal or hepatic disease and pulmonary insufficiency. Primidone is metabolized to phenobarbital and has the same drug interactions and toxicities (see Phenobarbital). In addition, primidone may cause vertigo, nausea, leukopenia, malignant lymphoma-like syndrome, diplopia, nystagmus, and systemic lupus-like syndrome. Monitor for suicidal behavior or ideation. Acetazolamide may decrease primidone absorption. **Adjust dose in renal failure (see Chapter 31).**

Monitor both primidone and phenobarbital levels. Therapeutic levels: 5–12 mg/L of primidone and 15–40 mg/L of phenobarbital. Recommended serum sampling time at steady state: trough level obtained within 30 min prior to the next scheduled dose after 1–4 days of continuous dosing.

PROBENECID
Various generics
Penicillin therapy adjuvant, uric acid–lowering agent

Tabs: 500 mg

To prolong penicillin levels.

Child (2–14 yr): 25 mg/kg PO ×1, then 40 mg/kg/24 hr ÷ QID; **max. single dose:** 500 mg/dose. Use adult dose if >50 kg.

Adult: 500 mg PO QID

Hyperuricemia with gout:

Adult: 250 mg PO BID ×1 wk, then 500 mg PO BID; may increase by 500 mg increments Q4 wk PRN up to a **max. dose** of 2–3 g/24 hr ÷ BID.

Gonorrhea, antibiotic adjunct (administer just prior to antibiotic):

≤45 kg: 23 mg/kg/dose PO ×1

>45 kg: 1 g PO ×1

Prevention of nephrotoxicity from cidofovir: see Cidofovir.

Use with caution in patients with peptic ulcer disease. **Contraindicated** in children <2 yr and patients with renal insufficiency. **Do not use** if GFR <30 mL/min.

Increases uric acid excretion. Inhibits renal tubular secretion of acyclovir, ganciclovir, ciprofloxacin, levofloxacin, nalidixic acid, moxifloxacin, organic acids, penicillins, cephalosporins, AZT, dapsone, methotrexate, nonsteroidal antiinflammatory agents, and benzodiazepines. Salicylates may decrease probenecid's activity. Alkalinize urine in patients with gout. May cause headache, GI

False-positive glucosuria with Clinitest may occur.

For explanation of icons, see p. 667

PROCAINAMIDE
Generics
Antiarrhythmic, class Ia

Injection: 100 mg/mL (10 mL), 500 mg/mL (2 mL); may contain methylparabens and bisulfites

NOTE: The IV infusion dosage units for adults are in mg/min; compared to mCg/kg/min for children.

Child (limited data):

IV: Load with 15 mg/kg/dose IV or IO ×1 over 30–60 min. Then followed by maintenance continuous IV infusion of 20–80 mCg/kg/min; **max. dose**: 2 g/24 hr.

IM: 20–30 mg/kg/24 hr ÷ Q4–6 hr; **max. dose**: 4 g/24 hr (peak effect in 1 hr).

Adult:

IV: Load: 50–100 mg/dose; repeat dose Q5 min PRN to a **max. total dose** of 1000–1500 mg.

Maintenance: 1–6 mg/min by continuous infusion

IM: 50 mg/kg/24 hr ÷ Q3–6 hr

Contraindicated in myasthenia gravis, complete heart block, SLE, and torsade de pointes. Use with caution in asymptomatic premature ventricular contractions, digitalis intoxication, CHF, renal or hepatic dysfunction. Adjust dose in renal failure (see Chapter 31).

May cause lupus-like syndrome, positive Coombs' test, thrombocytopenia, arrhythmias, GI complaints, and confusion. Increased LFTs and liver failure have been reported. Monitor BP and ECG when using IV. QRS widening by >0.02 sec suggests toxicity.

Do not use with desipramine and other TCAs. Cimetidine, ranitidine, amiodarone, β-blockers, and trimethoprim may increase procainamide levels. Procainamide may enhance the effects of skeletal muscle relaxants and anticholinergic agents. Therapeutic levels: 4–10 mg/L of procainamide or 10–30 mg/L of procainamide and NAPA levels combined.

Recommended serum sampling times:

IM intermittent dosing: Trough level within 30 min prior to the next scheduled dose after 2 days of continuous dosing (steady state).

IV continuous infusion: 2 and 12 hr after start of infusion and at 24-hr intervals thereafter.

PROCHLORPERAZINE
Compro and generics; previously available as Compazine
Antiemetic, phenothiazine derivative

Tabs (as maleate): 5, 10 mg
Suppository (Compro and generics): 25 mg (12s)
Injection (as edisylate): 5 mg/mL (2 mL); may contain benzyl alcohol

Antiemetic doses:

Child (≥2 yr and ≥9 kg):

PO or PR: 0.4 mg/kg/24 hr ÷ TID–QID (**max. dose**: 10 mg/dose) or alternative dosing by weight:

9–13 kg: 2.5 mg once daily–BID; **max. dose**: 7.5 mg/24 hr

>13–18 kg: 2.5 mg BID–TID; **max. dose**: 10 mg/24 hr

>18–39 kg: 2.5 mg TID or 5 mg BID; **max. dose**: 15 mg/24 hr

>39 kg: Use adult dose

IM: 0.1–0.15 mg/kg/dose BID–TID; **max. dose**: 10 mg/single dose or 40 mg/24 hr

Adult:

PO: 5–10 mg/dose TID–QID; **max. dose**: 40 mg/24 hr

PR: 25 mg/dose BID

PROCHLORPERAZINE *continued*

IM: 5–10 mg/dose Q3–4 hr
IV: 2.5–10 mg/dose; may repeat Q3–4 hr PRN
Max. IM/IV dose: 40 mg/24 hr

Psychoses:

Child 2–12 yr and >9 kg:

PO: Start with 2.5 mg BID–TID with a **max. first day dose** of 10 mg/24 hr. Dose may be increased as needed to 20 mg/24 hr for children 2–5 yr and 25 mg/24 hr for 6–12 yr.
IM: 0.13 mg/kg/dose ×1 and convert to PO immediately.

Adult:

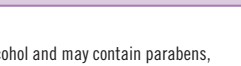
PO: 5–10 mg TID–QID; may be increased as needed to a **max. dose** of 150 mg/24 hr
IM: 10–20 mg Q2–4 hr PRN convert to PO immediately.

Intractable migraines:

Child (5–18 yr, limited data): 0.15 mg/kg/dose **(max. dose**: 10 mg/dose) IV over 10 min was effective in migraine headaches presenting in the emergency departments (see *Ann Emerg Med.* 2004;43:256–262).

Toxicity as for other phenothiazines (see Chlorpromazine). Extrapyramidal reactions (reversed by diphenhydramine) or orthostatic hypotension may occur. May mask signs and symptoms of overdosage of other drugs and may obscure the diagnosis and treatment of conditions such as intestinal obstruction, brain tumor, and Reye syndrome. May cause false-positive test for phenylketonuria, urinary amylase, uroporphyrins, and urobilinogen. **Do not use** IV route in children. Use only in management of prolonged vomiting of known etiology.

PROMETHAZINE
Phenergan, Phenadoz, Promethegan, and generics
Antihistamine, antiemetic, phenothiazine derivative



Tabs: 12.5, 25, 50 mg
Oral solution/syrup: 6.25 mg/5 mL (118, 473 mL); contains alcohol and may contain parabens, sodium benzoate, or phenol (many formulations exist)
Suppository (Phenadoz, Promethegan and generics): 12.5, 25, 50 mg (12s)
Injection: 25, 50 mg/mL (1 mL); may contain edetate disodium, sulfites, and phenol

Antihistaminic:

Child ≥2 yr: 0.1 mg/kg/dose (**max. dose:** 12.5 mg/dose) Q6 hr PO during the day hours and 0.5 mg/kg/dose (**max. dose:** 25 mg/dose) QHS PO PRN
Adult: 6.25–12.5 mg PO/PR TID and 25 mg QHS

Nausea and vomiting PO/IM/IV/PR (see remarks):

Child ≥2 yr: 0.25–1 mg/kg/dose Q4–6 hr PRN; **max. dose:** 25 mg/dose
Adult: 12.5–25 mg Q4–6 hr PRN

Motion sickness: (1st dose 0.5–1 hr before departure):

Child ≥2 yr: 0.5 mg/kg/dose Q12 hr PO/PR PRN; **max. dose:** 25 mg/dose
Adult: 25 mg PO Q8–12 hr PRN

Avoid use in children <2 yr because of risk for fatal respiratory depression. Toxicity similar to other phenothiazines (see Chlorpromazine). **Do not** administer SC or intra-arterially because of severe local reactions. IV route of administration is **not recommended** (IM preferred) due to severe tissue injury (tissue necrosis and gangrene). If using IV route, dilute 25 mg/mL strength product with 10–20 mL NS and administer over 10–15 min, consider lower initial doses, administer through a large-bore vein and check patency of line before administering, administer through an IV line at the port farthest from the

For explanation of icons, see p. 667

PROMETHAZINE *continued*

patient's vein, and monitor for burning or pain during or after injection. Administer oral doses with meals to decrease GI irritation.

May cause profound sedation, blurred vision, respiratory depression (use lowest effective dose in children and **avoid** concomitant use of respiratory depressants), and dystonic reactions (reversed by diphenhydramine). Cholestatic jaundice and neuroleptic malignant syndrome has been reported. May interfere with pregnancy tests (immunologic reactions between hCG and anti-hCG). **For nausea and vomiting, use only in management of prolonged vomiting of known etiology.**

PROPRANOLOL
Inderal, Inderal LA, Hemangeol, and generics
Adrenergic blocking agent (β), class II antiarrhythmic

Tabs: 10, 20, 40, 60, 80 mg
Extended-release caps (Inderal LA and others including generics): 60, 80, 120, 160 mg
Oral solution: 20 mg/5 mL, 40 mg/5 mL; contains parabens and saccharin
Hemangeol: 4.28 mg/mL (120 mL); alcohol, sugar and parabens free; contains saccharin
Injection: 1 mg/mL (1 mL)

Arrhythmias:
Child:
IV: 0.01–0.1 mg/kg/dose IV push over 10 min, repeat Q6–8 hr PRN; **max. dose:** 1 mg/dose for infant; 3 mg/dose for child
PO: Start at 0.5–1 mg/kg/24 hr ÷ Q6–8 hr; increase dosage Q3–5 days PRN. Usual dosage range: 2–4 mg/kg/24 hr ÷ Q6–8 hr; **max. dose**: 60 mg/24 hr or 16 mg/kg/24 hr
Adult:
IV: 1 mg/dose Q5 min up to total 5 mg
PO: 10–30 mg/dose TID–QID; increase PRN. Usual range 30–160 mg/24 hr ÷ TID–QID.
Hypertension (as alternative therapy):
Child:
PO: Initial: 0.5–1 mg/kg/24 hr ÷ Q6–12 hr. May increase dose Q5–7 days PRN; **max. dose:** 8 mg/kg/24 hr
Adult:
PO: 40 mg/dose PO BID or 60–80 mg/dose (sustained-release capsule) PO once daily. May increase 10–20 mg/dose Q3–7 days; **max. dose:** 640 mg/24 hr.
Migraine prophylaxis:
Child:
<35 kg: Start with 10 mg PO once daily and increase dose PRN weekly intervals at 10 mg increments. Usual dosage range: 10–20 mg PO TID.
≥35 kg: 20–40 mg PO TID
Adult: 80 mg/24 hr ÷ Q6–8 hr PO; increase dose by 20–40 mg/dose Q3–4 wk PRN. Usual effective dose range: 160–240 mg/24 hr.
Tetralogy spells:
IV: 0.15–0.25 mg/kg/dose slow IV push. May repeat in 15 min ×1. See also Chapter 7.
PO: Start at 2–4 mg/kg/24 hr ÷ Q6 hr PRN. Usual dose range: 4–8 mg/kg/24 hr ÷ Q6 hr PRN. Doses as high as 15 mg/kg/24 hr have been used with careful monitoring.
Thyrotoxicosis:
Neonate: 2 mg/kg/24 hr PO ÷ Q6–12 hr
Adolescent and adult:
IV: 1–3 mg/dose over 10 min. May repeat in 4–6 hr.

PROPRANOLOL *continued*

Infantile hemangioma (see remarks):

Infant (5 wk–5 mo and ≥2 kg; labeled dosing information for Hemangeol product): 0.6 mg/kg/dose BID PO (at least 9 hr apart) ×7 days, then increase to 1.1 mg/kg/dose BID PO ×14 days, followed by 1.7 mg/kg/dose BID PO ×6 mo.

Alternative dosing: Start at 1 mg/kg/24 hr ÷ Q8 hr PO. If tolerated after 1 day, increase dose to 2 mg/kg/24 hr ÷ Q8 hr PO

Contraindicated in asthma, Raynaud syndrome, heart failure, and heart block. **Not indicated** for the treatment of hypertensive emergencies. **Use with caution** in presence of obstructive lung disease, diabetes mellitus, or renal or hepatic disease. May cause hypoglycemia, hypotension, nausea, vomiting, depression, weakness, impotence, bronchospasm, and heart block. Cutaneous reactions, including Stevens-Johnson, TEN, exfoliative dermatitis, erythema multiforme, and urticaria have been reported. Acute hypertension has occurred after insulin-induced hypoglycemia in patients on propranolol.

Therapeutic levels for beta-blockade: 50–100 ng/mL; ventricular arrhythmia: 40–85 ng/mL. Drug is metabolized by CYP 450 1A2, 2C18, 2C19 and 2D6 isoenzymes. Concurrent administration with barbiturates, indomethacin, or rifampin may cause decreased activity of propranolol. Concurrent administration with cimetidine, hydralazine, flecainide, quinidine, chlorpromazine, or verapamil may lead to increased activity of propranolol. **Avoid** IV use of propranolol with calcium channel blockers; may increase effect of calcium channel blocker. Use with amiodarone may increase negative chronotropic effects.

For infantile hemangioma, monitor BP and HR 2 hr after initiating therapy and after dose increases. To reduce risk of hypoglycemia, administer doses during or right after a feeding; hold doses if child is not eating or is vomiting. Infants <6 mo must be fed every 4 hr. Common adverse effects (>10%) reported in clinical trials with Hemangeol include sleep disorders, aggravated respiratory tract infections (e.g., bronchitis and bronchiolitis) associated with cough/fever, diarrhea, and vomiting. Readjust dose periodically with changes (increases) in child's body weight.

Successful use in infantile hepatic hemangiomas has also been reported.

Pregnancy category changes to "D" if used in second or third trimesters.

PROPYLTHIOURACIL
PTU and generics
Antithyroid agent

Tabs: 50 mg
Oral suspension: 5 mg/mL
100 mg PTU = 10 mg methimazole

Dosages should be adjusted as required to achieve and maintain T_4, TSH levels in normal ranges.

Neonate: 5–10 mg/kg/24 hr ÷ Q8 hr PO

Child:

Initial: 5–7 mg/kg/24 hr ÷ Q8 hr PO, OR by age:

6–10 yr: 50–150 mg/24 hr ÷ Q8 hr PO

>10 yr: 150–300 mg/24 hr ÷ Q8 hr PO

Maintenance: Generally begins after 2 mo. Usually 1/3–2/3 the initial dose in divided doses (Q8–12 hr) when the patient is euthyroid.

Adult:

Initial: 300–400 mg/24 hr ÷ Q6–8 hr PO; some may require larger doses of 600–900 mg/24 hr

Maintenance: 100–150 mg/24 hr ÷ Q8 hr PO

Continued

For explanation of icons, see p. 667

PROPYLTHIOURACIL *continued*

Generally reserved for patients who are unable to tolerate methimazole and whom radioactive iodine or surgery are not appropriate. May be the antithyroid treatment of choice during or just prior to the first trimester of pregnancy because of risk of fetal abnormalities associated with methimazole.

May cause blood dyscrasias, fever, liver disease, dermatitis, urticaria, malaise, CNS stimulation or depression, and arthralgias. Glomerulonephritis, severe liver injury/failure, agranulocytosis, severe vasculitis, interstitial pneumonitis, exfoliative dermatitis, and erythema nodosum have also been reported. May decrease the effectiveness of warfarin. Monitor thyroid function. A dose reduction of β-blocker may be necessary when the hyperthyroid patient becomes euthyroid.

For neonates, crush tablets, weigh appropriate dose, and mix in formula/breast milk. **Adjust dose in renal failure (see Chapter 31).**

PROSTAGLANDIN E_1

See Alprostadil

PROTAMINE SULFATE

Various generics

Antidote, heparin

Injection: 10 mg/mL (5, 25 mL); preservative free

Heparin antidote, IV:

1 mg protamine will neutralize 115 U porcine intestinal heparin, or 100 U (1 mg) low-molecular-weight heparin.

Consider time since last heparin dose:

If <0.5 hr: give 100% of specified dose

If within 0.5–1 hr: give 50%–75% of aforementioned dose

If within 1–2 hr: give 37.5%–50% of aforementioned dose

If ≥2 hr: give 25%–37.5% of aforementioned dose

Max. dose: 50 mg/dose IV

Max. infusion rate: 5 mg/min

Max. IV concentration: 10 mg/mL

If heparin was administered by deep SC injection, give 1–1.5 mg protamine per 100 U heparin as follows:

Load with 25–50 mg via slow IV infusion followed by the rest of the calculated dose via continuous infusion over 8–16 hr or the expected duration of SC heparin absorption.

Enoxaparin overdosage, IV (see remarks): Approximately 1 mg protamine will neutralize 1 mg enoxaparin.

Consider time since last enoxaparin dose:

If <8 hr: give 100% of aforementioned dose.

If within 8–12 hr: Give 50% of aforementioned dose

If >12 hr: Protamine not required but if serious bleeding is present, give 50% of aforementioned dose.

If aPTT remains prolonged 2–4 hr after the first protamine dose or if bleeding continues, a second infusion of 0.5 mg protamine per 1 mg enoxaparin may be given.

Max. dose: 50 mg/dose. See aforementioned heparin antidote IV dosage for **max.** administration concentration and rate.

D

PROTAMINE SULFATE *continued*

Risk factors for protamine hypersensitivity include known hypersensitivity to fish and exposure to protamine-containing insulin or prior protamine therapy.
May cause hypotension, bradycardia, dyspnea, and anaphylaxis. Monitor aPTT or ACT. Heparin rebound with bleeding has been reported to occur 8–18 hr later.
Use in enoxaparin overdose may not be complete despite using multiple doses of protamine.

PSEUDOEPHEDRINE
Sudafed, Sudafed 12 Hour, Sudafed 24 Hour, and generics
Sympathomimetic, nasal decongestant

Tabs (OTC): 30, 60 mg
Extended-release tab (OTC):
Sudafed 12 Hour and generics: 120 mg
Sudafed 24 Hour: 240 mg
Oral liquid (OTC): 15 mg/5 mL, 30 mg/5 mL (120 mL); may contain sodium benzoate
Purchases of OTC products are limited to behind the pharmacy counter sales with monthly sale limits due to the methamphetamine epidemic.

Child <12 yr: 4 mg/kg/24 hr ÷ Q6 hr PO or by age:
<4 yr: 4 mg/kg/24 hr ÷ Q6 hr PO; **max. dose:** 60 mg/24 hr
4–5 yr: 15 mg/dose Q4–6 hr PO; **max. dose:** 60 mg/24 hr
6–12 yr: 30 mg/dose Q4–6 hr PO; **max. dose:** 120 mg/24 hr
Child ≥12 yr and adult:
Immediate release: 60 mg/dose Q4–6 hr PO; **max. dose:** 240 mg/24 hr
Sustained release:
Sudafed 12 Hour and generics: 120 mg PO Q12 hr
Sudafed 24 Hour: 240 mg PO Q24 hr

Contraindicated with MAO inhibitor drugs and in severe hypertension and severe coronary artery disease. **Use with caution** in mild/moderate hypertension, hyperglycemia, hyperthyroidism, and cardiac disease. May cause dizziness, nervousness, restlessness, insomnia, and arrhythmias. Pseudoephedrine is a common component of OTC cough and cold preparations and is combined with several antihistamines; these products are not recommended for children <6 yr. Since drug and active metabolite are primarily excreted renally, **doses should be adjusted in renal impairment.** May cause false-positive test for amphetamines (EMIT assay).

PSYLLIUM
Metamucil, Geri-Mucil, Konsyl, Reguloid, and many others including some generics
Bulk-forming laxative

Check specific product label for amount of psyllium per unit of measurement.
Granules [OTC]:
Konsyl: 4.3 g psyllium per rounded teaspoon or 6 g of granules (300 g); contains maltodextrin and 35 mg potassium for each 6 g dose; sugar and gluten free

Continued

For explanation of icons, see p. 667

PSYLLIUM *continued*

Powder [OTC]:
Metamucil: 3.4 g psyllium per rounded teaspoon; contains 5 mg sodium, 30 mg potassium, and 25 mg phenylalanine for each teaspoon. Other products may contain sucrose or maltodextrin instead of phenylalanine.

Caps [OTC]:
Reguloid and generics: 0.52 g; may contain potassium sorbate and polysorbate 80 and may be gluten and milk free; Reguloid is a fish derivative

3.4 g psyllium hydrophilic mucilloid is equivalent to 2 g soluble fiber

Constipation (granules or powder must be mixed with a full glass [240 mL] of water or juice):
<6 yr: 1.25–2.5 g/dose PO once daily–TID; **max. dose:** 7.5 g/24 hr
6–11 yr: 2.5–3.75 g/dose PO once daily–TID; **max. dose:** 15 g/24 hr
≥12 yr and adult: 2.5–7.5 g/dose PO once daily–TID; **max. dose:** 30 g/24 hr

Contraindicated in cases of fecal impaction or GI obstruction. **Use with caution** in patients with esophageal strictures and rectal bleeding. Phenylketonurics should be aware that certain preparations may contain aspartame. Should be taken or mixed with a full glass (240 mL) of liquid. Onset of action: 12–72 hr.

PYRANTEL PAMOATE
Reese's Pinworm Medicine and many other generics
Anthelmintic

C	2	No	Yes	No

Oral suspension (OTC): 50 mg/mL pyrantel base (144 mg/mL pyrantel pamoate) (30, 473 mL); may contain sodium benzoate, parabens, and saccharin
Tabs (OTC): 62.5 mg pyrantel base (180 mg pyrantel pamoate); scored tablet

All doses expressed in terms of pyrantel base.
Child (≥2 yr), adolescent, and adult:
Ascaris (roundworm) and Trichostrongylus: 11 mg/kg/dose PO ×1
Enterobius (pinworm): 11 mg/kg/dose PO ×1. Repeat same dose 2 wk later.
Hookworm or eosinophilic enterocolitis: 11 mg/kg/dose PO once daily ×3 days
Moniliformis: 11 mg/kg/dose PO Q2 wk ×3 doses.
Max. dose (all indications): 1 g/dose

Use with caution in liver dysfunction. **Do not use** in combination with piperazine because of antagonism. May cause nausea, vomiting, anorexia, transient AST elevations, headaches, rash, and muscle weakness. Limited experience in children <2 yr. May increase theophylline levels. Drug may be mixed with milk or fruit juice and may be taken with food.

PYRAZINAMIDE
Pyrazinoic acid amide, and generics
Antituberculous agent

C	2	Yes	Yes	No

Tab: 500 mg
Oral suspension: 100 mg/mL
In combination with isoniazid and rifampin (Rifater):
Tab: 300 mg with 50 mg isoniazid and 120 mg rifampin; contains povidone and propylene glycol

PYRAZINAMIDE *continued*

Tuberculosis: Use as part of a multidrug regimen for tuberculosis. See latest edition of the AAP Red Book for recommended treatment for tuberculosis.

Child:

Daily dose regimen: 30–40 mg/kg/24 hr PO once daily; **max. dose**: 2 g/24 hr

Twice-weekly dose regimen: 50 mg/kg/dose PO 2× per week; **max. dose**: 2 g/dose

Adult:

Daily dose regimen:

40–55 kg: 1000 mg PO once daily

56–75 kg: 1500 mg PO once daily

76–90 kg: 2000 mg PO once daily

Twice-weekly dose regimen:

40–55 kg: 2000 mg PO 2× per week

56–75 kg: 3000 mg PO 2× per week

76–90 kg: 4000 mg PO 2× per week

See latest edition of the AAP Red Book for recommended treatment for tuberculosis.

Contraindicated in severe hepatic damage and acute gout. The CDC and ATS **do not recommend** the combination of pyrazinamide and rifampin for latent TB infections. **Use with caution** in patients with renal failure (dosage reduction has been recommended), gout or diabetes mellitus. Monitor liver function tests (baseline and periodic) and serum uric acid.

Hepatoxicity is most common dose-related side effect; doses ≤30 mg/kg/24 hr minimizes effect. Hyperuricemia, maculopapular rash, arthralgia, fever, acne, porphyria, dysuria, and photosensitivity may occur. Severe hepatic toxicity may occur with rifampin use. May decrease isoniazid levels.

PYRETHRINS WITH PIPERONYL BUTOXIDE

A-200, Pronto Plus, RID, LiceMD, Licide, and many others

Pediculicide

C 2 No No No

All products are available OTC without a prescription.

Gel (LiceMD): 0.3% pyrethrins and 4% piperonyl butoxide (118 mL)

Shampoo (RID, Pronto Plus, Licide, A-200): 0.33% pyrethrins and 4% piperonyl butoxide (60, 120, 240 mL); may contain alcohol

Pediculosis (≥2 yr and adult): Apply to dry hair or affected body area for 10 min, then wash thoroughly and comb with fine-tooth comb or nit-removing comb; repeat in 7–10 days.

Contraindicated in ragweed hypersensitivity; drug is derived from the chrysanthemum flowers. For topical use only. **Avoid** use in and around the eyes, mouth, nose, or vagina. **Avoid** repeat applications in <24 hr. Low ovicidal activity requires repeat treatment. Dead nits require mechanical removal. Wash bedding and clothing to eradicate infestation.

Local irritation including erythema, pruritis, urticaria, edema, and eczema may occur.

For explanation of icons, see p. 667

PYRIDOSTIGMINE BROMIDE
Mestinon, Regonol, and generics
Cholinergic agent

Oral syrup (Mestinon): 60 mg/5 mL (473 mL); contains 5% alcohol and sodium benzoate
Tabs (Mestinon and generics): 30, 60 mg
Sustained-release tab (Mestinon and generics): 180 mg; scored tablet
Injection (Regonol): 5 mg/mL (2 mL); may contain 1% benzyl alcohol

Myasthenia gravis:
Neonate:
PO: 1 mg/kg/dose Q4 hr; **max.** dose: 7 mg/kg/24 hr
IM/IV: 0.05–0.15 mg/kg/dose Q4–6 hr; **max.** single IM/IV dose: 10 mg
Child:
PO: 7 mg/kg/24 hr in 5–6 divided doses
IM/IV: 0.05–0.15 mg/kg/dose Q4–6 hr; **max.** single IM/IV dose: 10 mg
Adult:
PO (immediate release): 60 mg TID; increase Q48 hr PRN. Usual effective dose: 60–1500 mg/24 hr.
PO (sustained release): 180–540 mg once daily–BID
IM/IV (use when PO therapy is not practical): Give 1/30 of the usual PO

Contraindicated in mechanical intestinal or urinary obstruction. **Use with caution** in patients with epilepsy, asthma, bradycardia, hyperthyroidism, arrhythmias, or peptic ulcer. May cause nausea, vomiting, diarrhea, rash, headache, and muscle cramps. Pyridostigmine is mainly excreted unchanged by the kidney. Therefore lower doses titrated to effect in renal disease may be necessary.
Changes in oral dosages may take several days to show results. **Atropine is the antidote.**

PYRIDOXINE
Vitamin B_6, and various names including generics
Vitamin, water soluble

Tabs (HCl) [OTC]: 25, 50, 100, 250, 500 mg
Oral solution (HCl): 1 mg/mL
Injection (HCl): 100 mg/mL (1 mL); some products may contain aluminum and 0.5% chlorobutanol

Deficiency, IM/IV/PO (PO preferred):
Child: 5–25 mg/24 hr ×3 wk, followed by 2.5–5 mg/24 hr as maintenance therapy (via multivitamin preparation)
Adolescent and adult: 10–20 mg/24 hr ×3 wk, followed by 2–5 mg/24 hr as maintenance therapy (via multivitamin preparation)
Drug-induced neuritis (PO):
Prophylaxis:
Child: 1 mg/kg/24 hr or 10–50 mg/24 hr
Adolescent and adult: 25–50 mg/24 hr
Treatment (optimal dose not established):
Child: 50–200 mg/24 hr
Adolescent and adult: 50–300 mg/24 hr

PYRIDOXINE *continued*

Pyridoxine-dependent seizures:
Neonate and infant:
Initial: 50–100 mg/dose IM or rapid IV ×1
Maintenance: 50–100 mg/24 hr PO
Recommended daily allowance: See Chapter 21.

Use caution with concurrent levodopa therapy. Chronic administration has been associated with sensory neuropathy. Nausea, headache, increased AST, decreased serum folic acid level, and allergic reaction may occur. May lower phenobarbital and phenytoin levels. See Chapter 20 for management of neonatal seizures.
Pregnancy category changes to "C" if dosage exceeds U.S. RDA recommendation.

PYRIMETHAMINE
Daraprim and generics
Antiparasitic agent

Tabs: 25 mg; scored tablet (see remarks for outpatient prescription process)
Oral suspension: 2 mg/mL

Congenital toxoplasmosis (administer with sulfadiazine and leucovorin; see remarks):
Load: 2 mg/kg/24 hr PO ÷ Q12 hr ×2 days
Maintenance: 1 mg/kg/24 hr PO once daily ×2–6 mo, then 1 mg/kg/24 hr 3× per wk to complete total 12 mo of therapy
Toxoplasmosis (administer with sulfadiazine or trisulfapyrimidines, and leucovorin):
Child:
Load: 2 mg/kg/24 hr PO ÷ BID (**max. dose**: 100 mg/24 hr) with the following duration:
Non-HIV exposed/positive: 2 days
HIV exposed/positive: 3 days
Maintenance:
Non-HIV exposed/positive: 1 mg/kg/24 hr PO once daily (**max. dose**: 25 mg/24 hr) ×6 mo, followed by 1 mg/kg/dose (**max. dose:** 25 mg/24 hr) 3 times per week to complete a total 12 mo therapy
HIV exposed/positive: 1 mg/kg/24 hr PO once daily (**max. dose**: 25 mg/24 hr) ≥6 wk
Adult:
Non-HIV exposed/positive: 50–75 mg/24 hr PO ×1–3 wk. Depending on tolerance and response, additional therapy at a 50% reduced dosage is continued ×4–5 wk.
HIV exposed/positive: 200 mg PO ×1 followed by 50–75 mg/24 hr once daily × ≥6 wk.

Pyrimethamine is a folate antagonist. Supplementation with folinic acid leucovorin at 5–15 mg/24 hr is recommended. **Contraindicated** in megaloblastic anemia secondary to folate deficiency. **Use with caution** in G6PD deficiency, malabsorption syndromes, alcoholism, pregnancy, and renal or hepatic impairment. Pyrimethamine can cause glossitis, bone marrow suppression, seizures, rash, and photosensitivity. For congenital toxoplasmosis, see *Clin Infect Dis* 1994;18:38–72. Zidovudine and methotrexate may increase risk for bone marrow suppression. Aurothioglucose, trimethoprim, and sulfamethoxazole may increase risk for blood dyscrasias. Administer doses with meals. Most cases of acquired toxoplasmosis do not require specific antimicrobial therapy.
Outpatient prescriptions may need to be processed through a specialty pharmacy program via the manufacturer; see http://www.daraprimdirect.com/healthcare-providers.

For explanation of icons, see p. 667

Q

QUETIAPINE

Seroquel, Seroquel XR, and generics

Antipsychotic, second generation

Tabs: 25, 50, 100, 200, 300, 400 mg

Extended release tabs (Seroqul XR and generics): 50, 150, 200, 300, 400 mg

Oral suspension: 40 mg/mL

Bipolar Mania (continue therapy at lowest dose to maintain efficacy and periodically assess maintenance treatment needs; PO):

Immediate release dosage forms:

Age	Dose Titration	Recommended Dose	Maximum Dose
Child ≥10 yr and adolescent	Day 1: 25 mg BID Day 2: 50 mg BID Day 3: 100 mg BID Day 4: 150 mg BID Day 5: 200 mg BID ≥Day 6: If needed, additional increases should be ≤100 mg/24 hr up to 600 mg/24 hr. Total daily doses may be divided TID based on response and tolerability.	400–600 mg/24 hr	600 mg/24 hr
Adult	Day 1: 50 mg BID Day 2: 100 mg BID Day 3: 150 mg BID Day 4: 200 mg BID ≥Day 5: If needed, additional increases ≤200 mg/24 hr up to 800 mg/24 hr by day 6.	400–800 mg/24 hr	800 mg/24 hr

Extended-release tabs (see remarks):

Age	Dose Titration	Recommended Dose	Maximum Dose
Child ≥10 yr and adolescent	Day 1: 50 mg once daily Day 2: 100 mg once daily Day 3–5: increase by 100 mg/24 hr increments each day until 400 mg once daily is achieved on day 5.	400–600 mg once daily	600 mg/24 hr
Adult	Day 1: 300 mg once daily Day 2: 600 mg once daily Day 3: Adjust dose to 400–800 mg once daily based on efficacy and tolerance	400–800 mg once daily	800 mg/24 hr (some may require 1200 mg/24 hr)

QUETIAPINE *continued*

Schizophrenia (continue therapy at lowest dose to maintain efficacy and periodically assess maintenance treatment needs; PO):

Immediate release dosage forms:

Age	Dose Titration	Recommended Dose	Maximum Dose
Adolescent (13–17 yr)	Day 1: 25 mg BID Day 2: 50 mg BID Day 3: 100 mg BID Day 4: 150 mg BID Day 5: 200 mg BID ≥Day 6: If needed, additional increases should be ≤100 mg/24 hr up to 800 mg/24 hr. Total daily doses may be divided TID based on response and tolerability.	400–800 mg/24 hr	800 mg/24 hr
Adult	Day 1: 25 mg BID Day 2 and 3: increase in increments of 25–50 mg divided 2–3 doses daily to 300–400 mg/24 hr divided BID–TID by day 4. If needed, increase dose by 50–100 mg/24 hr at intervals of at least 2 days.	150–750 mg/24 hr	800 mg/24 hr

Extended release tabs (see remarks):

Age	Dose Titration	Recommended Dose	Maximum Dose
Adolescent (13–17 yr)	Day 1: 50 mg once daily Day 2: 100 mg once daily Day 3: 200 mg once daily Day 4: 300 mg once daily Day 5: 400 mg once daily	400–800 mg once daily	800 mg/24 hr
Adult	Day 1: 300 mg once daily If needed, increase dose in increments of up to 300 mg/24 hr	400–800 mg once daily	800 mg/24 hr

Avoid use in patients with history of cardiac arrhythmias or prolonged QTc syndrome, concurrent medications that can prolong the QTc interval, and alcohol use. **Use with caution** in hypovolemia and diabetes mellitus.

Suicidal ideation/behavior or worsening depression may occur especially in children and young adults during the first few months of therapy or during dosage changes.

Common side effects in children include hypertension, hyperglycemia, hyperprolactinemia, and significant weight gain. Other common side effects include orthostatic hypotension, tachycardia, hypercholesterolemia, hypertriglyceridemia, abdominal pain, GI disturbances, increase appetite, xerostomia, increase serum transaminases, EPS, headache, dizziness, agitation, and fatigue. Anaphylactic reactions, DRESS, SJS, TEN, SIADH, cardiomyopathy, priapism, DKA, pancreatitis, eosinophilia, agranulocytosis, leukopenia, neutropenia, cataracts, hypothyroidism, neuroleptic malignant syndrome, and seizures have been reported. Anticholinergic side effects (e.g., constipation, urinary retention) may occur due to norquetiapine, its active metabolite.

Continued

For explanation of icons, see p. 667

QUETIAPINE *continued*

Do not abruptly discontinue medication as acute withdrawal symptoms occur. Dosage adjustment in hepatic impairment may be necessary as it is primarily hepatically metabolized. Quetiapine is a major substrate for CYP 450 3A4 and minor substrate for 2D6. Opioids and other CNS depressants may enhance CNS depressant effects. Carbamazepine may decrease the effects of quetiapine. Quetiapine may decrease dopamine agonist effects (e.g., anti-parkinson agents) but may enhance the anticholinergic and QTc prolongation effects to those medications processing these risks. Always check for drug interactions as effects can be mild to severe.

Non–extended release dosage forms may be administered with or without food. Extended-release tabs must be swallowed whole and administered preferably in the evening without food (a light meal of ≤300 calories is allowed). May convert patients from immediate-release to extended-release tablets at the equivalent total daily dose and administer once daily; individual dosage adjustments may be necessary.

QUINIDINE

Various generics

Class Ia antiarrhythmic, antimalarial agent

As gluconate (62% quinidine):

Slow-release tabs: 324 mg

As sulfate (83% quinidine):

Tabs: 200, 300 mg

Oral suspension: 10 mg/mL

Equivalents: 200 mg sulfate = 267 mg gluconate

NOTE: The intravenous dosage form is no longer available in the United States. Contact the CDC Marlaria Hotline at (770) 488–7788 or (855) 856–4713 for an alternative therapy.

All doses are expressed as salt forms.

Antiarrhythmic (not first line):

Child (as sulfate): 15–60 mg/kg/24 hr 24 hr PO ÷ Q 6 hr; **max. dose**: 2400 mg/24 hr.

Adult:

As sulfate: 100–600 mg/dose PO Q 4–6 hr. Begin at 200 mg/dose and titrate to desired effect.

As gluconate: 324–972 mg PO Q 8–12 hr.

Malaria:

Child and adult (give intravenously as gluconate; see remarks):

Loading dose: 10 mg/kg/dose IV (**max. dose**: 600 mg) over 1–2 hr followed by maintenance dose. Omit or decrease load if patient has received quinine or mefloquine.

Maintenance dose: 0.02 mg/kg/min IV as continuous infusion until oral therapy can be initiated. If more than 48 hr of intravenous therapy is required, reduce dose by 30%–50%.

Test dose is given to assess for idiosyncratic reaction to quinidine. Toxicity indicated by increase of QRS interval by ≥0.02 sec (skip dose or stop drug). May cause gastrointestinal (GI) symptoms, hypotension, tinnitus, TTP, rash, heart block and blood dyscrasias. When used alone, may cause 1:1 conduction in atrial flutter leading to ventricular fibrillation. Patients may develop idiosyncratic ventricular tachycardia with low levels, especially when therapy is being initiated.

QUINIDINE *continued*

Quinidine is a substrate of CYP 450 3A3/4 and 3A5–7 enzymes, and an inhibitor of CYP 450 2D6 and 3A3/4 enzymes. Can cause increase in digoxin levels. Quinidine potentiates the effect of neuromuscular blocking agents, beta blockers, anticholinergics, and warfarin. Amiodarone, antacids, delavirdine, diltiazem, grapefruit juice, saquinavir, ritonavir, verapamil, or cimetidine may enhance the drug's effect. Barbiturates, phenytoin, cholinergic drugs, nifedipine, sucralfate, or rifampin may reduce quinidine's effect. **Use with caution** in renal insufficiency (15%–25% of drug is eliminated unchanged in the urine), myocardial depression, sick sinus syndrome, G6PD deficiency, and hepatic dysfunction.

Therapeutic levels (antiarrhythmic): 3–7 mg/L. Recommended serum sampling times at steady state: trough level obtained within 30 min prior to the next scheduled dose after 1–2 days of continuous dosing (steady state).

MALARIA USE: Continuous monitoring of electrocardiogram, blood pressure, and serum glucose is recommended, especially in pregnant women and young children.

QUINUPRISTIN AND DALFOPRISTIN
Synercid
Antibiotic, streptogramin

Injection: 500 mg (150 mg quinupristin and 350 mg dalfopristin)

Doses expressed in mg of combined quinupristin and dalfopristin.

Vancomycin-resistant* Enterococcus faecium *(VREF):

Child < 16 yr (limited data), ≥16 yr and adult: 7.5 mg/kg/dose IV Q 8 hr

Complicated skin infections:

Child < 16 yr (limited data), ≥16 yr and adult: 7.5 mg/kg/dose IV Q 12 hr for at least 7 days

VREF endocarditis:

Child and adult: 7.5 mg/kg/dose IV Q 8 hr for at least 8 weeks

Not active against *Enterococcus faecalis*. **Use with caution** in hepatic impairment; dosage reduction may be necessary. Most common side effects include pain, burning, inflammation and edema at the intravenous infusion site, thrombophlebitis, and thrombosis, GI disturbances, rash, arthralgia, myalgia, increased liver enzymes, hyperbilirubinemia, and headache. Dose frequency reductions (Q 8 hr–Q 12 hr) or discontinuation can improve severe cases of arthralgia and myalgia. Use total body weight for obese patients when calculating dosages.

Drug is an inhibitor to the CYP 450 3A4 isoenzyme. **Avoid use** with CYP 450 3A4 substrates, which can prolong QTc interval. May increase the effects/toxicity of cyclosporine, tacrolimus, sirolimus, delavirdine, nevirapine, indinavir, ritonavir, diazepam, midazolam, carbamazepine, methylprednisolone, vinca alkaloids, docetaxel, paclitaxel, quinidine and some calcium channel blockers.

Pediatric (<16 yr old) pharmacokinetic studies are incomplete. Reduce dose for patients with hepatic cirrhosis (Child-Pugh A or B).

Drug is compatible with D_5W and incompatible with saline and heparin. Infuse each dose over 1 hr using the following **max. IV concentrations**: peripheral line: 2 mg/mL, central line: 5 mg/mL. If injection site reaction occurs, dilute infusion to <1 mg/mL.

For explanation of icons, see p. 667

R

RANITIDINE HCL

Zantac, Zantac 75 [OTC], Zantac 150 Maximum Strength [OTC], and generics

Histamine-2-antagonist

Tabs: 75 [OTC], 150 [OTC and Rx], 300 mg
Caps: 150, 300 mg
Oral syrup: 15 mg/mL (480 mL); may contain 7.5% alcohol and parabens
Injection: 25 mg/mL (2, 6, 40 mL); may contain 0.5% phenol

Neonate:
PO: 6 mg/kg/24 hr ÷ Q 8 hr
IV:
Pre-term: 1–3 mg/kg/24 hr ÷ Q 12 hr
Term: 1.5–4.5 mg/kg/24 hr ÷ Q 8 hr
ECMO: 2 mg/kg/dose IV Q 12–24 hr

Child ≥1 mo–16 yr:
Duodenal/gastric ulcer (see remarks):
PO:
Treatment: 4–8 mg/kg/24 hr ÷ Q 12 hr; **max. dose**: 300 mg/24 hr
Maintenance: 2–4 mg/kg/24 hr ÷ Q 12 hr; **max. dose**: 150 mg/24 hr
IV/IM: 2–4 mg/kg/24 hr ÷ Q 6–8 hr; **max. dose**: 200 mg/24 hr
Gastroesophageal reflux disease (GERD)/erosive esophagitis:
PO: 5–10 mg/kg/24 hr ÷ Q 8–12 hr; **max. dose**: 300 mg/24 hr
IV/IM: 2–4 mg/kg/24 hr ÷ Q 6–8 hr; **max. dose**: 50 mg per dose

Adolescent and adult:
PO: 150 mg/dose BID or 300 mg/dose QHS; doses as high as 6 g/24 hr have been used in patients with severe disease (e.g., Zollinger-Ellison syndrome).
IM/IV: 50 mg/dose Q 6–8 hr; **max. dose:** 400 mg/24 hr

Continuous infusion, all ages: Administer daily intravenous dosage over 24 hr (may be added to parenteral nutrition solutions). An initial loading dose (using the respective age-appropriate intermittent dose) may be administered.

May cause headache and gastrointestinal (GI) disturbance, malaise, insomnia, sedation, arthralgia, and hepatotoxicity. Acute interstitial nephritis has been reported. May increase levels of nifedipine and midazolam. May decrease levels of ketoconazole, itraconazole and delavirdine. May cause false-positive urine protein test (Multistix).

Duodenal/gastric ulcer doses for ≥1 mo–16 yr are extrapolated from clinical adult trials and pharmacokinetic data in children. Extemporaneously compounded carbohydrate-free oral solution dosage form is useful for patients receiving the ketogenic diet. The syrup dosage form has a peppermint flavor and may not be tolerated. **Adjust dose in renal failure (see Chapter 31).**

RASBURICASE
Elitek
Antihyperuricemic agent

Injection: 1.5, 7.5 mg; contains mannitol and L-alanine

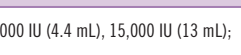
Hyperuricemia (all ages): 0.1–0.2 mg/kg/dose (rounded down to the nearest whole 1.5 mg multiple) IV over 30 min × 1. Patients generally respond to one dose but if needed dose may be repeated Q 24 hr for up to four additional doses.

Contraindicated in G6PD deficiency (risk for acute hemolytic anemia) or history of hypersensitivity, hemolytic reactions, or methemoglobinemia with rasburicase. **Use with caution** in asthma, allergies, hypersensitivity with other medications, and children <2 yr of age (decreased efficacy and increased risk for rash, vomiting, diarrhea, and fever).

Common side effects include nausea, vomiting, abdominal pain, discomfort, diarrhea, constipation, mucositis, fever, and rash. Serious and fatal hypersensitivity reactions have been reported in <1% of patients, including anaphylaxis, and can occur at any time; discontinue use immediately and permanently.

During therapy, uric acid blood samples must be sent to the laboratory immediately. Blood should be collected in prechilled tubes containing heparin, and placed in an ice-water bath to avoid potential falsely low uric acid levels (degradation of plasma uric acid occurs in the presence of rasburicase at room temperature). Centrifugation in a precooled centrifuge (4°C) is indicated. Plasma samples must be assayed within 4 hr of sample collection.

RH_0 (D) IMMUNE GLOBULIN INTRAVENOUS (HUMAN)
WinRho-SDF, Rhophylac
Immune Globulin



Injection (WinRho-SDF): 1500 IU (1.3 mL), 2500 IU (2.2 mL), 5000 IU (4.4 mL), 15,000 IU (13 mL); may contain polysorbate 80

Prefilled injection (Rhophylac): 1500 IU (2 mL)

Conversion: 1 mCg = 5 IU

IM route and IM dosage forms: indicated for prevention of Rh hemolytic disease of newborn by administering to Rh_0(D) negative mother or prevention of isoimmunization in Rh_0(D)-negative individuals who have been transfused with Rh_0(D)-positive blood/cell components.

All doses based on international units (IU)

Immune thrombocytopenic purpura (nonsplenectomized Rh_0(D)-positive patients):

WinRho-SDF (child, adolescent, and adult; see remarks):

Initial dose (may be given in two divided doses on separate days or as a single dose):

Hemoglobin ≥ 10 mg/dL: 250 IU/kg/dose IV × 1

Hemoglobin 8–<10 mg/dL: 125–200 IU/kg/dose IV × 1

Hemoglobin <8 mg/dL: Use alternative therapy.

Subsequent doses (actual dose and frequency of administration is determined by the patient's clinical response and subsequent hemoglobin level):

Hemoglobin <8 g/dL: Use alternative therapy.

Hemoglobin 8–10 g/dL: 125–200 IU/kg/dose IV × 1

Hemoglobin > 10 g/dL: 250–300 IU/kg/dose IV × 1

Rhophylac (child, adolescent, and adult; see remarks): 250 IU/kg/dose IV × 1

Continued

For explanation of icons, see p. 667

RH_0 (D) IMMUNE GLOBULIN INTRAVENOUS (HUMAN) *continued*

Contraindicated in IgA deficiency. **Use with caution** with history of atherosclerosis, known/suspected hyperviscosity, coagulation disorders, and other thrombotic risks. Adverse events associated with ITP indication include headache, chills, fever and reduction in hemoglobin (due to the destruction of Rh_0[D] antigen-positive red cells). Intravascular hemolysis resulting in anemia and renal insufficiency has been reported. May interfere with immune response to live virus vaccines (e.g., MMR, varicella).

Clinical response for ITP therapy requires monitoring of platelet counts, RBC, Hgb, and reticulocyte count. Rh_0(D)-positive patients should be monitored for signs and symptoms of intravascular hemolysis, anemia, and renal insufficiency.

Recommended IV administration rate:

WinRho-SDF: over 3–5 min

Rhophylac: each 1500 IU (2 mL) per 15–60 sec

RIBAVIRIN

Oral: Rebetol and generics

Inhalation: Virazole and generics

Antiviral agent

Oral solution (Rebetol): 200 mg/5 mL (100 mL); contains sodium benzoate and propylene glycol

Oral caps (Rebetol and generics): 200 mg

Tabs: 200, 400, 500, 600 mg

Aerosol (Virazole and generics): 6 g

Hepatitis C (PO, see remarks): Hepatitis C combination therapy is dependent on HCV genotype and treatment status. Specific treatment recommendations are dynamic with newer therapies; see the most recent American Association for the Study of Liver Diseases/Infectious Disease Society of America (AASLD/IDSA) treatment recommendations at www.hcvguidelines.org

Child: In combination with sofosbuvir for patients with genotypes 2 or 3 with/without cirrhosis:

Child <12 yr and ≥35 kg, child ≥12 yr and adolescent (see remarks):

<47 kg: 15 mg/kg/24 hr PO ÷ BID

47–49 kg: 300 mg PO BID

50–65 kg: 400 mg PO BID

66–80 kg: 500 mg PO BID

>80 kg: 600 mg PO BID

Duration of therapy:

Genotype 2: 12 weeks

Genotype 3: 24 weeks

Adult (see remarks):

Oral capsules or solution as part of a recommended combination therapy:

<75 kg: 500 mg PO BID

≥75 kg: 600 mg PO BID

Inhalation (see remarks):

Continuous: Administer 6 g by aerosol over 12–18 hr once daily for 3–7 days. The 6-g ribavirin vial is diluted in 300 mL preservative-free sterile water to a final concentration of 20 mg/mL. Must be administered with Viratek Small Particle Aerosol Generator (SPAG-2).

Intermittent (for nonventilated patients): Administer 2 g by aerosol over 2 hr TID for 3–7 days. The 6 g ribavirin vial is diluted in 100 mL preservative-free sterile water to a final concentration of 60 mg/mL. The intermittent use is not recommended in patients with endotracheal tubes.

RIBAVIRIN continued

ORAL RIBAVIRIN: Contraindicated in pregnancy, significant or unstable cardiac disease, autoimmune hepatitis, hepatic decompensation (Child-Pugh score >6; class B or C), hemoglobinopathies, and creatinine clearance <50 mL/min. **Use with caution** in preexisting cardiac disease, pulmonary disease and sarcoidosis. Anemia (most common), insomnia, depression, irritability, and suicidal behavior (higher in adolescent and pediatric patients) have been reported with the oral route.

Combination therapy with peginterferon for Hep C is no longer recommended due to poor efficacy. Tinnitus, hearing loss, vertigo, severe hypertriglyceridemia, and homicidal ideation have been reported in combination with interferon. Pancytopenia has been reported in combination with interferon and azathioprine. Increased risk for hepatic decompensation with cirrhotic chronic hepatitis C patients treated with α interferons or with HIV coinfection receiving HAART and interferon alfa-2a. Growth inhibition (delays in weight and height increases) was observed in children (5–17 years old) receiving combination therapy for up to 48 weeks.

May decrease the effects of zidovudine, stavudine; and increase risk for lactic acidosis with nucleoside analogues. **Reduce or discontinue dosage for toxicity as follows:**

Patient with no cardiac disease:

Hgb < 10 g/dL and ≥8.5 g/dL:

Child: 12 mg/kg/dose PO once daily; may further reduce to 8 mg/kg/dose PO once daily

Adult: 600 mg PO once daily (capsules or solution) or 200 mg PO QAM and 400 mg PO QPM (tablets)

Hgb < 8.5 g/dL: Discontinue therapy permanently.

Patient with cardiac disease:

≥2 mg/dL decrease in Hgb during any 4-week period during therapy:

Child: 12 mg/kg/dose PO once daily; may further reduce to 8 mg/kg/dose PO once daily (monitor weekly)

Adult: 600 mg PO once daily (capsules or solution) or 200 mg PO QAM and 400 mg PO QPM (tablets)

Hgb < 12 g/dL after 4 weeks of reduced dose: Discontinue therapy permanently

INHALED RIBAVIRIN: Use of ribavirin for RSV is controversial and not routinely indicated. Aerosol therapy may be considered for selected infants and young children at high risk for serious RSV disease (see most recent edition of the *AAP Redbook*). Most effective if begun early in course of RSV infection; generally in the first 3 days. May cause worsening respiratory distress, rash, conjunctivitis, mild bronchospasm, hypotension, anemia and cardiac arrest. **Avoid** unnecessary occupational exposure to ribavirin due to its teratogenic effects. Drug can precipitate in the respiratory equipment.

RIBOFLAVIN
Vitamin B_2 and various brands and generics
Water-soluble vitamin

Tabs [OTC]: 25, 50, 100 mg

Caps [OTC]: 50 , 400 mg

Riboflavin deficiency:

Child: 2.5–10 mg/24 hr ÷ once daily–BID PO

Adult: 5–30 mg/24 hr ÷ once daily–BID PO

U.S. RDA requirements: see Chapter 21.

Continued

For explanation of icons, see p. 667

RIBOFLAVIN *continued*

Migraine prophylaxis (limited data):
Child ≥8 yr and adolescent: 200–400 mg PO once daily

Hypersensitivity may occur. Administer with food. Causes yellow to orange discoloration of urine. For multivitamin information, see Chapter 21.
Pregnancy category changes to C if used in doses above the RDA.

RIFABUTIN
Mycobutin and generics
Antituberculous agent

B	3	Yes	Yes	No

Caps: 150 mg
Oral suspension: 20 mg/mL

MAC primary prophylaxis for first episode of opportunistic disease in HIV (see remarks for interactions and www.aidsinfo.nih.gov/guidelines):
Child >5 yr, adolescent, and adult: 300 mg PO once daily; doses may be administered as 150 mg PO BID if gastrointestinal (GI) upset occurs.
MAC secondary prophylaxis for recurrence of opportunistic disease in HIV (in combination with ethambutol and a macrolide antibiotic [clarithromycin or azithromycin]):
Infant and child: 5 mg/kg/24 hr PO once daily; **max. dose:** 300 mg/24 hr
Adolescent and adult: 300 mg PO once daily; doses may be administered 150 mg PO BID if GI upset occurs
MAC treatment:
Child: 10–20 mg/kg/24 hr PO once daily; **max. dose**: 300 mg/24 hr as part of a multidrug regimen for severe disease.
Adult: 300 mg PO once daily; may be used in combination with azithromycin and ethambutol.
Use in combination with HIV antiretroviral agents: see product information for dosage recommendations.

Should not be used for MAC prophylaxis with active TB. May cause GI distress, discoloration of skin and body fluids (brown-orange color) and marrow suppression. Rash, eosinophilia, and bronchospasm have been reported. **Use with caution** in renal and liver impairment. **Adjust dose in renal impairment (see Chapter 31).** May permanently stain contact lenses. Uveitis can occur when using high doses (>300 mg/24 hr in adults) in combination with macrolide antibiotics.
Rifabutin is an inducer of CYP 450 3A enzyme and is structurally similar to rifampin (similar drug interactions, see Rifampin). Clarithromycin, fluconazole, itraconazole, nevirapine and protease inhibitors increase rifabutin levels. Efavirenz may decrease rifabutin levels. May decrease effectiveness of dapsone, delavirdine, nevirapine, amprenavir, indinavir, nelfinavir, saquinavir, itraconazole, warfarin, oral contraceptives, digoxin, cyclosporine, ketoconazole and narcotics.
Doses may be administered with food if patient experiences GI intolerance.

RIFAMPIN
Rifadin and generics
Antibiotic, antituberculous agent, rifamycin

C	2	Yes	Yes	No

Caps (Rifadin and generics): 150, 300 mg
Oral suspension: 10, 15, 25 mg/mL
Injection (Rifadin and generics): 600 mg

RIFAMPIN *continued*

Staphylococcus aureus ***infections (as part of synergistic therapy with other antistaphylococcal agents):***

Neonate, infant, child, and adolescent: 10–20 mg/kg/24 hr ÷ Q 12 hr IV/PO; **max. dose**: 600 mg/24 hr

Prosthetic valve endocarditis:

Early infection (≤1 yr surgery): 20 mg/kg/24 hr ÷ Q 8 hr IV/PO; **max. dose:** 900 mg/24 hr

Late infection (>1 yr surgery): 15–20 mg/kg/24 hr ÷ Q 12 hr IV/PO; **max. dose**: 600 mg/24 hr

Adult: 600 mg once daily, or 300–450 mg Q 12 hr IV/PO

Prosthetic valve endocarditis: 300 mg Q 8 hr IV/PO for a minimum of 6 weeks in combination with antistaphylococcal penicillin with or without gentamicin for first 2 weeks.

Tuberculosis (see latest edition of the* AAP Red Book *for duration of therapy and combination therapy): Twice-weekly therapy may be used after 1–2 months of daily therapy.

Infant, child and adolescent:

Daily therapy: 15–20 mg/kg/24 hr ÷ Q 12–24 hr IV/PO; higher dose of 20–30 mg/kg/24 hr ÷ Q 12–24 hr has been recommended for infants and toddlers and for central nervous system (CNS) and disseminated disease.

Twice-weekly therapy: 15–20 mg/kg/24 hr PO twice weekly; higher dose of 20–30 mg/kg/24 hr twice weekly has been recommended for infants and toddlers and for CNS and disseminated disease.

Max. daily dose: 600 mg/24 hr

Adult:

Daily therapy: 10 mg/kg/24 hr PO once daily

Twice-weekly therapy: 10 mg/kg/24 hr once daily twice weekly

Max. daily dose: 600 mg/24 hr

Prophylaxis for Neisseria meningitidis (see latest edition of the* AAP Red Book *for additional information):

0–<1 mo: 10 mg/kg/24 hr ÷ Q12 hr PO × 2 days

≥1 mo: 15–20 mg/kg/24 hr ÷ Q12 hr PO × 2 days

Adult: 600 mg PO Q12 hr × 2 days

Max. dose (all ages): 1200 mg/24 hr.

Never use as monotherapy except when used for prophylaxis. Patients with latent tuberculosis infection should NOT be treated with rifampin and pyrazinamide because of the risk of severe liver injury. Use is **NOT recommended** in porphyria. **Use with caution** in diabetes.

May cause GI irritation, allergy, headache, fatigue, ataxia, muscle weakness, confusion, fever, hepatitis, transient LFT abnormalities, blood dyscrasias, interstitial nephritis, and elevated BUN and uric acid. Causes red discoloration of body secretions such as urine, saliva and tears (which can permanently stain contact lenses). Bleeding and vitamin K–dependent coagulation disorders have been reported.

Induces several hepatic enzymes and transporters (CYP 450 2C9, 2C19, and 3A4; UGT1A1, P-glycoprotein, and OATP1B1/1B3), which may decrease plasma concentration of digoxin, corticosteroids, buspirone, benzodiazepines, fentanyl, calcium channel blockers, β blockers, cyclosporine, tacrolimus, itraconazole, ketoconazole, oral anticoagulants, barbiturates, and theophylline. May reduce the effectiveness of oral contraceptives and anti-retroviral agents (protease inhibitors and nonnucleoside reverse transcriptase inhibitors). **Use is contraindicated** with praziquantel due to decreased praziquantel levels; rifampin should be discontinued 4 weeks prior to initiating praziquantel and rifampin can be restarted one day after completion of praziquantel. Hepatotoxicity is a concern when used in combination with pyrazinamide and ritonavir-boosted saquinavir **(use is contraindicated).**

Adjust dose in renal failure (see Chapter 31). Reduce dose in hepatic impairment. Give oral doses 1 hr before or 2 hr after meals.

For *Haemophilus influenzae* type b prophylaxis, see latest edition of the *Red Book.*

For explanation of icons, see p. 667

RIFAXIMIN
Xifaxan
Antibiotic, rifamycin derivative

Tabs: 200, 550 mg; may contain edetate disodium
Oral suspension: 20 mg/mL

Small intestinal bacterial overgrowth (SIBO; limited data):
Child ≥3 yr and adolescent: 200–550 mg PO TID × 7 days
Adult: 550 mg PO TID × 14 days
Irritable bowel syndrome with diarrhea:
Child ≥8 yr and adolescent (limited data): 10–30 mg/kg/24 hr PO ÷ TID; **max. dose**: 1200 mg/24 hr
Adult: 550 mg PO TID × 14 days; may repeat up to two times with the same dosage regimen
Travelers' diarrhea (caused by noninvasive strains of Escherichia coli):
Child ≥3–11 yr (limited data): 100 mg PO QID for up to 5 days
Child ≥12 yr and adult: 200 mg PO TID × 3 days
Recurrent or subsequent Clostridium difficile diarrhea:
Child ≥12 yr and adult: 400 mg PO TID × 20 days initiated after a 10-day course of oral vancomycin

Contraindicated with rifamycin hypersensitivity. **Avoid use** in diarrhea complicated by fever or blood in the stool. **Use with caution** in severe hepatic impairment (Child-Pugh class C).
Common side effects include peripheral edema, abdominal pain, nausea, ascites, dizziness, headache, and fatigue. Anaphylaxis, angioedema, and exfoliative dermatitis have been reported.
Substrate and inhibitor of OATP1A2/SLCOA2 transporter and substrate of P-glycoprotein ABCB1 and OATP1B1/1B3. May decrease the effects of warfarin and immunological effects of cholera and BCG vaccines. P-glycoprotein inhibitors (e.g., cyclosporine) may increase the effects/toxicity of rifaximin.
Doses may be administered with or without food.

RIMANTADINE
Flumadine and generics
Antiviral agent

Tabs: 100 mg
Oral suspension: 10 mg/1 mL

Influenza A prophylaxis (for at least 10 days after known exposure; usually for 6–8 weeks during influenza A season or local outbreak):
Child:
1–9 yr: 5 mg/kg/24 hr PO once daily–BID; **max. dose**: 150 mg/24 hr
≥10 yr:
<40 kg: 5 mg/kg/24 hr PO ÷ BID; **max. dose**: 150 mg/24 hr
≥40 kg: 100 mg per dose PO BID
Adult: 100 mg PO BID
Influenza A treatment (within 48 hr of illness onset):
Use the aforementioned prophylaxis dosage × 5–7 days.

Resistance to influenza A and recommendations against the use for treatment and prophylaxis have been reported by the Centers for Disease Control (CDC). Check with local microbiology laboratories and the CDC for seasonal susceptibility/resistance.

RIMANTADINE *continued*

Preferred over amantadine for influenza due to lower incidence of adverse events. Individuals immunized with live attenuated influenza vaccine (e.g., FluMist) should not receive rimantadine prophylaxis for 14 days after the vaccine. Chemoprophylaxis does not interfere with immune response to inactivated influenza vaccine.

May cause GI disturbance, xerostoma, dizziness, headache and urinary retention. CNS disturbances are less than with amantadine. **Contraindicated** in amantadine hypersensitivity. **Use with caution** in renal or hepatic insufficiency; dosage reduction may be necessary. A dosage reduction of 50% has been recommended in severe hepatic or renal impairment. Subjects with severe renal impairment have been reported to have an 81% increase in systemic exposure.

RISPERIDONE
Risperdal, Risperdal Consta, and generics
Atypical antipsychotic, serotonin (5-HT_2) and dopamine (D_2) antagonist

Tabs: 0.25, 0.5, 1, 2, 3, 4 mg
Oral solution: 1 mg/mL (30 mL); may contain benzoic acid
Orally disintegrating tabs: 0.25, 0.5, 1, 2, 3, 4 mg; contains phenylalanine
IM Injection (Risperdal Consta): 12.5, 25, 37.5, 50 mg (prefilled syringe with 2 mL diluent; includes one 21-gauge 1-in needle for deltoid administration and one 20-gauge 2-in needle for gluteal administration); for IM administration only

Irritability associated with autistic disorder:
5–16 yr (PO daily doses may be administered once daily–BID; patients experiencing somnolence may benefit from QHS or BID dosing or dose reduction):
Initial dose:
<20 kg: 0.25 mg/24 hr PO for a minimum of 4 days; use with caution if <15 kg as dosing recommendation is not established.
≥20 kg: 0.5 mg/24 hr PO for a minimum of 4 days
Dose increment (if needed) after 4 days of initial dose:
<20 kg: 0.5 mg/24 hr PO for a minimum of 14 days, if additional increments needed, increase dose by 0.25 mg/24 hr at intervals of at least 14 days.
≥20 kg: 1 mg/24 hr PO for a minimum of 14 days, if additional increments needed, increase dose by 0.5 mg/24 hr at intervals of at least 14 days.
Max. daily dose for plateau of therapeutic effect (from one pivotal clinical trial):
<20 kg: 1 mg/24 hr
≥20–45 kg: 2.5 mg/24 hr
>45 kg: 3 mg/24 hr

Bipolar mania: Oral doses may be administered once or twice daily; patients experiencing somnolence may benefit from QHS or BID dosing or dose reduction. Long-term use beyond 3 weeks and doses (all ages) >6 mg/24 hr have not been evaluated.
Child (10–17 yr): Start with 0.5 mg/24 hr PO once daily (QAM or QHS). If needed, increase dose at intervals ≥24 hr in increments of 0.5 or 1 mg/24 hr, as tolerated, up to a recommended dose of 2.5 mg/24 hr. Although efficacy has been demonstrated between 0.5–6 mg/24 hr, no additional benefit was seen above 2.5 mg/24 hr. Higher doses were associated with more adverse effects.
Adult: Start with 2–3 mg PO once. Dosage increases or decreases of 1 mg/24 hr can be made at 24-hr intervals. Dosage range: 1-6 mg/24 hr.

Continued

For explanation of icons, see p. 667

RISPERIDONE *continued*

Schizophrenia: Oral doses be administered once daily--BID and patients experiencing somnolence may benefit from BID dosing (see remarks).

Adolescent (13–17 yr): No data are available to support long-term use of >8 wk.

PO: Start with 0.5 mg once daily (QAM or QHS). If needed, increase dose at intervals ≥24 hr in increments of 0.5 to 1 mg/24 hr, as tolerated, to a recommended dose of 3 mg/24 hr. Although efficacy has been demonstrated between 1–6 mg/24 hr, no additional benefit and greater side effects were seen above 3 mg/24 hr. Doses >6 mg/24 hr have not been studied.

Adult:

PO: Start with 1 mg BID on day 1; if tolerated, increase to 2 mg BID on day 2 and to 3 mg BID thereafter. Dosage increases or decreases of 1–2 mg can be made on a weekly basis if needed. Usual effective dose: 2–8 mg/24 hr. Doses above 16 mg/24 hr have not been evaluated.

IM: Start with 25 mg Q 2 wk; if no response, dose may be increased to 37.5 mg or 50 mg at 4-week intervals. **Max. IM dose:** 50 mg Q 2 wk. PO risperidone should also be administered with the initial IM dose and continued × 3 weeks and discontinued to provide adequate plasma concentrations during the initial IM dosing period.

Use with caution in cardiovascular disorders, diabetes, renal or hepatic impairment (dose reduction necessary), hypothermia or hyperthermia, seizures, breast cancer or other prolactin dependent tumors, and dysphagia. Common side effects include abdominal pain and other GI disturbances, arthralgia, anxiety, dizziness, headache, insomnia, somnolence (use QHS dosing), EPS, cough, fever, pharyngitis, rash, rhinitis, sexual dysfunction, tachycardia, and weight gain. Weight gain, somnolence, and fatigue were common side effects reported in the autism studies. Priapism, QTc prolongation, hypothermia, sleep apnea syndrome, sleep walking, ileus, urinary retention, diabetes mellitus, and hypoglycemia have been reported in post marketing reports. Very rare cases of anaphylaxis have been reported with use of the IM dosage form in patients who have previously tolerated the oral dosage form.

In the presence of severe renal or hepatic impairment or risk for hypotension, the following adult dosing has been recommended: Start with 0.5 mg PO BID. Increase dose, if needed and tolerated, in increments no more than 0.5 mg BID. Increases to doses >1.5 mg BID should occur at intervals of at least 1 week; slower titration may be required in some patients.

Limited studies in pediatric related Tourette syndrome, schizophrenia, and aggressive behavior in psychiatric disorders are reported. Autistic disorder safety and efficacy in children <5 years of age have not been established. If therapy has been discontinued for a period of time, therapy should be reinitiated with the same initial titration regimen.

Drug is a CYP 450 2D6 and 3A4 isoenzyme substrate. Concurrent use of isoenzyme inhibitors (e.g., fluoxetine, paroxetine, sertraline, cimetidine) and inducers (e.g., carbamazepine, rifampin, phenobarbital, phenytoin) may increase and decrease the effects of risperidone, respectively. Alcohol, CNS depressants, and St. John's wort may potentiate the drug's side effect. Risperidone may enhance the hypotensive effects of levodopa and dopamine agonists.

Oral dosage forms may be administered with or without food. Oral solution can be mixed in water, coffee, orange juice, or low-fat milk but is incompatible with cola or tea. **Do not** split or chew the orally disintegrating tablet. Use IM suspension preparation within 6 hr after reconstitution.

RIZATRIPTAN BENZOATE

Maxalt, Maxalt-MLT, and generics

Antimigraine agent, selective serotonin agonist

Tabs:

Maxalt and generics: 5, 10 mg (12s, 18s, 30s)

Orally disintegrating tabs (ODT):

12s) Knowledge Bank

RIZATRIPTAN BENZOATE *continued*

Treatment of acute migraines with or without aura (tabs and ODT):

Child 6–17 yr (efficacy and safety with >1 dose within 24 hr has not been established):

<40 kg: 5 mg PO × 1

≥40 kg: 10 mg PO × 1

≥18 yr and adult (safety of an average of >4 headaches in a 30 day period has not been established; see remarks): 5–10 mg PO × 1. If needed in 2 hr, a second dose may be administered. **Max. daily dose:** 30 mg/24 hr.

Dosage adjustment if receiving propranolol:

Child 6–17 yr:

<40 kg: **DO NOT USE**

≥40 kg: 5 mg PO× 1; **max. dose:** 5 mg/24 hr period

≥18 yr and adult: 5 mg PO up to a **maximum** of three doses at 2-hr intervals; **max. dose:** 15 mg/24 hr period.

Contraindicated in hemiplegic or basilar migraine, coronary artery vasospasm, uncontrolled hypertension, ischemic bowel or coronary artery disease, peripheral vascular disease, history of stroke or transient ischemic attack (TIA), and current or recent use (within 2 weeks) of a MAO inhibitor.

Do not administer with any ergotamine-containing medication ergot-type medication, any other 5-HT1 agonist (e.g., triptans), methylene blue, or linezolid.

Use with **caution** in renal and hepatic impairment as a 44% increase in AUC for patients receiving hemodialysis and a 30% increase plasma concentration for patients with moderate hepatic dysfunction were reported.

Common adverse effects include nausea, asthenia, dizziness, somnolence, and fatigue. Serious adverse effects include chest pain, coronary artery spasm, hypertension, myocardial infarction (MI), peripheral ischemia, ventricular arrhythmia, ischemic colitis, anaphylaxis, angioedema, cerebrovascular accident, and serotonin syndrome. Transient and permanent vision loss have been reported.

When the ODT is being used, place the whole tablet on the tongue, allow the tablet to dissolve, and swallow with saliva. Administration with liquids is optional. Do not break the ODT tablet.

ROCURONIUM

Generics; previously available as Zemuron

Nondepolarizing neuromuscular blocking agent

Injection: 10 mg/mL (5, 10 mL)

Use of a peripheral nerve stimulator to monitor drug effect is recommended.

Infant:

IV: 0.5 mg/kg/dose; may repeat Q 20–30 min PRN

Child (3 mo–14 yr):

IV: 0.6 mg/kg/dose × 1; if needed, give maintenance doses of 0.075–0.125 mg/kg/dose Q20–30 min PRN when neuromuscular blockade returns to 25% of control. Alternatively, a maintenance continuous intravenous infusion may be used starting at 7–12 mCg/kg/min when neuromuscular blockade returns to 10% of control.

Adolescent and adult:

IV: Start with 0.6–1.2 mg/kg/dose × 1; if needed, maintenance doses at 0.1–0.2 mg/kg/dose Q 20–30 min PRN. Alternatively, a maintenance continuous intravenous infusion may be used starting at 10–12 mCg/kg/min (range: 4–16 mCg/kg/min).

For explanation of icons, see p. 667

ROCURONIUM *continued*

Use with caution in hepatic impairment and history of anaphylaxis with other neuromuscular blocking agents. Hypertension, hypotension, arrhythmia, tachycardia, nausea, vomiting, bronchospasm, wheezing, hiccups, rash, and edema at the injection site may occur. Myopathy after long-term use in an intensive care unit (ICU) and QT interval prolongation in pediatric patients receiving general anesthetic agents have been reported. Severe anaphylactic reactions and malignant hypothermia have been reported. Increased neuromuscular blockade may occur with concomitant use of aminoglycosides, clindamycin, tetracycline, magnesium sulfate, quinine, quinidine, succinylcholine and inhalation anesthetics (for continuous infusion, reduce infusion by 30%–50% at 45–60 min after intubating dose).

Caffeine, calcium, carbamazepine, phenytoin, phenylephrine, azathioprine, and theophylline may reduce neuromuscular blocking effects.

Use must be accompanied by adequate anesthesia or sedation. Peak effects occur in 0.5–1 min for children and in 1–3.7 min for adults. Duration of action: 30–40 min in children and 20–94 min in adults (longer in geriatrics). Recovery time in children 3 months to 1 year of age is similar to that in adults. To prevent residual paralysis, extubate patient **only** after the patient has sufficiently recovered from neuromuscular blockade. In obese patients, use actual body weight for dosage calculation.

RUFINAMIDE

Banzel

Anticonvulsant, triazole derivative

C 3 Yes Yes No

Tabs: 200, 400 mg

Oral suspension: 40 mg/mL (460 mL); contains parabens and propylene glycol

Lennox-Gastaut Syndrome (it is not known if doses lower than the targeted dosages are effective; see remarks):

Child 1–<17 yr (see remarks): Start at 10 mg/kg/24 hr PO ÷ BID, then increase dose by ~10 mg/kg/24 hr every other day up to the **maximum** targeted dose of 45 mg/kg/24 hr ÷ BID **not to exceed** 3200 mg/24 hr.

Child ≥17 yr and adult: Start at 400–800 mg/24 hr PO ÷ BID, then increase dose by 400–800 mg/24 hr every other day up to the **maximum** targeted dose of 3200 mg/24 hr ÷ BID.

Use with concurrent valproate therapy: Use lower initial dosages; <10 mg/kg/24 hr for child 1–<17 yr and <400 mg/24 hr for ≥17 yr and adult.

Contraindicated in Familial short-QT syndrome. Use is **not recommended** in severe hepatic impairment (Child-Pugh 10–15). Use with **caution** when taking other medications that can shorten the QT interval, performing tasks requiring mental alertness, and in mild/moderate hepatic impairment (Child-Pugh 5–9).

Common side effects include fatigue, blurred vision, diplopia, ataxia, dizziness, headache, somnolence, nausea, vomiting and shortening of cardiac QT interval. Serious side effects of leukopenia, severe dermatologic reactions (e.g., Stevens-Johnson syndrome), multiorgan hypersensitivity reactions (e.g., DRESS), and suicidal ideation have been reported.

Rufinamide is a weak inhibitor of CYP 450 2E1 and weak inducer of 3A4. May decrease levels/effects of nifedipine, nimodipine, piperaquine, calcifediol, clozapine, carbamazepine, lamotrigine, triazolam, orlistat, and hormonal contraceptives. May increase the levels/effects of phenytoin and phenobarbital. Primidone, phenobarbital, phenytoin, and carbamazepine may decrease the levels/effects of rufinamide. Whereas valproic acid may increase the levels/effects of rufinamide.

The effectiveness data for 1- to 4-year-old children is based on bridging pharmacokinetic (PK) and safety data as their PK and safety data are similar to children ≥4 years old and adults.

Consider dose adjustment for drug loss in patients receiving hemodialysis (rufinamide is dialyzable). For therapy discontinuation, reduce dose by ~25% every 2 days. Tablets may be crushed and all

S

SALMETEROL
Serevent Diskus
β-2-adrenergic agonist (long acting)

Dry powder inhalation (DPI; Diskus): 50 mCg/inhalation (28, 60 inhalations); contains lactose
In combination with fluticasone: see Fluticasone Propionate and Salmeterol

Persistent asthma (see remarks):
≥4 yr and adult: 1 inhalation (50 mCg) Q 12 hr
Prevention of exercise-induced bronchospasm:
≥4 yr and adult: 1 inhalation 30 to 60 min before exercise. Additional does should not be used for another 12 hr. Patients who are already using 12-hr dosing for persistent asthma should not use additional salmeterol doses for this indication and use alternative therapy (e.g., albuterol) prior to exercise.

For long-term asthma control, should be used in combination with inhaled corticosteroids. **Should not be used to relieve symptoms of acute asthma.** It is long acting and has its onset of action in 10 to 20 min with a peak effect at 3 hr. May be used at QHS (1 inhalation of the dry powder inhaler [DPI]) for nocturnal symptoms. Salmeterol is a chronic medication and is not used in similar fashion to short-acting β agonists (e.g., albuterol). Patients already receiving salmeterol every 12 hr should not use additional doses for prevention of exercise-induced bronchospasm; consider alternative therapy. Asthma exacerbations or hospitalizations were reported to be lower when this medication was used with an inhaled corticosteroid.

WARNING: Long-acting β-2-agonists as monotherapy increase the risks of asthma-related death and asthma-related hospitalizations. Monotherapy without concomitant use of an inhaled corticosteroid is **contraindicated** in asthma. Use salmeterol only as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly requires initiation of treatment with two maintenance therapies. **Contraindicated** in milk allergies; contains milk proteins.

Should not be used in conjunction with an inhaled, long-acting β-2 agonist and is not a substitute for inhaled or systemic corticosteroid. Use with strong CYP450 3A4 inhibitors (e.g., ketoconazole, HIV protease inhibitors, clarithromycin, itraconazole, nefazodone, and telithromycin) is **not recommended** due to risk for cardiovascular adverse events (e.g., QTc prolongation, tachycardia). Salmeterol is a CYP450 3A4 substrate.

Proper patient education is essential. Use with caution in hepatic impairment. Side effects are similar to those of albuterol. Hypertension and arrhythmias have been reported. See Chapter 24 for recommendations for asthma controller therapy.

SCOPOLAMINE HYDROBROMIDE
Transderm Scop and generics
Anticholinergic agent

Transdermal (Transderum Scop and generics): 1.5 mg/patch (4s, 10s, and 24s); delivers ~1 mg over 3 days

Transdermal (≥12 yr and adult; see remarks):
Motion sickness: Apply patch behind the ear at least 4 hr prior to exposure to motion; remove after 72 hr.

Continued

For explanation of icons, see p. 667

SCOPOLAMINE HYDROBROMIDE *continued*

Transdermal (≥12 yr and adult; see remarks):

Antiemetic prior to surgery: Apply patch behind the ear the evening before prior to surgery. Remove patch 24 hr after surgery.

Antiemetic prior to cesarean section: Apply patch behind the ear 1 hr prior surgery to minimize infant exposure. Remove patch 24 hr after surgery.

Toxicities similar to those of atropine. **Contraindicated** in closed-angle glaucoma and hypersensitivity to belladonna alkaloids. **Use with caution** in hepatic or renal dysfunction, GI and urinary disorders (discontinue use if there is difficulty in urination), cardiac disease, seizures, or psychosis. May cause dry mouth, drowsiness, and blurred vision. Generalized rash and erythema may indicate hypersensitivity to the medication or other ingredients in the formulation.

Transdermal route should **NOT** be used in children under 12 yr of age. Drug withdrawal symptoms (nausea, vomiting, headache, and vertigo) have been reported following removal of transdermal patch in patients using the patch for more than 3 days. For perioperative use, the patch should be kept in place for 24 hr following surgery.

Concurrent use with medications with known CNS adverse reactions or have anticholinergic properties may potentiate scopolamine's CNS effects. Use of this medication may delay the rate of orally administered drugs and will interfere with the gastric secretion test (discontinue use 10 days prior to testing).

REMOVE transdermal patch before undergoing an MRI; patch contains aluminum.

SELENIUM SULFIDE
Selsun Blue Max Strength, SelRx, and generics
Topical antiseborrheic agent

Shampoo:

1% (Selsun Blue Max Strength and others; OTC): 207, 325, 400, 420 mL; some products are available with conditioner. Be aware of different active ingredients in the Selsun Blue product line.

2.25%: 180 mL; may contain parabens and propylene glycol

2.3% (SelRx and generics): 180 mL; may contain parabens and propylene glycol

Topical lotion: 2.5% (120 mL)

≥2 yr and adult:

Seborrhea/Dandruff: Massage 5 to 10 mL of shampoo into wet scalp and leave on scalp for 2 to 3 min. Rinse thoroughly and repeat. Shampoo twice weekly for 2 weeks. Use maintenance application once every 1 to 4 wk.

Pityriasis (Tinea) versicolor: Apply 2.5% lotion to affected areas of skin. Allow to remain on skin for10 min. Rinse thoroughly. Repeat once daily for 7 days. Follow with weekly or monthly applications for 3 mo to prevent recurrences.

Rinse hands and body well after treatment. May cause local irritation, hair loss, and hair discoloration. **Avoid** eyes, genital areas, and skin folds. Shampoo may be used for tinea capitis to reduce risk of transmission to others (does not eradicate tinea infection).

For tinea versicolor, 15% to 25% sodium hyposulfite or thiosulfate (Tinver lotion) applied to affected areas twice daily for 2 to 4 wk is an alternative. Topical antifungals (e.g., clotrimazole, miconazole) may be used for small focal infections. **Do not use** for tinea versicolor during pregnancy.

SENNA/SENNOSIDES
Senokot, Senna-Lax, Ex-Lax, and many others
Laxative, stimulant

Based on mg of senna (all products are OTC):
Oral powder: 284 g
Oral syrup: 176 mg/5 mL, 218 mg/5 mL (60 mL, 240 mL); may contain parabens and propylene glycol
Tabs: 187, 217, 374 mg
187 mg senna extract is approximately 8.6 mg sennosides.
Based on mg of sennosides (all products are OTC):
Oral syrup: 8.8 mg/5 mL (40, 237 mL); may contain parabens and propylene glycol
Tabs: 8.6, 15, 17.2, 25 mg
Chewable tabs: 15 mg
8.6 mg sennosides is approximately 187 mg senna extract.

Constipation:

Dosing based on mg senna:
Child:
Oral: 10–20 mg/kg/dose PO QHS (**max. dose:** as shown below) or dosage by age:
1 mo–1 yr: 55–109 mg PO QHS to **max. dose:** 218 mg/24 hr
1–5 yr: 109–218 mg PO QHS to **max. dose:** 436 mg/24 hr
5–15 yr: 218–436 mg PO QHS to **max. dose**: 872 mg/24 hr
Adult:
Oral powder: 1/2 to 1 tsp PO once or twice daily
Syrup: 436–654 mg PO at bedtime; **max. dose**: 654 mg (15 mL) BID
Tabs: 374 mg PO at bedtime; **max. dose:** 748 mg BID
Dosing based on mg sennosides:
Child:
Syrup:
1 mo–2 yr: 2.2–4.4 mg (1.25–2.5 mL) PO QHS to **max. dose**: 8.8 mg/24 hr
2–5 yr: 4.4–6.6 mg (2.5–3.75 mL) PO QHS to **max. dose:** 6.6 mg BID
6–12 yr: 8.8–13.2 mg (5–7.5 mL) PO QHS to **max. dose:** 13.2 mg BID
Tabs:
2–5 yr: 4.3 mg PO QHS to **max. dose:** 8.6 mg BID
6–12 yr 8.6 mg PO QHS to **max. dose**: 17.2 mg BID
>12 yr and adult:
Granules: 15 mg PO QHS to **max. dose**: 30 mg BID
Syrup: 17.6–26.4 mg (10–15 mL) PO QHS to **max. dose:** 26.4 mg BID
Tabs: 17.2 mg PO QHS to **max. dose**: 34.4 mg BID

Effects occur within 6 to 24 hr after oral administration. Prolonged use (>1 wk) should be **avoided** as it may lead to dependency. May cause nausea, vomiting, diarrhea, and abdominal cramps. Active metabolite stimulates the Auerbach plexus. Syrup may be adminstered with juice, milk, or mixed with ice cream.

SERTRALINE HCL
Zoloft and generics
Antidepressant (selective serotonin reuptake inhibitor)

Tabs: 25, 50, 100 mg
Oral concentrate solution: 20 mg/mL (60 mL); may contain 12% alcohol and propylene glycol

For explanation of icons, see p. 667

SERTRALINE HCL *continued*

Depression (see remarks):

Child ≥6–12 yr (data limited in this age group): Start at 12.5–25 mg PO once daily. May increase dosage by 25 mg at weekly intervals up to a **max. dose** of 200 mg/24 hr.

Child ≥13 yr and adult: Start at 25–50 mg PO once daily. May increase dosage by 50 mg at weekly intervals up to a **max. dose** of 200 mg/24 hr.

Obesessive compulsive disorder (see remarks):

Child ≥6–12 yr: Start at 25 mg PO once daily. May increase dosage by 25 mg at 3- to 4-day intervals or by 50 mg at 7-day intervals up to a **max. dose** of 200 mg/24 hr.

Child ≥13 yr and adult: Start at 50 mg PO once daily. May increase dosage by 50 mg at weekly intervals up to **max. dose** of 200 mg/24 hr.

Drug is **contraindicated** in combination (or within 14 days of discontinuing use) with a monoamine oxidase (MAO) inhibitor (e.g., linezolid or intravenous methylene blue) or pimozide (increases adverse/toxic effects of pimozide). **Use with caution** in patients with abnormal bleeding, syndrome of inappropriate diuretic hormone (SIADH) secretion, and hepatic or renal impairment. Adverse effects include nausea, diarrhea, tremor, and increased sweating. Hyponatremia, diabetes mellitus, rhabdomyolysis, trismus, and platelet dysfunction have been reported. A positive correlation with length of QTc interval and serum sertraline and N-desmethylsertraline levels has been reported.

Monitor for clinical worsening of depression and suicidal ideation/behavior following the initiation of therapy or after dose changes. Use during the late third trimester of pregnancy may increase risk for withdrawal symptoms and persistent pulmonary hypertension in the newborn.

Use with drugs that interfere with hemostasis (e.g., NSAIDs, aspirin, warfarin) may increase risk for GI bleeds. Use with warfarin may increase PT. Inhibits the CYP 450 2D6 drug metabolizing enzyme. Serotonin syndrome may occur when taken with selective serotonin reuptake inhibitors (e.g., amitriptyline, amphetamines, buspirone, dihydroergotamine, sumatriptan, sympathomimetics).

Sertraline is a substrate for CYP 450 2B6, 2C9, 2C19, 2D6, and 3A4. Poor metabolizers of CYP 450 2C19 should initiate therapy at 50% of the recommended dosage and titrate to desired effect *or* consider using an alternative medication not predominantly metabolized by this enzyme. Ultrarapid 2C19 metabolizers should initiate therapy at the recommended starting dose and titrate to the recommended maintenance dosage *or* consider using a drug not predominantly metabolized by this enzyme.

Do not abruptly discontinue use; gradually taper dose (4–6 wk has been recommended) to reduce risk for withdrawal symptoms.

Mix oral concentrate solution with 4 oz of water, ginger ale, lemon/lime soda, lemonade, or orange juice. After mixing, a slight haze may appear; this is normal. This dosage form should be **used cautiously** in patients with latex allergy because the dropper contains dry natural rubber.

SILDENAFIL
Revatio, Viagra, and generics
Phosphodiesterase type-5 (PDE5) inhibitor

Tabs:
Revatio and generics: 20 mg
Viagra and generics: 25, 50, 100 mg
Oral suspension: 2.5 mg/mL
Revatio and generics: 10 mg/mL (112 mL); may contain sodium benzoate
Injection:
Revatio and generics: 0.8 mg/mL (12.5mL)

D

SILDENAFIL *continued*

Pulmonary hypertension:

Neonate (limited data from case reports and small clinical trials):

PO: Several dosages have been reported and have ranged from 0.5 to 3 mg/kg/dose Q 6–12 hr PO. A single dose of ~0.3 mg/kg PO has been used in select patients to facilitate weaning from inhaled nitric oxide.

IV (case report from 4 neonates >34 wk gestation and <72 hr old): Start with 0.4 mg/kg/dose IV over 3 hr followed by a continuous infusion of 1.6 mg/kg/24 hr (0.067 mg/kg/hr) for up to 7 days.

Infant and child (limited data):

PO: Start at 0.25 mg/kg/dose Q 6 hr or 0.5 mg/kg/dose Q 8 hr; if needed, titrate dose up to 1–2 mg/kg/dose Q 6–8 hr. A single dose of ~0.4mg/kg PO has been used in select patients to facilitate weaning from inhaled nitric oxide.

Child 1–17 yr (higher doses and long-term use are associated with increased risk for mortality; see remarks).

PO:

≥8–20 kg: 10 mg TID
>20–45 kg: 20 mg TID
>45 kg: 40 mg TID

Pulmonary arterial hypertension:

Adult:

PO: 20 mg TID (take at least 4–6 hr apart)
IV: 10 mg TID

Contraindicated with concurrent use of nitrates (e.g., nitroglycerin) and other nitric oxide donors; potentiates hypotensive effects. **Use with caution** in sepsis (high levels of cGMP may potentiate hypotension), hypotension, sickle cell anemia (use not established) and with concurrent CYP 450 3A4 inhibiting medications (see discussion that follows) and anti-hypertensive medications. Hepatic insufficiency or severe renal impairment (glomerular filtration rate [GFR] <30 mL/min) significantly reduces sildenafil clearance.

Findings from the dose-ranging study in 1- to 17-yr-olds with pulmonary arterial hypertension found an association of increased mortality risk with long-term use (>2 yr). Headache, pyrexia, upper respiratory tract infections (URTIs), vomiting, and diarrhea were the most frequently reported side effect in this study. Optimal dosing based on age and body weight still needs to be determined. Hazard ratios for mortality were 3.95 (95% CI: 1.46–10.65) for high versus low doses and 1.92 (95% CI: 0.65–5.65) for medium versus low doses in follow-up study for those receiving therapy for ≥3 yr. A subsequent extension open-label study on the same population for an additional 16 weeks reported a greater hazard ratio for mortality with high- versus low-dose therapy ($P = 0.007$).

In adults, a transient impairment of color discrimination may occur; this effect could increase risk of severe retinopathy of prematurity in neonates. Common side effects reported in adults have included flushing, rash, diarrhea, indigestion, headache, abnormal vision, and nasal congestion. Hearing loss has been reported.

Sildenafil is substrate for CYP 450 3A4 (major) and 2C8/9 (minor). Azole antifungals, cimetidine, ciprofloxacin, clarithromycin, erythromycin, nicardipine, propofol, protease inhibitors, quinidine, verapamil, and grapefruit juice may increase the effects/toxicity of sildenafil. Bosentin, efavirenz, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort, and high-fat meals may decrease sildenafil effects.

For explanation of icons, see p. 667

SILVER SULFADIAZINE
Silvadene, Thermazene, SSD Cream, and generics
Topical antibiotic

Cream: 1% (20, 25, 50, 85, 400, 1000 g); contains methylparabens and propylene glycol

Child (≥2 mo) and adult: Cover affected areas completely once or twice daily. Apply cream to a thickness of 1/16 inch using sterile technique.

Contraindicated in premature infants and infants up to 2 mo of age due to concerns of kernicterus; also contraindicated in pregnancy (approaching term). **Use with caution** in G6PD and renal and hepatic impairment. Discard product if cream has darkened. Significant systemic absorption may occur in severe burns. Adverse effects include pruritus, rash, bone marrow suppression, hemolytic anemia, hepatitis, interstitial nephritis, and life-threatening cutaneous reactions (e.g., Stevens-Johnson syndrome/toxic epidermal necrolysis [TEN] and exfoliative dermatitis). **Avoid** contact with the eye. Dressing may be used but is not necessary. See Chapter 4 for more information.

SIMETHICONE
Mylicon, Children's Mylicon, Phazyme, Mylanta Gas, Gas-X and generics
Antiflatulent

All dosage forms available OTC
Oral drops and suspension: 40 mg/0.6 mL (15, 30 mL); may contain sodium benzoate
Caps (Phazyme, Gas-X, and generics): 125, 180, 250 mg
Chewable tabs: 80, 125 mg
Children's Mylicon: 40 mg; contains 400 mg calcium carbonate
Strip, orally disintegrating (Gas-X): 40 mg (16s), 62.5 mg (18s); may contain alcohol

Infant and child <2 yr: 20 mg PO QID PRN; **max. dose:** 240 mg/24 hr
2–12 yr: 40 mg PO QID PRN
>12 yr and adult: 40–125 mg PO QPC and QHS PRN; **max. dose:** 500 mg/24 hr

Efficacy has not been demonstrated for treating infant colic. **Avoid** carbonated beverages and gas-forming foods. Oral liquid may be mixed with water, infant formula, or other suitable liquids for ease of oral administration.

SIROLIMUS
Rapamune and generics
Immunosuppressant agent

Tabs: 0.5, 1, 2 mg
Oral solution: 1 mg/mL (60 mL); contains 1.5%–2.5% ethanol

Child ≥13 yr (see remarks):
<40 kg: 3 mg/m^2/dose PO given once immediately after transplantation, followed by 1 mg/m^2/24 hr PO ÷ Q 12–24 hr on the next day. Adjust dose to achieve desired trough blood levels.
≥40 kg: use adult (low/moderate immunologic risk) ≥40 kg dosage below.

SIROLIMUS *continued*

Adult (see remarks):

Patients at low/moderate immunologic risk:

In combination with cyclosporine (adjust dose to achieve desired trough blood levels):

<40 kg: 3 mg/m^2/dose PO given once immediately after transplantation followed by 1 mg/m^2/dose PO once on the next day

≥40 kg: 6 mg PO once immediately after transplantation, followed by 2 mg PO once on the next day

Patients at high immunologic risk:

In combination with cyclosporine (withdrawal of cyclosporine is not recommended): 15 mg PO once immediately after transplantation, followed by 5 mg PO once on the next day. Adjust dose to achieve desired trough blood levels.

Increased susceptibility to infection and development of lymphoma may result from immunosuppression. **Fatal** bronchial anastomotic dehiscence has been reported in lung transplantation. Excess mortality, graft loss, and hepatic artery thrombosis have been reported in liver transplantation when used with tacrolimus. Patients with the greatest amount of urinary protein excretion prior to sirolimus conversion were those whose protein excretion increased the most after conversion. Increase risk of BK virus associated nephropathies have been reported. The following adverse effects have been reported when converting from a calcineurin inhibitor-based regimen to maintenance sirolimus:
Stable liver transplant: increased mortality
Kidney transplant: pneumonia, proteinuria, acute rejection, graft loss and death.

Monitor whole-blood trough levels (just prior to a dose at steady state); especially with pediatric patients; hepatic impairment; concurrent use of CYP 450 3A4 and/or P-gp inducers and inhibitors; and/or if cyclosporine dosage is markedly changed or discontinued. Steady-state is generally achieved after 5 to 7 days of continuous dosing. **Interpretation will vary based on specific treatment protocol and assay methodology (HPLC vs immunoassay vs LC/MS/MS). Younger children may exhibit faster sirolimus clearance compared with adolescents.**

Sirolimus is a substrate for CYP 450 3A4 and P-gp. Cyclosporine, diltiazem, protease inhibitors, erythromycin, grapefruit juice and other inhibitors of CYP 3A4 may increase the toxicity of sirolimus. Phenobarbital, carbamazepine, phenytoin, and St John's wort may decrease the effects of sirolimus. Strong inhibitors (e.g., azole antifungals and clarithromycin) and strong inducers (e.g., rifamycins) are **not recommended.**

Hypertension, peripheral edema, increase serum creatinine, dyspnea, epistaxis, headache, anemia, thrombocytopenia, hyperlipidemia, hypercholesterolemia, and arthralgia may occur. Progressive multifocal leukoencephalopathy (PML), diabetes mellitus, posterior reversible encephalopathy syndrome, ovarian cysts and menstrual disorders have been reported. Urinary tract infections have been reported in pediatric renal transplant patients with high immunologic risk.

Two milligrams of the oral solution have been demonstrated to be clinically equivalent to the 2-mg tablets. However, it is not known whether they are still therapeutically equivalent at higher doses. Reduce maintenance dosage by one-third in the presence of hepatic function impairment. Administer doses consistently with or without food. When administered with cyclosporine, give dose 4 hr after cyclosporine. **Do not** crush or split tablets. Measure the oral liquid dosage form with an amber oral syringe and dilute in a cup with 60 mL of water or orange juice only. Take dose immediately after mixing, add/mix additional 120 mL diluent into the cup, and drink immediately after mixing.

For explanation of icons, see p. 667

SODIUM BICARBONATE
Neut and generics
Alkalinizing agent, electrolyte

Injection: 4% (Neut) (0.48 mEq/mL) (5 mL), 4.2% (0.5 mEq/mL) (5, 10 mL), 7.5% (0.89 mEq/mL) (50 mL), 8.4% (1 mEq/mL) (10, 50 mL)
Tabs: 325 mg (3.8 mEq), 650 mg (7.6 mEq)
Powder: 1, 120, 500 g; contains 30 mEq Na^+ per 1/2 teaspoon
Each 1 mEq bicarbonate provides 1 mEq Na^+.

Cardiac arrest: See inside front cover.
Correction of metabolic acidosis: Calculate patient's dose with the following formulas.
Neonate, infant and child:
HCO_3^- (mEq) = 0.3× weight (kg) × base deficit (mEq/L), **OR**
HCO_3^- (mEq) = 0.5× weight (kg) × [24 – serum HCO_3^- (mEq/L)]
Adult:
HCO_3^- (mEq) = 0.2× weight (kg) × base deficit (mEq/L), **OR**
HCO_3^- (mEq) = 0.5× weight (kg) × [24 – serum HCO_3^- (mEq/L)]
Urinary alkalinization (titrate dose accordingly to urine pH):
Child: 84–840 mg (1–10 mEq)/kg/24 hr PO ÷ QID
Adult: 4 g (48 mEq) × 1 followed by 1–2 g (12–24 mEq) PO Q4 hr. Doses up to 16 g (192 mEq)/24 hr have been used.

Contraindicated in respiratory alkalosis, hypochloremia, and inadequate ventilation during cardiac arrest. **Use with caution** in congestive heart failure (CHF), renal impairment, cirrhosis, hypocalcemia, hypertension, and concurrent corticosteroids. Maintain high urine output. Monitor acid-base balance and serum electrolytes. May cause hypernatremia (contains sodium), hypokalemia, hypomagnesemia, hypocalcemia, hyperreflexia, edema, and tissue necrosis (extravasation). Oral route of administration may cause GI discomfort and gastric rupture from gas production.
For direct intravenous administration (cardiac arrest) in neonates and infants, use the 0.5 mEq/mL (4.2 %) concentration or dilute the 1 mEq/mL (8.4 %) concentration 1:1 with sterile water for injection and infuse at a rate **no greater than** 10 mEq/min. The 1 mEq/mL (8.4 %) concentration may be used in children and adults for direct intravenous administration.
For intravenous infusions (for all ages), dilute to a **max. concentration** of 0.5 mEq/mL in dextrose or sterile water for injection and infuse over 2 hr using a **max. rate** of 1 mEq/kg per hr.
Sodium bicarbonate should not be mixed with or be in contact with calcium, norepinephrine or dobutamine.

SODIUM CHLORIDE—INHALED PREPARATIONS
Hypersal, Nebusal, PulmoSal, Simply Saline, Ocean, Ayr Saline, Ayr Nasal Mist Allergy/Sinus, Rhinaris, many other brands, and generics
Electrolyte, inhalation

Nebulized solution (generics): 0.9% (3, 5, 15 mL), 3% (4, 15 mL), 7% (4 mL), 10% (4, 15 mL)
Hypersal (preservative-free): 3.5% (4 mL), 7% (4 mL)
Nebusal: 3% (4 mL), 6% (4 mL)
PulmoSal: 7% (4 mL)
Nasal solution spray/drops/mist (OTC): 0.2% (30 mL), 0.65% (15, 30, 45 mL), 0.9% (45, 90 mL), 2.65% (50 mL), 3% (100 mL); may contain benzalkonium chloride

SODIUM CHLORIDE—INHALED PREPARATIONS *continued*

Intranasal as moisturizer:

Child and adult:

Spray/Mist: 2–6 sprays into each nostril Q 2 hr PRN

Drops: 2–6 drops into each nostril Q 2 hr PRN

Cystic Fibrosis (Pre-treatment with albuterol is recommended to prevent bronchospasms; see remarks):

≥6 yr and adult: Nebulize 4 mL of 7% solution once or twice daily. If patient is unable to tolerate the 7% strength, lower strengths of 3%, 3.5% or 5% may be used.

Acute viral bronchiolitis (for hospitalized patients only; pretreatment with albuterol is recommended to prevent bronchospasms; see remarks):

Infant (>34 weeks' gestation up to 18 mo old): Nebulize 4 mL of 3% solution Q 2 hr for three doses followed by Q 4 hr for five doses followed by Q-6-hr dosing until discharge.

INTRANASAL USE: May be used as a nasal wash for sinuses, to restore moisture, to thin nasal secretions, or to relieve dry, crusted, and inflamed nasal membranes from colds, low humidity, allergies, nasal decongestant overuse, minor nose bleeds, and other irritations.

Nasal administration instructions:

Nasal drops: tilt head back and hold bottle upside down.

Nasal spray: hold head in upright position and give short, firm squeezes into each nostril. Sniff deeply.

NEBULIZATION: Hypertonic solutions lowers sputum viscosity and enhances mucociliary clearance.

Cystic Fibrosis: Improves FEV_1 and reduces pulmonary exacerbation frequency. May cause bronchospasm, cough, pharyngitis, hemoptysis, and acute decline in pulmonary function (administer first dose in a medical facility). It is recommended to withhold therapy in the presence of massive hemoptysis.

Acute viral bronchiolitis: Reduces length of hospitalization when compared to normal saline. May cause acute bronchospasm and local irritation.

SODIUM PHENYLACETATE AND SODIUM BENZOATE

Ammonul and generics

Ammonium detoxicant, Urea Cycle Disorder Treatment Agent

C ? Yes Yes Yes

Injection: 100 mg sodium phenylacetate and 100 mg sodium benzoate per 1 mL (50 mL)

IV via central line (administered with IV arginine, continue infusion until ammonia levels are in the normal range): See Chapter 13 for dosing information.

Indicated for hyperammonemia due to enzyme deficiencies of the urea cycle (e.g., carbamoyl phosphate synthetase [CPS] and ornithine transcarbamylase deficiency). **Use with caution** in renal and hepatic impairment. Significant amounts of sodium may be administered with prolonged durations of therapy. Ammonia clearance is most efficient with hemodialysis.

Side effects include hypotension, hypokalemia, hyperglycemia, injection site reaction, nausea/vomiting, altered mental status, fever, metabolic acidosis, cerebral edema, seizures, anemia, and disseminated intravascular coagulation. CNS side effects are more frequent with ornithine transcarbamylase (OTC) and CPS. Blood and lymphatic system disorders and hypotension are common in patients 30 days old or younger, whereas nausea, vomiting, and diarrhea are common in patients more than 30 days old.

Although no formal drug interaction studies have been completed, penicillin antibiotics and probenecid may increase serum concentrations of sodium phenylacetate and sodium benzoate by competing for renal tubular secretion. Use of valproic acid or corticosteroids may increase plasma ammonia levels.

Must be diluted and administered IV via central line; peripheral line administration may result in burning.

For explanation of icons, see p. 667

SODIUM PHOSPHATE
Fleet Enema, Fleet Pedia-Lax, Fleet Enema Extra, Fleet Phospho-Soda, OsmoPrep, and generics
Laxative, enema/oral

Enema [OTC]:
7 g dibasic sodium phosphate and 19 g monobasic sodium phosphate/118 mL; contains 4.4 g sodium per 118 mL
Pediatric size (Fleet Pedia-Lax): 66 mL
Adult size (Fleet Enema and generics): 133 mL
7 g dibasic sodium phosphate and 19 g monobasic sodium phosphate/197 mL; contains 4.4 g sodium per 197 mL
Fleet Enema Extra: 230 mL
Oral solution (Fleet Phospho-Soda and generics) [OTC]: 2.4 g monobasic sodium phosphate and 0.9 g dibasic sodium phosphate/5 mL (45 mL); contains 96.4 mEq Na per 20 mL and 62.25 mEq phosphate/5 mL
Oral tablets (OsmoPrep): 1.5 g (1.102 g monobasic sodium and 0.398 g per tablet)
Injection: see Phosphorus Supplements

Not to be used for phosphorus supplementation (see Phosphorus Supplements).
Enema (see remarks):
2–4 yr: 33 mL enema (half of Fleet Pedia-Lax) ×1
5–11 yr: 66 mL enema (Fleet Pedia-Lax) ×1
≥12 yr and adult: 133 mL enema (Fleet Enema or generics) **OR** 230 mL enema (Fleet enema Extra) ×1
Oral laxative (Fleet Phospho-Soda or generic); mix with a full glass of water:
5–9 yr: 7.5 mL PO ×1
10–11 yr: 15 mL PO ×1
≥12 yr and adult: 15–45 mL PO ×1
Bowel prep prior to colonoscopy:
Adult (PO):
Evening prior to colonoscopy: 4 tabs (OsmoPrep) with 8 ounces of clear liquids Q 15 min up to a total of 5 doses (20 tabs with 40 oz of clear liquids)
Day of colonoscopy, 3 to 5 hr prior to procedure: 4 tabs (OsmoPrep) with 8 oz of clear liquids Q 15 min up to a total of three doses (12 tabs with 24 oz of clear liquids)

Contraindicated in patients with severe renal failure, megacolon, bowel obstruction, and CHF. May cause hyperphosphatemia, hypernatremia, hypocalcemia, hypotension, dehydration, and acidosis. **Avoid** retention of enema solution and **do not exceed** recommended doses, as this may lead to severe electrolyte disturbances due to enhanced systemic absorption. **Use with caution** in cardiac arrhythmias. Colonic mucosal aphthous ulceration should be considered when interpreting colonoscopy findings with use in patients with known or suspected irritable bowel disease (IBD). A rare but serious form of kidney failure (acute phosphate nephropathy) has been reported with the use of bowel cleansing preparations such as Fleet Phospho-Soda.
Correct electrolyte abnormalities prior to use to minimize electrolyte side effects.
Onset of action: PO, 3–6 hr; PR, 2–5 min.

SODIUM POLYSTYRENE SULFONATE
SPS, Kionex, and generics; previously available as Kayexalate
Potassium-removing resin

Powder: 454 g
Oral suspension: 15 g/60 mL (60, 120, 500 mL); contains 21.5 mL sorbitol per 60 mL and 0.1%–0.3% alcohol
Rectal suspension: 30 g/120 mL (120 mL), 50 g/200 mL (200 mL)
Contains 4.1 mEq Na^+/g drug.

Note: Suspension may be given PO or PR. Practical exchange ratio is 1 mEq K per 1 g resin. May calculate dose according to desired exchange (see remarks).

Infant and child:
PO: 1 g/kg per dose (**max. dose**: 15 g per dose) Q 6 hr
PR: 1 g/kg per dose Q 2–6 hr; **max. dose**: 30–50 g per dose. Dosing by practical exchange (1 mEq K per 1 g resin) has been recommended for infants and smaller children.

Adult:
PO: 15 g once daily-QID
PR: 30–50 g Q 6 hr

Contraindicated in obstructive bowel disease, neonates with reduced gut motility, and oral administration in neonates. **Use cautiously** in presence of renal failure, CHF, hypertension or severe edema. May cause hypokalemia, hypernatremia, hypomagnesemia, and hypocalcemia. Cases of colonic necrosis, GI bleeding, ischemic colitis, and perforation have been reported with the concomitant use of sorbitol in patients with GI risk factors (prematurity, history of intestinal disease or surgery hypovolemia, and renal insufficiency/failure). Use in neonates generally **not recommended** due to complication concerns for hypernatremia and NEC.

1 mEq Na delivered for each mEq K removed. **Do not administer** with antacids or laxatives containing Mg^{2+} or Al^{3+}. Systemic alkalosis may result. May reduce absorption of other orally administered medication; administer other oral medications at least 3 hr before or 3 hr after sodium polystyrene sulfonate (patients with gastroparesis may require a 6-hr separation). Enema should be retained in the colon for at least 30–60 min.

SPIRONOLACTONE
Aldactone, CaroSpir, and generics
Diuretic, potassium sparing

Tabs: 25, 50, 100 mg
Oral suspension: 1, 5, 25 mg/mL
CaroSpir: 25 mg/5 mL (118, 473 mL); contains saccharin

Diuretic:
Neonate: 1–3 mg/kg/24 hr ÷ once or twice daily PO
Child: 1–3 mg/kg/24 hr ÷ BID–QID PO; **max. dose by indication**:
Hypertension: the lesser of 3.3 mg/kg/24 hr or 100 mg/24 hr
Edema: the lesser of 4–6 mg/kg/24 hr or 400 mg/24 hr
Adult: 25–200 mg/24 hr ÷ once daily–BID PO (see remarks); **max. dose**: 200 mg/24 hr

Diagnosis of primary aldosteronism:
Child: 125–375 mg/m^2/24 hr ÷ once or twice daily PO
Adult: 400 mg once daily PO × 4 days (short test) or 3–4 wk (long test), then 100–400 mg once or twice daily maintenance.

For explanation of icons, see p. 667

SPIRONOLACTONE *continued*

Hirsutism in women:

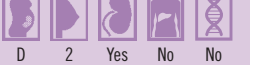
Adult: 50–200 mg/24 hr ÷ once or twice daily PO

Contraindicated in Addison disease, hyperkalemia, use with eplerenone, or severe renal failure (see Chapter 31). Use with caution in dehydration, hyponatremia, and renal or hepatic dysfunction. Precipitation of impaired neurologic function, worsening hepatic encephalopathy, and coma may occur with hepatic disease with cirrhosis and ascites. May cause hyperkalemia (especially with severe heart failure), GI distress, rash, lethargy, dizziness, and gynecomastia. May potentiate ganglionic blocking agents and other antihypertensives. Monitor potassium levels and be aware of other K+ sources, K+-sparing diuretics and angiotensin-converting enzyme inhibitors [ACEIs] (all of which can increase K+).

Do not use with other medications known to cause hyperkalemia (e.g., ACEIs, angiotensin II antagonists, aldosterone blockers, and other potassium-sparing diuretics). Hyperkalemic metabolic acidosis has been reported with concurrent cholestyramine use. May cause false elevation in serum digoxin levels measured by radioimmunoassay.

Although TID–QID regimens have been recommended, data suggest once- or twice-daily dosing to be adequate. Pregnancy category changes to D if used in pregnancy-induced hypertension.

STREPTOMYCIN SULFATE
Generics
Antibiotic, aminoglycoside; antituberculous agent



Powder for injection: 1 g

MDR tuberculosis: Use as part of multidrug regimen (see latest edition of *AAP Red Book*). IM route is preferred. Monitor levels.

Infant, child, and adolescent (<15 yr or ≤40 kg):

Daily therapy: 20–40 mg/kg/24 hr IM/IV once daily

Max. daily dose: 1 g/24 hr

Twice weekly therapy (under direct observation): 25–30 mg/kg/dose IM/IV twice weekly

Max. daily dose: 1 g/24 hr

Child, adolescent and adult (≥15 yr or >40 kg):

Daily therapy: 15 mg/kg/24 hr IM/IV once daily; **max. daily dose**: 1 g/24 hr

Twice weekly therapy (under direct observation): 15 mg/kg/dose IM/IV twice weekly; **max. daily dose**: 1 g/24 hr

Brucellosis, tularemia, plague and rat bite fever (See latest edition of the *Red Book*).

Contraindicated with aminoglycoside and sulfite hypersensitivity. **Use with caution** in preexisting vertigo, tinnitus, hearing loss and neuromuscular disorders. Drug is administered via deep IM injection **only.** Follow auditory status. May cause CNS depression, other neurologic problems, myocarditis, serum sickness, nephrotoxicity, and ototoxicity. Concomitant neurotoxic, ototoxic, or nephrotoxic drugs and dehydration may increase risk for toxicity.

Therapeutic levels: peak 15–40 mg/L; trough: <5 mg/L. Recommended serum sampling time at steady state: trough within 30 min prior to the third consecutive dose and peak at 30–60 min (60 min for IM) after the administration of the third consecutive dose. Therapeutic levels are not achieved in cerebrospinal fluid (CSF).

Adjust dose in renal failure (see Chapter 31).

SUCCIMER
Chemet, DMSA [dimercaptosuccinic acid]
Chelating agent

Cap: 100 mg

Lead chelation, child:
10 mg/kg/dose (or 350 mg/m²/dose) PO Q 8 hr ×5 days, then 10 mg/kg/dose (or 350 mg/m²/dose) PO Q 12 hr ×14 days. **Max. dose**: 500 mg per dose.
Manufacturer recommendation (see following table):

Weight (kg)	Dose (mg) Q 8 hr × 5 Days Followed by Same Dose Q 12 hr × 14 Days
8–15	100
16–23	200
24–34	300
35–44	400
≥45	500

Use caution in patients with compromised renal or hepatic function. Repeated courses may be necessary. Follow serum lead levels. Allow a minimum of 2 wk between courses unless blood levels require more aggressive management. Side effects: GI symptoms, increased negative liver function tests (LFTs) (10%), rash, headaches, and dizziness. Allergic reactions, such as urticaria and angioedema, and neutropenia have been reported. May cause false-positive urinary ketone readings with nitroprusside reagent tests such as Ketostix and can falsely lower measured serum uric acid and creatine phosphokinase (CPK). **Coadministration with other chelating agents is not recommended.**
Serum transaminases should be monitored at baseline and weekly during therapy. Treatment of iron deficiency is recommended as well as environmental remediation. Contents of capsule may be sprinkled on food for those who are unable to swallow a capsule.

SUCCINYLCHOLINE
Anectine, Quelicin
Neuromuscular blocking agent

Injection:
Anectine, Quelicin: 20 mg/mL (10 mL); contains parabens

Paralysis for intubation (see remarks):
Infant, child, and adolescent:
Initial:
IV:
Infant: 2–3 mg/kg/dose ×1
Child: 1–2 mg/kg/dose ×1
Adolescent: 1–1.5 mg/kg/dose ×1
IM:
Infant <6 mo: 4–5 mg/kg/dose ×1
Infant ≥6 mo and child: 4 mg/kg/dose ×1; **max. dose**: 150 mg per dose
Adolescent: 3–4 mg/kg/dose ×1; **max. dose**: 150 mg per dose

Continued

For explanation of icons, see p. 667

SUCCINYLCHOLINE *continued*

Paralysis for intubation (see remarks, cont.):

Adult:

Initial:

IV: 0.3–1.1 mg/kg/dose ×1

IM: 3–4 mg/kg/dose ×1; **max. dose:** 150 mg/dose

Maintenance for long surgical procedures: 0.04–0.07 mg/kg/dose IV Q 5–10 min PRN. Continuous infusion not recommended.

Contraindicated after the acute phase of an injury following major burns, multiple trauma, extensive denervation of skeletal muscle, or upper motor neuron injury because severe hyperkalemia and subsequent **cardiac arrest** may occur. Individuals carrying the *RYR1* or *CACNA1S* gene have an increased risk for developing malignant hyperthermia with succinylcholine or halogenated volatile anesthetics; use in these individuals is **contraindicated**. Succinylcholine should be **avoided** in patients who are susceptible to malignant hyperthermia.

Pretreatment with atropine is recommended to reduce incidence of bradycardia. For rapid sequence intubation, see Chapter 1.

Cardiac arrest has been reported in children and adolescents primarily with skeletal muscle myopathies (e.g., Duchenne muscular dystrophy). Identify developmental delays suggestive of a myopathy prior to use. Predose creatine kinase may be useful for identifying patients at risk. Monitoring of the electrocardiogram (ECG) for peaked T waves may be useful in detecting early signs of this adverse effect.

May cause malignant hyperthermia (use dantrolene to treat), bradycardia, hypotension, arrhythmia, and hyperkalemia. Severe anaphylactic reactions have been reported; **use caution** if previous anaphylactic reaction to other neuromuscular blocking agents. **Use with caution** in patients with severe burns, paraplegia, or crush injuries and in patients with preexisting hyperkalemia. Beware of prolonged depression in patients with liver disease, malnutrition, pseudocholinesterase deficiency, hypothermia and those receiving aminoglycosides, phenothiazines, quinidine, β blockers, amphotericin B, cyclophosphamide, diuretics, lithium, acetylcholine, and anticholinesterases. Diazepam may decrease neuromuscular blocking effects. Prior use of succinylcholine may enhance the neuromuscular blocking effect of vecuronium and its duration of action.

Duration of action 4–6 min IV, 10–30 min IM. Must be prepared to intubate within 1 min.

SUCRALFATE

Carafate and generics

Oral antiulcer agent

Tabs: 1 g

Oral suspension: 100 mg/mL (420 mL); contains sorbitol and parabens

Child:

Duodenal or gastric ulcer: 40–80 mg/kg/24 hr ÷ Q6 hr PO; **max. dose**: 1000 mg/dose

Stomatitis: 5–10 mL (500–1000 mg of suspension), swish and spit or swish and swallow QID

Adult:

Duodenal ulcer:

Treatment: 1 g PO QID (1 hr before meals and QHS) or 2 g PO BID ×4–8 wk

Maintenance/prophylaxis: 1 g PO BID

Stress ulcer:

Prophylaxis: 1 g PO QID

Stomatitis: 10 mL (1000 mg of suspension), swish and spit or swish and swallow QID

Proctitis (use oral suspension as rectal enema): 20 mL (2 g) PR once or twice daily

SUCRALFATE *continued*

May cause vertigo, constipation, and dry mouth. Hypersensitivity, including anaphylactic reactions, and hyperglycemia in diabetic patients have been reported. Aluminum may accumulate in patients with renal failure. This may be augmented by the use of aluminum-containing antacids. **Use with caution** in patients with dysphagia or other conditions that may alter gag or cough reflexes or diminish oropharyngeal coordination/motility who are receiving the oral tablet dosage form; cases of tablet aspiration with respiratory complications have been reported.

Decreases absorption of phenytoin, digoxin, theophylline, cimetidine, fat-soluble vitamins, ketoconazole, omeprazole, quinolones, and oral anticoagulants. Administer these drugs at least 2 hr before or after sucralfate doses.

Drug requires an acidic environment to form a protective polymer coating for damaged GI tract mucosa. Administer oral doses on an empty stomach (1 hr before meals and QHS).

SUGAMMADEX
Bridion
Neuromuscular blockade reversal agent

Injection: 100 mg/1 mL (2, 5 mL)

Infant, child, and adolescent (limited data):

Routine reversal of rocuronium-induced moderate blockade (see remarks):
2 mg/kg/dose IV once over 10 sec; some suggest administering over slow intravenous push to reduce risk for bradycardia or asystole.

Adult (use actual body weight):

Reversal rocuronium or vecuronium-induced neuromuscular blockade:

Deep block (spontaneous recovery of twitch response reaching 1 to 2 post-tetanic counts with no twitch responses to train-of-four stimulation): 4 mg/kg/dose IV ×1

Moderate block (spontaneous recovery of reappearance of the second twitch in response of train-of-four stimulation): 2 mg/kg/dose IV ×1

Reversal of neuromuscular blockade 3 min after rocuronium 1.2 mg/kg: 16 mg/kg/dose IV ×1. The recovery to T_1 of 10% baseline (relative to the time of administration of rocuronium or succinylcholine) was faster with rocuronium/sugammadex than with succinylcholine alone. This dose has not been evaluated for vecuronium-induced neuromuscular blockade.

Sugammadex is a modified gamma cyclodextrin that binds to rocuronium and vecuronium for reduced neuromuscular blockade.

Use is **not recommended** for GFR <30 mL/min or on dialysis. **Use with caution** in hepatic impairment, especially in the presence of coagulopathy or severe edema.

Common side effects include nausea, vomiting, and headache. Serious effects include bradycardia, prolonged QTc interval, hypersensitivity reactions/anaphylaxis, increase creatine kinase, and bronchospasms. Sugammadex may increase the effects/toxicity of anticoagulants, and decrease the effects of hormonal contraceptives. Fusidic acid and toremifene may decrease sugammadex activity.

Limited data in children (especially <2 yr) and dosing in a multicenter, randomized, parallel-group, dose-finding study in 63 children (28 days to 17 yr of age) and 28 adult surgical patients. Doses were well tolerated across all ages with dose-response relationship for those 2 yr of age or older. All had a median recovery time of 1.1 to 1.2 min after a 2 mg/kg dose (*Anesthesiology.* 2009;110:284–294).

For explanation of icons, see p. 667

SULFACETAMIDE SODIUM OPHTHALMIC
Bleph-10 and generics
Ophthalmic antibiotic, sulfonamide derivative

Ophthalmic solution (Bleph 10 and generics): 10% (5, 15 mL); may contain thimerosal or benzalkonium chloride
Ophthalmic ointment: 10% (3.5 g)

Conjunctivitis (usual duration of therapy for ophthalmic use is 7–10 days):
>2 mo and adult:
Ointment: Apply 0.5-in ribbon into conjunctival sac Q 3–4 hr and QHS initially, and reduce the dosing frequency with adequate response.
Drops: 1–2 drops to affected eye(s) Q 2–3 hr initially and reduce the dosing frequency with adequate response.

Hypersensitivity reactions between different sulfonamides can occur regardless of route of administration. May cause local irritation, stinging, burning, conjunctival hyperemia, excessive tear production, and eye pain. Rare toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported. Sulfacetamide preparations are incompatible with silver preparations.
To reduce risk of systemic absorption with ophthalmic solution, apply finger pressure to lacrimal sac during and 1–2 min after instillation.

SULFADIAZINE
Various generics
Antibiotic, sulfonamide derivative

Tabs: 500 mg
Oral suspension: 100, 200 mg/mL

Infant ≥2 mo, child and adolescent: 75 mg/kg/dose or 2000 mg/m²/dose PO ×1, followed by 150 mg/kg/24 hr or 4000 mg/m²/24 hr ÷ Q 4–6 hr (**max. dose**: 6000 mg/24 hr).
Adult: 2–4 g/dose ×1, followed by 2–4 g/24 hr PO ÷ Q 4–8 hr
Congenital toxoplasmosis (administer with pyrimethamine and folinic acid; see pyrimethamine for dosage information):
Infant: 100 mg/kg/24 hr PO ÷ BID × 12 mo
Acquired toxoplasmosis (administer with pyrimethamine and folinic acid; see Pyrimethamine for dosage information):
Infant ≥2 mo and child: 100–200 mg/kg/24 hr ÷ Q 6 hr PO for at least 4–6 wk; **max. dose**: 6000 mg/24 hr
Adult: 4–6 g/24 hr PO ÷ Q6 hr for at least 4–6 wk
Rheumatic fever prophylaxis:
≤27 kg: 500 mg PO once daily
>27 kg: 1000 mg PO once daily

Most cases of acquired toxoplasmosis do not require specific antimicrobial therapy. **Contraindicated** in porphyria and hypersensitivity to sulfonamides. **Use with caution** in premature infants and infants below 2 mo of age, because of risk of hyperbilirubinemia, and in hepatic or renal dysfunction (30%–44% eliminated in urine). Maintain hydration. May cause fever, rash, hepatitis, systemic lupus erythematosus (SLE)–like syndrome, vasculitis, bone marrow suppression, and hemolysis in patients with G6PD deficiency, and Stevens-Johnson syndrome.

SULFADIAZINE *continued*

May cause increased effects of warfarin, methotrexate, thiazide diuretics, uricosuric agents, and sulfonylureas due to drug displacement from protein binding sites. Large quantities of vitamin C or acidifying agents (e.g., cranberry juice) may cause crystalluria. Pregnancy category changes from C to D if administered near term. Administer on an empty stomach with plenty of water.

SULFAMETHOXAZOLE AND TRIMETHOPRIM

Trimethoprim-sulfamethoxazole, Co-Trimoxazole, TMP-SMX; Bactrim, Bactrin DS, Sulfatrim, and generics; previously available as Septra

Antibiotic, sulfonamide derivative

Tabs:

Reg. strength (Bactrim and generics): 80 mg TMP/400 mg SMX

Double strength (Bactrim DS and generics): 160 mg TMP/800 mg SMX

Oral suspension (Sulfatrim and generics): 40 mg TMP/200 mg SMX per 5 mL (100, 480 mL)

Injection: 16 mg TMP/mL and 80 mg SMX/mL (5, 10, 30 mL); some preparations may contain propylene glycol and benzyl alcohol

Doses based on TMP component.

Minor/moderate infections (PO or IV):

Child: 8–12 mg/kg/24 hr ÷ BID; **max. dose** 160 mg/dose

Adult (>40 kg): 160 mg/dose BID

Severe infections (PO or IV):

Child and adult: 20 mg/kg/24 hr ÷ Q6–8 hr

UTI prophylaxis:

Child: 2–4 mg/kg/24 hr PO once daily

Pneumocystis jiroveci (carinii) pneumonia (PCP):

Treatment (≥2 mo and adult, PO or IV): 15–20 mg/kg/24 hr ÷ Q 6–8 hr × 21 days

Prophylaxis (PO or IV):

≥1 mo and child: 150 mg/m^2/24 hr ÷ BID for 3 consecutive days per wk; **max. dose**: 320 mg/24 hr; see Chapter 17 for use criteria for perinatal HIV PCP prophylaxis.

Adolescent and adult: 80 or 160 mg once daily or 160 mg 3 days per wk.

Not recommended for use in infants below 2 mo of age (excluding PCP prophylaxis).

Contraindicated in patients with sulfonamide or trimethoprim hypersensitivity and megaloblastic anemia due to folate deficiency. May cause kernicterus in newborns; may cause blood dyscrasias, crystalluria, glossitis, renal or hepatic injury, GI irritation, rash, Stevens-Johnson syndrome, or hemolysis in patients with G6PD deficiency. Severe hyponatremia may occur during treatment of Pneumocystic jiroveci pneumonia. Hyperkalemia may appear in HIV/AIDS patients.

Use with caution in renal and hepatic impairment and in G6PD deficiency. QT prolongation resulting in ventricular tachycardia has been reported. Slow acetylators may be prone to idiosyncratic reactions to sulfonamides. Intravenous dosage form contains propylene glycol and benzyl alcohol, which may result in adverse toxic effects when used at igher dosages, especially in neonates. Use of an adjusted body weight ([ABW] ABW = ideal body weight + 0.4 × [total body weight − ideal body weight]) has been recommended for determining doses for obese patients.

Epidemiologic studies suggest that use during pregnancy may be associated with increase risk of congenital malformations (particularly neural tube defects), cardiovascular malformations, urinary tract defects, oral clefts, and club foot.

Sulfamethoxazole is a CYP 450 2C9 substrate and inhibitor. Trimethoprim is a CYP 450 2C9, 3A4 substrate and 2C8/9 inhibitor. **Reduce dose in renal impairment (see Chapter 31).**

D

For explanation of icons, see p. 667

SULFASALAZINE
Azulfidine, Azulfidine EN-tabs, Salicylazosulfapyridine, and generics
Anti-inflammatory agent

Tabs: 500 mg
Delayed-release tabs (Azulfidine EN-tabs and generics): 500 mg
Oral suspension: 100 mg/mL

Inflammatory bowel disease:
Child ≥6 yr:
Initial dosing:
Mild: 40–50 mg/kg/24 hr ÷ Q 6 hr PO
Moderate/severe: 50–75 mg/kg/24 hr ÷ Q 4–6 hr PO
Max. initial dose: 4 g/24 hr
Maintenance: 30–70 mg/kg/24 hr ÷ Q 4–8 hr PO; **max. dose**: 4 g/24 hr
Adult:
Initial: 3–4 g/24 hr ÷ Q 4–8 hr PO
Maintenance: 2 g/24 hr ÷ Q 6 hr PO
Max. dose: 6 g/24 hr
Juvenile idiopathic arthritis:
Child 6–16 yr: Start with 10 mg/kg/24 hr ÷ BID PO and increase by 10 mg/kg/24 hr Q7 days until planned maintenance dose is achieved. Usual maintenance dose is 30–50 mg/kg/24 hr ÷ BID PO up to a **max.** of 2 g/24 hr.

Contraindicated in sulfa or salicylate hypersensitivity, porphyria and GI or genitourinary (GU) obstruction. Discontinue use if a serious infection develops. **Use with caution** in renal impairment, blood dyscrasias, or asthma. Maintain hydration. May cause orange-yellow discoloration of urine and skin. May permanently stain contact lenses. May cause photosensitivity, hypersensitivity (which may result in hepatits and nephritis), blood dyscrasias, CNS changes, nausea, vomiting, anorexia, diarrhea and renal damage. Hepatotoxicity/hepatic failure, anaphylaxis, angioedema, severe drug rash with eosinophilia and systemic symptoms (DRESS), and interstitial lung disease have been reported. May cause hemolysis in patients with G6PD deficiency. Pseudomononucleosis, myocarditis, folate deficiency (decreases folic acid absorption), nephrolithiasis and oropharyngeal pain have been reported.
Reduces serum digoxin and cyclosporine levels. Slow acetylators may require lower dosage due to accumulation of active sulfapyridine metabolite. May cause false-positive test for urinary normetanephrine if using liquid chromatography methods.
Pregnancy category changes to D if drug is administered near term. Bloody stools or diarrhea have been reported in breastfed infants of mothers receiving sulfasalazine.

SUMATRIPTAN SUCCINATE
Imitrex, Imitrex STAT dose, Sumavel Dose Pro, Zembrace SymTouch, Tosymra, and generics
In combination with naproxen:
Treximet
Antimigraine agent, selective serotonin agonist

Injection, for subcutaneous use:
Zembrace SymTouch: 3 mg/0.5 mL (0.5 mL)
Imitrex, Imitrex STAT dose, Sumavel DosePro, and generics: 4 mg/0.5 mL (0.5 mL), 6 mg/0.5 mL (0.5 mL)

D

SUMATRIPTAN SUCCINATE *continued*

Tabs: 25, 50, 100 mg
Oral suspension: 5 mg/mL
Nasal spray (as a unit-dose spray device):
Imitrex and generics: 5 mg dose in 100 microliters (six units per pack); 20 mg dose in 100 microliters (six units per pack)
Tosymra: 10 mg dose in 100 microliters (six units per pack)
Nasal powder (Onzetra): 11 mg capsule with nasal inhalation nosepiece (two each per pouch; box of eight pouches)
In combination with naproxen:
Tab (Treximet and generics): 85 mg sumatriptan and 500 mg naproxen sodium (nine tabs)

Adolescent ≥18 yr and adult (see remarks):
PO: 25, 50, or 100 mg as soon as possible after onset of headache. If no relief in 2 hr, give 25–100 mg Q 2 hr up to a daily **max.** of 200 mg. Safety of treating more than four headaches in a 30-day period has not been established.
Max. single dose: 100 mg/dose.
Max. daily dose: 200 mg/24 hr (with exclusive PO dosing or with an initial SC dose and subsequent PO dosing).
SC: 3, 4, or 6 mg ×1 as soon as possible after onset of headache. If no response, may give an additional dose 1 hr later; **max. daily dose**: 12 mg/24 hr. Use lower subsequent dose if side effects occur.
Nasal (safety of treating more than four headaches in a 30-day period has not been established):
Nasal spray (Imitrex, Tosymra, and generics): 5, 10, or 20 mg per dose into one nostril or divided into each nostril after onset of headache. Dose may be repeated in 2 hr up to a **max.** of 40 mg/24 hr.
Nasal powder (Onzetra): Inhale 22 mg (11 mg per nostril) after onset of headache. Dose may be repeated in 2 hr up to a **max.** of 44 mg/24 hr. If using a combination of different dosage forms, the **max. dose** is one dose of Onzetra (22 mg) and one dose of another sumatriptan product.
In combination with naproxen sodium:
Treximet and generics:
Child 12–17 yr: 1 tablet (85 mg sumatriptan +500 mg naproxen sodium) after the onset of headache ×1; **max. dose:** 1 tab/24 hr. Safety of treating more than two headaches in a 30-day period has not been established.
Adult: 1 tablet (85 mg sumatriptan + 500 mg naproxen sodium) after the onset of headache ×1, if response is unsatisfactory in 2 hr, a second dose may be administered. **Max. dose:** 2 tabs/24 hr. Safety of treating more than five headaches in a 30-day period has not been established.

Contraindicated with concomitant administration of ergotamine derivatives, MAO inhibitors (and use within the past 2 wk), or other vasoconstrictive drugs. **Not** for migraine prophylaxis. **Use with caution** in renal or hepatic impairment. **A max. single** PO dose of 50 mg has been recommended in adults with hepatic dysfunction. Acts as selective agonist for serotonin receptor. Induration and swelling at the injection site; flushing; dizziness; as well as chest, jaw, and neck tightness may occur with SC administration. Weakness, hyperreflexia, incoordination, and serotonin syndrome (may be life-threatening) have been reported with use in combination with selective serotonin reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline).
May cause coronary vasospasm if administered intravenously. **Use injectable form SC only**! Onset of action is 10–120 min SC, 60–90 min PO, and 15–120 min intranasal.
PO and SC efficacy studies were not conclusive in clinical trials for children. Some do not recommend use in patients less than 18 yr of age owing to poor efficacy and reports of serious adverse events (e.g., stroke, visual loss, and death) in both children and adults with all dosage forms.
To minimize infant exposure to sumatriptan, **avoid** breastfeeding for 12 hr after treatment. See naproxen remarks if using the combination sumatriptan and naproxen dosage form.

For explanation of icons, see p. 667

SURFACTANT, PULMONARY/BERACTANT
Survanta
Bovine lung surfactant

Suspension for inhalation: 25 mg/mL phospholipids (4, 8 mL); contains 0.5–1.75 mg triglycerides, 1.4–3.5 mg free fatty acids and <1 mg protein per 1 mL drug

Prophylactic therapy: 4 mL/kg/dose intratracheally as soon as possible; up to four doses may be given at intervals no shorter than Q 6 hr during the first 48 hr of life.

Rescue therapy (treatment): 4 mL/kg/dose intratracheally immediately following the diagnosis of respiratory distress syndrome (RDS). May repeat dose as needed Q 6 hr to **max.** of four doses total.

Method of administration for previously listed therapies (see remarks): Suction infant prior to administration. Each dose is divided into four aliquots of 1 mL/kg each; administer 1 mL/kg in each of four different positions (slight downward inclination with head turned to the right, head turned to the left; slight upward inclination with the head turned to the right, head turned to the left).

Transient bradycardia, O_2 desaturation, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypercarbia, hypercapnea, apnea, and hypertension may occur during the administration process. Other side effects may include pulmonary interstitial emphysema, pulmonary air leak, and posttreatment nosocomial sepsis. Monitor heart rate and transcutaneous O_2 saturation during dose administration and arterial blood gases for postdose hyperoxia and hypocarbia after administration.

All doses are administered intratracheally via a 5-french feeding catheter. If the suspension settles during storage, gently swirl the contents; **do not shake.** Drug is stored in the refrigerator, protected from light, and must be warmed by standing at room temperature for at least 20 min or warmed in the hand for at least 8 min. Artificial warming methods should **NOT** be used.

SURFACTANT, PULMONARY/CALFACTANT
Infasurf
Bovine lung surfactant

Intratracheal suspension: 35 mg/mL phospholipids (3, 6 mL); contains 26 mg phosphatidylcholine, 0.7 mg protein, and 0.26 mg surfactant protein B per 1 mL

Prophylactic therapy: 3 mL/kg/dose intratracheally as soon as possible; up to a total of three doses may be given Q 12 hr.

Rescue therapy (treatment; see remarks): 3 mL/kg/dose intratracheally immediately after the diagnosis of RDS. May repeat dose as needed Q12 hr to **max.** of 3 doses total.

Method of administration for previously listed therapies (see remarks): Suction infant prior to administration. Manufacturer recommends administration through a side-port adapter into the endotracheal tube with two attendants (one to instill drug and another to monitor and position patient). Each dose is divided into two aliquots of 1.5-mL/kg each; administer 1.5 mL/kg in each of two different positions (infant positioned with either the right or left side dependent). Drug is administered while ventilation is continued over 20 to 30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of respiratory status and repositioning should separate the two aliquots. The drug has also been administered by divided dose into four equal aliquots and administered with repositioning in the prone, supine, right, and left lateral positions.

SURFACTANT, PULMONARY/CALFACTANT *continued*

Common adverse effects include cyanosis, airway obstruction, bradycardia, reflux of surfactant into the endotracheal (ET) tube, requirement for manual ventilation, and reintubation. Monitor O_2 saturation and lung compliance after each dose such that oxygen therapy and ventilator pressure are adjusted as necessary.

All doses administered intratracheally via a 5-french feeding catheter. If suspension settles during storage, gently swirl the contents; **do not shake.** Drug is stored in the refrigerator, protected from light, and does not need to be warmed before administration. Unopened vials that have been warmed to room temperature (once only) may be refrigerated within 24 hr and stored for future use.

For rescue therapy, repeat doses may be administered as early as 6 hr after the previous dose for a total of up to four doses if the infant is still intubated and requires at least 30% inspired oxygen to maintain a $PaO_2 \geq 80$ torr.

SURFACTANT, PULMONARY/PORACTANT ALFA
Curosurf
Porcine lung surfactant

Intratracheal suspension: 80 mg/mL (1.5, 3 mL): contains 76 mg phospholipids, 1 mg protein (0.45 mg surfactant protein B, and 0.59 mg surfactant protein C) per 1 mL drug

Rescue therapy (treatment): 2.5 mL/kg/dose × 1 intratracheally, immediately following the diagnosis of RDS. May administer 1.25 mL/kg/dose Q 12 hr × 2 doses as needed up to a **max. total dose** of 5 mL/kg.

Method of administration (see remarks): Suction infant prior to administration. Each dose is divided into two aliquots, with each aliquot administered into one of the two main bronchi by positioning the infant with either the right or left side dependent. After the first aliquot is administered, remove the catheter from the ET tube and manually ventilate the infant with 100% oxygen at a rate of 40–60 breaths/min for 1 min. When the infant is stable, reposition the infant and administer the second dose with the same procedures. Then remove the catheter without flushing.

Currently approved by the US Food and Drug Administration (FDA) for the treatment (rescue therapy) of RDS. Transient episodes of bradycardia, decreased oxygen saturation, reflux of surfactant into the ET tube, and airway obstruction have occurred during dose administration. Monitor O_2 saturation and lung compliance after each dose and adjust oxygen therapy and ventilator pressure as necessary. Pulmonary hemorrhage has been reported.

All doses administered intratracheally via a 5-french feeding catheter. Suction infant prior to administration and 1 hr after surfactant instillation (unless signs of significant airway obstruction).

Drug is stored in the refrigerator and protected from light. Each vial of drug should be slowly warmed to room temperature and gently turned upside down for uniform suspension (**do not shake**) before administration. Unopened vials that have been warmed to room temperature (once only) may be refrigerated within 24 hr and stored for future use.

SYMDEKO

See Tezacaftor and Ivacaftor

For explanation of icons, see p. 667

T

TACROLIMUS

Prograf, Astagraf XL, Envarsus XR, Protopic, FK506, and generics

Immunosuppressant

Caps (Prograf and generics): 0.5, 1, 5 mg
Extended release caps (Astagraf XL): 0.5, 1, 5 mg (Q24 hr dosing; see remarks)
Extended release tabs (Envarsus XR): 0.75, 1, 4 mg (Q24 hr dosing; see remarks)
Oral suspension: 0.5, 1 mg/mL
Injection (Prograf): 5 mg/mL (1 mL); contains alcohol and polyoxyl 60 hydrogenated castor oil (cremophor)
Topical ointment (Protopic and generics): 0.03%, 0.1% (30, 60, 100 g)

SYSTEMIC USE:

Infant, child, and adolescent (initial immediate release doses; titrate to therapeutic levels and convert IV to PO as soon as possible; see remarks):
Liver transplantation:
IV: 0.03–0.05 mg/kg/24 hr by continuous infusion
PO: 0.15–0.2 mg/kg/24 hr ÷ Q12 hr
Renal transplantation:
IV: 0.06 mg/kg/24 hr by continuous infusion
PO: 0.2–0.3 mg/kg/24 hr ÷ Q12 hr
Astagraf XL (in combination with other immunosuppressants): *0.3 mg/kg/24 hr PO Q24 hr, initiated within 24 hr following reperfusion.*
Cardiac transplantation:
IV: 0.01–0.03 mg/kg/24 hr by continuous infusion
PO: 0.1–0.3 mg/kg/24 hr ÷ Q12 hr
Adult (initial immediate release doses; titrate to therapeutic levels):
IV: 0.01–0.05 mg/kg/24 hr by continuous infusion
PO: 0.075–0.2 mg/kg/24 hr ÷ Q12 hr
Liver transplantation: 0.1–0.15 mg/kg/24 hr PO ÷ Q12 hr
Kidney transplantation: 0.1–0.2 mg/kg/24 hr PO ÷ Q12 hr
Cardiac transplantation: 0.075 mg/kg/24 hr PO ÷ Q12 hr

TOPICAL USE:

Atopic dermatitis (continue treatment for 1 wk after clearing of signs and symptoms; see remarks):
Child ≥2 to 15 yr old: Apply a thin layer of the 0.03% ointment to the affected skin areas BID and rub in gently and completely.
Adolescent ≥16 yr and adult: Apply a thin layer of the 0.03% or 0.1% ointment to the affected skin areas BID and rub in gently and completely.

Avoid use in patients with prolonged cardiac QT intervals. IV dosage form **contraindicated** in patients allergic to polyoxyl 60 hydrogenated castor oil (cremophor). Experience in pediatric kidney transplantation is limited. Pediatric patients may require higher mg/kg doses than adults. For BMT use (beginning 1 day before BMT), dose and therapeutic levels similar to those in liver transplantation have been used.

Major adverse events include tremor, headache, insomnia, diarrhea, constipation, hypertension, nausea, and renal dysfunction. Hypokalemia, hypomagnesemia, hyperglycemia, confusion, depression, infections, lymphoma, liver enzyme elevation, optic neuropathy, and coagulation disorders may also occur. GI perforation, agranulocytosis, and hemolytic anemia have been reported.

D

TACROLIMUS *continued*

Tacrolimus is a substrate of the CYP 450 3A4 drug metabolizing enzyme and Pgp transporter. A 1.5–2-fold higher initial standard dose up to a max. dose of 0.3 mg/kg/24 hr has been recommended for intermediate or extensive metabolizers for CYP 450 3A5. Calcium channel blockers, imidazole antifungals (ketoconazole, itraconazole, fluconazole, clotrimazole, posaconazole), macrolide antibiotics (erythromycin, clarithromycin, troleandomycin), cisapride, cimetidine, cyclosporine, danazol, herbal products containing schisandra sphenanthera extracts, methylprednisolone, grapefruit juice, seville oranges, and severe diarrhea can increase tacrolimus serum levels. In contrast, carbamazepine, caspofungin, phenobarbital, phenytoin, rifampin, rifabutin, and sirolimus may decrease levels. Use with sirolimus may increase risk for hepatic artery thrombosis. **Avoid use** of live attenuated vaccines. Use with other CYP 450 3A inhibitors and substrates has the potential to prolong the cardiac QT interval. Reduce dose in renal or hepatic insufficiency.

Monitor trough levels (just prior to a dose at steady state). Steady state is generally achieved after 2–5 days of continuous dosing. Interpretation will vary based on treatment protocol and assay methodology (whole blood ELISA vs. MEIA vs. HPLC). Whole blood trough concentrations of 5–20 ng/mL have been recommended in liver transplantation at 1–12 mo. Trough levels of 7–20 ng/mL (whole blood) for the first 3 mo and 5–15 ng/mL after 3 mo have been recommended in renal transplantation. African Americans may need to be titrated to higher dosages.

Tacrolimus therapy generally should be initiated 6 hr or more after transplantation. PO is the preferred route of administration and all PO dosage forms should be administered on an empty stomach (1 hr before and 2 hr after meals).

Astagraf XL (extended release capsule): Safety and efficacy has been established for de novo and stable (receiving immediate-release dosage form) pediatric kidney transplant patients. A mg per mg conversion from immediate release dosage form to Astagraf XL has been recommended.

Envarsus XR (extended release tablet): Currently labeled for use in adult kidney transplant patients (de novo and stable on immediate-release tacrolimus). When converting to Envarsus XR from immediate-release dosage form, initiate at 80% of the established immediate-release dosage form.

All extended-release formulations are NOT interchangeable. IV infusions should be administered at concentrations between 0.004 and 0.02 mg/mL diluted with NS or D_5W.

TOPICAL USE: Not recommended for use in patients with skin conditions with a skin barrier defect with the potential for systemic absorption. **Do not use** in children <2 yr, immunocompromised patients, or with occlusive dressings (promotes systemic absorption). Approved as a second-line therapy for short-term and intermittent treatment of atopic dermatitis for patients who fail to respond, or do not tolerate, other approved therapies. Long-term safety is unknown. Skin burn sensation, pruritus, flu-like symptoms, allergic reaction, skin erythema, headache, and skin infection are the most common side effects. Application site edema has been reported. Although the risk is uncertain, the FDA has issued an alert about the potential cancer risk with the use of this product. See www.fda.gov/medwatch for the latest information.

TAZAROTENE
Avage, Fabior, Tazorac, and generics
Topical retinoid acid prodrug, keratolytic agent for acne or psoriasis

Topical Cream:
Tazorac: 0.05%, 0.1% (30, 60 g); contains benzyl alcohol
Avage: 0.1% (30 g); contains benzyl alcohol
Generics: 0.05% (30 g), 0.1% (30, 60 g); may contain benzyl alcohol

For explanation of icons, see p. 667

TAZAROTENE *continued*

Topical Foam:
Fabior: 0.1% (50, 100 g)
Topical Gel:
Tazorac: 0.05%, 0.1% (30, 100 g); contains benzyl alcohol

Acne:
≥***12 yr and adult:*** Apply a small amount of 0.1% strength dosage forms to affected areas QHS. Use thin film (2 mg/cm²) for cream or gel dosage form and small amount for foam dosage form.
Psoriasis:
≥***12 yr and adult:*** Apply a small amount of 0.05% gel (2 mg/cm²) to affected areas QHS initially. If needed and tolerated, increase to 0.1% gel QHS. The cream dosage form may also be used the same way as the gel but it is currently labeled for use in adults (≥18 yr).

Contraindicated in pregnancy. Pregnancy testing 2 wk prior to use and initiate use during menstrual period has been recommended. **Avoid** use in abraded or eczematous skin, with other medications or cosmetics with drying effects, or medications that can cause photosensitivity.
Tazarotene is a retinoid prodrug which is converted to its active form, the cognate carboxylic acid of tazarotene (AGN 190299), by rapid deesterification in animals and man.
Common side effects include erythema, dry skin, skin irritation/pain (including blistering and skin desquamation), pruritus, and worsening of psoriasis.
Avoid contact with mucous membranes. The foam dosage form is flammable; **avoid** fire, flame, or smoking during or immediately after use.

TERBINAFINE

Previously available as Lamisil, Lamisil AT, and generics
Antifungal

Tabs: 250 mg
Oral suspension: 25 mg/mL
Topical cream:
Lamisil AT and generics [OTC]: 1% (12, 15, 30 g); contains benzyl alcohol
Topical spray:
Lamisil AT [OTC]: 1% (30, 125 mL); contains alcohol and propylene glycol

Tinea capitis:
Child: 4–6 mg/kg/dose (**max. dose**: 250 mg) PO once daily, OR by the following once daily dosage by weight category:
10–20 kg: 62.5 mg
20–40 kg: 125 mg
>40 kg: 250 mg
Duration of therapy: T. tonsurans: 2–6 wk; M canis: 8–12 wk
Adult: 250 mg PO once daily × 4–6 wk
Onychomycosis:
Child and adolescent (limited data): PO once daily by weight category:
10–20 kg: 62.5 mg
20–40 kg: 125 mg
>40 kg: 250 mg
Adult: 250 mg PO once daily

TERBINAFINE *continued*

Duration of therapy:
Fingernail infection: 6 wk
Toenail infection: 12 wk

Topical Use for dermal mycosis:

≥12 yr:

Tinea pedis: Apply topically (cream or spray) interdigitally BID × 1 wk; if needed, apply the cream to the bottom or sides of the foot BID × 2 wk

Tinea cruris/Tinea corporis: Apply topically (cream or spray) to affected area once daily × 1 wk

Pityriasis (tinea) versicolor: Apply spray to affected area once daily × 1 wk

SYSTEMIC USE: Contraindicated in chronic or acute liver disease. Common side effects include headache, fever, cough, diarrhea, taste disorder, increased LFTs, GI disturbances, and rash. Severe dermatological reactions (e.g., SJS, TEN), hearing loss, neutropenia, thrombotic microangiopathy, and liver failure (some fatal) have been reported. Monitor AST/ALT at baseline and repeat with CBC if therapy is >6 wk. Signs and symptoms of liver disease may include persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain, or jaundice. Discontinue use immediately if biochemical or clinical evidence of liver injury develops.

Use with caution in renal impairment as terbinafine's clearance has been shown to decrease by ~50% in adults with CrCl ≤50 mL/min. Terbinafine inhibits CYP 450 2D6, thus increasing the effects/toxicity of 2D6 substrates such as amphetamines, risperidone, and fluoxetine.

Doses may be administered with or without food.

TOPICAL USE: Do not use on/in the eyes, mouth, nails, scalp, or vaginal areas. Local irritation, skin rash, xeroderma, pruritus, and contact dermatitis may occur. Apply to clean and dry affected area, and wash hands after each use. If using topical spray, hold spray 4–6 inches from the affected area during dose administration.

TERBUTALINE
Various generics; previously available as Brethine
β_2-adrenergic agonist

Tabs: 2.5, 5 mg
Oral suspension: 1 mg/mL
Injection: 1 mg/mL (1 mL)

Acute asthma exacerbation:

SC injection:

≤12 yr: 0.005–0.01 mg/kg/dose (**max. dose:** 0.4 mg/dose) Q15–20 min × 3; if needed, Q2–6 hr PRN.

>12 yr and adult: 0.25 mg/dose Q20 min PRN × 3; **max. total dose:** 0.75 mg.

Continuous infusion, IV: 2–10 mCg/kg loading dose followed by infusion of 0.1–0.4 mCg/kg/min. May titrate in increments of 0.1–0.2 mCg/kg/min Q30 min depending on clinical response. Doses as high as 10 mCg/kg/min have been used. To prepare infusion: See IV infusions on page i.

Nebulization (use IV dosage form):

<2 yr: 0.5 mg in 2.5 mL NS Q4–6 hr PRN

2–9 yr: 1 mg in 2.5 mL NS Q4–6 hr PRN

>9 yr: 1.5–2.5 mg in 2.5 mL NS Q4–6 hr PRN

Continued

For explanation of icons, see p. 667

TERBUTALINE *continued*

Prevention and reversal of bronchospasms with asthma:
Oral:
≤**12 yr: Initial:** 0.05 mg/kg/dose Q8 hr, increase as required. **Max. dose:** 0.15 mg/kg/dose Q8 hr or total of 5 mg/24 hr.
>12 yr and adult: 2.5–5 mg/dose PO Q6–8 hr
Max. dose:
12–15 yr: 7.5 mg/24 hr
>15 yr: 15 mg/24 hr

Use of the IV and PO route should not be used for the prevention or prolonged treatment of preterm labor because of the potential for serious maternal cardiac events and even death. Nervousness, tremor, headache, nausea, tachycardia, arrhythmias and palpitations may occur. Paradoxical bronchoconstriction may occur with excessive use; if it occurs, discontinue drug immediately. Injectable product may be used for nebulization. For acute asthma, nebulizations may be given more frequently than Q4–6 hr.
Monitor heart rate, blood pressure, respiratory rate, and serum potassium when using the continuous IV infusion route of administration. **Adjust dose in renal failure (see Chapter 31).**

TETRACYCLINE HCL

Various generics; previously available as Sumycin
Antibiotic

Caps: 250, 500 mg
Oral suspension: 25 mg/mL

Do not use in children <8 yr.
Child ≥8 yr: 25–50 mg/kg/24 hr PO ÷ Q6 hr; **max. dose:** 3 g/24 hr
Acne: 500 mg PO BID
Adult: 250–500 mg PO Q6–12 hr

Not recommended in patients <8 yr owing to tooth staining and decreased bone growth. Also **not recommended** for use in pregnancy because these side effects may occur in the fetus. The risk for these adverse effects is highest with long-term use. May cause nausea, GI upset, hepatotoxicity, stomatitis, rash, fever, and superinfection. Photosensitivity reaction may occur. **Avoid** prolonged exposure to sunlight.
Never use outdated tetracyclines because they may cause Fanconi-like syndrome. **Do not** give with dairy products or with any divalent cations (i.e., Fe^{2+}, Ca^{2+}, Mg^{2+}). Give 1 hr before or 2 hr after meals.
May decrease the effectiveness of oral contraceptives, increase serum digoxin levels, and increase effects of warfarin. Use with methoxyflurane increases risk for nephrotoxicity and use with isotretinoin is associated with pseudotumor cerebri. **Adjust dose in renal failure (see Chapter 31).**
Short-term maternal use is not likely to cause harm to breast-feeding infants.

TEZACAFTOR AND IVACAFTOR

Symdeko
Cystic Fibrosis Transmembrane Conductance Regulator Corrector and Potentiator

Tabs (4-week supply in 4 weekly blister packs):
Tezacaftor 50 mg and Ivacaftor 75 mg (white tabs; 28 tabs) and Ivacaftor 75 mg (light blue tabs; 28 tabs)
Tezacaftor 100 mg and Ivacaftor 150 mg (yellow tabs; 28 tabs) and Ivacaftor 150 mg (light blue

TEZACAFTOR AND IVACAFTOR *continued*

Child 6 to <12 yr:

<30 kg: one tezacaftor 50 mg/75 mg ivacaftor PO QAM and one ivacaftor 75 mg PO every evening administered ~12 hr apart

≥30 kg: one tezacaftor 100 mg/150 mg ivacaftor PO QAM and one ivacaftor 150 mg PO every evening administered ~12 hr apart

Child ≥12 yr–adult: one tezacaftor 100 mg/150 mg ivacaftor PO QAM and one ivacaftor 150 mg PO every evening administered ~12 hr apart

Dosage Modification with Hepatic Impairment:

Child-Pugh Class	Morning Dose		Evening Dose
	Age 6 to <12 yr and <30 kg:	Age 6 to <12 yr and ≥30 kg, and ≥12 yr—adult:	All Patients
Class A	No adjustment	No adjustment	No adjustment
Class B	One tablet of tezacaftor 50 mg/ivacaftor 75 mg PO QAM	One tablet of tezacaftor 100 mg/ivacaftor 150 mg PO QAM	No Ivacaftor
Class C	One tablet of tezacaftor 50 mg/ivacaftor 75 mg PO QAM or less frequently	One tablet of tezacaftor 100 mg/ivacaftor 150 mg PO QAM or less frequently	No Ivacaftor

Dosage Modification with CYP 450 3A4 inhibitors:

Moderate inhibitors (e.g., fluconazole, erythromycin): Do not administer any evening doses.

Child 6 to <12 yr and <30 kg: Administer the following tablet PO on the following days only in the morning:

Tablet	Day 1	Day 2	Day 3	Day 4[a]
Tezacaftor 50 mg/ivacaftor 75 mg tab	One tablet		One tablet	
Ivacaftor 75 mg tab		One tablet		One tablet

[a]Continue dosing with tezacaftor 50 mg/ivacaftor 75 mg or ivacaftor 75 mg on alternate days.

Child 6 to <12 yr and ≥30 kg, and ≥12 yr–adult: Administer the following tablet PO on the following days only in the morning:

Tablet	Day 1	Day 2	Day 3	Day 4[a]
Tezacaftor 100 mg/ivacaftor 150 mg tab	One tablet		One tablet	
Ivacaftor 150 mg tab		One tablet		One tablet

[a]Continue dosing with tezacaftor 100 mg/ivacaftor 150 mg or ivacaftor 150 mg on alternate days.

Strong inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin): Do not administer any evening doses.

Child 6 to <12 yr and <30 kg: One tezacaftor 50 mg/ivacaftor 75 mg PO in the morning on days 1 and 4, then continue with the same one tablet twice weekly (administered 3–4 days apart).

Child 6 to <12 yr and ≥30 kg, and ≥12 yr–adult: One tezacaftor 100 mg/ivacaftor 150 mg PO in the morning on days 1 and 4, then continue with the same one tablet twice weekly (administered 3–4 days apart).

Works on CFTR trafficking defect by acting as a CFTR corrector (tezacaftor) and in combination with a CFTR potentiator (ivacaftor). Indicated for individuals with homozygous F508del CFTR mutation or who have at least one CFTR mutation that is responsive to this drug based on in vitro data and/or clinical evidence.

Continued

For explanation of icons, see p. 667

TEZACAFTOR AND IVACAFTOR *continued*

Common side effects include headache, nausea, sinus congestion, and dizziness. Increased liver enzymes and cataracts may occur; monitor baseline AST/ALT and ocular exam at baseline. Repeat AST/ALT every 3 months for the first year followed by annual assessments. Repeat ocular exams annually. May cause a false positive urine drug screen for cannabinoids.

Use with caution with CrCl ≤30 mL/min and ESRD. Reduce dose with moderate/severe hepatic impairment or when initiating therapy while taking a CYP 450 3A4 inhibitor (see dosing section).

Tezacaftor and ivacaftor are substrates for CYP 450 3A4/3A5. Use with strong CYP 450 3A inducers (e.g., rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's wort) is not recommended. Tezacaftor and ivacaftor may increase the effects/toxicity of cyclosporine, digoxin, everolimus, sirolimus, tacrolimus, and warfarin. Always evaluate potential drug-drug interactions; see https://www.symdekohcp.com/drug-interactions. **Avoid** food or drink containing grapefruit or Seville oranges.

Administer all doses with high-fat foods to assure absorption. If a dose (all dosage forms) is missed within 6 hrs of a scheduled dose, administer a dose immediately. However, if the missed dose is >6 hr, skip that dose and resume therapy at the next scheduled dose. Never take a double dose for a missed dose.

THEOPHYLLINE

Theo-24, Elixophyllin, and generics

Bronchodilator, methylxanthine

Other dosage forms may exist.

Immediate release:

Oral elixir/solution (Elixophyllin and generics): 80 mg/15 mL (473 mL); may contain up to 20% alcohol (alcohol-free preparations may be available).

Sustained/extended release (see remarks):

Tabs:

Q12 hr dosing (generics): 100, 200, 300, 450 mg

Q24 hr dosing (generics): 400, 600 mg

Caps (Q24 hr dosing: Theo-24 and generics): 100, 200, 300, 400 mg

Sustained-release forms should **not** be chewed or crushed. Capsules may be opened and contents may be sprinkled on food.

Dosing intervals are for immediate-release preparations.

For sustained-release preparations, divide daily dose >Q8–24 hr based on product.

Neonatal apnea:

Loading dose: 5 mg/kg/dose PO × 1

Maintenance: 3–6 mg/kg/24 hr PO ÷ Q6–8 hr

Bronchospasm; PO:

Loading dose: 1 mg/kg/dose for each 2 mg/L desired increase in serum theophylline level.

Maintenance, infant (<1 yr):

Preterm:

<24 days old (postnatal): 1 mg/kg/dose PO Q12 hr

≥24 days old (postnatal): 1.5 mg/kg/dose PO Q12 hr

Full-term up to 1 yr old: Total daily dose (mg) = [(0.2 × age in weeks) + 5] × (kg body weight)

≤6 mo: Divide daily dose Q8 hr

>6 mo: Divide daily dose Q6 hr

THEOPHYLLINE *continued*

Maintenance, child >1 yr and adult without risk factors for altered clearance (see remarks):

<45 kg: Begin therapy at 12–14 mg/kg/24 hr ÷ Q4–6 hr up to **max. dose** of 300 mg/24 hr. If needed based on serum levels, gradually increase to 16–20 mg/kg/24 hr ÷ Q4–6 hr. **Max. dose**: 600 mg/24 hr.

≥45 kg: Begin therapy with 300 mg/24 hr ÷ Q6–8 hr. If needed based on serum levels, gradually increase to 400–600 mg/24 hr ÷ Q6–8 hr.

Drug metabolism varies widely with age, drug formulation, and route of administration. Most common side effects and toxicities are nausea, vomiting, anorexia, abdominal pain, gastroesophageal reflux, nervousness, tachycardia, seizures, and arrhythmias.

Serum levels should be monitored. Therapeutic levels: bronchospasm: 10–20 mg/L; apnea: 7–13 mg/L. Half-life is age-dependent: 30 hr (newborns); 6.9 hr (infants); 3.4 hr (children); 8.1 hr (adults). See Aminophylline for guidelines for serum level determinations. Liver impairment, cardiac failure, and sustained high fever may increase theophylline levels. Theophylline is a substrate for CYP 450 1A2. Levels are increased with allopurinol, alcohol, ciprofloxacin, cimetidine, clarithromycin, disulfiram, erythromycin, estrogen, isoniazid, propranolol, thiabendazole, and verapamil. Levels are decreased with carbamazepine, isoproterenol, phenobarbital, phenytoin, and rifampin. May cause increased skeletal muscle activity, agitation, and hyperactivity when used with doxapram, and increase quinine levels/toxicity.

Use ideal body weight in obese patients when calculating dosage because of poor distribution into body fat. Risk factors for increased clearance include: smoking, cystic fibrosis, hyperthyroidism, and high-protein diet. Factors for decreased clearance include CHF, correction of hyperthyroidism, fever, viral illness, sepsis, and high carbohydrate diet.

Suggested dosage intervals for sustained-released products (see following table):

THEOPHYLLINE SUSTAINED-RELEASE PRODUCTS

Trade Name	Available Strengths	Dosage Interval
CAPSULES:		
Theo-24	100, 200, 300, 400 mg	Q24 hr
TABLETS:		
Theochron and generics	100, 200, 300, 450 mg	Q12 hr
Generics	400, 600 mg	Q24 hr

THIAMINE

VITAMIN B1, many generic products

Water-soluble vitamin

Tabs (OTC): 50, 100, 250 mg

Caps (OTC): 50 mg

Oral suspension: 25, 100 mg/mL

Injection: 100 mg/mL (2 mL); may contain benzyl alcohol

For US RDA, see Chapter 21.

Beriberi (thiamine deficiency):

Child: 10–25 mg/dose IM/IV once daily (if critically ill) or 10–50 mg/dose PO once daily × 2 wk, followed by 5–10 mg/dose once daily × 1 mo.

Adult: 5–30 mg/dose IM/IV TID (if critically ill) × 2 wk, followed by 5–30 mg/24 hr PO ÷ once daily or TID × 1 mo.

Continued

For explanation of icons, see p. 667

THIAMINE *continued*

Wernicke's encephalopathy syndrome:

Adult: 100 mg IV × 1, then 50–100 mg IM/IV once daily until patient resumes a normal diet. (Administer thiamine before starting glucose infusion.)

Multivitamin preparations contain amounts meeting RDA requirements. Allergic reactions and anaphylaxis may occur, primarily with IV administration. Therapeutic range: 1.6–4 mg/dL. High carbohydrate diets or IV dextrose solutions may increase thiamine requirements. Large doses may interfere with serum theophylline assay. Pregnancy category changes to "C" if used in doses above the RDA.

THIORIDAZINE

Various generics, previously available as Mellaril

Antipsychotic, phenothiazine derivative

Tabs: 10, 25, 50, 100 mg

Schizophrenia:

Child ≥6 yr–adolescent: Start with 0.5 mg/kg/24 hr PO ÷ BID–TID (**initial max.:** 50 mg/dose); dosage range: 0.5–3 mg/kg/24 hr PO ÷ BID–TID. **Max. dose**: 3 mg/kg/24 hr.

Adult: Start with 75–300 mg/24 hr PO ÷ TID. Then gradually increase PRN to **max. dose** 800 mg/24 hr ÷ BID–QID.

Indicated for schizophrenia unresponsive to standard therapy. **Contraindicated** in severe CNS depression, brain damage, narrow-angle glaucoma, blood dyscrasias, and severe liver or cardiovascular disease. **DO NOT** co-administer with drugs which may inhibit the CYP 450 2D6 isoenzymes (e.g., SSRIs such as fluoxetine, fluvoxamine, paroxetine; and beta-blockers such as propranolol and pindolol); drugs which may widen the QTc interval (e.g., disopyramide, procainamide, quinidine); and in patients with known reduced activity of CYP 450 2D6.

May cause drowsiness, extrapyramidal reactions, autonomic symptoms, ECG changes (QTc prolongation in a dose-dependent manner), arrhythmias, paradoxical reactions, and endocrine disturbances. Long-term use may cause tardive dyskinesia. Pigmentary retinopathy may occur with higher doses; a periodic eye exam is recommended. More autonomic symptoms and less extra-pyramidal effects than chlorpromazine. Concurrent use with epinephrine can cause hypotension. Increased cardiac arrhythmias may occur with tricyclic antidepressants.

In an overdose situation, monitor ECG and avoid drugs that can widen QTc interval.

TIAGABINE

Gabitril and generics

Anticonvulsant

Tabs: 2, 4, 12, 16 mg

Oral suspension: 1 mg/mL

Adjunctive therapy for refractory seizures (see remarks):

Child ≥2 yr (limited data from a safety and tolerability study in 52 children 2–17 yr, mean 9.3 + 4.1): Initial dose of 0.25 mg/kg/24 hr PO ÷ TID × 4 wk. Dosage was increased at 4-wk intervals to 0.5, 1, and 1.5 mg/kg/24 hr until an effective and well-tolerated dose was established. Criteria for dose increase required tolerance of the current dosage level and <50% reduction in seizures. Patients receiving enzyme-inducing antiepileptic drugs (AEDs) received a **max. daily dose** of 0.73 + 0.44 mg/kg/24 hr and patients receiving non-enzyme inducing AEDs received a **max.** of 0.61 + 0.32 mg/kg/24 hr.

TIAGABINE *continued*

Adjunctive therapy for partial seizures (dosage based on use with enzyme-inducing AEDs; see remarks). NOTE: Patients receiving non-enzyme-inducing AEDs had tiagabine blood levels about two times higher than patients receiving enzyme-inducing AEDs.

≥***12 yr and adult:*** Start at 4 mg PO once daily × 7 days. If needed, increase dose to 8 mg/24 hr PO ÷ BID. Dosage may be increased further by 4–8 mg/24 hr at weekly intervals (daily doses may be divided BID–QID) until a clinical response is achieved or up to specified **max. dose.**

Max. dose:

12–18 yr: 32 mg/24 hr

Adult: 56 mg/24 hr

Use with caution in hepatic insufficiency (may need to reduce dose and/or increase dosing interval). Most common side effects include dizziness, somnolence, depression, confusion, and asthenia. Nervousness, tremor, nausea, abdominal pain, confusion, and difficulty in concentrating may also occur. Cognitive/neuropsychiatric symptoms resulting in nonconvulsive status epilepticus requiring subsequent dose reduction or drug discontinuation have been reported. Suicidal behavior or ideation, bullous dermatitis, and blurred vision have been reported. **Off-label use in patients WITHOUT epilepsy is discouraged** due to reports of seizures in these patients.

Tiagabine's clearance is increased by concurrent hepatic enzyme-inducing antiepileptic drugs (e.g., phenytoin, carbamazepine, and barbiturates), and St. John's Wort. Lower doses or a slower titration for clinical response may be necessary for patients receiving non-enzyme-inducing drugs (e.g., valproate, gabapentin, and lamotrigine). **Avoid** abrupt discontinuation of drug.

TID dosing schedule may be preferred since BID schedule may not be well tolerated. Doses should be administered with food.

TIOTROPIUM
Spiriva HandiHaler, Spiriva Respimat
Anticholinergic agent, long-acting

Aerosol inhaler:

Spiriva Respimat:

For asthma: 1.25 mCg/actuation (each cartridge weighs 4 g and provides either 28 or 60 actuations/inhaler); contains benzalkonium chloride and disodium EDTA

For COPD: 2.5 mCg/puff (each cartridge weighs 4 g and provides either 10, 28, or 60 actuations/inhaler); contains benzalkonium chloride and disodium EDTA

Inhalational capsules:

Spiriva HandiHaler: 18 mCg (boxes of 5s, 30s, or 90s with one HandiHaler device); contains milk protein

Asthma (maintenance therapy, see remarks):

Child ≥6 yr, adolescent, and adult:

Spiriva Respimat: Inhale two 1.25 mCg actuations once daily.

Contraindicated in patients with ipratropium hypersensitivity reactions (e.g., angioedema, itching, or rash). Common side effects include headache, constipation, xerostomia, UTI, bronchitis, cough, pharyngitis, sinusitis, and URI. Bowel obstruction, angle-closure glaucoma, urinary retention, and bronchospasm have been reported. The pediatric adverse reaction profile is similar to adults.

Use as an add-on maintenance therapy for asthma along with inhaled corticosteroid. Maximum benefits may take up to 4–8 wk of continuous use. Doses >2.5 mCg/24 hr were not associated with greater efficacy in FEV_1 for asthmatic adults.

For explanation of icons, see p. 667

TIOTROPIUM *continued*

Monitor for anticholinergic side effects in patients with moderate/severe renal impairment (eGFR <60 mL/min).

Administration of Spiriva Respimat 1.25 mCg × 2 delivered with the AeroChamber Plus Flow-Vu holding chamber with/without facemask by an in vitro study utilizing inspiratory flow rates for children 6–12 mo, 2–5 yr, and >5 yr has been shown to deliver a comparable adult dose on a mCg per body weight basis. Despite a report of similar adverse reaction profile to adolescents and adults from a 12-wk placebo control trial (2.5 mCg/24 hr) in children 1–5 yr, the clinical efficacy and safety have not been fully established for children <6 years of age with asthma.

TOBRAMYCIN

Tobrex, TOBI, TOBI Podhaler, Bethkis, Kitabis Pak, and generics; previously available as Nebcin

Antibiotic, aminoglycoside

Injection: 10 mg/mL (2 mL), 40 mg/mL (2, 30, 50 mL); may contain phenol and bisulfites
Powder for injection: 1.2 g; preservative free
Ophthalmic ointment (Tobrex): 0.3% (3.5 g)
In combination with dexamethasone (TobraDex): 0.3% tobramycin with 0.1% dexamethasone (3.5 g); contains 0.5% chlorobutanol
Ophthalmic solution (Tobrex and generics): 0.3% (5 mL)
In combination with dexamethasone as an ophthalmic suspension (both products contain 0.01% benzalkonium chloride and EDTA):
TobraDex and generics: 0.3% tobramycin with 0.1% dexamethasone (2.5, 5, 10 mL)
TobraDex ST: 0.3% tobramycin with 0.05% dexamethasone (5 mL)
Nebulizer solution:
Bethkis: 300 mg/4 mL (56s); preservative free
TOBI, Kitabis Pak, and generics: 300 mg/5 mL (56s); preservative free
170 mg/3.4 mL (mixed in 0.45% NS, preservative free, use with eFlow/Trio nebulizer)
Powder for inhalation:
TOBI Podhaler: 28 mg capsules (224 capsules in 4 weekly packs with 2 Podhaler inhalation devices)

Initial empiric dosage; patient-specific dosage defined by therapeutic drug monitoring (see remarks).

Neonate/Infant, IM/IV (see following table):

Post-conceptional age (wk)	Postnatal age (days)	Dose (mg/kg/dose)	Interval (hr)
≤29[a]	0–7	5	48
	8–28	4	36
	>28	4	24
30–34	0–7	4.5	36
	>7	4	24
≥35	ALL	4	24[b]

[a]Or significant asphyxia, PDA, indomethacin use, poor cardiac output, reduced renal function.
[b]Use Q36 hr interval for HIE patients receiving whole-body therapeutic cooling.

Child: 7.5 mg/kg/24 hr ÷ Q8 hr IV/IM
Cystic fibrosis (if available, use patient's previous therapeutic mg/kg dosage):
Conventional Q8 hr dosing: 7.5–10.5 mg/kg/24 hr ÷ Q8 hr IV
High dose extended interval (once daily) dosing: 10–12 mg/kg/dose Q24 hr IV

TOBRAMYCIN *continued*

Adult:

Conventional Q8 hr dosing: 3–6 mg/kg/24 hr ÷ Q8 hr IV/IM

High dose extended interval: 4–7 mg/kg/dose Q24 hr IV/IM

Ophthalmic:

Tobramycin:

Child and adult:

Ophthalmic ointment: Apply 0.5-inch ribbon into conjunctival sac(s) BID–TID; for severe infections, apply Q3–4 hr initially then reduce dose frequency

Ophthalmic drop: Instill 1–2 drops of solution to affected eye(s) Q4 hr; for severe infections, instill 2 drops Q30–60 min initially, then reduce dosing frequency.

Tobramycin with dexamethasone:

≥2 yr and adult:

Ophthalmic ointment: Apply 0.5-inch ribbon of ointment into conjunctival sac(s) TID–QID

Ophthalmic drop: Instill 1–2 drops of solution to affected eye(s) Q2 hr × 24–48 hr, then 1–2 drops Q4–6 hr.

Inhalation:

Cystic fibrosis prophylaxis therapy:

≥6 yr and adult:

TOBI, Bethkis, Kitabis Pak, and generic nebs: 300 mg Q12 hr administered in repeated cycles of 28 days on drug followed by 28 days off drug.

Use with eFlow/Trio nebulizer: 170 mg Q12 hr administered in repeated cycles of 28 days on drug followed by 28 days off drug.

TOBI Podhaler: Inhale four 28-mg capsules (112 mg) Q12 hr administered in repeated cycles of 28 days on drug followed by 28 days off drug.

Use with caution in combination with neurotoxic, ototoxic, or nephrotoxic drugs; anesthetics or neuromuscular blocking agents; pre-existing renal, vestibular, or auditory impairment; and in patients with neuromuscular disorders. May cause ototoxicity, nephrotoxicity, and neuromuscular blockade. Serious allergic reactions including anaphylaxis and dermatologic reactions including exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome have been reported rarely. **Ototoxic effects synergistic with furosemide.**

Higher doses are recommended in patients with cystic fibrosis, neutropenia, or burns. **Adjust dose in renal failure (see Chapter 31).** Monitor peak and trough levels.

Therapeutic peak levels with conventional Q8 hr dosing:

6–10 mg/L in general

8–10 mg/L in pulmonary infections, neutropenia, osteomyelitis, and severe sepsis

Therapeutic trough levels with conventional Q8 hr dosing: <2 mg/L. Recommended serum sampling time at steady state: trough within 30 min prior to the third consecutive dose and peak 30–60 min after the administration of the third consecutive dose.

Therapeutic peak and trough goals for high-dose extended-interval dosing for cystic fibrosis:

Peak: 20–40 mg/L; recommended serum sampling time at 30–60 min after the administration of the first dose.

Trough: <1 mg/L; recommended serum sampling time within 30 min before the second dose.

Serum levels should be rechecked with changing renal function, poor clinical response, and at a minimum of once weekly for prolonged therapies.

To maximize bactericidal effects, an individualized peak concentration to target a peak/MIC ratio of 8–10:1 may be applied.

For initial dosing in obese patients, use an adjusted body weight (ABW). ABW = Ideal Body Weight + 0.4 (Total Body Weight – Ideal Body Weight).

For explanation of icons, see p. 667

TOBRAMYCIN *continued*

INHALATIONAL USE: Transient voice alteration, bronchospasm, dyspnea, pharyngitis, and increased cough may occur. Transient tinnitus, decreased appetite, and hearing loss have been reported with nebulized dosage forms. Aphonia, discolored sputum, and malaise have been reported with the powder for inhalation. Use is not recommended with nephrotoxic, neurotoxic, or ototoxic medications, or when intravenous antibiotic therapy is prescribed. When used with other inhaled medications in cystic fibrosis, use the following order of administration: bronchodilator first, chest physiotherapy, other inhaled medications (if indicated), and tobramycin last. For TOBI Podhaler, inhale the entire contents of each capsule. To improve adherence with prophylactic inhalation therapy, initiate each 28-day inhalation cycle on the first day of an odd or even numbered month.

Pregnancy category is a "D" for injection and inhalation routes of administration and a "B" for the ophthalmic route.

TOLNAFTATE
Tinactin, many other brands and generics
Antifungal agent

Topical aerosol liquid [OTC]: 1% (150 g); may contain 29% vol/vol or 41% wt/wt alcohol
Aerosol powder [OTC]: 1% (133 g); contains 11% vol/vol alcohol and talc
Cream [OTC]: 1% (15, 30, 114 g)
Topical powder [OTC]: 1% (45 g)
Topical solution [OTC]: 1% (10, 15, 30 mL); may contain propylene glycol and/or parabens

Child (≥2 yr), adolescent, and adult:
Topical for Tinea pedis, Tinea corporis, and Tinea cruris: apply 1–3 drops of solution, or small amount of liquid, cream, or powder to affected areas BID for 2–4 wk.

May cause mild irritation and sensitivity. Contact dermatitis has been reported. **Avoid** eye contact. **Do not use** for nail or scalp infections. Discontinue use if sensitization develops.

Pregnancy category not formally assigned by FDA.

TOPIRAMATE
Topamax, Topamax Sprinkle, Trokendi XR, Qudexy XR, and generics
Anticonvulsant

Caps, sprinkle:
Topamax Sprinkle and generics: 15, 25 mg
Tabs:
Topamax and generics: 25, 50, 100, 200 mg
Extended-release caps, sprinkle (Q24 hr dosing; see remarks):
Qudexy XR and generics: 25, 50, 100, 150, 200 mg
Extended-release caps (Q24 hr dosing; see remarks):
Trokendi XR: 25, 50, 100, 200 mg
Oral suspension: 6, 14, 20 mg/mL

Adjunctive therapy for partial onset seizures or Lennox-Gastaut syndrome:
Child 2–16 yr: Start with 1–3 mg/kg/dose (**max. dose**: 25 mg/dose) PO QHS × 7 days, then increase by 1–3 mg/kg/24-hr increments at 1- to 2-wk intervals (divided daily dose BID) to response. Usual maintenance dose is 5–9 mg/kg/24 hr PO ÷ BID

TOPIRAMATE *continued*

≥***17 yr and adult:*** Start with 25–50 mg PO QHS × 7 days, then increase by 25–50 mg/24 hr increments at 1-wk intervals until adequate response. Doses >50 mg should be divided BID. Usual maintenance dose: 100–200 mg/24 hr. Doses above 1600 mg/24 hr have not been studied.

Adjunctive therapy for primary generalized tonic clonic seizures:

Child 2–16 yr: Use above initial dose and slower titration rate by reaching 6 mg/kg/24 hr by the end of 8 weeks

≥***17 yr and adult:*** Use above initial dose and slower titration rate by reaching 200 mg BID by the end of 8 weeks; **max. dose:** 1600 mg/24 hr.

Monotherapy for partial onset seizures or primary generalized tonic clonic seizures:

Child 2 to <10 yr: Start with 25 mg PO QHS × 7 days, if needed and tolerated, may increase dose to 25 mg PO BID. May further increase by 25–50 mg/24 hr at weekly intervals over 5–7 weeks up to the lower end the following daily target maintenance dosing range (if needed and tolerated, increase to higher end of dosing range by increasing by 25–50 mg/24hr at weekly intervals):

≤***11 kg:*** 150–250 mg/24 hr ÷ BID

12–22 kg: 200–300 mg/24 hr ÷ BID

23–31 kg: 200–350 mg/24 hr ÷ BID

32–38 kg: 250–350 mg/24 hr ÷ BID

>38 kg: 250–400 mg/24 hr ÷ BID

Child ≥10 yr and adult: Start with 25 mg PO BID × 7 days, then increase by 50 mg/24 hr increments at 1-wk intervals up to a **max. dose** of 100 mg PO BID at wk 4. If needed, dose may be further increased at weekly intervals by 100 mg/24 hr up to a recommended **max. dose** of 200 mg PO BID.

Migraine prophylaxis:

Child 6 to <12 yr and ≥20 kg (limited data): Start with 15 mg PO once daily × 7 days, then increase to 25 mg PO BID × 7 days, then gradually increase dose to effect up to a target dose of 2–3 mg/kg/24 hr ÷ BID (**max. dose:** 200 mg/24 hr).

Child ≥12 yr and adult: titrate dosage to 50 mg PO BID with the following schedule:

	Morning PO Dose	Evening PO Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4 and beyond	50 mg	50 mg

Use clinical outcome to guide dose and titration. Longer intervals between dose adjustments can be used.

Use with caution in renal and hepatic dysfunction (decreased clearance) and sulfa hypersensitivity. **Reduce dose by 50% when creatinine clearance is <70 mL/min.** Common side effects (incidence lower in children) include ataxia, cognitive dysfunction, dizziness, nystagmus, paresthesia, sedation, visual disturbances, nausea, dyspepsia, and kidney stones (incidence higher in children). Secondary angle closure glaucoma characterized by ocular pain, acute myopia, and increased intraocular pressure has been reported and may lead to blindness if left untreated. Patients should be instructed to seek immediate medical attention if they experience blurred vision or periorbital pain. Oligohidrosis and hyperthermia has been reported primarily in children and should be monitored especially during hot weather and with use of drugs that predispose patients to heat-related disorders (e.g., carbonic anhydrase inhibitors and anticholinergics). Low serum bicarbonate levels have been reported in pediatric and adult clinical trials. Hyperchloremic, non-anion gap metabolic acidosis, hyperammonemia (with or without encephalopathy), suicidal behavior or ideation, and false-positive sweat chloride test for cystic fibrosis have been reported.

Continued

For explanation of icons, see p. 667

TOPIRAMATE *continued*

Drug is metabolized by and inhibits the CYP 450 2C19 isoenzyme. Phenytoin, valproic acid, and carbamazepine may decrease topiramate levels. Topiramate may decrease valproic acid, digoxin, warfarin, and ethinyl estradiol (to decrease oral contraceptive efficacy) but may increase phenytoin levels/effects. Alcohol and CNS depressants may increase CNS side effects. Carbonic anhydrase inhibitors (e.g., acetazolamide) may increase risk of metabolic acidosis, nephrolithiasis, or paresthesia. Use with valproic acid may result in the development of hyperammonemia.

Safety and efficacy in migraine prophylaxis in pediatrics have not been established; an increase in serum creatinine has been reported in a clinical trial.

Qudexy XR and Trokendi XR are not bioequivalent and should not be interchanged. Doses may be administered with or without food. Capsule may be opened and sprinkled on small amount of food (e.g., 1 teaspoonful of applesauce) and swallowed whole (do not chew). Maintain adequate hydration to prevent kidney stone formation. If discontinuing therapy, gradually taper dosage.

TRAZODONE

Generics, previously available as Desyrel

Antidepressant, serotonin reuptake inhibitor/antagonist, triazolopyridine-derivative

Tabs: 50, 100, 150, 300 mg

Oral suspension: 10 mg/mL

Insomnia with comorbid psychiatric disorders (limited data):

18 mo to <3 yr: Start at 25 mg PO QHS. If needed, increase by 25 mg Q2 week up to a **max.** of 100 mg/24 hr.

3–5 yr: Start at 50 mg PO QHS, if needed, increase by 25 mg Q2 week up to a **max.** of 150 mg/24 hr.

5 yr–adolescent: 25–50 mg PO QHS, if needed, increase by 25–50 mg Q2 week up to a **max.** of 200 mg/24 hr. Daily dose may be divided BID–TID when used for palliative care.

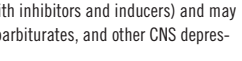
Use with caution in pre-existing cardiac disease, initial recovery phase of MI, in patients receiving antihypertensive medications, renal and hepatic impairment (has not been evaluated), and electroconvulsive therapy. Common side effects include dizziness, drowsiness, dry mouth, and diarrhea. May cause angle-closure glaucoma in patients with anatomically narrow angles who do not have an iridectomy. Seizures, tardive dyskinesia, EPS, arrhythmias, priapism, blurred vision, neuromuscular weakness, anemia, orthostatic hypotension, and rash have been reported. Monitor for clinical worsening of depression and suicidal ideation/behavior following the initiation of therapy or after dose changes.

Trazodone is CYP 450 3A4 isoenzyme substrate (may interact with inhibitors and inducers) and may increase digoxin levels and increase CNS effects of alcohol, barbiturates, and other CNS depressants. **Max.** antidepressant effect is seen at 2–6 wk.

TREPROSTINIL

Remodulin, Tyvaso, Orenitram

Prostaglandin I2 analogue, vasodilator



Injection:

Remodulin: 1 mg/mL (20 mL), 2.5 mg/mL (20 mL), 5 mg/mL (20 mL), 10 mg/mL (20 mL); contains metacresol

Inhalation solution:

Tyvaso: 0.6 mg/mL (2.9 mL; 4s and 28s); use with Tyvaso inhalation system

Extended release tab:

TREPROSTINIL *continued*

Pulmonary arterial hypertension (PAH):

IV/SC infusion:

Child (limited data): Initial dose of 2 nanogram/kg/min has been recommended with careful titration. Stable doses have been reported at 50–80 nanogram/kg/min with an unknown maximum dosage. Dosages as high as 350 and 170 nanogram/kg/min have been reported with the SC and IV routes, respectively.

Adult: Start at 1.25 nanogram/kg/min. If not tolerated, reduce to 0.625 nanogram/kg/min. If needed, increase dose at increments of 1.25 nanogram/kg/min per week for the first 4 wk followed by 2.5 nanogram/kg/min per week thereafter. Limited experience with doses >40 nanogram/kg/min.

Inhalation:

Child (limited data): 1–9 (6–54 mCg) patient-activated breaths Q6 hr. A retrospective report of 29 children with PAH receiving background therapy initially received 3 breaths (18 mCg) via oral inhalation QID and titrated doses weekly as tolerated to a **maximum** of 9 breaths (54 mCg) QID for ≥6 wk. 19 of 29 children had WHO functional class improvement (significant improvements in exercise tolerance and peak oxygen consumption). Four children had to discontinue therapy for reasons of O_2 desaturation (1), progression of PAH (1), and chest tightness with bronchospasms (2).

Adult: Start at 3 breaths (18 mCg) via oral inhalation Q4 hr four times a day during waking hours. Reduce dose to 1 or 2 breaths if not tolerated and subsequently increase to 3 breaths. If tolerated, increase dose by 3 additional inhalations at ~1–2 wk intervals to the target and **maximum** maintenance dose of 9 breaths (54 mCg) QID.

Use with caution in liver or renal impairment by titrating doses slowly. **Avoid use** with the oral dosage form in Child-Pugh class B and C. Treprostinil is primarily metabolized by the liver via CYP 450 2C8 and its metabolites are excreted primarily via the urinary route. Inhibitors (e.g., gemfibrozil) and inducers (e.g., rifampin) may increase and decrease treprostinil effects, respectfully.

Flushing, muscle pain (especially with SC route), headaches, and diarrhea are common side effects with injectable routes. Central line gram-negative catheter infections have been reported with the IV route. Recommendations for reducing this risk include using watertight seals in the drug delivery system and closed-hub systems, replacing the diluent with the diluent used for epoprostenol, and using the SC route. Thrombocytopenia has been reported with SC administration. Worsening of reactive airway symptoms, cough, dizziness, bone pain, headache, syncope, and flushing may occur with the inhaled route. Headache, diarrhea, nausea, and flushing are common side effects with the oral dosage form in clinical trials.

Treprostinil has a longer T1/2 than epoprostenol with better room temperature stability (depending on specific diluent used).

Do not abruptly withdrawal therapy and have a backup plan for interruptions with IV/SC continuous therapies (e.g., backup pumps and medications).

TRETINOIN—TOPICAL PREPARATIONS

Retin-A, Retin-A Micro, Altreno, Atralin, Avita, Renova, Refissa, and many others

In combination with clindamycin: Veltin, Ziana, and generics

Retinoic acid derivative, topical acne product

Cream (all strengths may contain parabens, benzyl alcohol, and edetate disodium):

0.02% (20, 40, 60 g): Renova

0.025% (20, 45 g): Avita, Retin-A, and generics

0.05% (20, 40, 45 g): Refissa and generics

0.1% (20, 45 g): generics

For explanation of icons, see p. 667

TRETINOIN—TOPICAL PREPARATIONS *continued*

Topical gel (all strengths may contain 90% alcohol, benzyl alcohol, propylene glycol, and trolamine):
0.01% (15, 45 g): Retin-A and generics
0.025% (15, 45 g): Avita and generics
0.04% (20, 45, 50 g): Retin-A Micro and generics
0.05% (45 g): Atralin and generics
0.06% and 0.08% (50 g): Retin-A Micro
0.1% (20, 45, 50 g): Retin-A Micro and generics

Lotion (Altreno):
0.05% (20, 45 g), contains benzyl alcohol, parabens, and trolamine

In combination with clindamycin:
Topical gel: 0.025% tretinoin and 1.2% clindamycin (30, 60 g); may contain parabens, trometh-amine, and propylene glycol

Topical:
Child ≥12 yr and adult (may be used as young as 8 yr as reported in the literature and specific product labeling; see remarks): Gently wash face with a mild soap, pat the skin dry, and wait 20 to 30 min before use. Initiate therapy with lower strengths (0.02% or 0.025% cream, or 0.01% gel) and apply a small pea-size amount to the affected areas of the face QHS or on alternate days. See remarks.

In combination with clindamycin:
Child ≥12 yr and adult: Gently wash face with a mild soap, pat the skin dry, and wait 20 to 30 min before use. Apply a pea-size amount to entire face QHS.

Contraindicated in sunburns. **Avoid** excessive sun exposure. If stinging or irritation occurs, decrease frequency of administration to every other day. **Avoid** contact with eyes, ears, nostrils, mouth, or open wounds. Local adverse effects include irritation, erythema, excessive dryness, blistering, crusting, hyperpigmentation or hypopigmentation, and acne flare-ups. Concomitant use of other topical acne products may lead to significant skin irritation. Onset of therapeutic benefits may be experienced within 2–3 wk with optimal effects in 6 wk. The gel dosage form is flammable and should not be exposed to heat or temperatures >120°F.

Lower minimum age (<12 yr) for use by specific product labeling:
Atralin gel: ≥10 yr
Altreno lotion: ≥9 yr

In combination with clindamycin (additional remarks from above): **Contraindicated** in regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis. Prolonged use may result in fungal and bacterial superinfection, including *C. difficile* associated diarrhea.

TRIAMCINOLONE

C/D 2 Yes Yes No

Nasal preparations: Nasacort Allergy 24HR Children, Nasacort Allergy 24HR, Nasal Allergy 24 Hour, and generics
Topical preparations: Triderm, Kenalog, Oralone, Trianex, and generics
Injection preparations: Kenalog-10, Kenalog-40, Kenalog-80, generics, and others in kits
Corticosteroid

Nasal spray:
Nasacort Allergy 24HR, Nasal Allergy 24 Hour, and generics [OTC]: 55 mCg/actuation (60 actuations per 10.8 mL, 120 actuations per 16.9 mL); contains benzalkonium chloride, polysorbate 80, and EDTA.
Nasacort Allergy 24 HR Children [OTC]: 55 mCg/actuation (60 actuations per 10.8 mL); contains DTA

TRIAMCINOLONE *continued*

Cream:
Triderm and generics: 0.1% (15, 28.4, 30, 85.2, 454 g); contains propylene glycol
Generics: 0.025% (15, 80, 454 g), 0.5% (15 g)
Ointment:
Generics: 0.025%, 0.1% (15, 80, 454 g)
Trianex and generics, 0.5% (15, 430 g)
Lotion: 0.025%, 0.1% (60 mL)
Topical aerosol:
Kenalog and generics: 0.2 mg/2 second spray, each g of spray contains 0.147 mg triamcinolone acetate (63, 100 g); contains 10.3% alcohol
Dental paste:
Oralone and generics: 0.1% (5 g)
See Chapter 10 for potency rankings and sizes of topical preparations.
Injection as acetonide: 10 mg/mL (Kenalog-10 and generics) (5 mL), 40 mg/mL (Kenalog-40 and generics) (1, 5, 10 mL), 80 mg/mL (Kenalog-80) (1, 5 mL); contains benzyl alcohol and polysorbate 80
Kits (all contain benzyl alcohol and polysorbate 80):
P-Care K40, Pod-Care 100K: 40 mg/mL (1 × 1 mL)
P-Care K80, Pro-C-Dure 5: 40 mg/mL (2 × 1 mL)
Pro-C-Dure 6: 40 mg/mL (3 × 1 mL)

Intranasal (titrate to lowest effective dose after symptoms are controlled; discontinue use if no relief of symptoms occurs after 3 weeks of use):
Child 2–5 yr: 1 spray in each nostril once daily (110 mCg/24 hr; starting and **max. dose**).
Child 6–11 yr: Start with 1 spray in each nostril once daily (110 mCg/24 hr). If no benefit in 1 wk, dose may be increased to the **max. dose** of 2 sprays in each nostril once daily (220 mCg/24 hr). Decrease dose back to 1 spray each nostril when symptoms are controlled.
≥12 yr and adult: 2 sprays in each nostril once daily (220 mCg/24 hr; starting and **max. dose**). Decrease dose to 1 spray each nostril when symptoms are controlled.
Topical cream or ointment:
Infant, child, and adult: Apply a thin film to affected areas BID–TID for topical concentrations of 0.1% or 0.5% and BID–QID for 0.025% or 0.05%.
Topical spray or lotion:
Infant, child, and adult: Spray or apply to affected area TID–QID
SYSTEMIC USE (see remarks):
Anti-inflammatory and allergic condition:
Child and adolescent (use 40 or 80 mg/mL strength, deep IM into gluteal muscle):
0.11–1.6 mg/kg/24 hr IM ÷ TID–QID
Intralesional for dermatosis:
≥12 yr and adult (use 10 mg/mL strength): Inject up to 1 mg/site × 1 and may be repeated × 1 or more times weekly. May give separate doses in sites ≥1 cm apart, **not to exceed** 30 mg.

NASAL USE: Rare reports of bone mineral density loss and osteoporosis have been reported with prolonged use of inhaled dosage form. Nasal preparations may cause epistaxis, cough, fever, nausea, throat irritation, dyspepsia, and fungal infections (rarely). Shake intranasal dosage forms before each use.
TOPICAL USE: Topical preparations may cause dermal atrophy, telangiectasias, and hypopigmentation. HPA axis suppression, Cushing syndrome, and intracranial hypertension have been reported in children with topical use. Topical steroids should be used with caution on the face and in intertriginous areas. See Chapter 8. **Avoid** spraying the eye or inhaling the topical aerosol dosage form. Aerosol dosage form is flammable.

For explanation of icons, see p. 667

TRIAMCINOLONE *continued*

INJECTABLE USE: Anaphylaxis has been reported with use of the injectable dosage form. Dosage adjustment for hepatic failure with systemic use may be necessary. Triamcinolone is a substrate of the CYP 450 3A4 enzyme; inhibitors of this enzyme may increase risk for side effects. **Use with caution** in thyroid dysfunction, respiratory TB, ocular herpes simplex, peptic ulcer disease, osteoporosis, hypertension, CHF, myasthenia gravis, ulcerative colitis, and renal dysfunction. With systemic use, pregnancy category changes to "D" if used in the first trimester. **Avoid** IV administration with injectable dosage forms. Injectable forms contain benzyl alcohol.

TRIAMTERENE
Dyrenium and generics
Diuretic, potassium sparing

Caps: 50, 100 mg

Hypertension:
Child: 1–2 mg/kg/24 hr PO ÷ BID. May increase up to a **max.** of 3–4 mg/kg/24 hr up to 300 mg/24 hr.
Adult: 50–100 mg/24 hr ÷ once daily–BID PO; **max. dose:** 300 mg/24 hr.

Do not use if GFR <10 mL/hr or in severe hepatic disease. **Adjust dose in renal impairment (see Chapter 31)** and cirrhosis. Monitor serum electrolytes. May cause hyperkalemia, hyponatremia, hypomagnesemia, and metabolic acidosis. Interstitial nephritis, thrombocytopenia, and anaphylaxis have been reported.

Concurrent use of ACE inhibitors may increase serum potassium. **Use with caution** when administering medications with high potassium load (e.g., some penicillins) and in patients with hepatic impairment or on high potassium diets. Cimetidine may increase effects. This drug is also available as a combination product with hydrochlorothiazide; erythema multiforme and toxic epidermal necrolysis have been reported with this combination product. Administer doses with food to minimize GI upset. Pregnancy category changes to "D" if used in pregnancy-induced hypertension.

TRIFLURIDINE
Generics; previously available as Viroptic
Antiviral, ophthalmic

Ophthalmic solution: 1% (7.5 mL); contains thimerosal

Herpes keratoconjunctivitis:
≥6 yr, adolescent and adult: Instill 1 drop into affected eye(s) Q2 hr while awake up to a **maximum** of 9 drops/24 hr. Reduce dose when there is re-epithelialization of the corneal ulcer to 1 drop Q4 hr (**minimum** 5 drops/24 hr) × 7 days. If improvement does not occur in 7–14 days, consider alternative therapy. **DO NOT EXCEED** 21 days of treatment.

Burning sensation in eyes and palpebral edema are common side effects. Rare cross sensitivity with idoxuridine, increased intraocular pressure, keratoconjunctivitis, and ocular hyperemia have been reported.

Avoid touching the applicator tip to eye, fingers, or other surfaces, and do not wear contact lenses during treatment of ocular infections. Apply pressure to the lacrimal sac during and for 1–2 min after dose administration to reduce risk of systemic absorption.

Store medication in the refrigerator (2–8°C). Storage at room temperature will result in a decrease in pH to cause stinging and ocular discomfort when in use.

TRIKAFTA

See Elexacaftor/Tezacaftor/Ivacaftor

TRILISATE

See Choline Magnesium Trisalicylate

TRIMETHOBENZAMIDE HCL

Tigan and generics

Antiemetic

Caps: 300 mg

Injection (Tigan): 100 mg/mL (2, 20 mL); multidose vials may contain 0.45% phenol

Child (PO): 15–20 mg/kg/24 hr ÷ TID–QID.

Alternative dosing:

<13.6 kg: 100 mg TID–QID

13.6–40 kg: 100–200 mg/dose TID–QID

>40 kg: 300 mg/dose TID–QID

Adult:

PO: 300 mg/dose TID–QID

IM: 200 mg/dose TID–QID

Do not use in premature or newborn infants. **Avoid** use in patients with hepatotoxicity, acute vomiting, medications with CNS depressant effects, or allergic reaction. CNS disturbances are common in children (extrapyramidal symptoms, drowsiness, confusion, dizziness). Hypotension, especially with IM use, may occur. **IM not recommended in children.** Consider reducing dosage in the presence of renal impairment since a significant amount of drug is excreted and eliminated by the kidney.

TRIMETHOPRIM AND SULFAMETHOXAZOLE

See Sulfamethoxazole and Trimethoprim

U

URSODIOL

Actigall, Urso 250, Urso Forte, and generics

Gallstone solubilizing agent, cholelitholytic agent

Oral suspension: 20, 25, 50, 60 mg/mL

Caps (Actigall and generics): 300 mg

Tabs:

Urso 250 and generics: 250 mg

Urso Forte and generics: 500 mg

Continued

For explanation of icons, see p. 667

URSODIOL *continued*

Biliary atresia:
Infant and child (limited data): 10–20 mg/kg/24 hr ÷ BID–TID PO
Pruritis from cholestasis:
Infant, child, and adolescent (limited data): 15–30 mg/kg/24 hr ÷ once daily –BID PO
TPN-induced cholestasis:
Infant and child (limited data): 30 mg/kg/24 hr ÷ TID PO
Cystic fibrosis (to improve fatty acid metabolism in liver disease; limited data):
Child: 15–30 mg/kg/24 hr ÷ BID–TID PO
Gallstone dissolution:
Adult: 8–10 mg/kg/24 hr ÷ BID–TID PO

Contraindicated in calcified cholesterol stones, radiopaque stones, bile pigment stones, or stones >20 mm in diameter. **Use with caution** in patients with nonvisualizing gallbladder and chronic liver disease. May cause GI disturbance, rash, arthralgias, anxiety, headache, and elevated liver enzymes (elevated ALT, AST, alkaline phosphatase, bilirubin, GGT). Monitor LFTs every month for the first 3 months after initiating therapy and every 6 months thereafter. Thrombocytopenia has been reported in clinical trials.

Aluminum-containing antacids, cholestyramine, and oral contraceptives decrease ursodiol effectiveness. Dissolution of stones may take several months. Stone recurrence occurs in 30% to 50% of patients within 5 yr.

V

VALACYCLOVIR
Valtrex and generics
Antiviral agent

Tabs/Caplets: 500, 1000 mg
Oral suspension: 50 mg/mL

Child: Recommended dosages based on steady-state pharmacokinetic data in immunocompromised children. Efficacy data is incomplete.
To mimic an IV acyclovir regimen of 250 mg/m²/dose or 10 mg/kg/dose TID:
30 mg/kg/dose PO TID OR alternatively by weight:
4–12 kg: 250 mg PO TID
13–21 kg: 500 mg PO TID
22–29 kg: 750 mg PO TID
≥30 kg: 1000 mg PO TID
To mimic a PO acyclovir regimen of 20 mg/kg/dose 4 or 5 times a day:
20 mg/kg/dose PO TID OR alternatively by weight:
6–19 kg: 250 mg PO TID
20–31 kg: 500 mg PO TID
≥32 kg: 750 mg PO TID
Chickenpox (immunocompetent patient; initiate therapy at earliest signs or symptoms, within 24 hr of rash onset):
Infant ≥3 mo, child, and adolescent: 20 mg/kg/dose PO TID × 5 days; **max. dose**: 1 g/dose TID
HSV treatment (immunocompetent):
Child 3 mo–11 yr: 20 mg/kg/dose PO BID (**max. dose**: 1000 mg/dose) × 7–10 days

VALACYCLOVIR *continued*

Herpes zoster (shingles; see remarks):

Adult (immunocompetent): 1 g/dose PO TID × 7 days within 48–72 hours of onset of rash.

Genital herpes:

Adolescent and adult:

Initial episodes: 1 g/dose PO BID × 10 days.

Recurrent episodes: 500 mg/dose PO BID × 3 days

Suppressive therapy:

Immunocompetent patient: 500–1000 mg/dose PO once daily × 1 year, then reassess for recurrences. Patients with <9 recurrences per yr may be dosed at 500 mg/dose PO once daily × 1 yr.

Herpes labialis (cold sores; initiated at earliest symptoms):

≥12 yr and adult:

Immunocompetent: 2 g/dose PO Q12 hr × 2 doses (1 day)

HIV positive: 1 g/dose PO Q12 hr × 5–10 days

This pro-drug is metabolized to acyclovir and L-valine with better oral absorption than acyclovir. **Use with caution in hepatic or renal insufficiency (adjust dose; see Chapter 31).** Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) has been reported in patients with advanced HIV infection and in bone marrow and renal transplant recipients. Probenecid or cimetidine can reduce the rate of conversion to acyclovir. Headache, nausea, and abdominal pain are common adverse events in adults. Headache is common in children. See Acyclovir for additional drug interactions and adverse effects.

For initial episodes of genital herpes, therapy is most effective when initiated within 48 hr of symptom onset. Therapy should be initiated immediately after the onset of symptoms in recurrent episodes (no efficacy data when initiating therapy >24 hr after onset of symptoms). Data are not available for use as suppressive therapy for periods >1 yr.

Valacyclovir **CANNOT** be substituted for acyclovir on a one-to-one basis. Doses may be administered with or without food.

VALGANCICLOVIR
Valcyte and generics
Antiviral agent

Tabs: 450 mg

Oral solution: 50 mg/mL (88 mL); contains saccharin and sodium benzoate

Oral suspension: 60 mg/mL

Neonate and infant:

Symptomatic congenital CMV (from pharmacokinetic [PK] data in 8 infants 4–90 days old (mean: 20 days) and 24 neonates 8–34 days old): 15–16 mg/kg/dose PO BID produced similar levels to IV ganciclovir 6 mg/kg/dose BID. A comparison of 6 weeks vs. 6 months of therapy in 96 neonates (>32 wk gestation and ≥1.8 kg) showed modest improvement in long-term hearing and developmental outcomes at 1–2 yr of age with the longer duration of therapy of 6 months.

Child (1 mo–16 yr):

CMV prophylaxis in kidney (4 mo–16 yr), heart (1 mo–16 yr), or liver (4 mo–16 yr) transplantation (see remarks): Once daily PO dosage initiated within 10 days of transplantation is calculated with the following equation:

Daily mg dose (**max. dose**: 900 mg) = 7 X BSA X CrCl. BSA is determined by the Mosteller equation and CrCL is determined by a modified Schwartz equation (**max. value**: 150 mL/min/1.73m^2).

Mosteller BSA (m^2) equation: square root of [(height (cm) X weight (kg)) ÷ 3600]

For explanation of icons, see p. 667

VALGANCICLOVIR *continued*

Modified Schwartz (mL/min/1.73 m²) equation (max. value: 150 mL/min/1.73 m²): k X height (cm) ÷ serum creatinine (mg/dL); where k = 0.33 if patient is <1 yr old with low birth weight for gestational age; k = 0.45 if patient is <1 yr old with birth weight appropriate for gestational age or if patient is 1 to <2 yr old; k = 0.55 for males 2 to <13 yr old and females aged 2 to <16 yr old or; k = 0.7 if males 13–16 yr old.

Duration of therapy:

Kidney transplantation (≥4 mo to 16 yr): 200 days

Heart transplantation (≥1 mo to 16 yr): 100 days

Liver transplantation (≥4 mo to 16 yr): 100–200 days; limited data.

Adolescent (>16 yr) and adult:

CMV retinitis:

Induction therapy: 900 mg PO BID × 14–21 days with food

Maintenance therapy: 900 mg PO once daily with food for a minimum of 3–6 mo.

CMV prophylaxis in heart, kidney, and kidney-pancreas transplantation: 900 mg PO once daily starting within 10 days of transplantation until 100 days post heart or kidney-pancreas transplantation; or until 200 days post kidney transplantation.

This pro-drug is metabolized to ganciclovir with better oral absorption than ganciclovir. **Contraindicated** with hypersensitivity to valganciclovir/ganciclovir; ANC <500 mm³; platelets <25,000 mm³; hemoglobin <8 g/dL; and patients on hemodialysis. **Use with caution in renal insufficiency (adjust dose; see Chapter 31)**, preexisting bone marrow suppression, or receiving myelosuppressive drugs or irradiation. Has not been evaluated in hepatic impairment. May cause headache, insomnia, peripheral neuropathy, diarrhea, vomiting, neutropenia, anemia, and thrombocytopenia. Neutropenia incidence is greater at day 200 versus day 100 in pediatric kidney transplant patients.

Use effective contraception during and for at least 90 days after therapy; may impair fertility in men and women. See Ganciclovir for drug interactions and additional adverse effects.

Monitor CBC with differential, platelets, and serum creatinine at baseline and periodically during therapy. Consider changes in serum creatinine and body changes to height and body weight for prophylaxis dosing.

Valganciclovir **CANNOT** be substituted for ganciclovir on a one-to-one basis. All doses are administered with food. **Avoid** direct skin or mucous membrane contact with broken or crushed tablets.

VALPROIC ACID
Generics; previously available as Depakene (PO) and Depacon (IV)
[Depakote: See Divalproex Sodium]
Anticonvulsant

Caps: 250 mg
Oral solution: 250 mg/5 mL (473 mL); may contain parabens
Injection: 100 mg/mL (5mL)

Seizures (PO):

Initial: 10–15 mg/kg/24 hr ÷ once daily–TID

Increment: 5–10 mg/kg/24 hr at weekly intervals to **max. dose** of 60 mg/kg/24 hr.

Maintenance: 30–60 mg/kg/24 hr ÷ BID–TID. Due to drug interactions, higher doses (up to 100 mg/kg/24 hr ÷ TID–QID) may be required in children on other anticonvulsants. If using divalproex sodium, administer BID.

VALPROIC ACID *continued*

Intravenous route (use only when PO is not possible):

Use same PO daily dose ÷ Q6 hr. Convert back to PO as soon as possible.

Rectal route (use syrup, diluted 1:1 with water, given PR as a retention enema):

Load: 20 mg/kg/dose

Maintenance: 10–15 mg/kg/dose Q8 hr

Migraine prophylaxis:

Child (limited data): Start at 10–15 mg/kg/24 hr PO ÷ BID (**max. initial dose:** 250 mg/dose). If needed, increase dose over 4–6 wk to 40–45 mg/kg/24 hr PO ÷ BID up to a **maximum** of 1000 mg/24 hr. Alternative dosing for child ≥12 yr is 250 mg PO BID (**max. dose**: 1000 mg/24 hr).

Adult: Start with 500 mg/24 hr ÷ PO BID. Dose may be gradually increased to a **max.** of 1000 mg/24 hr ÷ PO BID. If using divalproex sodium extended-release tablets, administer daily dose once daily.

Contraindicated in hepatic disease, pregnancy (for migraine indication), urea cycle disorders (e.g., OTC deficiency), mitochondrial disorders with mutations in DNA polymerase γ (e.g., Alpers-Huttenlocher syndrome), and children <2 yr suspected of the aforementioned mitochondrial disorder. May cause GI, liver, blood, and CNS toxicity; weight gain; transient alopecia; pancreatitis (potentially life-threatening); nausea; sedation; vomiting; headache; thrombocytopenia (dose-related); platelet dysfunction; rash (especially with lamotrigine); and hyperammonemia. Hepatic failure has occurred especially in children <2 yr (especially those receiving multiple anticonvulsants, with congenital metabolic disorders, with severe seizure disorders with mental retardation, and with organic brain disease). Idiosyncratic life-threatening pancreatitis has been reported in children and adults. Hyperammonemic encephalopathy has been reported in patients with urea cycle disorders. Suicidal behavior or ideation, male infertility, elevated testosterone, decreased bone mineral density, DRESS, encephalopathy without elevated ammonia levels, hair texture/color changes, and nail/nail bed disorders have been reported.

Valproic acid is a substrate for CYP 450 2C19 isoenzyme and an inhibitor of CYP 450 2C9, 2D6 and 3A3/4 (weak). It increases amitriptyline/nortriptyline, rufinamide, phenytoin, propofol, diazepam, and phenobarbital levels. Concomitant estrogen-containing contraceptives, phenytoin, phenobarbital, topiramate, meropenem, cholestyramine, and carbamazepine may decrease valproic acid levels. Amitriptyline or nortriptyline may increase valproic acid levels. May interfere with urine ketone and thyroid tests.

Do not give syrup with carbonated beverages. Use of IV route has not been evaluated for >14 days of continuous use. Infuse IV over 1 hr up to a **max. rate** of 20 mg/min. Depakote and Depakote ER are **NOT** bioequivalent; see package insert for dose conversion.

Therapeutic levels: 50–100 mg/L. Recommendations for serum sampling at steady state: Obtain trough level within 30 min prior to the next scheduled dose after 2–3 days of continuous dosing. Levels of 50–60 mg/L and as high as 85 mg/L have been recommended for bipolar disorders. Monitor CBC and LFTs prior to and during therapy.

Valproic acid and divalproex should not be used in pregnant women. Increased risk of neural tube defects, decreased child IQ scores, craniofacial defects, and cardiovascular malformations have been reported in babies exposed to valproic acid and divalproex sodium.

Pregnancy category is "X" when used for migraine prophylaxis and is "D" for all other indications.

VALSARTAN

Diovan and generics

Angiotensin II Receptor Blocker, antihypertensive agent

Tabs: 40, 80, 160, 320 mg

Oral suspension: 4 mg/mL

For explanation of icons, see p. 667

VALSARTAN *continued*

Hypertension (see remarks):

Child 1–5 yr (≥8 kg; limited data): A reported range of 0.4–3.4 mg/kg/dose PO once daily with the following **maximum doses:**

<18 kg: 40 mg/24 hr

≥18 kg: 80 mg/24 hr

Child 6–16 yr: Start at 1.3 mg/kg/dose (**max. dose**: 40 mg) PO once daily. Dose may be increased up to the 2.7 mg/kg/dose up to 160 mg (whichever is lower); doses greater than this have not been studied.

Adolescent ≥17 yr and adult (non-volume depleted status): Start 80 or 160 mg PO once daily; usual dose range is 80–320 mg once daily. **Max. dose**: 320 mg/24 hr.

Contraindicated with aliskiren use in diabetic patients. Discontinue use immediately after when pregnancy is detected. **Use with caution** in renal (CrCl <30 mL/min) and liver insufficiency, heart failure, post-myocardial infarction, renal artery stenosis, renal function changes, and volume depletion.

Hypotension, dizziness, headache, cough, and increases in BUN and sCr are common side effects. Hyperkalemia (most commonly reported in children <6 yr with underlying renal disease in clinical trials; also consider salt substitutes, foods, and medications which may increase potassium levels), bullous dermatitis, angioedema, acute renal failure, and dysgeusia have been reported. May increase lithium levels resulting in toxicity for those receiving concurrent lithium therapy; monitor lithium levels closely.

Onset of initial antihypertensive effects is 2 hr with maximum effects after 2–4 wk of chronic use. Patients may require higher doses of oral tablet dosage form than with the oral suspension due to increased bioavailability with the oral suspension.

VANCOMYCIN

Vancomycin, Firvanq, and generics

Antibiotic, glycopeptide

Injection: 0.25, 0.5, 0.75, 1, 1.5, 5, 10 g

Premixed injection:

In D5W or NS: 500 mg/100 mL, 750 mg/150 mL, 1000 mg/200 mL

In water and polyethylene glycol: 500 mg/100 mL, 1000 mg/200 mL, 1500 mg/300 mL, and 2000 mg/400 mL; contains D-alanine and L-lysine

Caps: 125, 250 mg

Oral solution: 25 mg/mL

Firvanq and generics: 25 mg/mL (80, 150, 300 mL); may contain sodium benzoate

Firvanq: 50 mg/mL (150, 210, 300 mL); may contain sodium benzoate

Initial empiric dosage; patient-specific dosage defined by therapeutic drug monitoring (see remarks).

Neonate, IV (see following table for dosage interval):

Bacteremia: 10 mg/kg/dose

Meningitis, pneumonia: 15 mg/kg/dose

Post-menstrual age (weeks)[a]	Post-natal age (days)	Dosage interval (hr)
≤29	0–14	18
	>14	12
30–36	0–14	12
	>14	8
37–44	0–7	12
	>7	8
≥45	All	6

VANCOMYCIN *continued*

Infant, child, adolescent, and adult, IV:

Age	General dosage	CNS infections, endocarditis, osteomyelitis, pneumonia, and septic arthritis
1 mo–12 yr	15 mg/kg/dose Q6 hr	20 mg/kg/dose Q6 hr
Adolescent (>12 to <18 yr)[a]	15 mg/kg/dose Q6–8 hr	20 mg/kg/dose Q6–8 hr
Adult (\ge 18 yr)	15 mg/kg/dose Q8–12 hr	20 mg/kg/dose (max. 2 g) Q8--12 hr

[a]Use Q8 hr dosing interval for older adolescent

Clostridium difficile colitis (PR route of administration may be preferable for complete ileus):

Child: 40–50 mg/kg/24 hr ÷ Q6 hr PO × 7–10 days

Max dose: 500 mg/24 hr; higher maximum of 2 g/24 hr have also been used for severe/fulminant disease.

Adult: 125 mg/dose PO Q6 hr × 7–10 days; dosages as high as 2 g/24 hr ÷ Q6–8 hr have also been used for severe/fulminant disease.

Endocarditis prophylaxis for GU or GI (excluding esophageal) procedures (complete all antibiotic dose infusion(s) within 30 min of starting procedure):

Moderate-risk patients allergic to ampicillin or amoxicillin:

Child: 20 mg/kg/dose (max. 1 g/dose) IV over 1–2 hr × 1

Adult: 1 g/dose IV over 1–2 hr × 1

High-risk patients allergic to ampicillin or amoxicillin:

Child and adult: Same dose as moderate-risk patients plus gentamicin 1.5 mg/kg/dose (**max. dose**: 120 mg/dose) IV/IM ×1

Ototoxicity and nephrotoxicity may occur and may be exacerbated with concurrent aminoglycoside use. Greater nephrotoxicity risk has been associated with higher therapeutic serum trough concentrations (≥15 mg/mL), concurrent piperacillin/tazobactam therapy, and receiving furosemide in the intensive care unit. **Adjust dose in renal failure (see Chapter 31).** Use total body weight for obese patients when calculating dosages. Low concentrations of the drug may appear in CSF with inflamed meninges. Nausea, vomiting, and drug-induced erythroderma are common with IV use. "Red man syndrome" associated with rapid IV infusion may occur. Infuse over 60 min (may infuse over 120 min if 60-min infusion is not tolerated). **NOTE:** Diphenhydramine is used to reverse red man syndrome. Allergic reactions (including drug rash with eosinophilia and systemic symptoms [DRESS]), neutropenia, and immune-mediated thrombocytopenia have been reported.

Although current extrapolated adult guidelines suggest measuring only trough levels, an additional post-distributional level may be useful in characterizing enhanced/altered drug clearance for quicker dosage modification to attain target levels; this may be useful for infants with known faster clearance and patients in renal compromise. Consult a pharmacist.

The following therapeutic trough level recommendations are based on the assumption that the pathogen's Vancomycin MIC is ≤ 1 mg/L.

Indication	Goal trough level
Uncomplicated skin and soft tissue infection, uncomplicated bacteremia, febrile neutropenia, sepsis	10–15 mg/L
CNS infections, endocarditis, pneumonia, osteomyelitis, septic arthritis	15–19 mg/L

Peak level measurement (20–50 mg/L) has also been recommended for patients with burns, clinically nonresponsive in 72 hr of therapy, persistent positive cultures, and CNS infections (≥30 mg/L).

For explanation of icons, see p. 667

VANCOMYCIN *continued*

Recommended serum sampling time at steady state: Trough within 30 min prior to the fourth consecutive dose and peak 60 min after the administration of the fourth consecutive dose. Infants with faster elimination (shorter $T_{1/2}$) may be sampled around the third consecutive dose.

Recent evidence strongly suggests moving away from serum trough vancomycin monitoring to a pharmacokinetic/pharmacodynamics (PK/PD) target of area under the curve (AUC) to MIC ratio. An $AUC_{(24)}$ of 400–600 mg*h/L is associated with clinical efficacy and reduced risk for AKI. Vancomycin therapeutic monitoring guidelines are currently being revised by the IDSA in collaboration with PIDS, SIDP, and ASHP and are forthcoming. Consult with an ID specialist and pharmacist to see how best this monitoring method is operationalized at your institution.

ORAL USE for C. difficile: Vancomycin (PO) or metronidazole (PO) are currently the recommended first-line therapy for children, whereas vancomycin (PO) or fidaxomicin is recommended for adults. See Clinical Infectious Diseases 66(7):e1–e48 for the 2017 IDSA/SHEA Clinical Practice Guidelines. Common adverse effects with oral vancomycin capsules in adults include nausea, abdominal pain, and hypokalemia.

Pregnancy category "C" for the intravenous route and "B" for the oral route of administration.

VARICELLA-ZOSTER IMMUNE GLOBULIN (HUMAN)
VariZig, VZIG
Hyperimmune globulin, varicella-zoster


C 2 No No No

Injection: 125 Units (1.2 mL); contains 10% maltose, 0.03% polysorbate 80, and <40 mCg/mL IgA; preservative free. May contain low levels of anti-Protein S antibodies.

Dose should be given within 48 hr of varicella exposure and no later than 96 hr post exposure. IM administration:
<2 kg: 62.5 Units
2.1–10 kg: 125 Units
10.1–20 kg: 250 Units
20.1–30 kg: 375 Units
30.1–40 kg: 500 Units
>40 kg: 625 Units
Max. dose: 625 Units/dose

If patient is high risk and re-exposed to varicella for more than 3 weeks after a prior dose, another full dose may be given.

Contraindicated in severe thrombocytopenia due to IM injection, immunoglobulin A-deficiency (anaphylactic reactions may occur), and known immunity to varicella zoster virus. See Chapter 16 for indications. Local discomfort, redness, and swelling at the injection site, and headache may occur.

Hyperviscosity of the blood may increase risk for thrombotic events. Interferes with immune response to live virus vaccines such as measles, mumps and rubella; defer administration of live vaccines 6 mo or longer after VZIG dose. See latest AAP Red Book for additional information.

Avoid IM injection into the gluteal region due to risk for sciatic nerve damage and **do not exceed** age-specific **single max. IM injection** volume.

VASOPRESSIN
Vasostrict, generics, 8-Arginine Vasopressin; previously available as Pitressin
Antidiuretic hormone analog

Injection: 20 Units/mL (aqueous) (1, 10 mL); may contain 0.5% chlorobutanol, especially in the 10 mL multidose vial

Diabetes insipidus: Titrate dose to effect (see remarks).
SC/IM:
Child: 2.5–10 Units BID–QID
Adult: 5–10 Units BID–TID
Continuous infusion (adult and child): Start at 0.5 milliunit/kg/hr (0.0005 Units/kg/hr). Increase dosage by 0.5 milliunit/kg/hr every 10 min PRN up to **max. dose** of 10 milliunit/kg/hr (0.01 Units/kg/hr).
Growth hormone and corticotropin provocative tests:
Child: 0.3 Units/kg IM; **max. dose**: 10 Units
Adult: 10 Units IM
GI hemorrhage (IV; NOTE: dosage metric is Units/kg/min for children and Units/min for adults):
Child: Start at 0.002–0.005 Units/kg/min. Increase dose as needed to **max. dose** of 0.01 Units/kg/min.
Adult: Start at 0.2–0.4 Units/min. Increase dose as needed to **max. dose** of 0.8 Units/min.
Cardiac arrest, ventricular fibrillation, and pulseless ventricular tachycardia:
Child (use following 2 doses of epinephrine; limited data): 0.4 Units/kg IV × 1
Vasodilatory shock with hypotension (unresponsive to fluids and pressors; NOTE: dosage metric is Units/kg/min for children and Units/min for adults):
Infant, child, adolescent (various reports): 0.00017–0.008 Units/kg/min via continuous IV infusion in combination with pressors.
Adult: 0.01–0.04 Units/min via continuous IV infusion in combination with pressors.

Use with caution in seizures, migraine, asthma, and renal, cardiac, or vascular diseases. Side effects include tremor, sweating, vertigo, abdominal discomfort, nausea, vomiting, urticaria, anaphylaxis, hypertension, and bradycardia. May cause vasoconstriction, water intoxication, and bronchoconstriction. Drug interactions: lithium, demeclocycline, heparin, and alcohol reduces activity; carbamazepine, tricyclic antidepressants, fludrocortisone, and chlorpropamide increases activity.
Do not abruptly discontinue IV infusion (taper dose). Patients with variceal hemorrhage and hepatic insufficiency may respond to lower dosages. Monitor fluid intake and output, urine specific gravity, urine and serum osmolality, plasma osmolality, and sodium.

VECURONIUM BROMIDE
Various generics; previously available as Norcuron
Nondepolarizing neuromuscular blocking agent

Injection: 10, 20 mg; contains mannitol

Neonate:
Initial: 0.1 mg/kg/dose IV
Maintenance: 0.03–0.15 mg/kg/dose IV Q1–2 hr PRN
Infants (>7 wk to 1 yr) (see remarks):
Initial: 0.08–0.1 mg/kg/dose IV
Maintenance: 0.05–0.1 mg/kg/dose IV Q1 hr PRN; may administer via continuous infusion at 0.06–0.09 mg/kg/hr IV

For explanation of icons, see p. 667

VECURONIUM BROMIDE *continued*

>1 yr–adult (see remarks):

Initial: 0.08–0.1 mg/kg/dose IV

Maintenance: 0.05–0.1 mg/kg/dose IV Q1 hr PRN; may administer via continuous infusion at 0.09–0.15 mg/kg/hr IV.

Use with caution in patients with renal or hepatic impairment, and neuromuscular disease. Dose reduction may be necessary in hepatic insufficiency. Infants (7 wk to 1 yr) are more sensitive to the drug and may have a longer recovery time. Children (1–10 yr) may require higher doses and more frequent supplementation than adults. Enflurane, isoflurane, aminoglycosides, β-blockers, calcium channel blockers, clindamycin, furosemide, magnesium salts, quinidine, procainamide, and cyclosporine may increase the potency and duration of neuromuscular blockade. Calcium, caffeine, carbamazepine, phenytoin, steroids (chronic use), acetylcholinesterases, and azathioprine may decrease effects. May cause arrhythmias, rash, and bronchospasm. Severe anaphylactic reactions have been reported.

Neostigmine, pyridostigmine, or edrophonium are antidotes. Onset of action within 1–3 min. Duration is 30–40 min. **See Chapter 1 for rapid sequence intubation.**

VERAPAMIL

Calan, Calan SR, Verelan, Verelan PM, and generics

Calcium channel blocker

C | 2 | Yes | Yes | No

Tabs: 40, 80, 120 mg

Extended/sustained-release tabs (Calan SR and generics): 120, 180, 240 mg

Extended/sustained-release caps (Verelan, Verelan PM and generics; for q24 hr dosing): 100, 120, 180, 200, 240, 300, 360 mg

Injection: 2.5 mg/mL (2, 4 mL)

Oral suspension: 50 mg/mL

IV for dysrhythmias: Give over 2–3 min. May repeat once after 30 min.

1–16 yr, for PSVT: 0.1–0.3 mg/kg/dose × 1 may repeat dose in 30 min; **max. dose:** 5 mg first dose, 10 mg second dose.

Adult, for SVT: 5–10 mg (0.075–0.15 mg/kg) × 1 may administer second dose of 10 mg (0.15 mg/kg) 15–30 min later.

Hypertension (PO):

Adult:

Immediate release dosage forms: 120–360 mg/24 hr PO ÷ TID

Sustained release dosage forms: 200–480 mg/24 hr PO once daily. **Max. dose**: 480 mg/24 hr (400 mg/24 hr for Verelan PM).

No longer recommended as an antihypertensive agent for children. **Contraindications** include hypersensitivity, cardiogenic shock, severe CHF, sick sinus syndrome, or AV block. **Use with caution** in hepatic and renal **(reduce dose in renal insufficiency; see Chapter 31)** impairment. **Owing to negative inotropic effects, verapamil should not be used to treat SVT in an emergency setting in infants. Avoid IV use** in neonates and young infants due to apnea, bradycardia and hypotension. May cause constipation, headache, dizziness, edema, and hypotension. EPS has been reported.

Monitor ECG. **Have calcium and isoproterenol available to reverse myocardial depression.** May decrease neuromuscular transmission in patients with Duchenne muscular dystrophy and worsen myasthenia gravis.

VERAPAMIL *continued*

Drug is a substrate of CYP 450 1A2 and 3A3/4, and an inhibitor of CYP 3A4 and P-gp transporter. Barbiturates, sulfinpyrazone, phenytoin, vitamin D, and rifampin may decrease serum levels/effects of verapamil; erythromycin, quinidine, and grapefruit juice may increase serum levels/effects. Verapamil may increase effects/toxicity of β-blockers (severe myocardial depression), carbamazepine, cyclosporine, sirolimus, everolimus, digoxin, ethanol, fentanyl, lithium, nondepolarizing muscle relaxants, prazosin, and tizanidine. Use with telithromycin has resulted in hypotension, bradyarrhythmias, and lactic acidosis. Bradycardia has been reported with concurrent use of clonidine, and increased bleeding times has been reported with use with aspirin.

Do not crush or chew extended-release dosage forms.

VIGABATRIN
Sabril, Vigadrone, and generics
Anticonvulsant

Tabs (Sabril and generics): 500 mg
Powder for oral solution (Sabril, Vigadrone, and generics): 500 mg per packet to be dissolved in 10 mL water (50s)

Infantile spams (1 mo–2 yr; see remarks for discontinuation of therapy): Start at 50 mg/kg/24 hr ÷ BID PO, if needed and tolerated, may titrate dosage upwards by 25–50 mg/kg/24 hr increments Q3 days up to a **maximum** of 150 mg/kg/24 hr ÷ BID. Withdrawal therapy if no clinical benefit is seen in 2–4 weeks.

Adjunctive therapy for refractory complex partial seizures (withdrawal therapy if no clinical benefit is seen in 3 months; see remarks for discontinuation of therapy):

Child ≥2 yr and ≥10 kg, and adolescent ≥16 yr: Start at 40 mg/kg/24 hr ÷ BID PO, if needed and tolerated, adjust dose to the following maintenance dose:

10–15 kg: 500–1000 mg/24 hr ÷ BID
16–30 kg: 1000–1500 mg/24 hr ÷ BID
31–50 kg: 1500–3000 mg/24 hr ÷ BID
>50 kg: 2000–3000 mg/24 hr ÷ BID

Adolescent (≥16 yr) and adult (see remarks for discontinuation of therapy): Start at 500 mg BID PO, if needed and tolerated, increase daily dose by 500 mg increments at 7-day intervals. Usual recommended dose: 1500 mg BID; **max. dose**: 6000 mg/24 hr. Doses >3 g/24 hr has not shown to provide additional benefit and is associated with more side effects.

Use with caution in renal impairment **(reduce dose; see Chapter 31)** and other CNS depressants (enhanced effects). Can cause progressive and permanent vision loss (risk increases with dose and duration); periodic vision testing is required. Common side effects in children and adults include rash, weight gain, GI disturbances, arthralgia, visual disturbances, vertigo, sedation, headache, confusion, and URIs. Liver failure, anemia, psychotic disorder, angioedema, Stevens Johnson syndrome, TEN, alopecia, and suicidal ideation have been reported. Dose-dependent abnormal MRIs and intramyelinic edema (in postmortem exams) have been reported in infants treated for infantile spasms.

Ketorolac, naproxen, and mefloquine may decrease the effect of vigabatrin. Vigabatrin may decrease the effects/levels of phenytoin but increase the levels/toxicity of carbamazepine.

Use in adjunctive therapy for refractory complex partial seizure has labeled indication for ≥10-yr-old patients when potential benefits outweigh the risk of vision loss.

Continued

For explanation of icons, see p. 667

VIGABATRIN *continued*

DO NOT rapidly withdrawal therapy. Dosage needs to be tapered when discontinuing therapy to minimize increased seizure frequency. The following tapering guidelines have been recommended:
Infant: decrease by 25–50 mg/kg every 3–4 days
Child: decrease dose by 1/3 every 7 days for 3 weeks
Adult: decrease by 1 g/24 hr every 7 days.
Doses may be administered with or without food. Access to this medication is restricted to prescribers and pharmacies registered under a special restricted distribution program (SABRIL REMS Program) in the United States. Call 888-457-4273 or see www.SabrilREMS.com for more information.

VITAMIN A
Aquasol A and generics
Vitamin, fat soluble

Caps [OTC]: 7,500, 8,000, 10,000, 25,000 IU
Tabs [OTC]: 10,000, 15,000 IU
Injection for IM use (Aquasol A): 50,000 IU/mL (2 mL); contains polysorbate 80 and chlorobutanol
Conversion: 10,000 IU is equivalent to 3000 mCg vitamin A

US RDA: See Chapter 21.
Supplementation in measles (a third dose may be administered 2–4 wk after the second dose if patient has ocular signs of vitamin A deficiency or is severely malnourished; see remarks):
<6 mo: 50,000 IU/dose once daily PO × 2 days.
Infant 6 mo to <1 yr: 100,000 IU/dose once daily PO × 2 days.
Child 1–5 yr: 200,000 IU/dose once daily PO × 2 days.
Malabsorption syndrome prophylaxis:
Child >8 yr and adult: 10,000–50,000 IU/dose once daily PO of water miscible product.
Cystic fibrosis (usually dosed in cystic fibrosis specific multi-vitamins; monitor serum concentrations):
Infant: 1,500 IU/dose once daily PO
Child 1–3 yr: 5,000 IU/dose once daily PO
Child 4–8 yr: 5,000–10,000 IU/dose once daily PO
Child ≥9 yr and adolescent: 10,000 IU/dose once daily PO

High doses above the U.S. RDA are teratogenic (category X). The use of vitamin A in measles is recommended in children 6 mo–2 yr of age who are either hospitalized or who have any of the following risk factors: immunodeficiency, ophthalmologic evidence of vitamin A deficiency, impaired GI absorption, moderate to severe malnutrition, and recent immigration from areas with high measles mortality. May cause GI disturbance, rash, headache, increased ICP (pseudotumor cerebri), papilledema, and irritability. Large doses may increase the effects of warfarin. Mineral oil, cholestyramine and neomycin will reduce vitamin A absorption. **Do not** access vitamin A levels during an acute inflammatory condition as falsely low levels have been reported.

VITAMIN B1

See Thiamine

VITAMIN A *continued*

VITAMIN B2

See Riboflavin

VITAMIN B3

See Niacin

VITAMIN B6

See Pyridoxine

VITAMIN B12

See Cyanocobalamin

VITAMIN C

See Ascorbic Acid

VITAMIN D2

See Ergocalciferol

VITAMIN D3

See Cholecalciferol

VITAMIN E/α-TOCOPHEROL
Aqueous Vitamin E, Nutr-E-Sol, and many others including generics
Vitamin, fat soluble

Tabs [OTC]: 100, 200, 400 IU
Caps [OTC]: 100, 200, 400, 1000 IU
Oral solution (Aqueous Vitamin E and generics [OTC]: 50 IU/mL (12, 30 mL); may contain propylene glycol, polysorbate 80, and saccharin
Oral liquid (Nutr-E-sol) [OTC]: 400 IU/15 mL (473 mL)
Conversion: 400 IU is equivalent to 180 mg of vitamin E

Continued

For explanation of icons, see p. 667

VITAMIN E/α-TOCOPHEROL *continued*

US RDA: See Chapter 21.

Vitamin E deficiency, PO: Follow levels.

Use water miscible form with malabsorption.

Neonate: 25–50 IU/24 hr × 1 week followed by recommended dietary intake.

Child: 1 IU/kg/24 hr

Adult: 60–75 IU/24 hr; doses as high as 300 IU/24 hr may be necessary

Cystic fibrosis (use water miscible form; usually dosed in cystic fibrosis specific multi-vitamins):

5–10 IU/kg/24 hr PO once daily; **max. dose**: 400 IU/24 hr.

Adverse reactions include GI distress, rash, headache, gonadal dysfunction, decreased serum thyroxine and triiodothyronine, and blurred vision. Necrotizing enterocolitis has been associated with large doses (>200 units/24 hr) of a hyperosmolar product administered to low birth weight infants. May increase hypoprothrombinemic response of oral anticoagulants (e.g., warfarin), especially in doses >400 IU/24 hr.

In malabsorption, water miscible preparations are better absorbed. Therapeutic levels: 6–14 mg/L.

Pregnancy category changes to "C" if used in doses above the RDA.

VITAMIN K

See Phytonadione

VORICONAZOLE

Vfend and generics

Antifungal, triazole

Tabs: 50, 200 mg; contains povidone

Oral suspension: 40 mg/mL (75 mL); may contain sodium benzoate

Injection: 200 mg; contains 3200 mg sulfobutyl ether β-cyclodextrin (SBECD) (see remarks)

Empiric doses and consider pharmacogenomic based recommendations (see remarks). Between patient and inter-occasion pharmacokinetic variability is high. ***Monitor trough level and adjust dose accordingly.***

Infant and child <2 yr (limited data): Start with 9 mg/kg/dose IV/PO Q12 hr; monitor levels and adjust dose.

Child 2–≤ 12 yr and 12–14 yr weighing <50 kg:

Invasive aspergillosis, candidemia (nonneutropenic), other deep tissue candida infections or other rare molds (e.g., Scedosporium and Fusarium):

Loading dose: 9 mg/kg/dose IV Q12 hr × 2 followed by maintenance dose

Maintenance dose: 8 mg/kg/dose IV Q12 hr and convert to the oral suspension dosage form after significant clinical improvement at a dose of 9 mg/kg/dose PO Q12 hr (**max. dose**: 350 mg Q12 hr). The oral suspension dosage form was used in clinical trials and the bioequivalence of this dosage form and tablets has not been evaluated in children. Dosage increments and decrements of 1 mg/kg (or 50 mg) steps has been recommended for those with inadequate response and who are unable to tolerate their dosage level, respectively.

VORICONAZOLE *continued*

Esophageal candidiasis:

Treatment:

IV: 4 mg/kg/dose Q12 hr

PO: 9 mg/kg/dose Q12 hr; **max. dose:** 350 mg Q12 hr.

Prophylaxis for candidiasis in high-risk AML, ALL, and allogeneic HSCT patients (limited data):

IV: 9 mg/kg/dose Q12 hr × 2 doses followed by 8 mg/kg/dose Q12 hr

PO (oral suspension): 9 mg/kg/dose Q12 hr; **max. dose**: 350 mg/dose.

Child 12–14 yr weighing ≥50 kg, >15 yr (any weight), and adult:

Invasive aspergillosis, candidemia (nonneutropenic), Fusarium/Scedosporiosis, or other serious fungal infections:

Loading dose: 6 mg/kg/dose IV Q12 hr × 2 doses followed by maintenance dose

Maintenance dose:

Candidemia (nonneutropenic): 3–4 mg/kg/dose IV Q12 hr

Invasive aspergillosis, Fusarium/Scedosporiosis, or other serious fungal infections: 4 mg/kg/dose IV Q12 hr; if patient unable to tolerate, reduce dose to 3 mg/kg/dose IV Q12 hr

PO maintenance dose: Initial dose may be increased to the maximum dose when response is inadequate; if dose is not tolerated, reduce dose by 50 mg decrements, until tolerated, with minimum of the initial recommended dose.

<40 kg: 100 mg Q12 hr; **max. dose**: 300 mg/24 hr

≥40 kg: 200 mg Q12 hr; **max. dose**: 600 mg/24 hr

Esophageal candidiasis (treat for a minimum of 14 days and until 7 days after resolution of symptoms): Initial dose may be increased to the maximum dose when response is inadequate by 50 mg increments for patients <40 kg and by 100 mg increments for ≥40 kg. If a titrated dose is not tolerated, reduce dose by 50 mg decrements until tolerated with the minimum of the initial recommended dose.

<40 kg: 100 mg Q12 hr PO; **max. dose**: 300 mg/24 hr

≥40 kg: 200 mg Q12 hr PO; **max. dose**: 600 mg/24 hr

Contraindicated with concomitant administration with rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, rifabutin, ergot alkaloids, or St. John's Wort (decreases voriconazole levels); and with terfenadine, astemizole, cisapride, pimozide, quinidine, or sirolimus (voriconazole increases levels of these drugs to increase side effects). **Use with caution** in proarrhythmic conditions (e.g., congenital/acquired QTc prolongation, cardiomyopathy, and sinus bradycardia), severe hepatic disease, galactose intolerance, and concurrent use with CYP 450 3A4 substrates that can lead to prolonged QTc interval (e.g., cisapride, pimozide, and quinidine).

Drug is a substrate and inhibitor for CYP 450 2C9, 2C19 (major substrate), and 3A4 isoenzymes. Specific CYP 2C19 phenotype and use recommendation for children and adults are as follows:

CYP 450 2C19 Phenotype	Pediatric Use Recommendation	Adult Use Recommendation
Ultrarapid metabolizer	Use alternative medication[a]	Use alternative medication[a]
Rapid metabolizer	Initiate with standard dosing with TDM[b]	Use alternative medication[a]
Intermediate metabolizer	Initiate with standard dosing with TDM[b]	Initiate with standard dosing with TDM[b]
Poor metabolizer	Use alternative medication[a]; if voriconazole must be used, use a lower dose with TDM[b]	Use alternative medication[a]; if voriconazole must be used, use a lower dose with TDM[b]

[a]Alternative medication should not be dependent on CYP 2C19 metabolism and may include agents such as isavuconazole, liposomal amphotericin B, and posaconazole.

[b]TDM= therapeutic drug monitoring

Continued

For explanation of icons, see p. 667

VORICONAZOLE *continued*

Currently approved for use in invasive aspergillosis; candidemia and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds; candidal esophagitis; and serious infections caused by Fusarium species and Scedosporium apiospermum in children ≥2 yr of age.

Common side effects include GI disturbances, fever, headache, hepatic abnormalities, photosensitivity (higher incidence in children; **avoid** direct sunlight and use protective measures), rash (6%), and visual disturbances (30%). Serious but rare side effects include anaphylaxis, liver or renal failure, and Stevens-Johnsons syndrome. Pancreatitis has been reported in children. Monitor serum transaminase and bilirubin levels weekly for the first month of therapy followed by reduced frequency has been recommended. Higher frequency of LFT elevations has reported with children. Dermatological follow up is recommended for those who develop photosensitivity reactions as squamous cell carcinoma has been reported in those who experience this adverse reaction.

Correct potassium, magnesium, and calcium levels before and during voriconazole therapy. **Adjust dose in hepatic impairment** by decreasing only the maintenance dose by 50% for patients with a Child-Pugh Class A or B. **Do not use** IV dosage form for patients with GFR <50 mL/min because of accumulation of the cyclodextrin excipient; switch to oral therapy if possible. Patients receiving concurrent phenytoin should increase their voriconazole maintenance doses (IV: 5 mg/kg/dose Q 12 hr; PO: double the usual dose).

Inter-occasion pharmacokinetic variability is high, thus requiring serum level monitoring. Therapeutic levels: trough: 1–5.5 mg/L. Levels <1 mg/L have resulted in treatment failures and levels >5.5 mg/L have resulted in neurotoxicity such as encephalopathy. Recommended serum sampling time: obtain trough within 30 min prior to a dose. Steady state is typically achieved after 5–7 days of initiating therapy.

Oral bioequivalence of the oral suspension and tablet has not been evaluated in children. Administer IV over 1–2 hr with a **max. rate** of 3 mg/kg/hr at a concentration ≤ 5 mg/mL. Administer oral doses 1 hr before and after meals.

W

WARFARIN
Coumadin, Jantoven, and generics
Anticoagulant

Tabs: 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg

Infant and child (see remarks): To achieve an INR between 2 and 3.5 directed by specific indication.

Loading dose on day 1:

Baseline INR ≤1.3: 0.2 mg/kg/dose PO; **max. dose:** 7.5 mg/dose

Liver dysfunction, baseline INR >1.3, cardiopulmonary bypass within previous 10 days, NPO status/poor nutrition, receiving broad spectrum antibiotics, receiving medications that significantly inhibit CYP 450 2C9, or slow metabolizers of warfarin (see remarks): 0.05–0.1 mg/kg/dose PO; **max. dose:** 5 mg/dose

Immediate post-operative period after a Fontan procedure: 0.05 mg/kg/dose PO; **max. dose:** 2.5 mg/dose

WARFARIN *continued*

Loading dose on days 2–4:

Day 2		Days 3 & 4	
INR level	**Dose Adjustment**	**INR level**	**Dose Adjustment**
1.1–1.3	Repeat day 1 loading dose	1.1–1.4	Increase previous dose by 20%–50%
1.4–1.9	Decrease day 1 loading dose by 50%	1.5–1.9	Continue current dose
≥2	Hold dose for 24 hr, then give 50% of day 1 loading dose on day 3	2–3	Use 25%–50% of day 1 loading dose
		3.1–3.5	Use 25% of day 1 loading dose
		>3.5	Hold dose until INR < 3.5, then restart at ≤ 25% of day 1 loading dose

Maintenance dose (therapy day ≥5):

Goal INR 2–3		Goal INR 2.5–3.5	
INR	**Dose Adjustment**	**INR**	**Dose Adjustment**
1.1–1.4	Increase previous dose by 20%	1.1–1.9	Increase previous dose by 20%
1.5–1.9	Increase previous dose by 10%	2–2.4	Increase previous dose by 10%
2–3	No change	2.5–3.5	No change
3.1–3.5	Decrease previous dose by 10%	3.6–4	Decrease previous dose by 50% for one dose, then restart at a dose (prior to 50% dose decrease) decreased by 20% the next day
>3.5	Hold dose until INR <3.5, then restart at 20% less than the last dose	>4	Hold dose for one day, then restart at a dose decreased by 20% of the last dose

Usual maintenance dose for INR goal of 2–3 (see remarks): ~0.1 mg/kg/24 hr PO once daily; range: 0.05–0.34 mg/kg/24 hr. Reported average dosages include the following:
Infant < 1 yr: 0.33 mg/kg/24 hr PO once daily
Adolescent 11–18 yr: 0.09 mg/kg/24 hr PO once daily
Adult (see remarks): 5–10 mg PO once daily × 2–5 days. Adjust dose to achieve the desired INR or PT. Maintenance dose range: 2–10 mg/24 hr PO once daily.

Contraindicated in severe liver or kidney disease, uncontrolled bleeding, GI ulcers, and malignant hypertension. Acts on vitamin K-dependent coagulation factors II, VII, IX, and X. Side effects include fever, skin lesions, skin necrosis (especially in protein C deficiency), anorexia, nausea, vomiting, diarrhea, hemorrhage, and hemoptysis.

Warfarin is a substrate for CYP 450 1A2, 2C8, 2C9, 2C18, 2C19, and 3A3/4. Amiodarone, azole antifungals (e.g., fluconazole, voriconazole), broad spectrum antibiotics (e.g., cefepime, meropenem, piperacillin/tazobactam), chloramphenicol, chloral hydrate, cimetidine, corticosteroids, delavirdine, fluoroquinolones (e.g., ciprofloxacin, levofloxacin), fluoxetine, metronidazole, indomethacin, large doses of vitamins A or E, nonsteroidal anti-inflammatory agents, omeprazole, oxandrolone, quinidine, salicylates, SSRIs (e.g., fluoxetine, paroxetine, sertraline), sulfonamides, and zafirlukast may increase warfarin's effect. Ascorbic acid, barbiturates, carbamazepine, cholestyramine, dicloxacillin, griseofulvin, oral contraceptives, nafcillin, ribavirin, rifampin, spironolactone, sucralfate, and vitamin K (including foods with high content) may decrease warfarin's effect.

Continued

For explanation of icons, see p. 667

WARFARIN *continued*

Younger children generally require higher doses to achieve desired effect. Children receiving Fontan cardiac surgery may require smaller doses than children with either congenital heart disease (without Fontan) or no congenital heart disease. (See Chest 2004;126:645–687S and Blood 1999;94[9]:3007–3014 for additional information.)

Lower doses should be considered for patients with pharmacogenetic variations in CYP 2C9 (e.g., *2 and *3 alleles) and VKORC1 (e.g., 1639G>A allele) enzymes, especially in European ancestry. Elderly and/or debilitated patients, and patients with a potential to exhibit greater than expected PT/INR response to warfarin should also consider using of lower doses.

Z

ZIDOVUDINE

Retrovir, AZT, and generics

Antiviral agent, nucleoside analogue reverse transcriptase inhibitor

Caps: 100 mg
Tabs: 300 mg
Oral syrup: 50 mg/5 mL (240 mL); contains 0.2% sodium benzoate
Injection: 10 mg/mL (20 mL); preservative free solution (vial stoppers may contain latex)
In combination with lamivudine (3TC) as Combivir and generics:
Tabs: 300 mg zidovudine + 150 mg lamivudine
In combination with abacavir and lamivudine (3TC) as Trizivir and generics:
Tabs: 300 mg zidovudine + 300 mg abacavir + 150 mg lamivudine

HIV: See www.aidsinfo.nih.gov/guidelines.

Prevention of HIV vertical transmission:

14–34 weeks of pregnancy (maternal dosing):

Until labor (see Perinatal guidelines for currently recommended combination antiretroviral therapies which may or may not include zidovudine): *600 mg/24 hr PO ÷ BID–TID*

During labor: 2 mg/kg/dose IV over 1 hour followed by 1 mg/kg/hr IV infusion until umbilical cord clamped.

Premature infant (initiate therapy within 6–12 hr of birth and continue until 4–6 wk of age):

Gestational age (wk)	Oral (PO) Dosage	Intravenous (IV) Dosage[a]
<30	2 mg/kg/dose Q12 hr, increase to 3 mg/kg/dose Q12 hr at 4 wk of age	1.5 mg/kg/dose Q12 hr, increase to 2.3 mg/kg/dose Q12 hr at 4 wk of age
30—34	2 mg/kg/dose Q12 hr, increase to 3 mg/kg/dose Q12 hr at postnatal age of 15 days	1.5 mg/kg/dose Q12 hr, increase to 2.3 mg/kg/dose Q12 hr at postnatal age of 15 days
\ge 35	4 mg/kg/dose Q12 hr, increase to 12 mg/kg/dose Q12 hr at 4 wk of age	3 mg/kg/dose Q12 hr, increase to 9 mg/kg/dose Q12 hr at 4 wk of age

[a]Convert to PO route when possible

Term neonate and infant <6 wk (initiate therapy within 6–12 hr of birth and continue until 4–6 wk of age):

PO: 2 mg/kg/dose Q6 hr, or 4 mg/kg/dose Q12 hr, increase dose to 12 mg/kg/dose Q12 hr at 4 wk of age

IV: 1.5 mg/kg/dose Q6 hr or 3 mg/kg/dose Q12 hr, administered over 60 min. Increase dose to 9

ZIDOVUDINE *continued*

HIV post exposure prophylaxis (all therapies to begin within 2 hr of exposure if possible for a total of 28 days): See www.aidsinfo.nih.gov/guidelines for the most recent preferred and alternative regimens. Zidovudine is dosed using HIV treatment doses and used in combination with lamivudine and additional antiretroviral agent(s).

HIV treatment (see www.aidsinfo.nih.gov/guidelines for additional antiretroviral therapies and dosing information):

Neonate:

Gestational age (wk)	Oral (PO) Dosage	Intravenous (IV) Dosage[a]
<30	**Birth to 4 wk of age:** 2 mg/kg/dose Q12 hr **4 wk to 8—10 wk of age:** 3 mg/kg/dose Q12 hr **> 8—10 wk of age:** 12 mg/kg/dose Q12 hr	**Birth to 4 wk of age:** 1.5 mg/kg/dose Q12 hr **4 wk to 8—10 wk of age:** 2.3 mg/kg/dose Q12 hr **> 8—10 wk of age:** 9 mg/kg/dose Q12 hr
30—34	**Birth to 2 wk of age:** 2 mg/kg/dose Q12 hr **>2 wk to 6—8 wk of age:** 3 mg/kg/dose Q12 hr **> 6—8 wk of age:** 12 mg/kg/dose Q12 hr	**Birth to 2 wk of age:** 1.5 mg/kg/dose Q12 hr **>2 wk to 6—8 wk of age:** 2.3 mg/kg/dose Q12 hr **> 6—8 wk of age:** 9 mg/kg/dose Q12 hr
\ge 35	**Birth to 4 wk of age:** 4 mg/kg/dose Q12 hr **>4 wk of age:** 12 mg/kg/dose Q12 hr	**Birth to 4 wk of age:** 3 mg/kg/dose Q12 hr **>4 wk of age:** 9 mg/kg/dose Q12 hr

[a]Convert to PO route when possible.

Infant (≥ 35 wk PCA, > 4 wk of age, and ≥ 4 kg), child, and adolescent:

PO: 180–240 mg/m^2/dose BID or the following by weight category:

4 to <9 kg: 12 mg/kg/dose BID or 8 mg/kg/dose TID

9 to <30 kg: 9 mg/kg/dose BID or 6 mg/kg/dose TID

≥ 30 kg: 300 mg BID or 200 mg TID

IV:

Infant (≥ 3 mo), child, and adolescent (<30 kg): 120 mg/m^2/dose Q6 hr; **max. dose:** 160 mg/dose

Adolescent ≥ 30 kg: 1–2 mg/kg/dose Q4 hr

See www. aidsinfo.nih.gov/guidelines for additional remarks.

Use with caution in patients with impaired renal or hepatic function. Dosage reduction is recommended in severe renal impairment and may be necessary in hepatic dysfunction. Drug penetrates well into the CNS. Most common side effects include: anemia, granulocytopenia, nausea, and headache (dosage reduction, erythropoietin, filgrastim/GCSF, or discontinuance may be required depending on event). Seizures, confusion, rash, myositis, myopathy (use > 1 yr), hepatitis, and elevated liver enzymes have been reported. Macrocytosis is noted after 4 wk of therapy and can be used as an indicator of compliance. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Neutropenia and severe anemia have been reported in advanced HIV disease. Use of injectable dosage form may cause allergic reactions in latex-sensitive individuals.

Do not use in combination with stavudine because of poor antiretroviral effect. Effects of interacting drugs include: increased toxicity (acyclovir, trimethoprim-sulfamethoxazole); increased hematological toxicity (ganciclovir, interferon-alpha, marrow suppressive drugs); and granulocytopenia (drugs which affect glucuronidation). Methadone, atovaquone, cimetidine, valproic acid, probenecid, and fluconazole may increase levels of zidovudine, whereas rifampin, rifabutin, and clarithromycin may decrease levels.

For explanation of icons, see p. 667

ZIDOVUDINE *continued*

Do not administer IM. IV form is incompatible with blood product infusions and should be infused over 1 hr (intermittent IV dosing). Despite manufacturer recommendations of administering oral doses 30 min prior to or 1 hr after meals, doses may be administered with food.

ZINC SALTS, SYSTEMIC
Galzin, Orazinc, and generics
Trace mineral

Sulfate salt (23% elemental Zn):
Tabs as sulfate (Orazinc and generics) [OTC]: 66, 110, 220 mg
Caps as sulfate (Orazinc, and generics) [OTC]: 220 mg
Liquid as sulfate: 10 mg elemental Zn/mL
Injection as sulfate: 5 mg elemental Zn/mL (5 mL); may contain benzyl alcohol
Acetate salt (30% elemental Zn):
Caps as acetate (Galzin): 25, 50 mg elemental per capsule
Liquid as acetate: 5 mg elemental Zn/mL
Chloride salt (48% elemental Zn):
Injection as chloride: 1 mg elemental Zn/mL (10 mL)

Zinc deficiency (see remarks):
Infant and child: 0.5–1 mg elemental Zn/kg/24 hr PO ÷ once daily–TID
Adult: 25–50 mg elemental Zn/dose (100–220 mg Zn sulfate/dose) PO TID
Wilson disease:
Child (≥ 10 yr): 75 mg/24 hr elemental Zn PO ÷ TID; if needed, may increase to 150 mg/24 hr elemental Zn PO ÷ TID
U.S. RDA: See Chapter 21.
For supplementation in parenteral nutrition, see Chapter 21.

Nausea, vomiting, GI disturbances, leukopenia, and diaphoresis may occur. Gastric ulcers, hypotension, and tachycardia may occur at high doses. Patients with excessive losses (burns) or impaired absorption require higher doses. Therapeutic levels: 70–130 mCg/dL.
Parenteral products may contain aluminum; **use with caution** in renal impairment. May decrease the absorption of penicillamine, tetracycline, and fluoroquinolones (e.g., ciprofloxacin). Drugs that increase gastric pH (e.g., H_2 antagonists and proton pump inhibitors) can reduce the absorption of zinc. Excessive zinc administration can cause copper deficiency.
Approximately 20%–30% of oral dose is absorbed. Oral doses may be administered with food if GI upset occurs. Pregnancy category is "A" for zinc acetate and "C" for all other salt forms.

ZOLMITRIPTAN
Zomig, Zomig ZMT, and generics
Antimigraine agent, selective serotonin agonist

Tabs:
Zomig and generics: 2.5 mg (scored), 5 mg
Oral disintegrating tabs (ODT):
Zomig ZMT and generics: 2.5, 5 mg; contains aspartame
Nasal spray:
Zomig: 2.5 mg single unit nasal spray (6s), 5 mg single unit nasal spray (6s)

D

ZOLMITRIPTAN *continued*

Treatment of acute migraines with or without aura:

Nasal (safety of an average of > 4 headaches in a 30-day period has not been established; see remarks):

≥ 12 yr and adult: Start with 2.5 mg inhaled into a single nostril × 1. If needed in 2 hr, a second dose may be administered. Dose may be increased to a **maximum** single dose of 5 mg if needed. **Max. daily dose:** 10 mg/24 hr.

Patients receiving concurrent cimetidine: Limit maximum doses to 2.5 mg as the **max. single dose** and **do not exceed** 5 mg in any 24 hr period.

Oral (Safety and efficacy in children have not been established with the oral route. One randomized placebo-controlled trial in 696 adolescents 12–17 yr old did not establish efficacy and had similar adverse events as seen in adult trials):

Adult (Safety of an average of > 3 headaches in a 30-day period has not been established; see remarks):

PO tabs: Start with 1.25–2.5 mg PO × 1. If needed in 2 hr, a second dose may be administered. Dose may be increased to a **maximum** single dose of 5 mg if needed. **Max. daily dose**: 10 mg/24 hr.

ODT tabs: Use the same dosage recommendation for PO tabs but with a 2.5 mg initial dose.

Patients receiving concurrent cimetidine: Limit **maximum** doses to 2.5 mg as the **max. single dose** and **do not exceed** 5 mg in any 24 hr period for both PO and ODT tabs.

Contraindicated in ischemic bowel disease; ischemic coronary artery disease; uncontrolled hypertension; peripheral vascular disease; history of stroke or TIA, arrhythmias, hemiplegic, or basilar migraine; significant cardiovascular disease; and coronary artery vasospasm.

Do not administer with any ergot-containing medications, any other 5-HT1 agonist (e.g., triptans), methylene blue, or within 2 wk of discontinuing a MAO inhibitor or linezolid. Cimetidine may increase the zolmitriptan levels; see dosage section for reduced maximum dosage. Patients with multiple cardiovascular risk factors and negative cardiovascular evaluation should have their first dose administered in a medically supervised facility.

Use **not** recommended in moderate/severe hepatic impairment. Severe renal impairment (CrCl 5–25 mL/min) reduces zolmitriptan clearance by 25%.

Common adverse reactions for all dosage forms unless otherwise indicated include nausea, taste alteration (nasal route), xerostomia, dizziness, hyperesthesia (nasal route), paresthesia, somnolence, sensation of hot and cold, throat pain, and asthenia (oral route). Hypertension, coronary artery spasm, MI, cerebral hemorrhage, and headaches have been reported.

For intranasal use, blow nose gently prior to dosing. Block opposite nostril while administering dose by breathing in gently.

When using the ODT, place the whole tablet on the tongue, allow the tablet to dissolve, and swallow with saliva. Administration with liquids is optional. **Do not** break the ODT tablet.

ZONISAMIDE
Zonegran and generics
Anticonvulsant

Caps: 25, 50, 100 mg
Oral syrup: 10 mg/mL

Infant and child (data is incomplete):

Suggested dosing from a review of Japanese open-label studies for partial and generalized seizures: Start with 1–2 mg/kg/24 hr PO ÷ BID. Increase dosage by 0.5–1 mg/kg/24 hr Q2 wk to the usual dosage range of 5–8 mg/kg/24 hr PO ÷ BID.

For explanation of icons, see p. 667

ZONISAMIDE *continued*

Infant and child (data is incomplete; cont.):

Recommended higher alternative dosing: Start with 2–4 mg/kg/24 hr PO ÷ BID–TID. Gradually increase dosage PRN at 2-wk intervals to 4–8 mg/kg/24 hr; **max. dose**: 12 mg/kg/24 hr.

Infantile spasms (regimen that was effective in a small study from Japan; additional studies needed): Start with 2–4 mg/kg/24 hr PO ÷ BID. Then increase by 2–5 mg/kg/24 hr every 2–4 day until seizures disappear, up to a **maximum** of 20 mg/kg/24 hr.

> 16 yr–adult:

Adjunctive therapy for partial seizures: 100 mg PO once daily × 2 wk. Dose may be increased to 200 mg PO once daily × 2 wk. Additional dosage increments of 100 mg/24 hr can be made at 2-wk intervals to allow attainment of steady-state levels. Effective doses have ranged from 100–600 mg/24 hr ÷ once daily–BID (BID dosing may provide better efficacy). No additional benefit has been shown for doses > 400 mg/24 hr.

Because zonisamide is a sulfonamide, it is **contraindicated** in patients allergic to sulfonamides (may result in Stevens-Johnson syndrome or TEN). Common side effects of drowsiness, ataxia, anorexia, gastrointestinal discomfort, headache, rash, and pruritis usually occur early in therapy and can be minimized with slow dose titration. Children are at increased risk for hyperthermia and oligohydrosis, especially in warm or hot weather. Suicidal behavior or ideation, acute pancreatitis, urolithiasis, metabolic acidosis (more frequent and severe in younger patients), DRESS/multi-organ hypersensitivity, rhabdomyolysis, and elevated creatinine phosphokinase have been reported.

Although not fully delineated, therapeutic serum levels of 20–30 mg/L have been suggested as higher rates of adverse reactions have been seen at levels > 30 mg/L.

Zonisamide is a CYP 450 3A4 substrate. Phenytoin, carbamazepine, and phenobarbital can decrease levels of zonisamide.

Use with caution in renal or hepatic impairment; slower dose titration and more frequent monitoring is recommended. **Do not use** if GFR is <50 mL/min. **Avoid** abrupt discontinuation or radical dose reductions. Swallow capsules whole and **do not** crush or chew.

Chapter 31

Drugs in Renal Failure

Elizabeth A.S. Goswami, PharmD and Namrata Trivedi, PharmD

I. DOSE ADJUSTMENT METHODS

A. Maintenance Dose

In patients with renal insufficiency, the dose may be adjusted using the following methods:

1. **Interval extension (I):** Lengthen intervals between individual doses, keeping dose size normal. For this method, a suggested interval is shown.
2. **Dose reduction (D):** Reduce number of individual doses, keeping interval between doses normal; recommended when relatively constant blood level of drug is desired. For this method, percentage of usual dose is shown. For some medications and indications, specific dosing is provided.
3. **Interval extension and dose reduction (DI):** Both lengthen interval and reduce dose.
4. **Interval extension or dose reduction (D, I):** In some instances, either dose or interval can be changed.

NOTE: These dose adjustment methods do not apply to patients in the neonatal period. For neonatal renal dosing, please consult a neonatal dosage reference (see Chapter 18). Dose modifications given are only approximations and may not be appropriate for all patients or indications. **Each patient must be monitored closely for signs of drug toxicity, and serum levels must be measured when available; drug doses and intervals should be adjusted accordingly.** When in doubt, always consult a nephrologist or pharmacist who has expertise in renal dosing.

B. Dialysis

General recommendations are provided when available. However, factors such as patient age, indication for use, residual native kidney function, specific peritoneal dialysis (PD) or intermittent hemodialysis (IHD) settings, etc., will affect the medication dosing needs of each individual patient. **Consult with a nephrologist or pharmacist who is familiar with medication dosing in dialysis prior to prescribing medications for a dialysis patient.**

II. ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE (Table 31.1)

TABLE 31.1

ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE[1-5]

	Pharmacokinetics				Adjustments in Renal Failure		
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Acyclovir (IV)	Renal (60%–90%)	2–3	Q8 hr	D, I	25–50 10–25 <10/IHD[b]/PD	100% 100% 50%	Q12 hr Q24 hr Q24 hr
Amantadine[c] **Note:** On day 1, give normal dose, then decrease subsequent doses based on renal function.	Renal (80%–90%)	10–30	Q12–24 hr	D, I	30–50 15–29 <15/IHD/PD	50% 50% 100%	Q24 hr Q48 hr Q7 days
Amikacin	Renal (>95%)	1.5–3	Q8–12 hr	I	<60/IHD/PD	Administer a standard one-time dose. Determine the appropriate interval for redosing based on serum concentrations. For IHD, redose based on concentrations.	
Amoxicillin **Note:** Do not administer 875 mg immediate release or 775 mg extended release tablets with eGFR <30 mL/min/1.73 m².	Renal (60%)	1–2	Q8–12 hr	D, I	10–30 <10/IHD[b]/PD	50–100% 50–100%	Q12 hr Q24 hr
Amoxicillin/clavulanate **Note:** Do not administer 875 mg immediate release or 1000 mg XR extended release tablet with eGFR <30 mL/min/1.73 m².	Renal (60%/25%–40%)	1–2/1	Q8–12 hr	D, I	10–30 <10/IHD[b]/PD	50%–100% 50%–100%	Q12 hr Q24 hr

Amphotericin B	Renal (40%)	Initial: 12–25 Terminal: 15 days	Q24 hr		No guidelines established.		
Amphotericin B lipid complex (Abelcet)	Renal (1%)	Terminal: 7 days	Q24 hr		No guidelines established.		
Amphotericin B, liposomal (AmBisome)	Renal (10%)	Initial: 7–10 Terminal: 4–6 days	Q24 hr		No guidelines established.		
Ampicillin (IV)	Renal (90%)	1–2	Q4–6 hr	I	10–30 <10/IHD[d]/PD	100% 100%	Q8 hr Q12 hr
Ampicillin/sulbactam	Renal (90%/75%–85%)	1–2/1	Q4–6 hr	I	15–29 <15/IHD[d]/PD	100% 100%	Q12 hr Q24 hr
Aztreonam **Note:** Administer full dose for initial dose, then adjust subsequent doses for kidney function.	Renal (60%–70%) (hepatic)	1-2	Q6–8 hr	DI	10–30 <10/IHD/PD IHD: Administer 12% of the full dose as an additional supplemental dose after dialysis in severe infections.[6]	50%–66% 25%–33%	Q8 hr Q12 hr
Cefaclor	Renal (80%)	0.5–1	Q8–12 hr	D	<10/IHD[d]/PD	50%	Q8–12 hr
Cefadroxil	Renal (>90%)	1–2	Q12 hr	I	10–25/IHD[b] <10/PD	100% 100%	Q24 hr Q36 hr
Cefazolin **Note:** Administer full dose for initial dose, then adjust subsequent doses for kidney function.	Renal (80%–100%)	1.5–2	Q8 hr	DI	11–30 ≤10/IHD[b]/PD	25 mg/kg 25 mg/kg	Q12 hr Q24 hr

Continued

TABLE 31.1

ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics				Adjustments in Renal Failure		
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Cefdinir	Renal (10%–20%)	1–2	Q12–24 hr	D, I	<30 IHD[d]/PD	7 mg/kg (max 300 mg) 7 mg/kg (max 300 mg)	Q24 hr Q48 hr
Cefepime **Note:** Administer full dose for initial dose, then adjust subsequent doses for kidney function.	Renal (85%)	2	Q8 hr	D, I	30-60 10-29 <10/PD/HD	100% 100% 50%	Q12 hr Q24 hr Q24 hr
Cefixime[c]	Renal (50%)/ (biliary)	3–4	Q12–24 hr	D	21–60/IHD <20/PD	65% 45%	Q12–24 hr Q12–24 hr
Cefotaxime	Renal (60%)	1–1.5	Q6–8 hr	I	30–50 10–29 <10/IHD[b]/PD	100% 100% 100%	Q8–12 hr Q12 hr Q24 hr
Cefotetan	Renal (50%–80%) (biliary)	3–4.5	Q12 hr	D, I	10–30 <10/IHD[d]/PD	50% 50%	Q12 hr Q24 hr
Cefoxitin	Renal (85%)	0.75–1	Q4–8 hr	I	30–50 10–30 <10/IHD[b]/PD	100% 100% 100 %	Q8 hr Q12 hr Q24 hr
Cefpodoxime	Renal (30%)	2–3	Q12 hr	I	<30 IHD	100% Administer thrice weekly after dialysis sessions	Q24 hr
Cefprozil	Renal (60%)	1.5	Q12–24 hr	D	<30/IHD[b]/PD	50%	Q12–24 hr

Ceftaroline[c]	Renal (88%)	1.5–2.5	Q8–12 hr	D, I	31–50 15–30 <15 IHD[b]	66% 50% 33% 33%	Q8–12 hr Q8–12 hr Q8–12 hr Q12 hr
Ceftazidime **Note:** Administer full dose for initial dose, then adjust subsequent doses for kidney function.[3]	Renal (80%–90%)	1–2	Q8 hr	D, I	30–50 10–30 <10/IHD[b]/PD	100% 100% 50%	Q12 hr Q24 hr Q24 hr
Ceftibuten	Renal (60%)	2–2.5	Q24 hr	D	30–49 5–29 IHD	50% 25% 100%	Q24 hr Q24 hr After each dialysis session.
Cefuroxime (IV)	Renal (>90%)	1.5–2	Q8 hr	I	10–29 <10/IHD[d]/PD	100% 100%	Q12 hr Q24 hr
Cephalexin	Renal (>90%)	0.5–2.5	Q6–12 hr	I	30–50 10–29 <10/IHD[b]/PD	100% 100% 100%	Q8 hr Q12 hr Q24 hr
Ciprofloxacin	Renal (30%–50%) (hepatic)	3–5	Q8–12 hr	I	10–29 <10/IHD[b]/PD	100% 100%	Q18 hr Q24 hr

Continued

TABLE 31.1

ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics				Adjustments in Renal Failure		
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Clarithromycin	Renal (20%–40%) (hepatic)	3–7	Q12 hr	D, I	<30	50%	Q12 hr
					<10/IHD[b]/PD	50%	Q24 hr
Ertapenem[c]	Renal (80%) (hepatic)	2.5–4	Q12–24 hr	D	≤30/IHD/PD	50%	Q12–24 hr
					IHD: If administered within 6 hr before dialysis, administer 30% of the daily dose as a supplemental dose after dialysis		
Erythromycin	Hepatic (renal [<15%])	1.5–2	Q6–12 hr	D	<10/IHD/PD	50%–75%	Q6–12 hr
Ethambutol[7]	Renal (50%) (hepatic)	2.5–3.5	Q24 hr	I	<30, IHD[b]	100%	3 times weekly
					PD	Data are not available. Begin with IHD dosing. Monitor closely and consider therapeutic drug monitoring[7]	

Famciclovir[c]	Renal (73%) (hepatic)	Penciclovir: 2–3	Q8 hr	D, I	**Herpes Zoster Treatment**[c]		
					40–59	500 mg	Q12 hr
					20–39	500 mg	Q24 hr
					<20	250 mg	Q24 hr
					IHD	250 mg	After each dialysis session
					Recurrent Genital Herpes Treatment—Single Day Regimen[c]		
					40–59	500 mg	Q12 hr ×1 day
					20–39	500 mg	Once
					<20	250 mg	Once
					IHD	250 mg	Once after dialysis
					Recurrent Genital Herpes Suppression[c]		
					20–39	125 mg	Q12 hr
					<20	125 mg	Q24 hr
					IHD	125 mg	After each dialysis session
					Recurrent Herpes Labialis—Single Dose Regimen[c]		
					40–59	750 mg	Once
					20–39	500 mg	Once
					<20	250 mg	Once
					IHD	250 mg	Once after dialysis
					Recurrent Orolabial or Genital Herpes in HIV-Infected Patients[c]		
					20–39	500 mg	Q24 hr
					<20	250 mg	Q24 hr
					IHD	250 mg	After each dialysis session

Continued

TABLE 31.1

ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics				Adjustments in Renal Failure		
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Fluconazole	Renal (80%)	20–25	Q24 hr	D, I	10–50 <10/PD IHD	50% 50% 100%	Q24 hr Q48 hr After each dialysis session
Flucytosine[8] **Note:** If available, therapeutic drug monitoring should be used to guide optimal dosing. Avoid flucytosine in children with severe kidney impairment.[9]	Renal (90%)	3–8	Q6 hr	I	20–40 10–20 <10/PD IHD	100% 100% 100% 100%	Q12 hr Q24 hr Q48 hr After each dialysis session
Foscarnet	Renal (80%–90%)	Plasma: 3–4 Terminal: 88	Induction: Q8 h Maintenance: Q24 hr	D, I	See package insert for adjustments for induction and maintenance.[10]		
Ganciclovir	Renal (>80%)	2.5–3.5	Induction: Q12 hr Maintenance: Q24 hr	D, I	**Induction IV** 50–69 25–49 10–24 <10/PD/IHD[b]	 2.5 mg/kg 2.5 mg/kg 1.25 mg/kg 1.25 mg/kg	 Q12 hr Q24 hr Q24 hr Thrice weekly

					Maintenance IV		
					50–69	2.5 mg/kg	Q24 hr
					25–49	1.25 mg/kg	Q24 hr
					10–24	0.625 mg/kg	Q24 hr
					<10/PD/IHD[b]	0.625 mg/kg	Thrice weekly
Gentamicin	Renal (70%)	1.5–3	Q8–12 hr	I	<50/IHD/PD	Administer standard initial dose. Determine appropriate interval for redosing based on serum concentrations.	
Imipenem/cilastatin[c] **Note:** Patients with eGFR ≤15 should not receive imipenem/cilastatin unless dialysis will be initiated within 48 hr.[11]	Renal (70%)	1	Q6 hr	D, I	60-89	75%	Q8 hr
					30–59	50%	Q6 hr
					10–29	50%	Q12 hr
					<10/IHD[b]/PD	50%	Q24 hr
Isoniazid	Renal (75%–95%) (hepatic)	Slow acetylator: 2–5 Fast acetylator: 0.5–1.5	Q24 hr		IHD[b]	100%	Q24 hr
Lamivudine[12,c] **Note:** Administer full dose for initial dose, then adjust subsequent doses for kidney function. If eGFR <5 or IHD, administer 50% of full dose as initial dose.	Renal	2	Q12 hr	D, I	30–49	100%	Q24 hr
					15–29	66%	Q24 hr
					5–14	33%	Q24 hr
					<5/IHD[b]/PD	17%	Q24 hr

Continued

TABLE 31.1

ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics				Adjustments in Renal Failure		
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Levofloxacin	Renal (90%)	5–8	Q12	I	10–29	100%	Q24 hr
					<10/IHD/PD	100%	Q48 hr
Note: Administer full dose for initial dose, then adjust subsequent doses for kidney function.			Q24h	D, I	10–29	100%	Q48h
					<10/IHD/PD	67%	Q48h
Meropenem	Renal (70%)	1–1.5	Q8 hr	D, I	30–50	100%	Q12 hr
					10–29	50%	Q12 hr
					<10/IHD[b]/PD	50%	Q24 hr
Metronidazole	Hepatic [renal (15%)]	6–12	Q6–12 hr	D	<10	Renally eliminated metabolites may accumulate and lead to adverse events. Monitor patient. Some recommend a dose of 4 mg/kg at standard intervals.[1,2]	
					IHD[d]	4 mg/kg	Q6 hr
					PD	4 mg/kg	Q6 hr
Norfloxacin[c]	Hepatic (renal [30%])	3–4	Q12 hr	I	<30	100%	Q24 hr

Oseltamivir[c]	Oseltamivir carboxylate: Renal (>99%)	Oseltamivir carboxylate: 6–10	Q12–24 hr	D, I

Influenza Treatment		
31–60	50%	Q12 hr
11–30	50%	Q24 hr
<10/IHD	25–40%	Once, then after each dialysis session
PD	50%	Once
Influenza Prophylaxis		
31–60	50%	Q24 hr
10–30	50%	Q48 hr
<10	No recommended dosage regimen.	
IHD	50%	Once, then after every other dialysis session
PD	50%	Weekly for duration of prophylaxis

Continued

TABLE 31.1

ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics				Adjustments in Renal Failure		
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Penicillin G—aqueous (K^+, Na^+) (IV) **Note:** Administer full dose for initial dose, then adjust subsequent doses for kidney function.	Renal (60%–85%) (hepatic)	0.5–1.2 hr	Q4–6 hr	D	10–50 <10/IHD[b]/PD	75% 50%	Q4–6 hr Q4–6 hr
Penicillin V K^+ (PO)	Renal (20-40%) (hepatic)	0.5 hr	Q6–8 hr	I	<10/IHD[b]/PD	100%	Q8 hr
Pentamidine[2]	Renal	5–9	Q24 hr	I	10–30 <10/IHD[b]/PD	100% 100%	Q36 hr Q48 hr
Piperacillin/tazobactam[1,2]	Renal (75%–90%/>80%)	0.7–1/0.7–1.5	Q6 hr	D, I	20–40 <20 IHD[b]/PD	70% 70% 70%	Q6 hr Q8 hr Q8–12 hr
Posaconazole	Fecal (Renal)	24–36	Oral suspension: Q8h Oral extended release, IV: Q12–24 hr	NA	<50	Consider risks and benefits of use of the IV product as solubilizing agent may accumulate. With PO products, exposure may vary, and breakthrough infections may occur.	

Rifabutin	Metabolites: Renal (50%) (hepatic)	35–45	Q24 hr	D	<30	50%-100%	Q24 hr
Streptomycin sulfate[c] **Note:** Determine appropriate interval for redosing based on serum concentration when available.	Renal (30%–90%)	2–5	Q24 hr	I	10–50 <10 IHD/PD	100% 100% 100%	Q24–72 hr Q48–96 hr. Administer 2–3 times weekly after dialysis
Sulfamethoxazole/trimethoprim	Renal (85%)/Renal (65%)	Sulfamethoxazole: 9–12 Trimethoprim: 3–8	Q8–12 hr	D	<30, IHD[b]/PD	50%	Q8–12 hr
Tetracycline[2,b]	Renal (30%–60%) (hepatic)	6–12	Q6 hr	I	50–80 10–50 <10	100% 100% 100%	Q8–12 hr Q12–24 hr Q24 hr
Tobramycin	Renal (>90%)	1.5–3	Q8–24 hr	I	<60	Administer standard initial dose. Determine appropriate interval for redosing based on serum concentrations.	

Continued

TABLE 31.1

ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics				Adjustments in Renal Failure		
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Valacyclovir[c] **Note:** For IHD for all indications, dose for eGFR <10 and administer dose after dialysis. For PD for all indications, administer 500 mg Q48 hr.[4]	Hepatic to acyclovir.	Valacyclovir: ~30 min Acyclovir: 2–3	Q8–24 hr	D, I	**Herpes Zoster (Adults)**		
					30–49	100%	Q12 hr
					10–29	100%	Q24 hr
					<10	50%	Q24 hr
					Genital Herpes (Adolescents/Adults): Initial Episode		
					10–29	100%	Q24 hr
					<10	50%	Q24 hr
					Genital Herpes (Adolescents/Adults): Recurrent Episode		
					<30	100%	Q24 hr
					Genital Herpes (Adolescents/Adults): Suppressive		
					<30	500 mg *OR* 500 mg	Q24 hr (for usual dose of 1 g Q24 hr) Q48 hr (for usual dose of 500 mg Q24 hr)
					Herpes Labialis (Adolescents/Adults)		
					30–49	50%	Q12 hr ×2 doses
					10–29	25%	Q12 hr ×2 doses
					<10	25%	Single dose

Valganciclovir **Note:** For dosing in children, a maximum eGFR value of 150 mL/min/1.73 m^2 should be used to calculate the dose. Calculate eGFR using modified Schwartz formula where k = 0.33 in infants aged <1 year, with low birth weight for gestational age, 0.45 in infants aged <1 year, with birth weight appropriate for gestational age, 0.45 in children aged 1 to <2 years, 0.55 in boys aged 2 to <13 years and girls aged 2 to <16 years, and 0.7 in boys aged 13–16 years. Consider use of k = 0.413 when enzymatic creatinine assays are used.	Ganciclovir: Renal (>80%)	Valganciclovir: 0.4–0.6 Ganciclovir: 2.5–3.5	Q12–24 hr	D, I

Children

Normal dosing accounts for kidney function:

Once daily dose (mg) = 7× body surface area × creatinine clearance.

Adults–Induction		
40–59	450 mg	Q12 hr
25–39	450 mg	Q24 hr
10–24	450 mg	Q48 hr
<10/IHD[b] (limited data-consider ganciclovir)	200 mg	Thrice weekly
Adults–Maintenance		
40–59	450 mg	Q24 hr
25–39	450 mg	Q48 hr
10–24	450 mg	Twice weekly
<10/IHD[b] (limited data-consider ganciclovir)	200 mg	Thrice weekly

Continued

TABLE 31.1

ANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics				Adjustments in Renal Failure		
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Vancomycin	Renal (80%–90%)	2.2–8	Q6–12 hr	I	<50	Administer standard initial dose. Determine appropriate interval for redosing based on serum concentrations.	
					IHD/PD	Administer standard initial dose. Obtain serum concentration after dialysis to determine need to redose. Obtain levels 4–6 hr after dialysis to allow for redistribution from peripheral compartment. If patient is unstable, may obtain sooner with knowledge that concentration may be lower than steady state.	

[a]Percentage in parenthesis represents the amount of drug and/or metabolites excreted in the urine. Route in parentheses indicates secondary route of excretion.

[b]For IHD administer after dialysis on dialysis days.

[c]In adults; guidelines not established in children.

[d]Administer a supplemental dose after dialysis

D, Dose reduction; *eGFR*, estimated glomerular filtration rate; *HIV*, human immunodeficiency virus; *hr*, hour; *I*, interval extension; *IHD*, intermittent hemodialysis; *IM*, intramuscular; *IV*, intravenous; *K+*, potassium; *NA*, not applicable; *Na+*, sodium; *PD*, peritoneal dialysis; *PO*, oral; *Q*, every; $t_{½}$, half-life with normal renal function.

III. NONANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE (Table 31.2)

TABLE 31.2

NONANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE[1–5]

	Pharmacokinetics			Adjustments in Renal Failure			
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Acetaminophen	Hepatic	2–4	Q4–6 hr	I	10–50 <10/IHD/PD	100% 100%	Q6 hr Q8 hr
Acetazolamide	Renal (>70%)	2.4–5.8	Q6–24 hr	I	10–50 IHD[b] <10/PD	100% 12.5%—titrate to effect Avoid use	Q12 hr Q12–24 hr
Allopurinol	Renal	1–3	Q6–24 hr	D	10–50 <10/IHD/PD	50% 30%	Q6–24 hr Q6–24 hr
Aminocaproic acid	Renal (76%)	1–2	Q4–6 hr, continuous	D	Oliguria/ESRD	12%–25%	Q4–6 hr, continuous
Aspirin	Hepatic (renal)	Dose dependent: 3–10	Q4–24 hr	I	10–50 IHD[b] <10/PD	100% 100% Avoid use for analgesia and antiinflammatory indications	Q4–24 hr Q24 hr
Atenolol	Renal (50%)	3.5–7	Q12–24 hr	D, I	15–35 <15/IHD[b]/PD	1 mg/kg up to 50 mg 1 mg/kg up to 25 mg	Q24 hr Q48 hr
Azathioprine	Hepatic to 6-mercaptopurine (renal)	2	Q24 hr	D	10–50 <10/IHD[b]/PD	75% 50%	Q24 hr Q24 hr

Continued

TABLE 31.2

NONANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics			Adjustments in Renal Failure			
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Bismuth subsalicylate	Hepatic (renal)	Salicylate: 2–5 Bismuth: 21–72 days	Q3–4 hr		Avoid use in patients with renal failure.		
Bosentan	Hepatic (renal)	5	Q12 hr		Dose adjustment not required. Significant clearance by dialysis is not expected.		
Calcium supplements	GI (renal [20%])	Variable	Variable		<25	May require dosage adjustment depending on calcium level.	
Captopril	Renal (95%) (hepatic)	1.5–2	Q6–24 hr	D	10–50 <10/IHD[b]PD	75% 50%	Q6–24 hr Q6–24 hr
Carbamazepine **NOTE:** Avoid use of IV product in moderate to severe kidney dysfunction. Solubilizing agent may accumulate and lead to toxicity.	Hepatic (renal)	Initial: 25–65 Subsequent: 8–17	Q6–12 hr	D	<10/IHD[b]/PD	75%	Q6–12 hr
Cetirizine[2]	Renal (70%) (hepatic)	6–8	Q12–24 hr	D	10-29/IHD/PD ≤10	50% Use not recommended.	Q24 hr
Chloroquine	Renal (70%) (hepatic)	3–5 days	Weekly	D	<10/IHD/PD	50%	Weekly
Chlorothiazide	Renal (>90%)	0.75–2	Q12–24 hr	NA	<30 <10	May be ineffective. Use not recommended.	

Cimetidine	Renal (50%) (hepatic)	1.5–2	Q6–12 hr	D, I	10–50 <10/IHD[b]/PD	50% 100%	Q6–12 hr Q8–12 hr
Clobazam	Renal (82%) (Hepatic, GI)	Children: 16 Adults: 36–42	Q12–24 hr	D	<30	Use with caution; has not been studied.	
Desloratadine[c]	Renal (87%) (GI)	27	Q24 hr	I	<50	100%	Q48 hr
Digoxin	Renal (50%–70%) (GI)	18–48		D, I			
					Digitalizing Dose		
					ESRD	50%	NA
					Maintenance Dose		
					30–50	75%	Q12–24 hr
					10–29	50% *OR* 100%	Q12–24 hr Q36 hr
					<10/IHD/PD	25% *OR* 100%	Q12–24 hr Q48 hr
Disopyramide[c]	Renal (40%–60%) (GI)	3–10	Q6 hr	I	30–40 15–30 <15	100% 100% 100%	Q8 hr Q12 hr Q24 hr

Continued

TABLE 31.2

NONANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics			Adjustments in Renal Failure			
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
EDTA calcium disodium[c] **Note:** Do not administer in patients with anuria or severe oliguria.	Renal	1.5 (IM) 0.3–1 (IV)	IM: Q8–12 hr IV: Q24 hr	D, I	**IV: Adult Serum Creatinine-Based Dosing** ≤2 mg/dL 2–3 mg/dL 3–4 mg/dL >4 mg/dL	 1 g/m² 500 mg/m² 500 mg/m² 500 mg/m²	 Q24 hr ×5 days Q24 hr ×5 days Q48 hr ×3 doses Once weekly
Enalapril (IV: enalaprilat)	Renal (60%–80%) (hepatic)	1.5–6 (PO) 5–20 (IV)	Q6–24 hr	D	10–50 <10 Manufacturer does not recommend in infants and children aged ≤16 years with GFR <30 mL/min/1.73 m².	75% 50%	Q6–24 hr Q6–24 hr
Enoxaparin[c]	Renal (40%)	4.5–7	Q12–24 hr	I	<30 IHD/PD	100% Serious bleeding complications may occur in this population. Avoid use. If used, reduce dose and monitor anti-Xa activity.[5]	Q24 hr
Epoprostenol	Hydrolyzed to renally eliminated metabolites (85%)	6 min	Continuous infusion	D	Manufacturer does not recommend renal dose reduction. Titrate to clinical effect.		
Famotidine	Renal (70%)	2–3	Q12–24 hr	D, I	30–50 10–29 <10/IHD/PD	100% 50% 25%	Q24 hr Q24 hr Q24 hr

Felbamate[c]	Renal (50%)	20–30	Q6–8 hr	D	<50	50%	Q6–8 hr
Fentanyl	Hepatic (renal [75%])	Single dose: 2–4 Prolonged infusion: 21	Q30 min–1 hr, continuous Patch: Q72 hr	D	**Injection** <50 **Patch** Mild–moderate impairment Severe impairment	 Manufacturer does not recommend dose reduction. Titrate to clinical effect. Initial dose: 50% Not recommended.	 Q72 hr
Fexofenadine	GI (renal [12%])	14	Q12 hr	I	<50	100%	Q24 hr
Flecainide[c]	Hepatic (Renal [>80%])	8–20	Q8–12 hr	D	<35	50%	Q12 hr
Furosemide	Renal (50%–80%) (hepatic)	0.5	PO: Q6–24 hr IV: Q6–12 hr		Avoid use in oliguria.		
Gabapentin	Renal (>75%) (GI)	5	Q8 hr	D, I	30–59 15–29 <15/IHD[d]/PD	75% 75% 75%	Q12 hr Q24 hr Q48 hr
Hydralazine[e]	Hepatic (renal [14%])	2–8	IV: Q4–6 hr PO: Q6–12 hr	I	10–50 <10/IHD/PD	100% 100%	Q8 hr (fast acetylator) Q8–16 hr Q12–24 hr (slow acetylator)
Iloprost[c]	Renal (70%) [Hepatic]	20–30 min	Q2–4 hr inhalation, continuous inhalation	D, I	<10/IHD/PD	Use with caution; has not been studied.	
Insulin (regular)[f]	Hepatic (renal)	IV: 0.5–1 Subcutaneous: 1.5	Variable	D	10–50 <10/IHD/PD	75% 50%	No change No change

Continued

TABLE 31.2

NONANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics			Adjustments in Renal Failure			
Drug	**Route of Excretion[a]**	**Normal $t_{1/2}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Ivacaftor	Hepatic (>85%)	12	Q12 hr	NA	<30	Use with caution.	
Lacosamide[c]	Renal (95%) (GI)	13	Q12 hr	D	<30	Maximum dose: 300 mg/24-hr period	
					IHD	Administer 50% dose supplementation after 4-hr dialysis session.	
Levetiracetam	Renal (66%)	5–8	Q12 hr	D, I	**Children**		
					<50	50%	Q12 hr
					IHD[g]/PD	50%	Q24 hr
					Adults		
					50–80	500–1000 mg	Q12 hr
					30–50	250–750 mg	Q12 hr
					<30	250–500 mg	Q12 hr
					IHD[g]/PD	500–1000 mg	Q24 hr
Lisinopril	Renal	11–13	Q24 hr	D	10–50	50%	Q24 hr
					<10/IHD[b]/PD	25%	Q24 hr
					Per manufacturer, use not recommended for children with eGFR <30 mL/min/1.73 m².		
Lithium[1] **Note:** Monitor serum concentrations. Due to high volume of distribution, lithium concentrations rebound after dialysis.[2]	Renal (>90%)	18–36	Q8–12 hr	D	10–50	50–75%	Q8–12 hr
					<10	25–50%	Q8–12 hr
					IHD	Dose after dialysis. Doses may vary, use serum concentrations to guide.	

Loratadine	Hepatic (renal 40%])	Loratadine: 8.4 Metabolite: 28	Q24 hr	I	<10/IHD	100%	Q48 hr
Lumacaftor + Ivacaftor	Hepatic (renal)	Lumacaftor: 26 Ivacaftor: 9	Q12 hr	NA	<30	Use with caution.	
Meperidine **Note:** Accumulation of normeperidine can lead to tremors and seizures. Limit duration to ≤48 hr in all patients. Avoid use in patients with kidney dysfunction.[1]	Renal (hepatic) (normeperidine, renal)	Meperidine: 2.3–4 Normeperidine: 8-20	Q3–4 hr	D	10–50 <10 IHD/PD	75% 50% Avoid use.	Avoid use, especially repeat administrations. Avoid use, especially repeat administrations.
Methadone	Hepatic (renal [<10%])	20–35	Q6–12 hr	D	<10/IHD/PD	50%–75%	Q6–12 hr
Methyldopa	Hepatic (renal [70%])	1–3	PO: Q6–12 hr IV: Q6–8 hr	I	>50 10–50 <10/IHD[b]/PD	100% 100% 100%	Q8 hr Q8–12 hr Q12–24 hr
Metoclopramide	Renal (85%)	2.5–6	PO: Q6 hr IV: Q6–8 hr	D	30–50 10–30 <10/IHD/PD	75% 50% 25%	No change No change No change

Continued

TABLE 31.2

NONANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics			Adjustments in Renal Failure			
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Midazolam **Note:** Metabolite α-hydroxymidazolam can accumulate in kidney failure, leading to prolonged sedation after midazolam is discontinued.[4]	Hepatic (renal [>60% as α-hydroxymidazolam])	2.5–4.5	Variable	D	<10	50%	No change
Milrinone	Renal (>85%)	1.5–2.5	Continuous infusion	D	50 40 30 20 10 5		0.43 mCg/kg/min 0.38 mCg/kg/min 0.33 mCg/kg/min 0.28 mCg/kg/min 0.23 mCg/kg/min 0.2 mCg/kg/min
Morphine	Hepatic (renal [5%–15%])	1–8	Variable	D	10–50 <10/IHD/PD	75% 50%	No change No change
Neostigmine	Hepatic (renal [50%])	0.5–2	Variable	D	10–50 <10	50% 25%	No change No change
Oxcarbazepine	Hepatic (Renal)	Oxcarbazepine: 2 MHD metabolite: 9	Q12 hr	D	<30	Initial dose: 50%. Titrate slowly.	Q12 hr
Pancuronium bromide	Renal (40%) (hepatic)	1.5–2.5	Q30–60 min *OR* continuous infusion	D	10–50 <10/IHD/PD	50% Avoid use.	No change

Phenazopyridine	Renal (65%) (hepatic)	Unavailable	Q8 hr for 2 days	I	50–80 <50	100% Contraindicated	Q8–16 hr
Phenobarbital	Hepatic (renal [20%–50%])	35–140	Q8–12 hr	I	<10/IHD[b]	100%	Q24 hr
Primidone **Note:** Due to complex metabolism, it is preferred to use other options when available for patients with kidney failure.[5]	Hepatic (renal [20%])	Primidone: 10–12 PEMA metabolite: 16 Phenobarbital: 35–140	Q6–12 hr	I	>50 10–50 <10/IHD[b]	100% 100% 100%	Q12 hr Q12–24 hr Q24 hr
Procainamide	Hepatic (renal [Procainamide 50%, NAPA 80%])	Procainamide: 1.7–4. 7 NAPA: 6	PO: Q4–6 hr IV: continuous	D	**IV Loading Dose** <10 **IV Maintenance**[c] <10 IHD	12 mg/kg Initiate at low end of dosing range and titrate to effect. Monitor levels. Supplementation may be needed.	Once
Quinidine	Renal (15%–25%)	2.5–8	Q6–12 hr	D	<10/IHD[b]/PD	75%	Q6–12 hr
Ranitidine	Renal (30%–70%) (hepatic)	1.5–2.5	PO: Q12 hr IV/IM: Q6–8 hr	D, I	30–50 10–29 <10/IHD[b]/PD	100% 50% 50%	Q12 hr Q12 hr Q24 hr
Sodium phenylacetate and sodium benzoate	Renal	Unavailable	Continuous	D	<50	Use with caution and close monitoring.	

Continued

TABLE 31.2

NONANTIMICROBIALS REQUIRING ADJUSTMENT IN RENAL FAILURE—cont'd

	Pharmacokinetics			Adjustments in Renal Failure			
Drug	**Route of Excretion[a]**	**Normal $t_{½}$ (hr)**	**Normal Dose Interval**	**Method**	**eGFR (mL/min/1.73 m²)**	**Percentage of Usual Dose**	**Interval**
Spironolactone	Renal (hepatic/biliary)	Spironolactone: 1.3–1.4 Metabolite: 13–24	Q6–24 hr	I	30–50 <30	100% Avoid use.	Q24 hr
Terbutaline	Renal (60%) (hepatic)	2.9–14	PO: Q8 hr Subcutaneous: Q2–6 hr IV: Continuous	D	<50	Manufacturer does not recommend dose reduction. Use with caution.	
Tezacaftor + Ivacaftor	Hepatic (renal)	Tezacaftor: 15 Ivacaftor:13	Combo product in AM, ivacaftor 12 hr after	NA	<30	Use with caution.	
Treprostinil	Renal (80%)	4	Oral: Q8–12 hr SubQ/IV: continuous	D, I	Manufacturer does not recommend dose reduction. Use with caution.		
Triamterene	Hepatic (renal [21%])	1.6–2.5	Q12–24 hr	I	<30	Do not use due to risk of hyperkalemia.[1]	
Verapamil	Renal (70%) (hepatic)	2–8	Variable	D	<10	Dose reduction may be needed; use caution. Monitor blood pressure, ECG for PR prolongation, and other signs of overdose.	

Vigabatrin	Renal (80%)	5–10	Q12 hr	D	50–80	75%	Q12 hr
					30–50	50%	Q12 hr
					10–30	25%	Q12 hr

[a]Percentage in parentheses represents the amount of drug and/or metabolites excreted in the urine. Route in parentheses indicates secondary route of excretion.

[b]For IHD administer after dialysis on dialysis days.

[c]In adults; guidelines not established in children.

[d]Administer supplemental dose after every 4 hours of dialysis, based on daily dose as follows (daily dose/recommended supplemental dose): 100 mg/125 mg; 125 mg/150 mg; 150 mg/200 mg; 200 mg/250 mg; 300 mg/350 mg.

[e]Dose interval varies for rapid and slow acetylators with normal and impaired renal function.

[f]Renal failure may cause hyposensitivity or hypersensitivity to insulin. Empiric dosing recommendations may not be appropriate for all patients; adjust to clinical response and blood glucose.

[g]Administer a supplemental dose after dialysis.

D, Dose reduction; *ECG*, electrocardiogram; *EDTA*, ethylenediaminetetraacetic acid; *eGFR*, estimated glomerular filtration rate; *ESRD*, end-stage renal disease; *GI*, gastrointestinal; *I*, interval extension; *IHD*, hemodialysis; *IM*, intramuscular; *IV*, intravenous; *MHD*, 10-monohydroxy metabolite; *NA*, not applicable; NAPA, *N*-acetylprocainamide; *PD*, peritoneal dialysis; *PO*, oral; *Q*, every; *SubQ*, subcutaneous; $t_{1/2}$, half-life.

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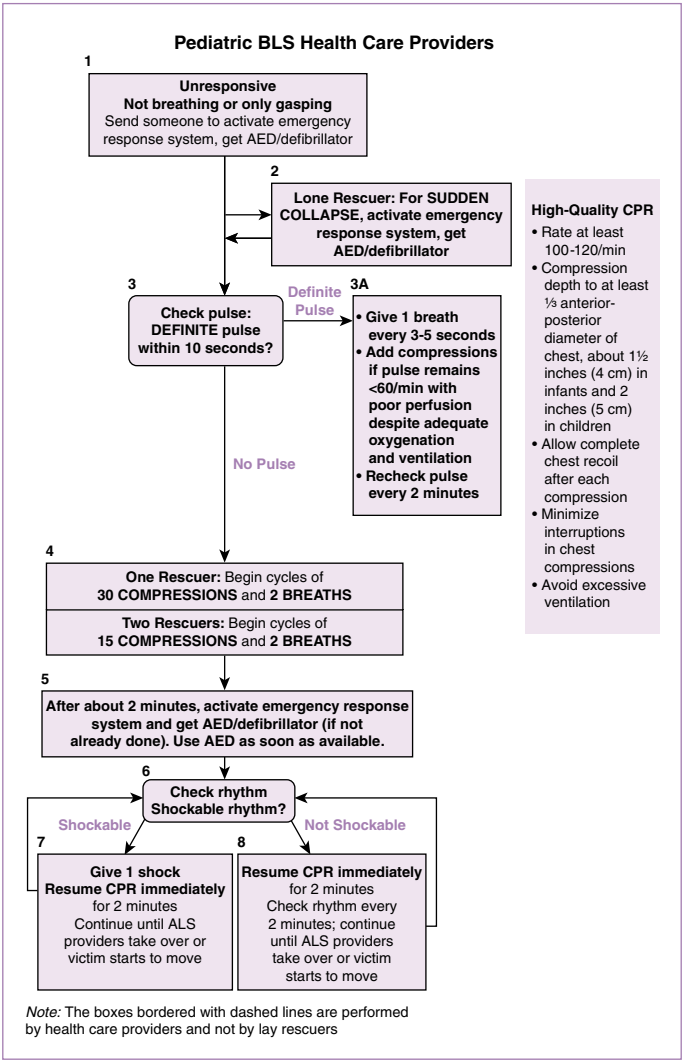
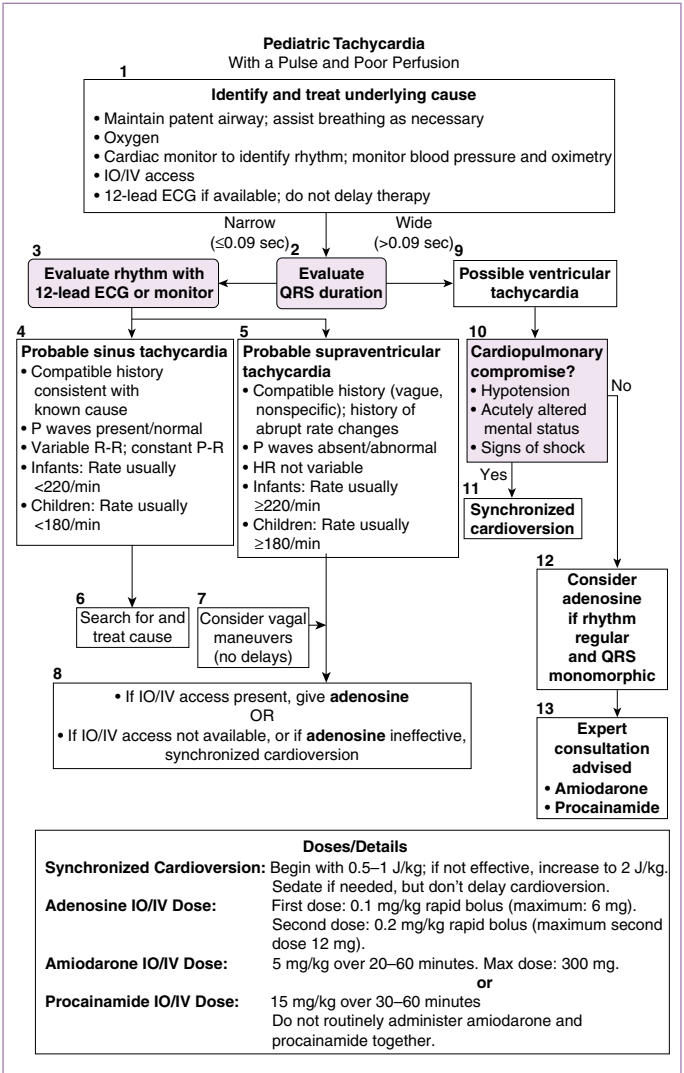
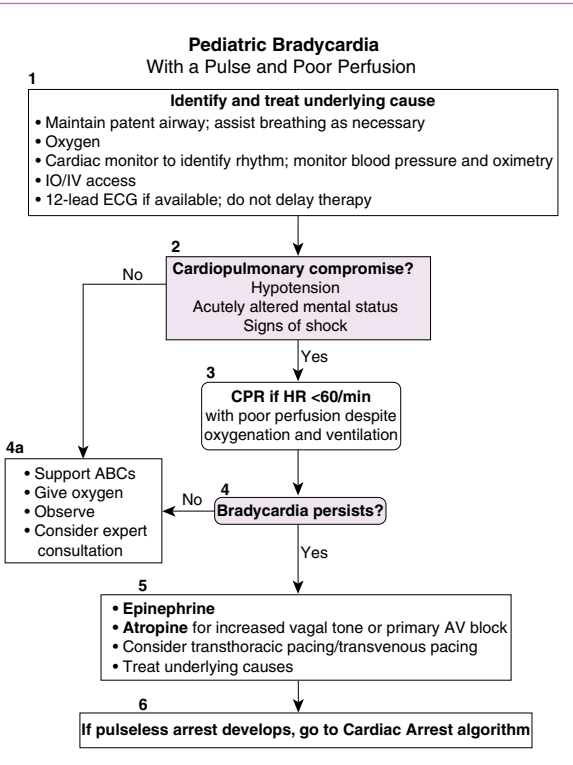


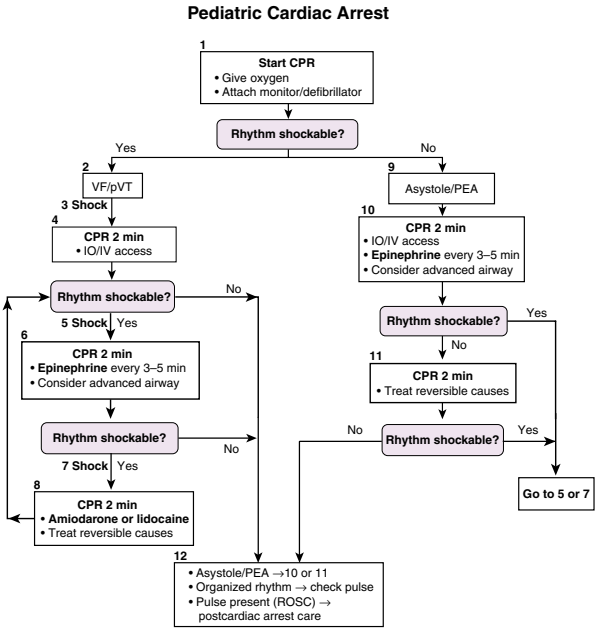
Pediatric BLS health care providers algorithm. (Reprinted with permission. Atkins DL, Berger S, Duff JP, et al. Part 11: pediatric basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Associated Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132(suppl 2):S519-S525.)



Pediatric tachycardia algorithm. (Reprinted with permission. 2015 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 14: Pediatric advanced life support. *Circulation.* 2015;122:S888. *© 2015 American Heart Association, Inc.*)



Pediatric bradycardia algorithm. (Reprinted with permission. 2015 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 14: Pediatric advanced life support. *Circulation.* 2015;122:S887. *© 2015 American Heart Association, Inc.*)



CPR Quality
- Push hard (≥⅓ of anterior-posterior diameter of chest) and fast (100–120/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes or sooner if fatigued
- If no advanced airway, 15:2 compression-ventilation ratio.

Shock Energy for Defibrillation

First shock 2 J/kg, second shock 4 J/kg, subsequent shocks ≥4 J/kg, maximum 10 J/kg or adult dose.

Drug Therapy
- **Epinephrine IO/IV Dose:** 0.01 mg/kg (0.1 mg/mL concentration). Max dose: 1 mg (10 mL). Repeat every 3–5 minutes. If no IO/IV access, may give endotracheal dose: 0.1 mg/kg (1 mg/mL concentration, max 2.5 mg).
- **Amiodarone IO/IV Dose:** 5 mg/kg bolus during cardiac arrest. Max dose: 300 mg. May repeat up to 2 times for refractory VF/pulseless VT.
- **Lidocaine IO/IV Dose:** Initial: 1 mg/kg loading dose. Max dose: 100 mg. Maintenance: 20–50 mcg/kg per minute infusion (repeat bolus dose if infusion initiated >15 min after initial bolus therapy).

Advanced Airway
- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor endotracheal tube placement
- Once advanced airway in place give 1 breath every 6 seconds (10 breaths per minute) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)
- Pulse and blood pressure
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes
- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypoglycemia
- Hypokalemia/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

Pediatric cardiac arrest algorithm. (Reprinted with permission. de Caen AR, Berg MD, Chameides L, et al. Part 12: pediatric advanced life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2015;132(suppl):S526-S542.)