THE HARRIET LANE HANDBOOK

THE JOHNS HOPKINS HOSPITAL

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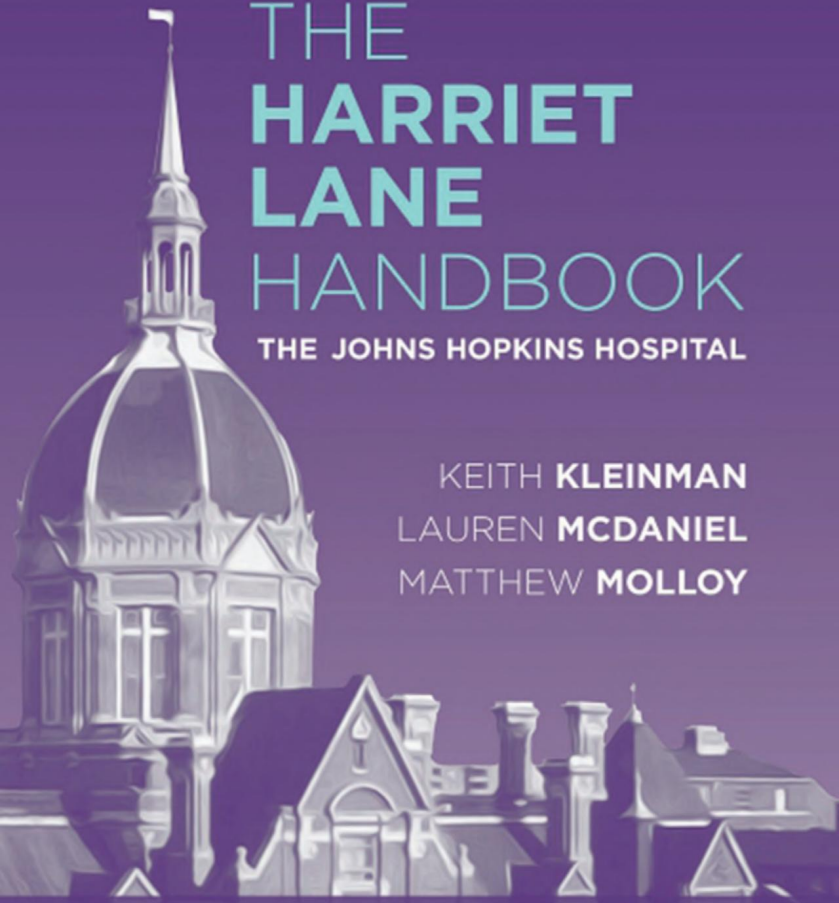

TWENTY-SECOND EDITION

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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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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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Elsevier
1600 John F. Kennedy Blvd.
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Philadelphia, PA 19103-2899

THE HARRIET LANE HANDBOOK, 22ND EDITION ISBN: 978-0-323-67407-2
INTERNATIONAL EDITION ISBN: 978-0-323-67408-9

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Previous editions copyrighted 2018, 2015, 2012, 2009, 2005, 2002, 2000, 1996, 1993, 1991, 1987, 1984, 1981, 1978, 1975, 1972, and 1969.

Library of Congress Control Number: 2020932209

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Design Direction: Patrick Ferguson

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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.

Valerie and Richard McDaniel, thank you for all of the sacrifices you have made to prioritize my education and support me in achieving my goals. From an early age, you instilled in me a love of books, a passion for medicine, and an unwavering belief that with hard work and a sense of humor, anything is possible. Michael McDaniel, thank you for being the best brother I could ever ask for and for always believing in and supporting me.

Patrick and Patricia Molloy, thank you for always being my constant supporters no matter where life takes me. Tim, Megan, and Kelly Molloy, your friendship keeps me smiling and has shown me that family is home. Molly Smith Molloy, I can't imagine being on this journey with anyone else. You know me better than I know myself; thank you for all the love, laughs, and acts of service. To my daughters, Maggie and Katie, I am so proud of you. You make every day an adventure and push me to be an advocate for children. The future is yours.

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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11	Fluids and Electrolytes	Lauren Burgunder, MD, MPH	Rebecca Ruebner, MD, MSCE Leonard Feldman, MD
12	Gastroenterology	Matthew Buendia, MD Natalie Thoni, MD	Darla Shores, MD, PhD
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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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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

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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]

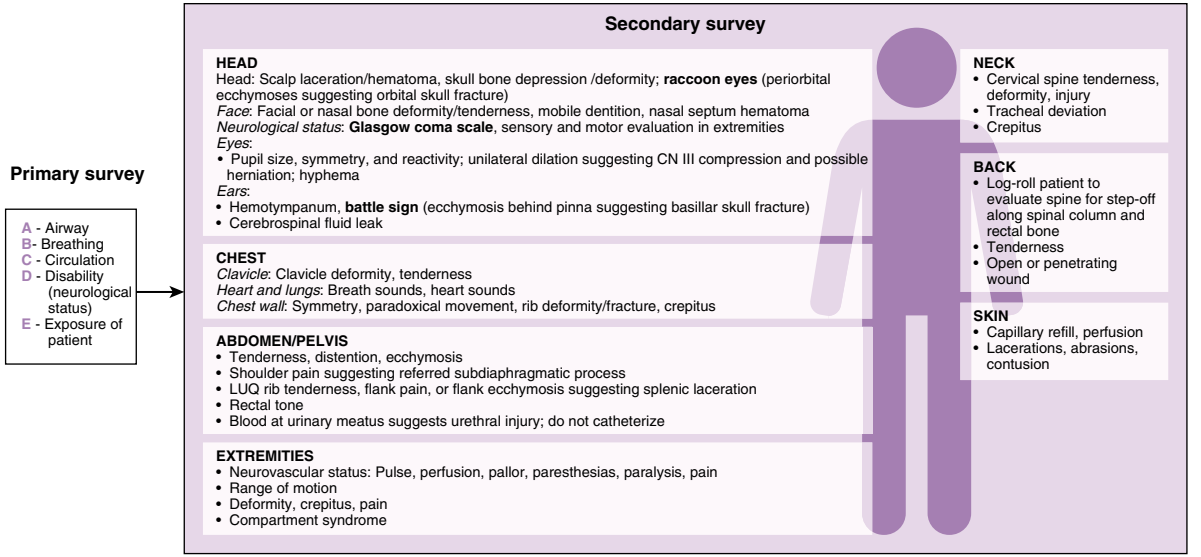


FIGURE 2.1
Trauma primary and secondary survey.

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

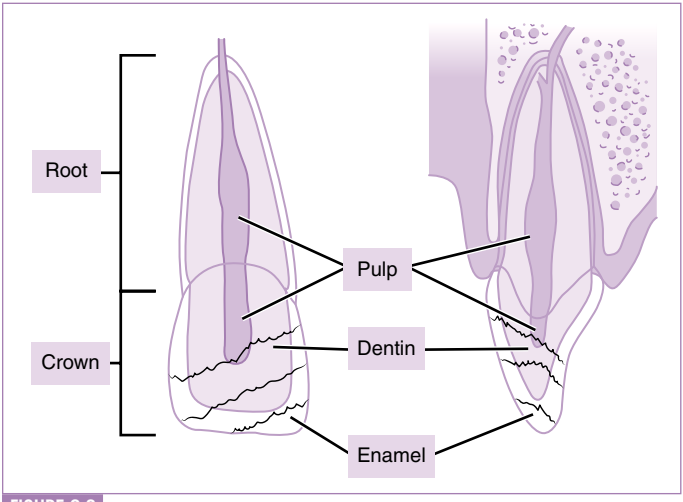


FIGURE 2.3
Normal anatomy of a tooth. (*Modified from Textbook of Pediatric Emergency Medicine.*[18])

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!

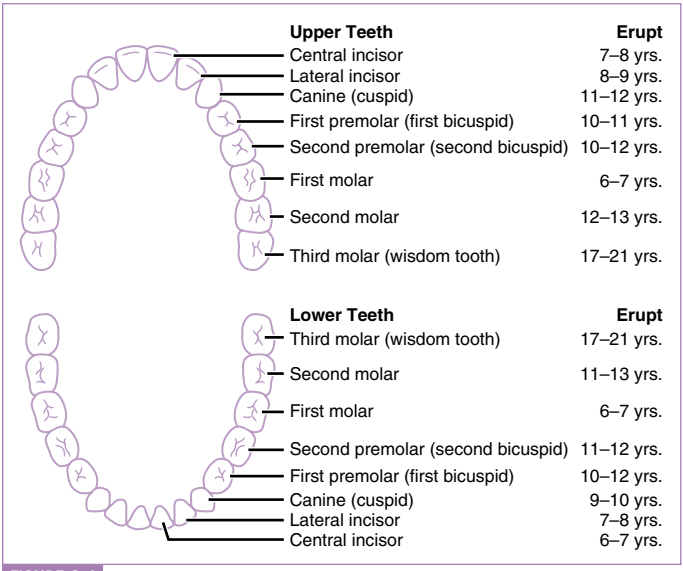


FIGURE 2.4

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.

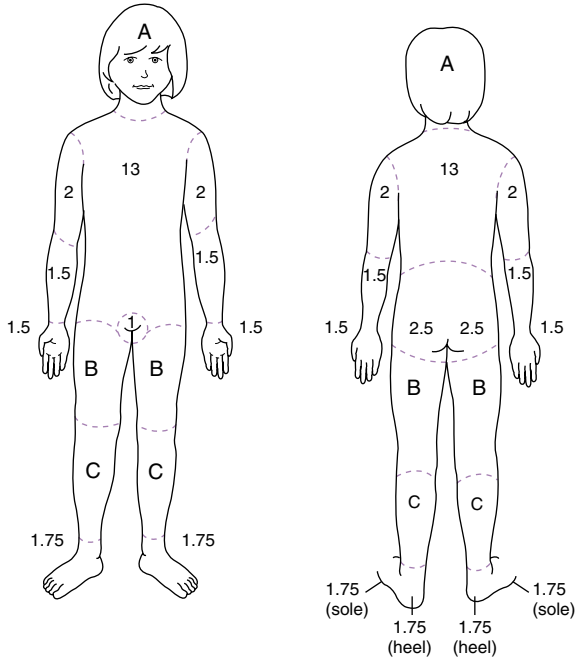
C. Estimation of the Depth of Burns (Table 2.5)

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

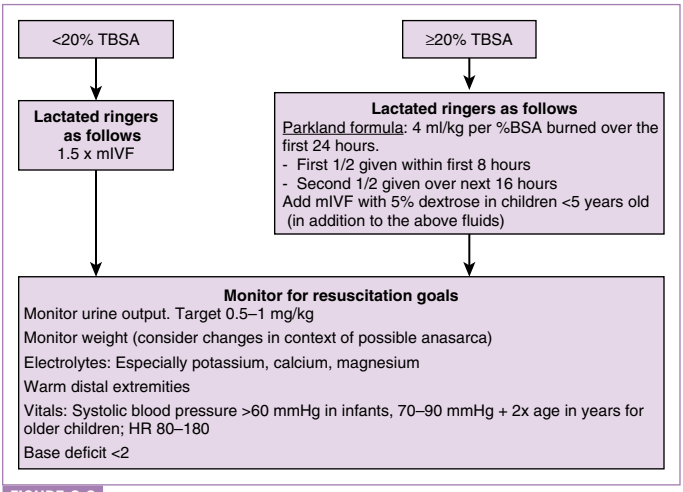


FIGURE 2.6

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.

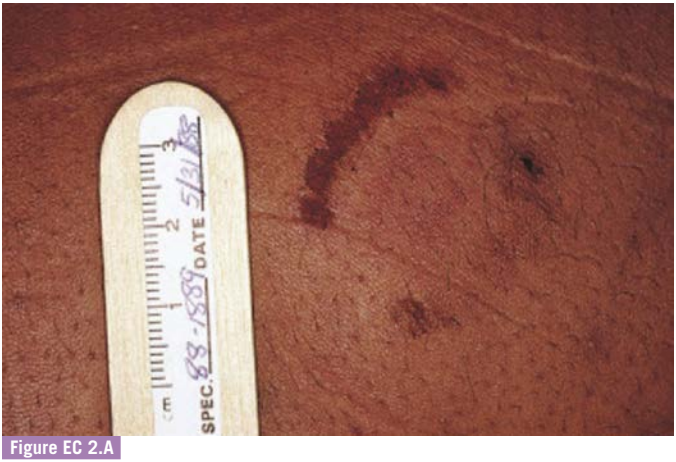


Figure EC 2.A

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]

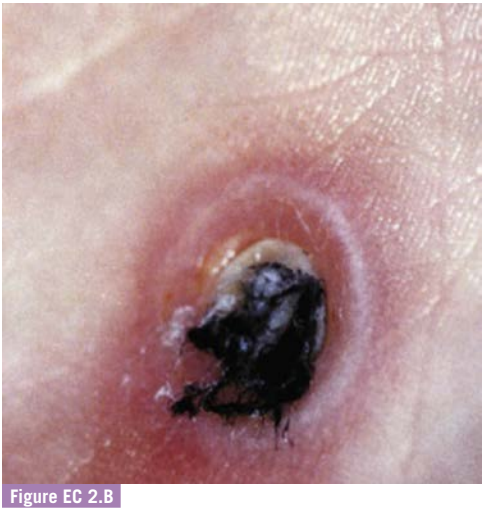


Figure EC 2.B

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]

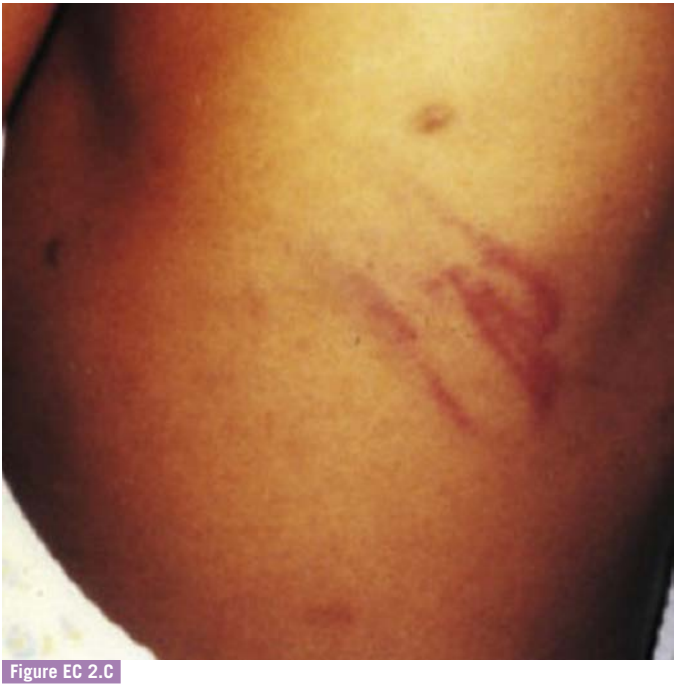


Figure EC 2.C
Loop marks from a cord or cable. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

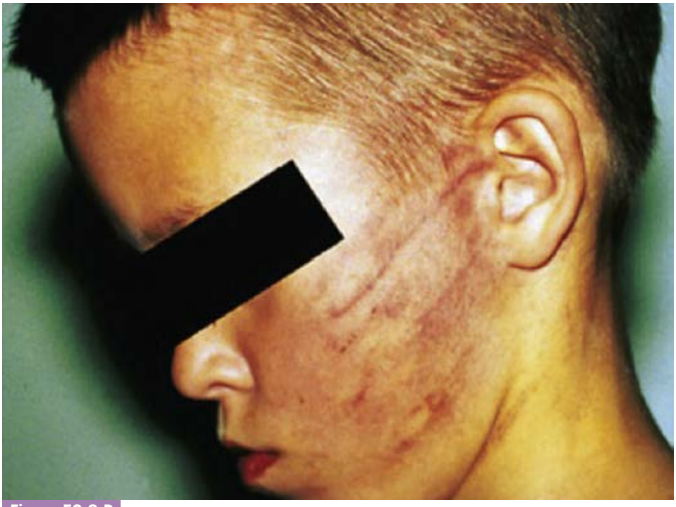


Figure EC 2.D

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.

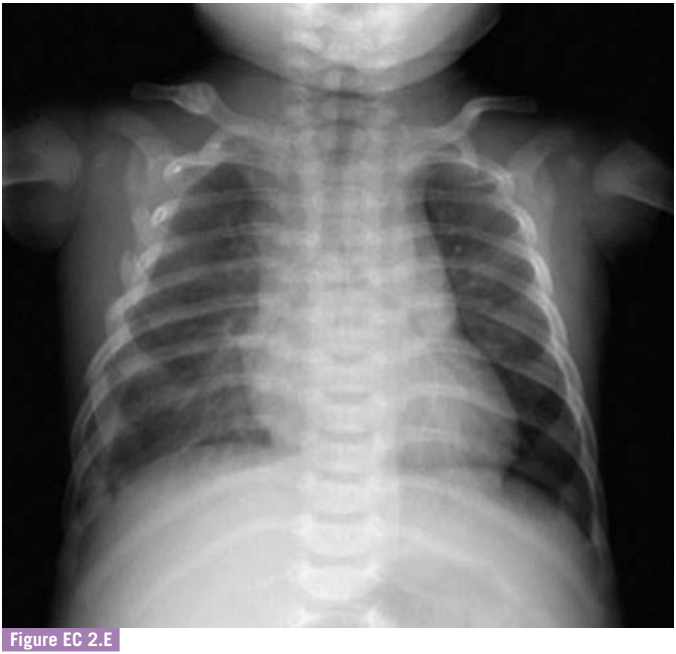


Figure EC 2.E

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]

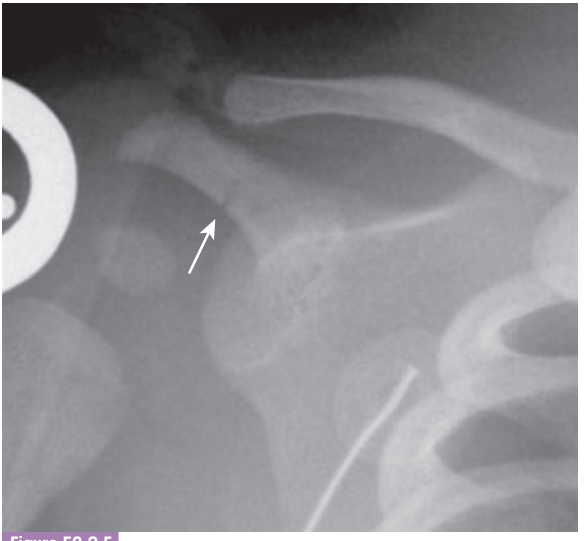


Figure EC 2.F
Right acromial fracture (arrow). (*Modified from Coley BD.* Caffey's Pediatric Diagnostic Imaging. *13th ed. Philadelphia: Elsevier; 2019.*)[40]

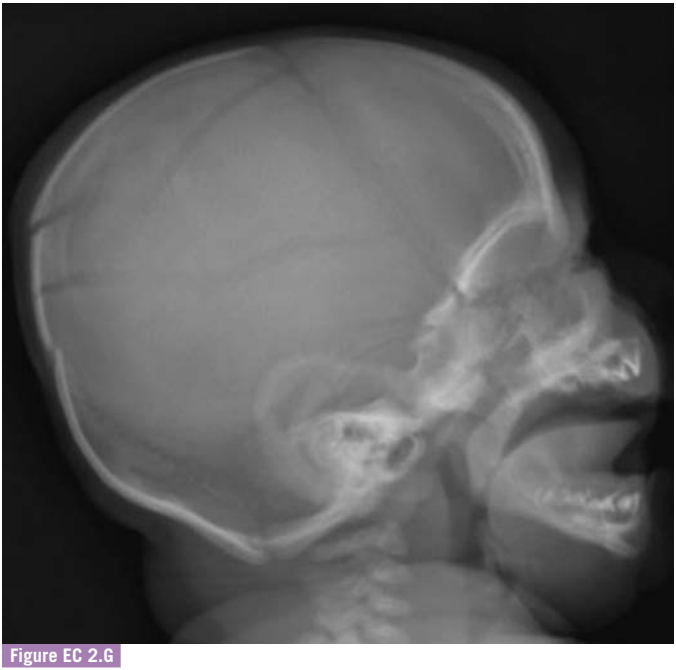


Figure EC 2.G

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

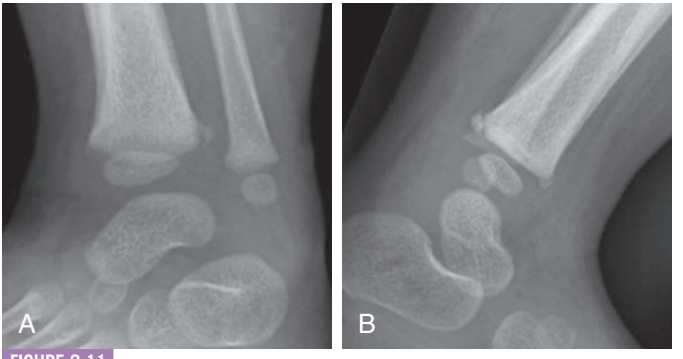


FIGURE 2.11

"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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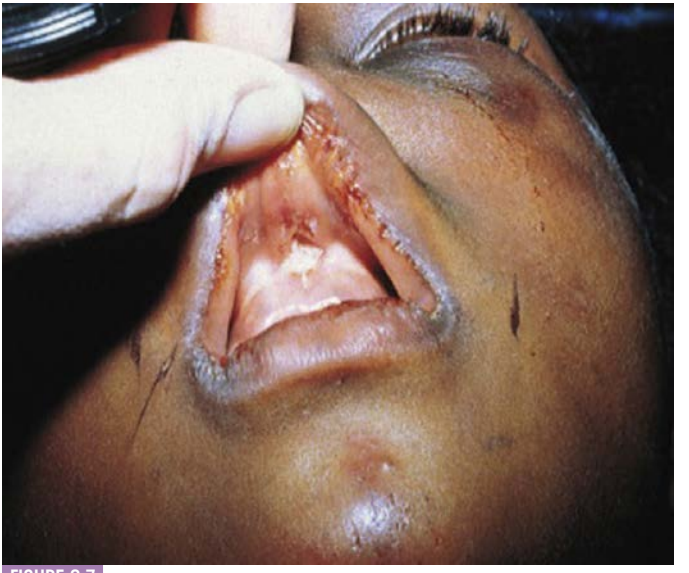

FIGURE 2.7

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]

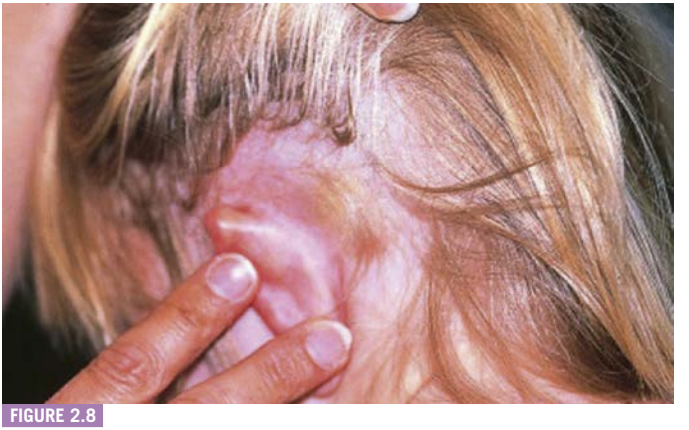

FIGURE 2.8

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

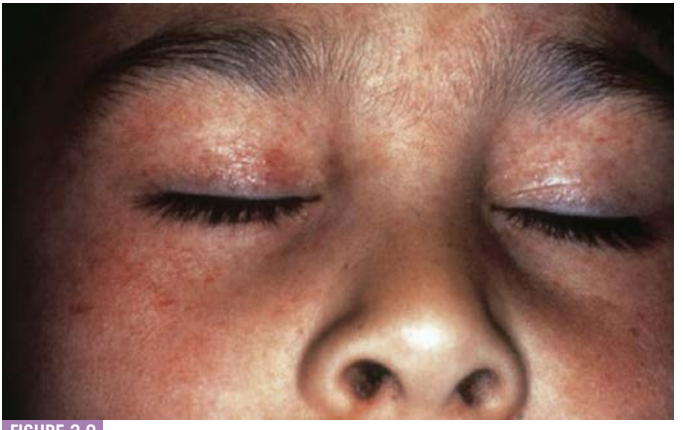

FIGURE 2.9
Petechial lesions due to choking. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

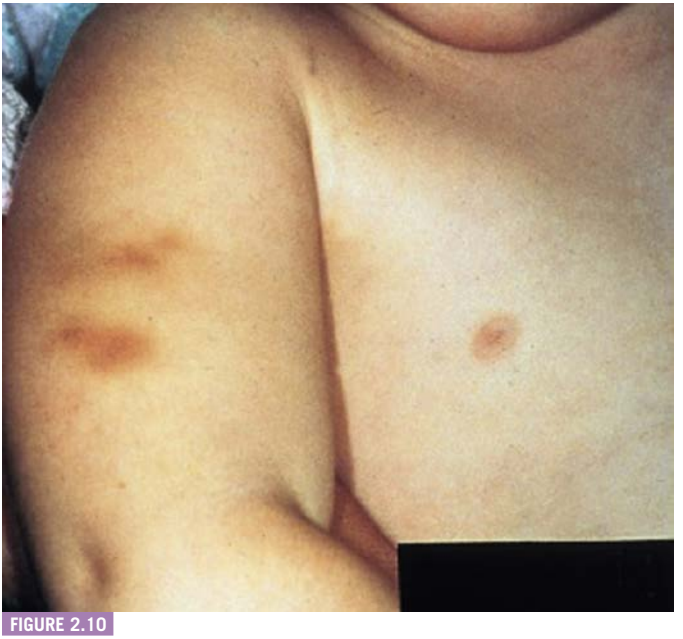

FIGURE 2.10
Pinch marks signified by two small bruises separated by clear space. (*Modified from Zitelli BJ, McIntire SC, Nowalk, AJ.* Atlas of Pediatric Physical Diagnosis. *7th ed. Philadelphia: Elsevier; 2018.*)[39]

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.

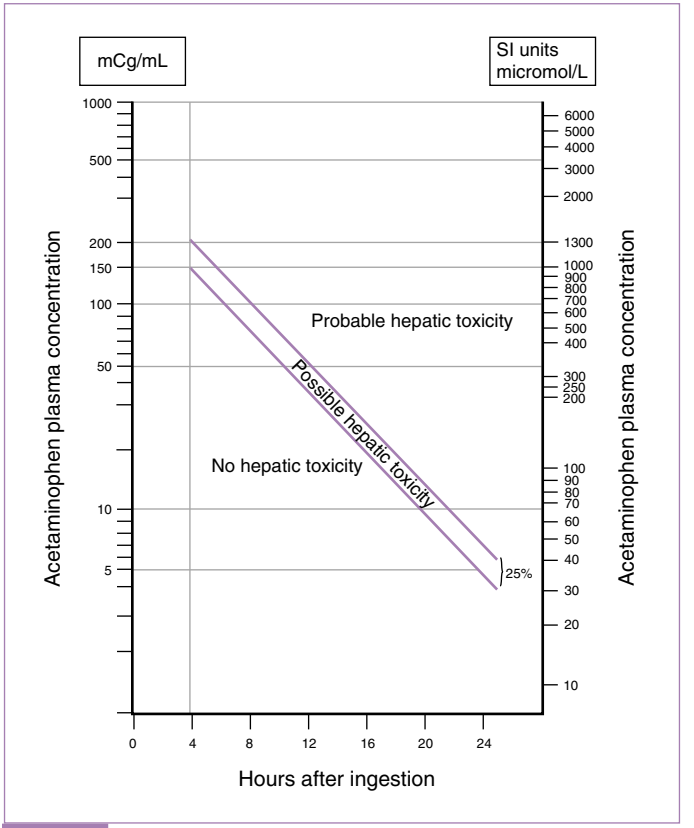

FIGURE. 3.1

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

REFERENCES

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

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Chapter 4

Procedures

Andrew Percy, MD

See additional content on Expert Consult

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.

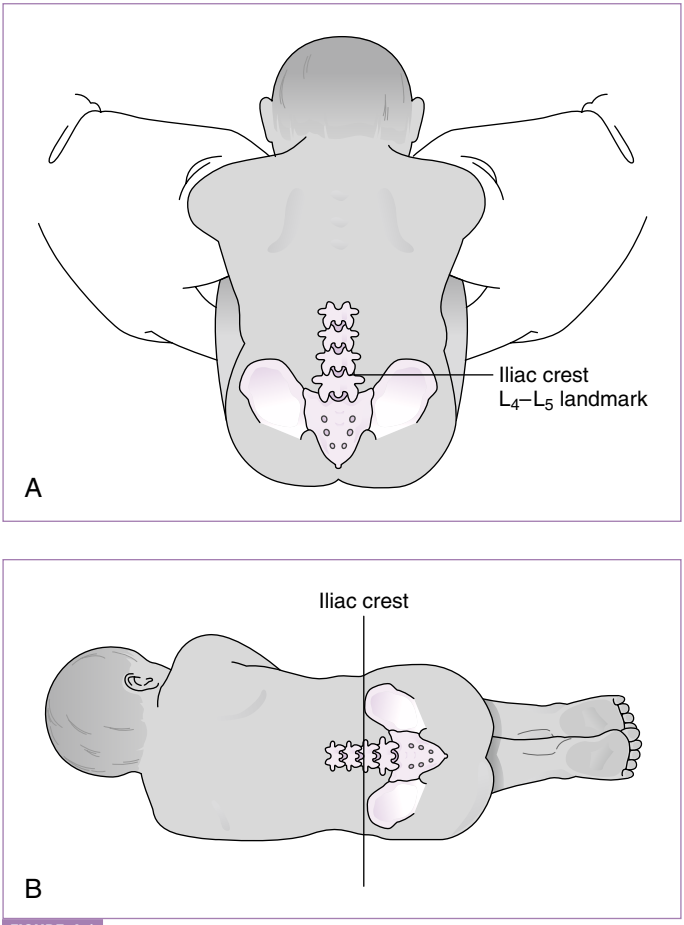

FIGURE 4.1
Lumbar puncture site. (A) Infant placed in sitting position. (B) Infant placed in lateral (recumbent) position. (*From Dieckmann R, Fiser D, Selbst S.* Pediatric Emergency and Critical Care Procedures. *St. Louis: Mosby; 1997.*)

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

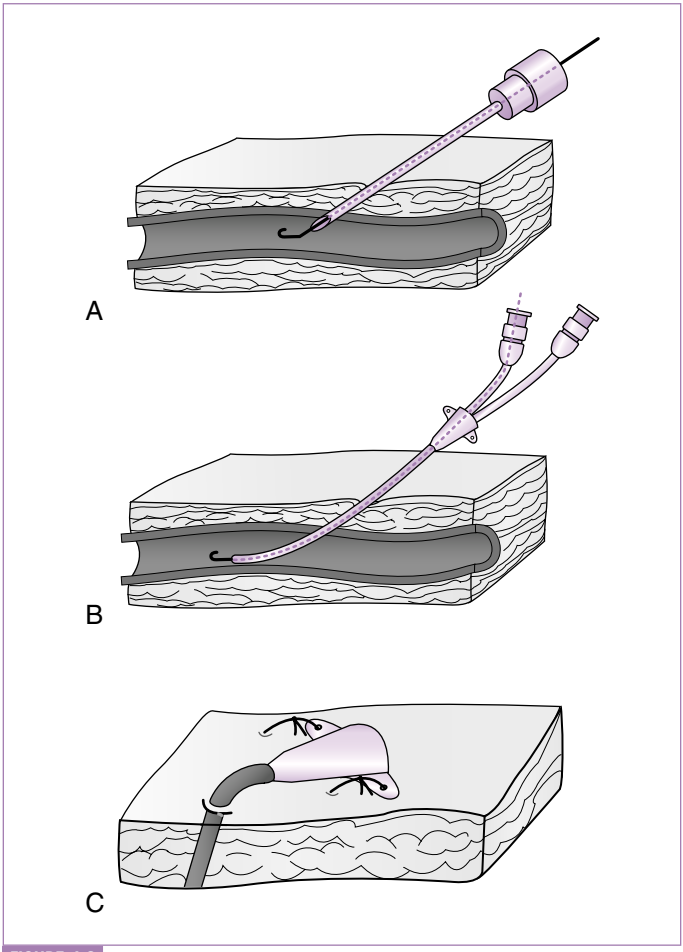

FIGURE 4.2
Seldinger technique. (A) Guidewire is placed through introducer needle into lumen of vein. (B) Catheter is advanced into vein lumen along guidewire. (C) Hub of catheter is secured to skin with suture. (*Modified from Fuhrman B, Zimmerman J.* Pediatric Critical Care. *4th ed. Philadelphia: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

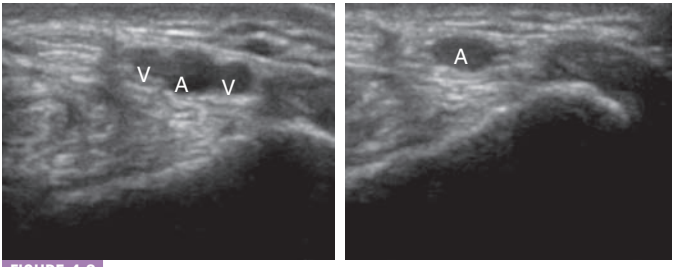

FIGURE 4.3
Ultrasound transverse view of radial artery. In the left image, the radial artery is seen in cross section with veins on either side. On the right image, pressure has been applied and the veins are collapsed while the artery remains patent. *A,* Artery; *V,* vein. (*From Weiner MM, Geldard 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.

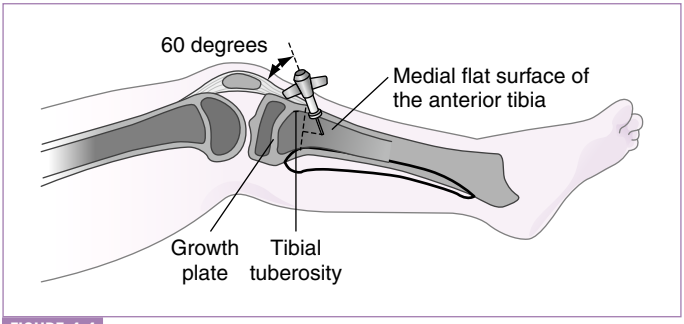

FIGURE 4.4

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):

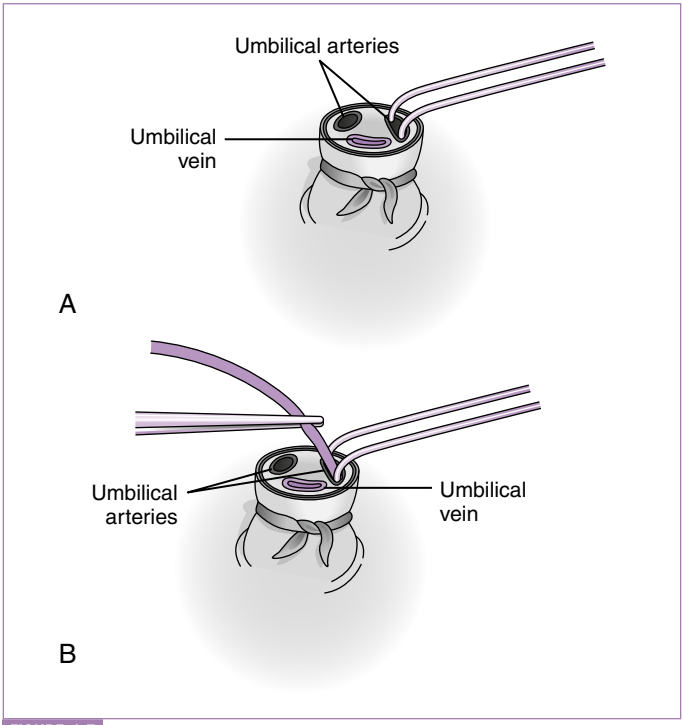

FIGURE 4.5

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.**

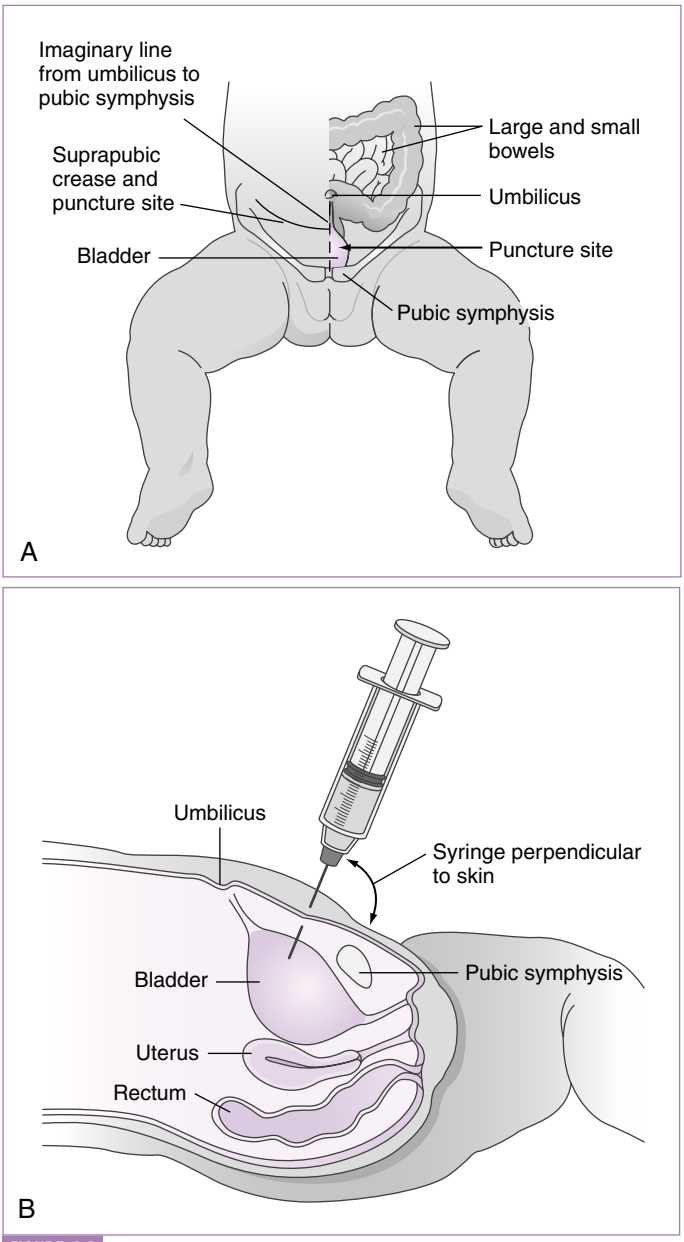

FIGURE 4.6

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

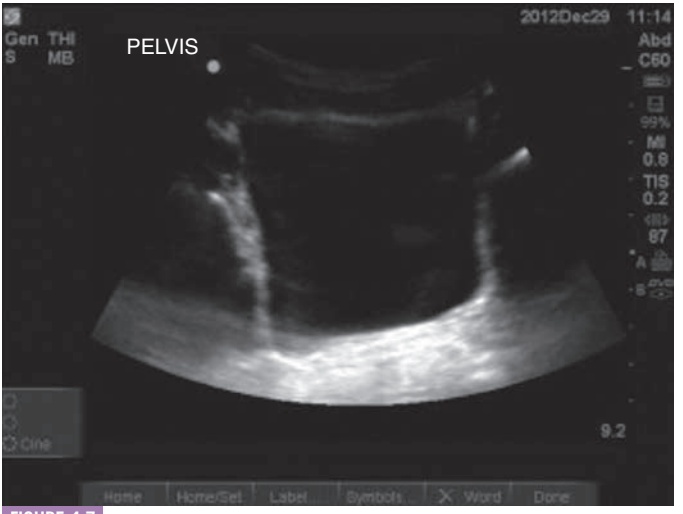

FIGURE 4.7
Ultrasound of bladder. In this transverse midline view of the pelvis the bladder appears black (anechoic) and cuboid in the midline. This is the typical appearance of a full bladder on ultrasound, although the shape may vary. (*From Leeson K, Leeson B. Pediatric ultrasound: applications in 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.

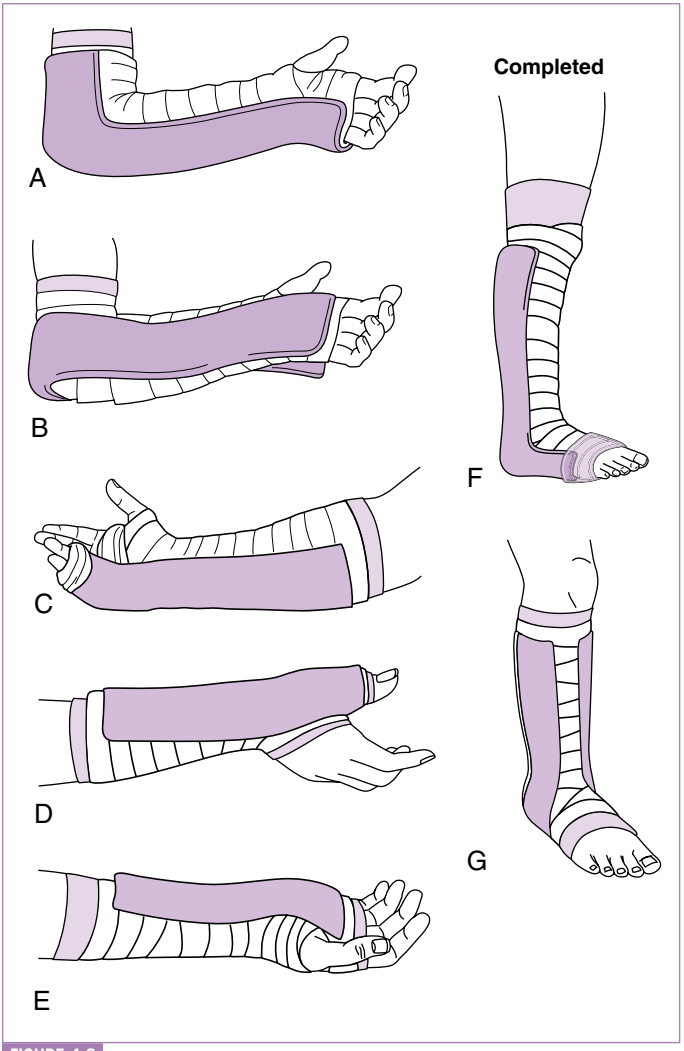

FIGURE 4.8

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

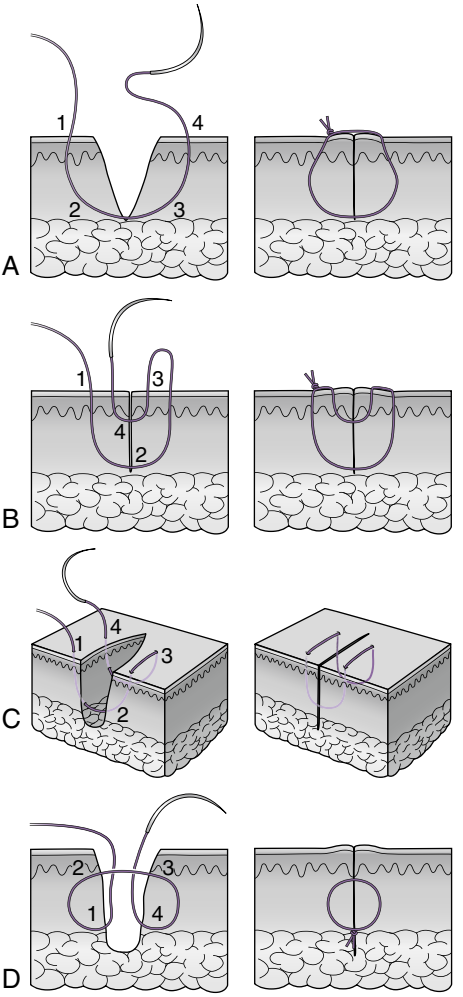

FIGURE 4.9

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.

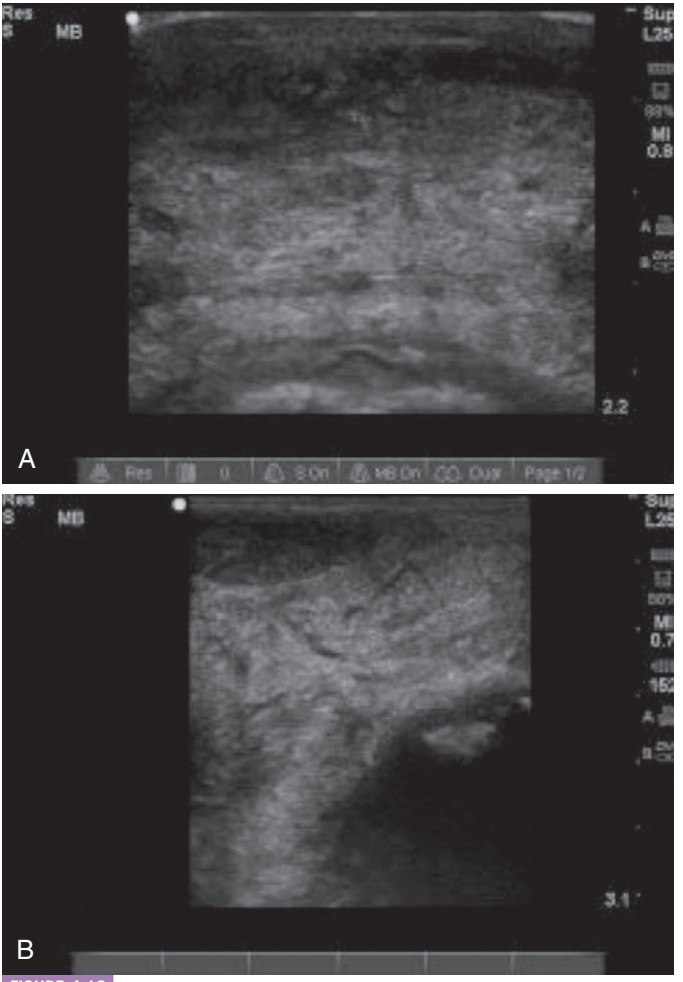

FIGURE 4.10
Ultrasound characteristics of soft tissue cellulitis and abscess. (A) Cellulitis characterized by bright (hyperechoic) tissue due to edema and inflammation in the tissue. (B) This image demonstrates the classic "cobblestone" appearance which is a later ultrasound finding in cellulitis.

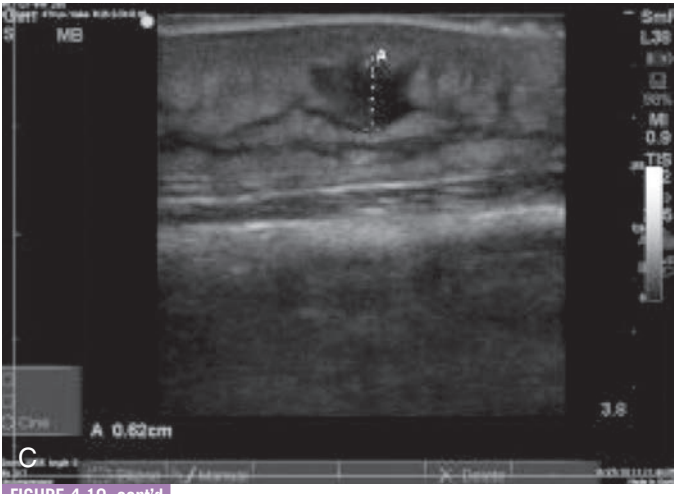

FIGURE 4.10, cont'd

(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.

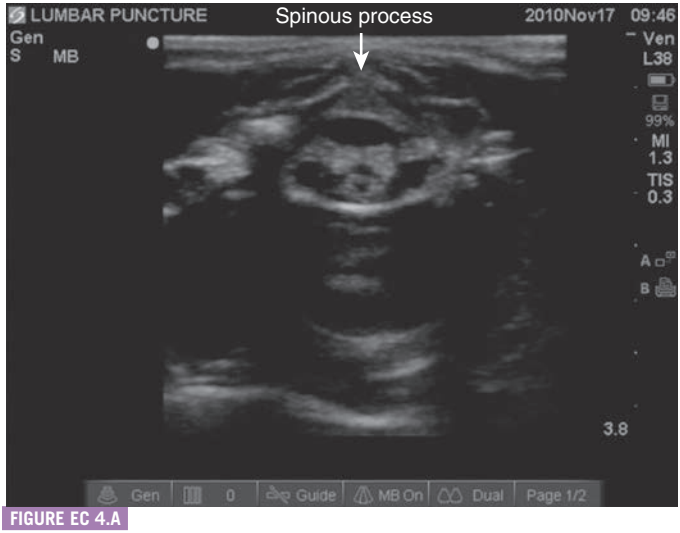

FIGURE EC 4.A

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.*)

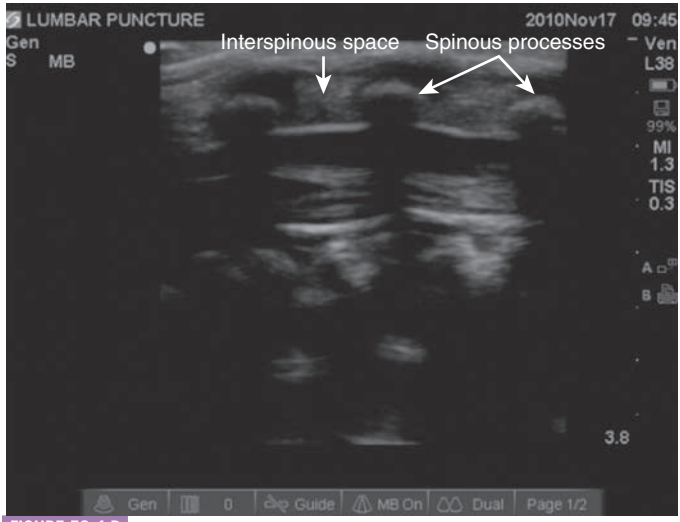

FIGURE EC 4.B

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.*)

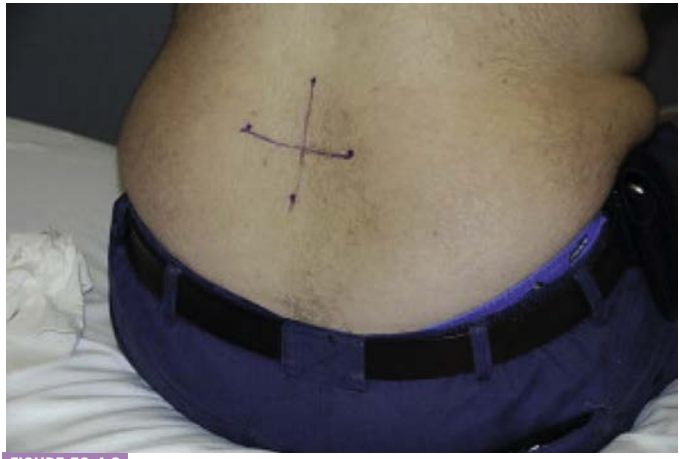

FIGURE EC 4.C

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.

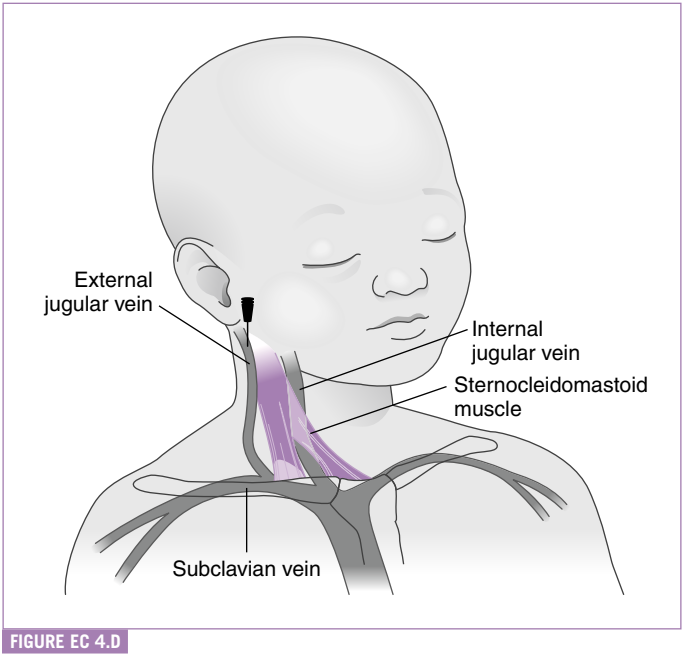

FIGURE EC 4.D

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.

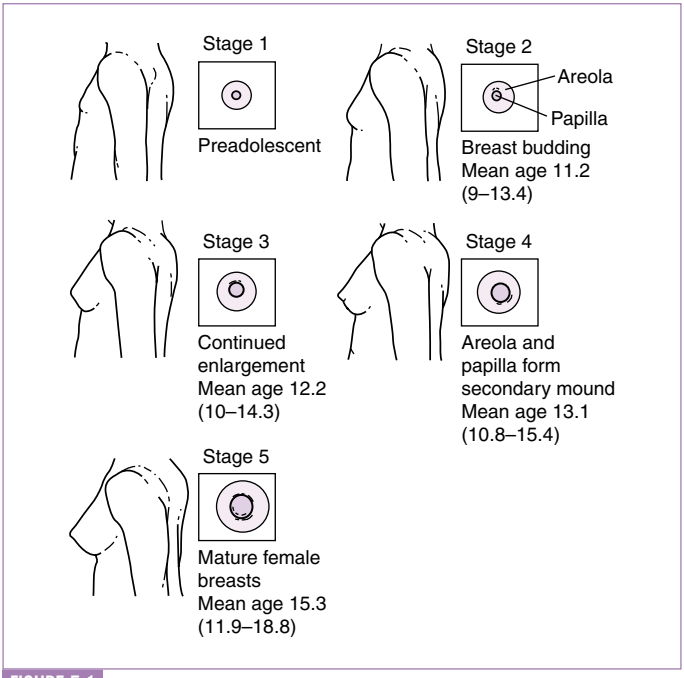


FIGURE 5.1

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.

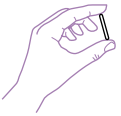
D. Contraception[32,33]

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.

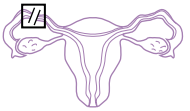
Less than 1 pregnancy per 100 women in a year

Permanent

Male Sterilization (Vasectomy)

0.15%

Female Sterilization (Abdominal, Laparoscopic, Hysteroscopic)



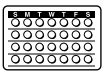
0.5%

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

Injectable

6%

Pill



9%

Patch

9%

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

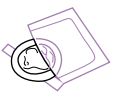
Ring

9%

Diaphragm

12%

Male Condom

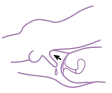


18%

Female Condom

21%

Withdrawal



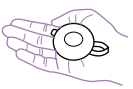
22%

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.

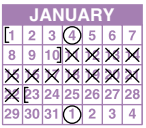
18 or more pregnancies per 100 women in a year

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]

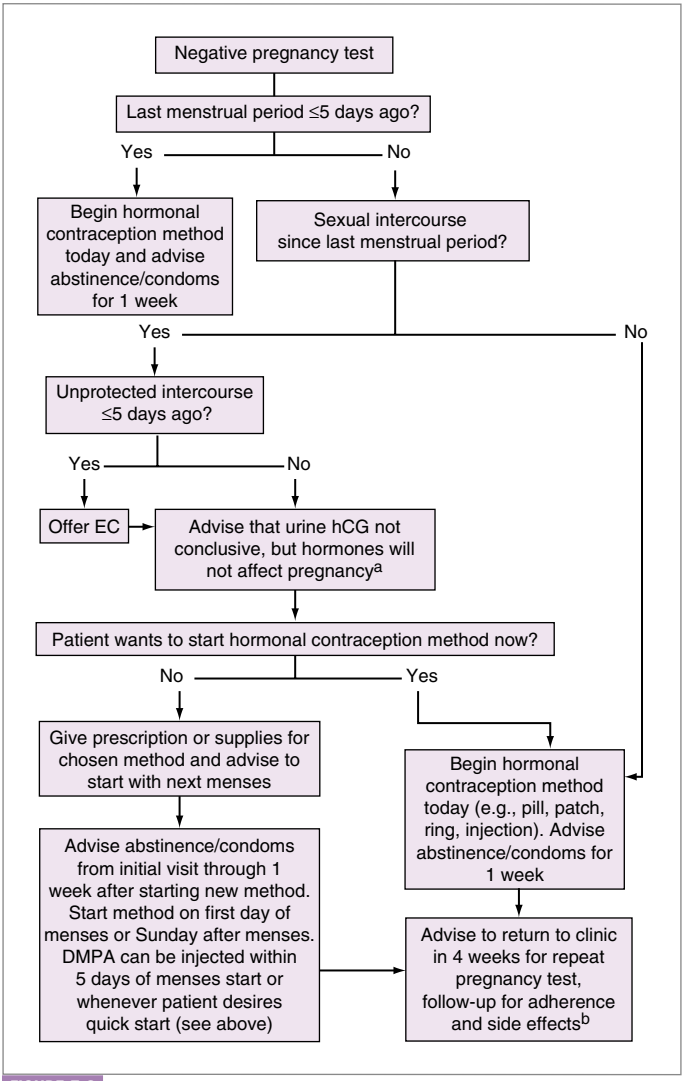


FIGURE 5.3

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.

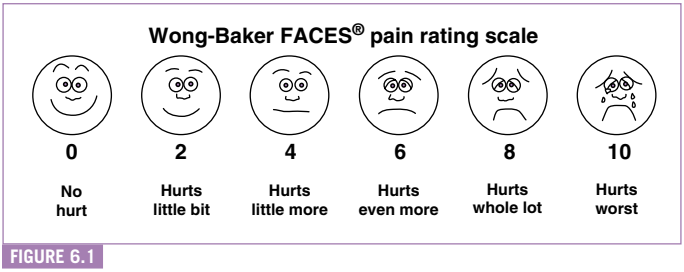

FIGURE 6.1

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.

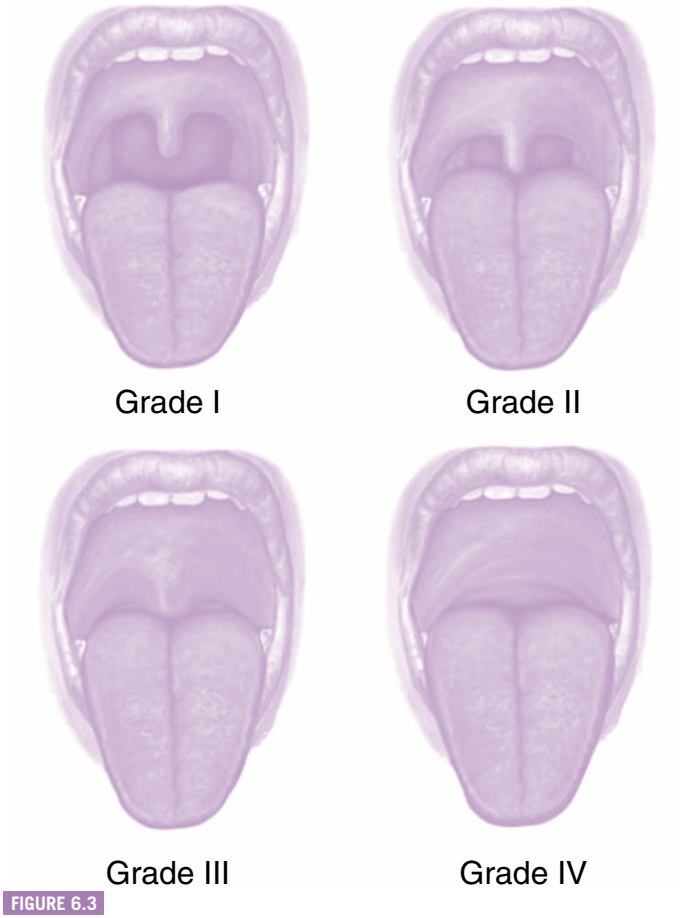

FIGURE 6.3
Mallampati classification system.

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).

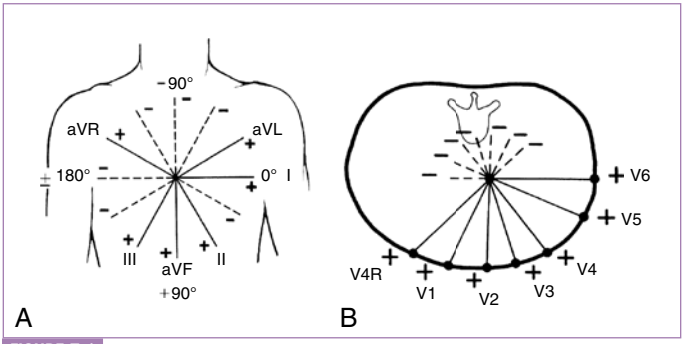

FIGURE 7.1

(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.

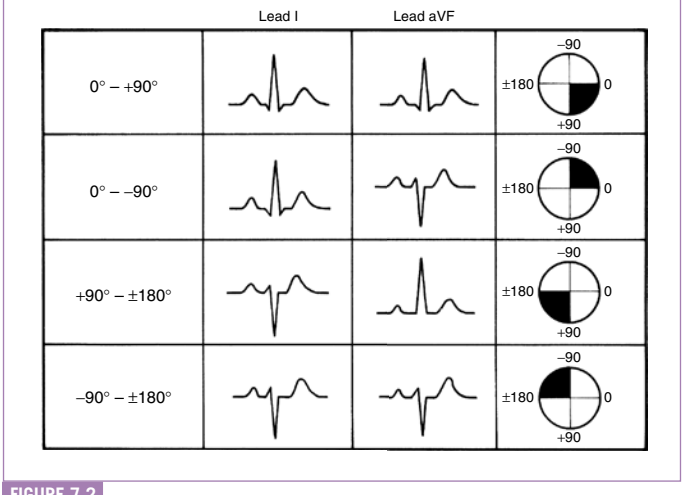

FIGURE 7.2

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.)

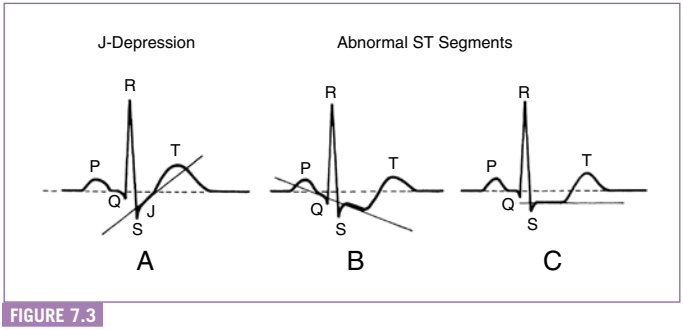

FIGURE 7.3

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.

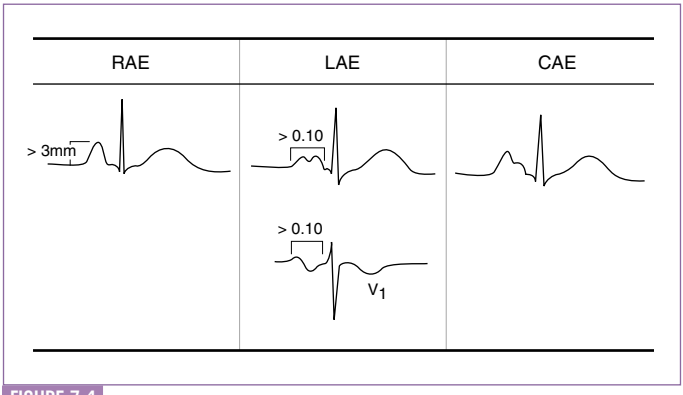

FIGURE 7.4

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.

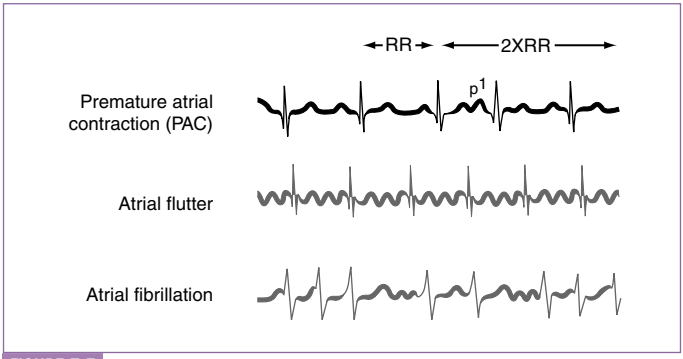

FIGURE 7.5

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.

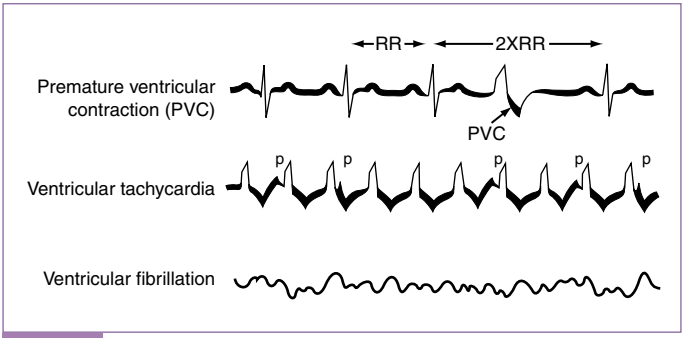

FIGURE 7.6

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.

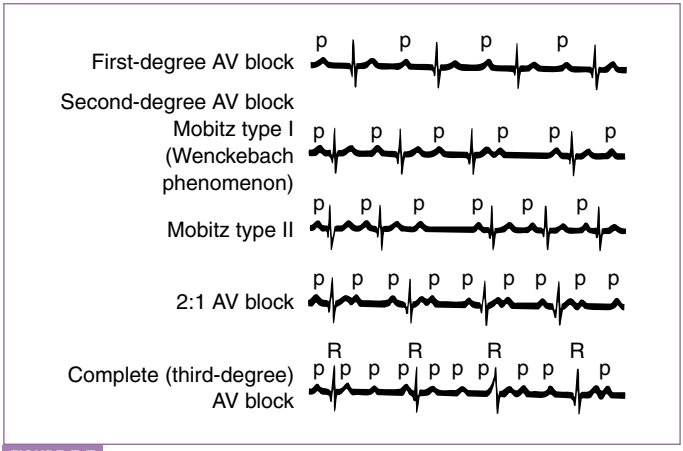

FIGURE 7.7

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.

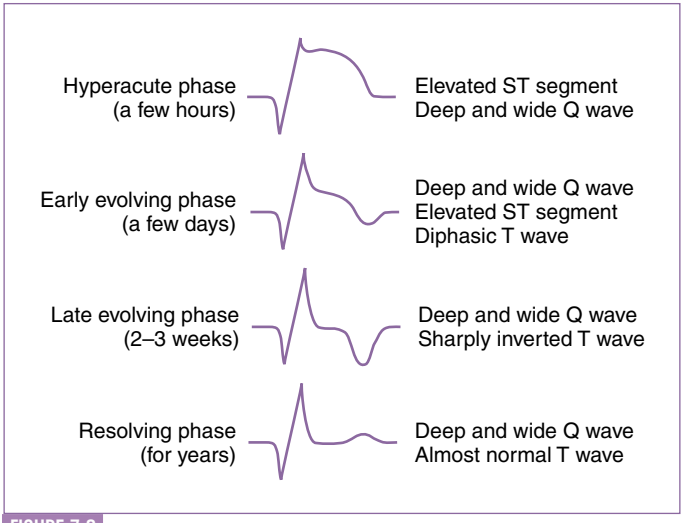

FIGURE 7.8

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]

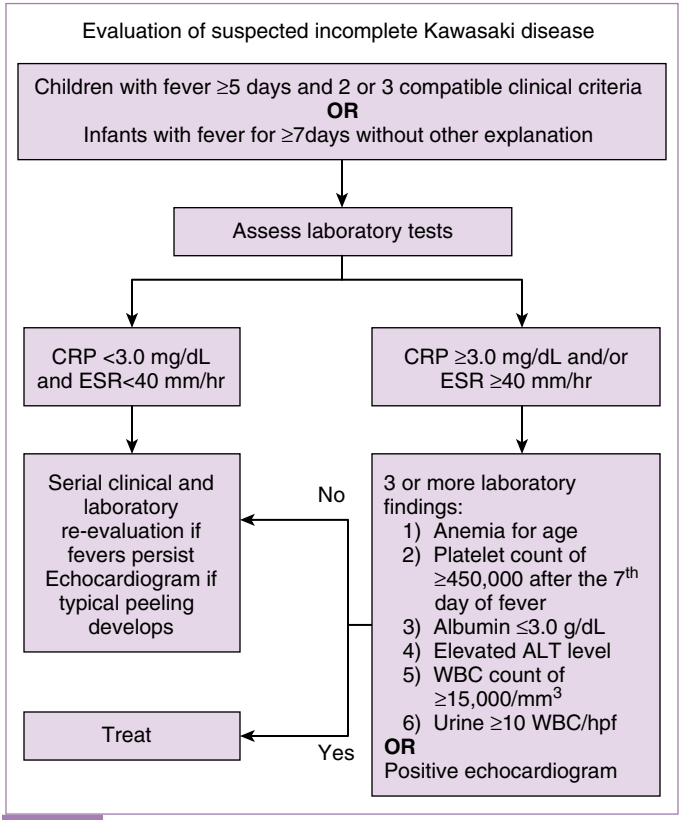

FIGURE 7.9

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,

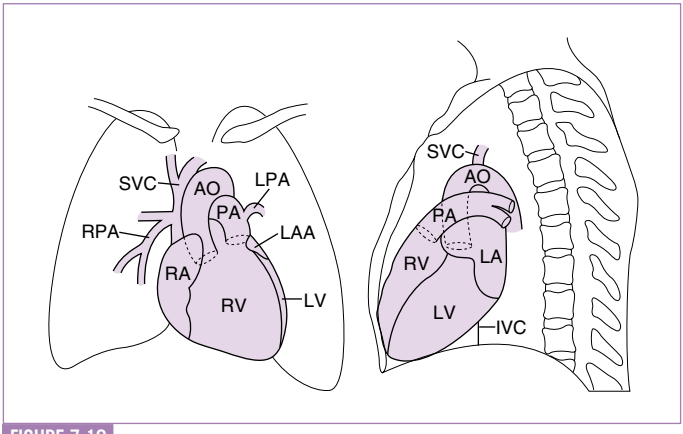

FIGURE 7.10

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

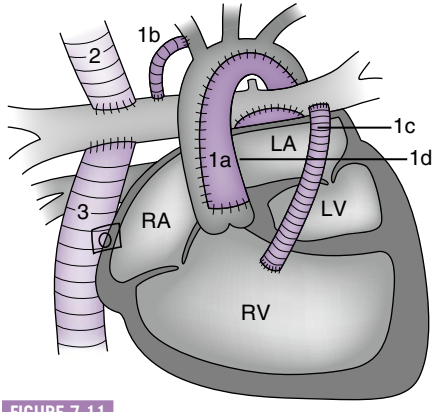

FIGURE 7.11
Schematic diagram of cardiac shunts, including the modified Blalock-Taussig *(BT)*, Sano modification, bidirectional Glenn, and Fontan shunts.

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.

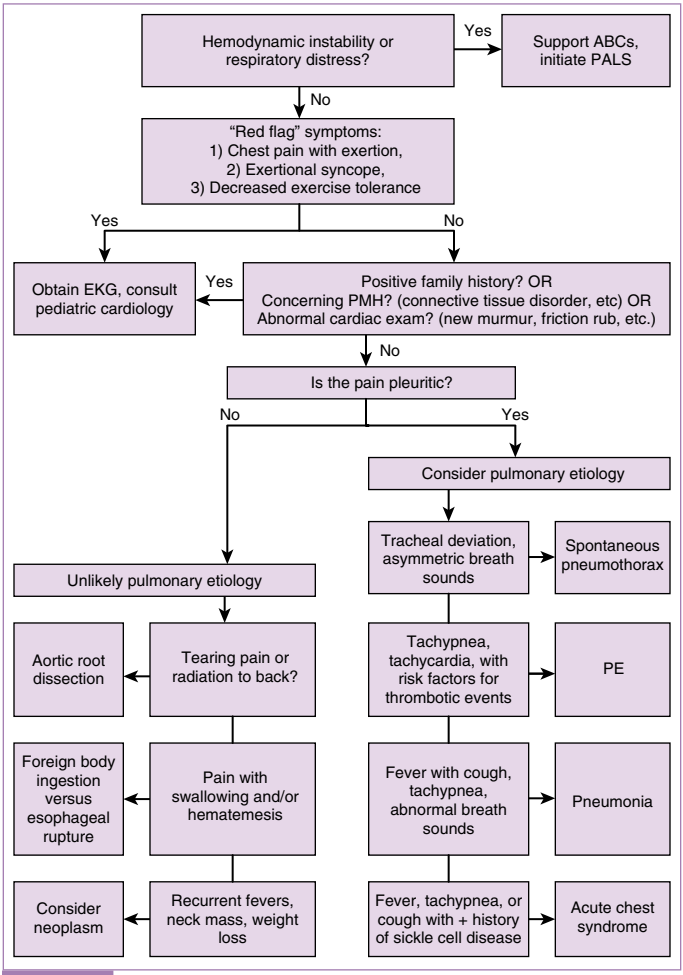

FIGURE 7.12

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.

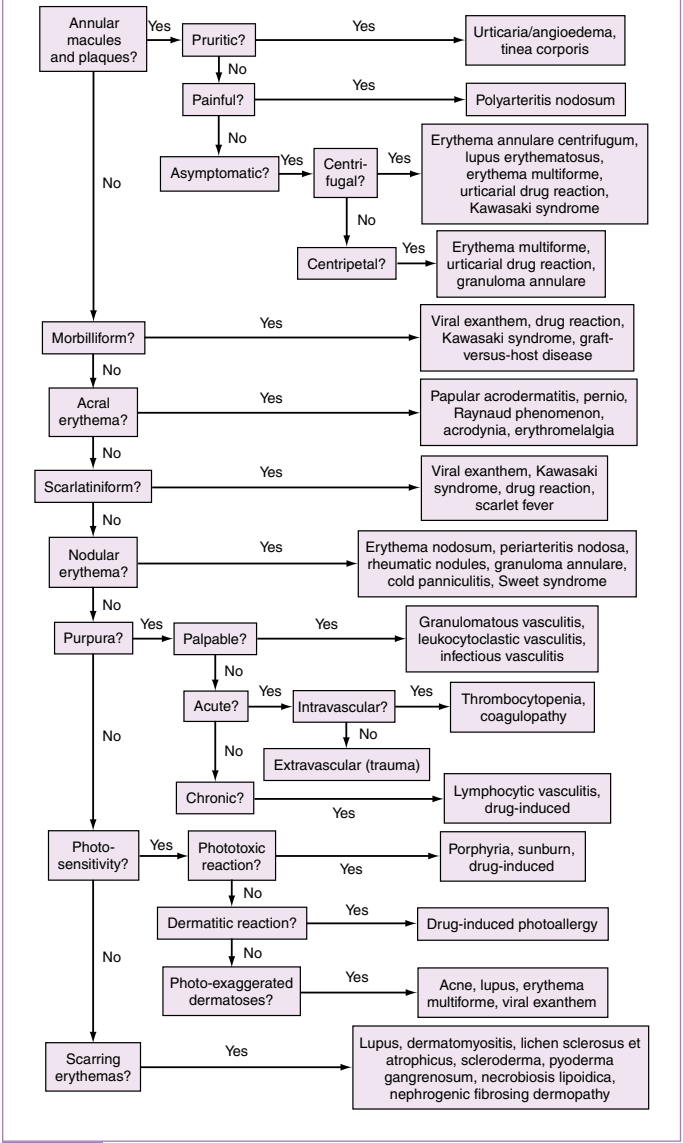

FIGURE 8.4

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.

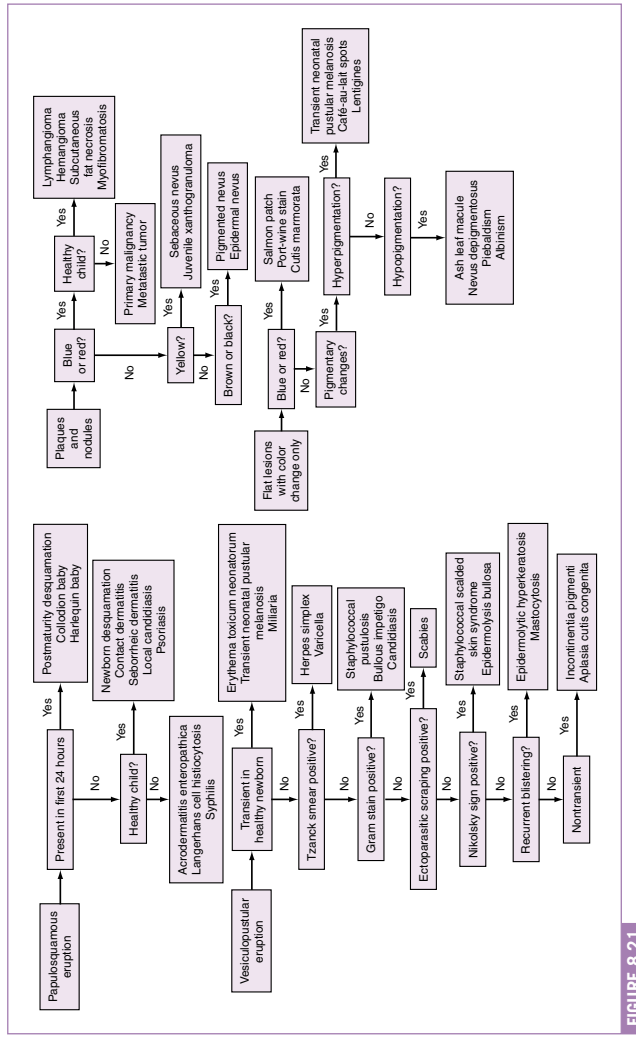

FIGURE 8.21
Evaluation of neonatal rashes. (Modified from Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:62.)

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.

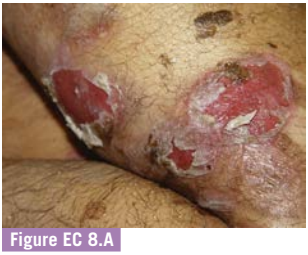

Figure EC 8.A

Pemphigus vulgaris. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

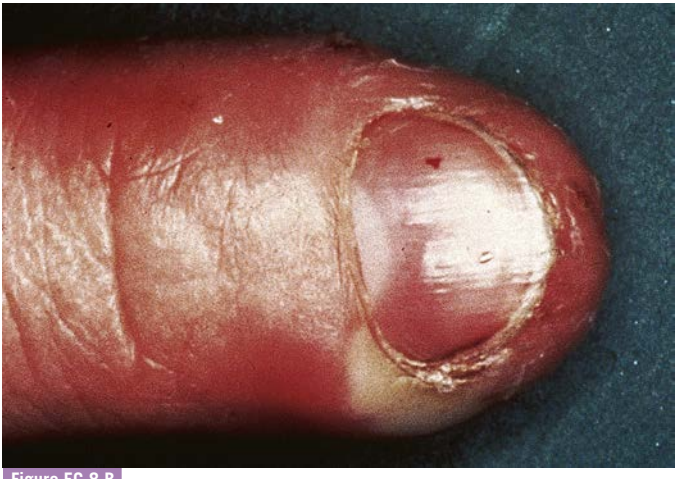

Figure EC 8.B
Acute paronychia. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

(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.

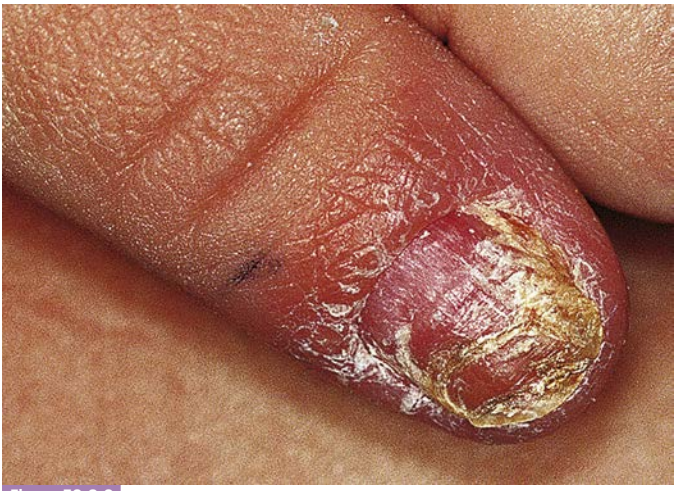

Figure EC 8.C

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.

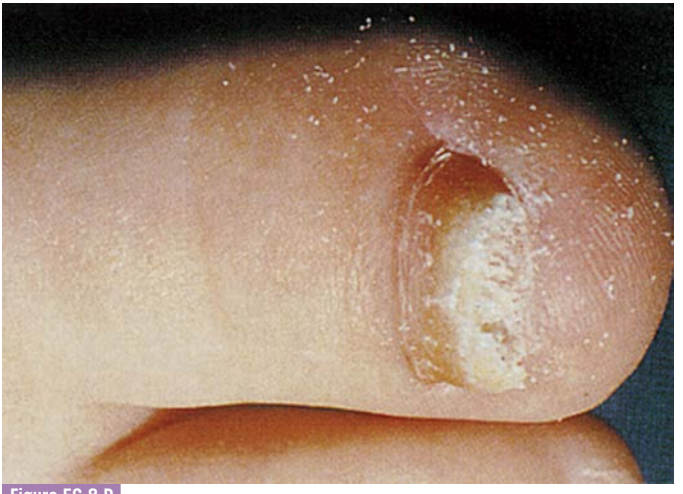

Figure EC 8.D
Onychomycosis. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

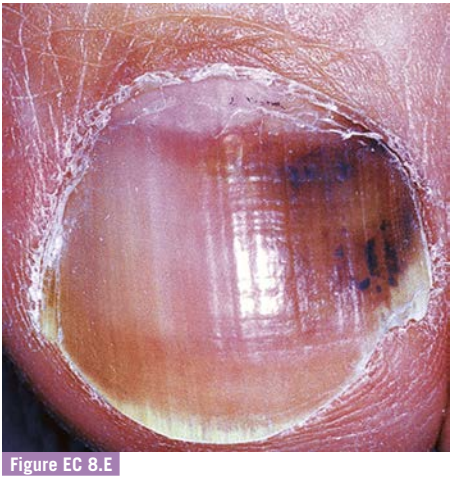

Figure EC 8.E
Traumatic subungual hemorrhage. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

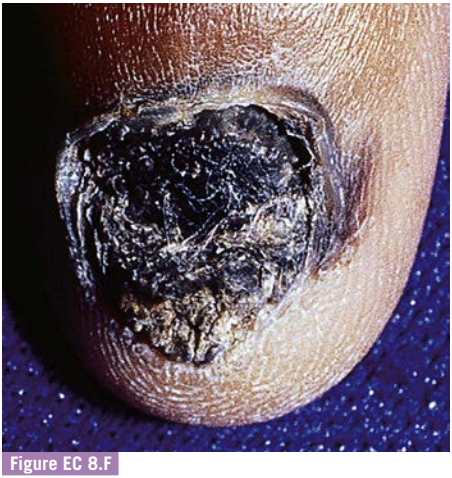

Figure EC 8.F

Acral melanoma. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

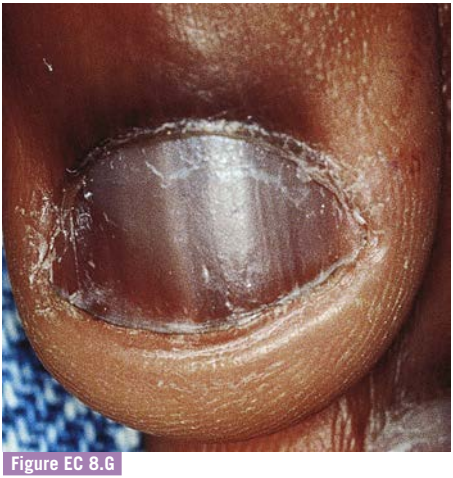

Figure EC 8.G

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.)

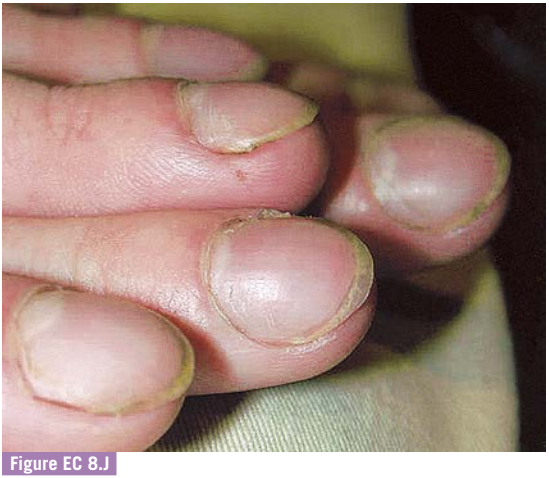

Figure EC 8.J
Nail clubbing. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

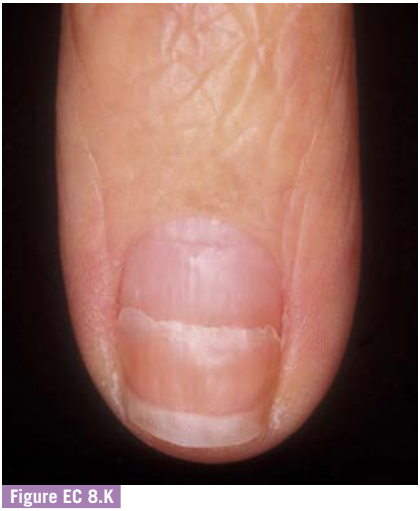

Figure EC 8.K
Beau lines. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

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.

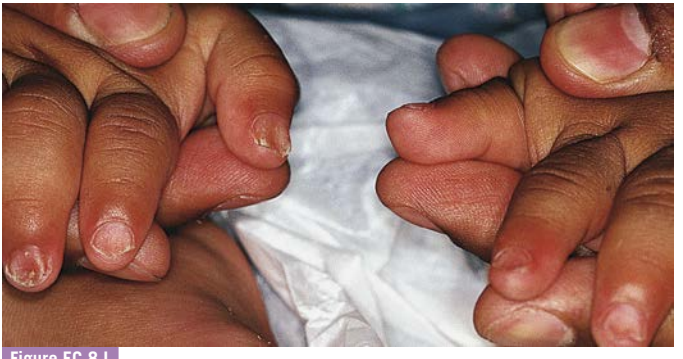

Figure EC 8.L
Koilonychia. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

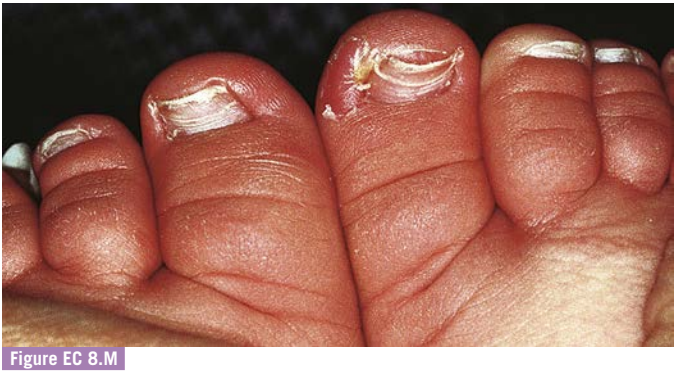

Figure EC 8.M
Congenital ingrown nails. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

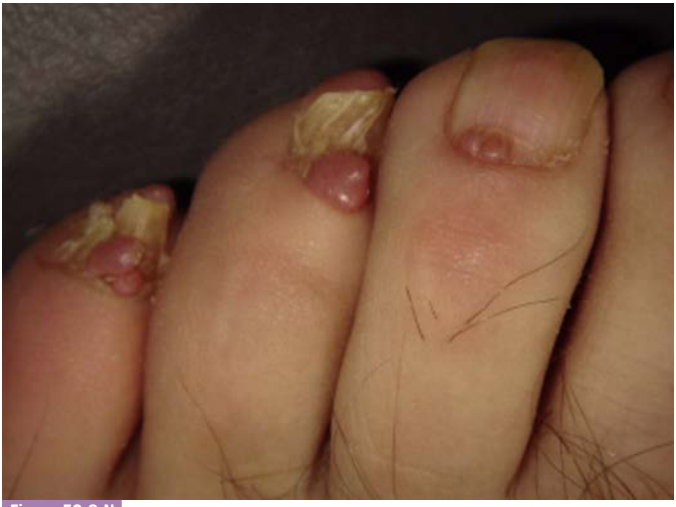

Figure EC 8.N
Periungual fibromas. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

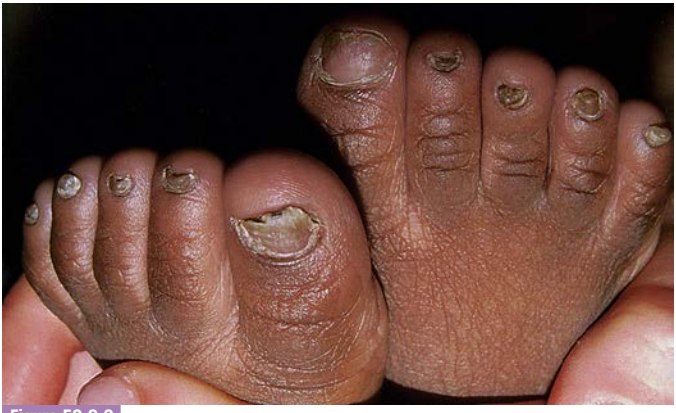

Figure EC 8.O
Fetal alcohol syndrome with congenital hypoplastic and dysplastic nails. (From Cohen BA. Disorders of the hair and nails. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:211–239.)

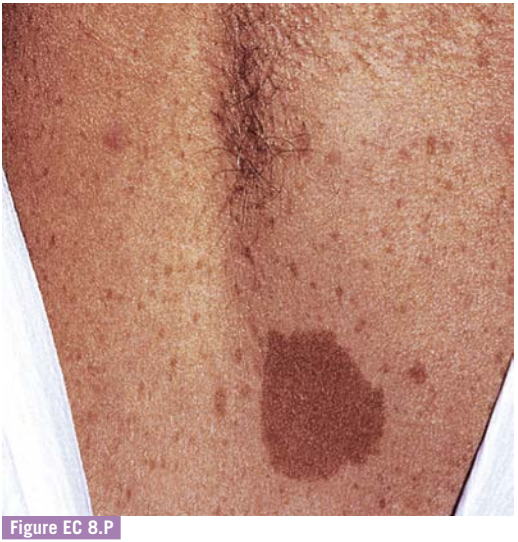

Figure EC 8.P

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

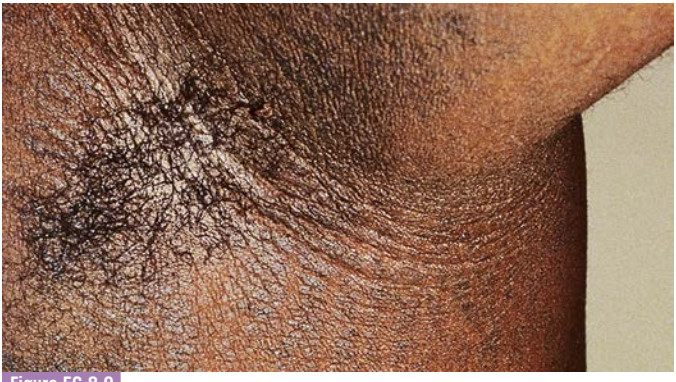

Figure EC 8.Q
Acanthosis nigricans, axilla. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

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

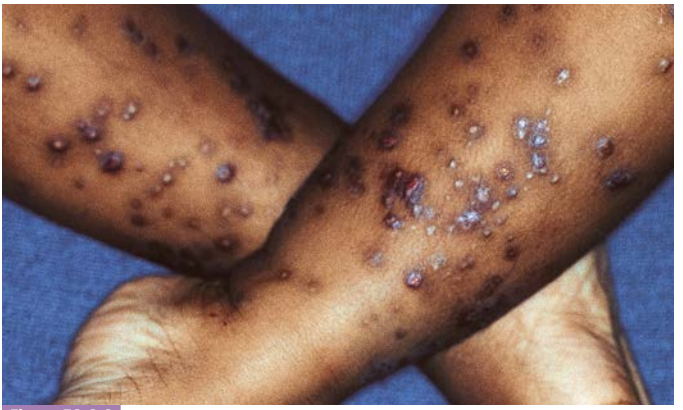

Figure EC 8.S

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.

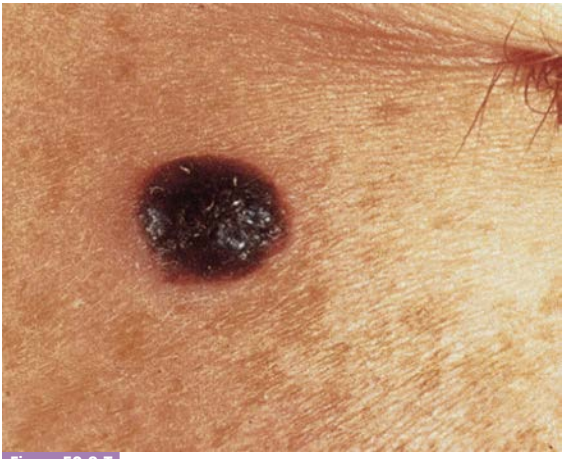

Figure EC 8.T
Compound nevomelanocytic nevus. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

(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,

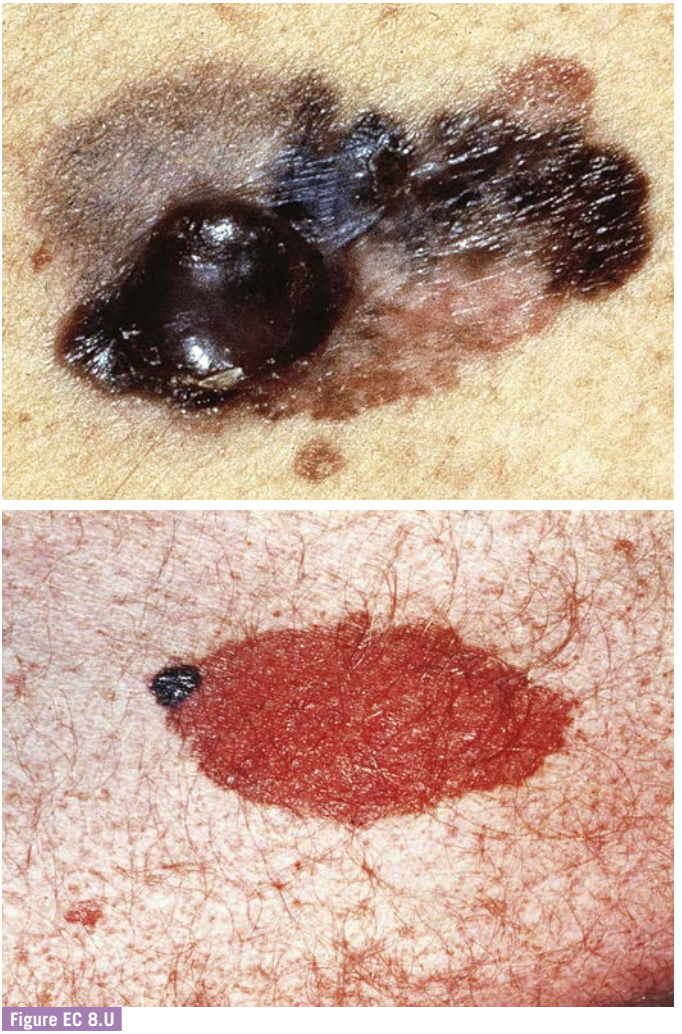

Figure EC 8.U

Melanoma. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

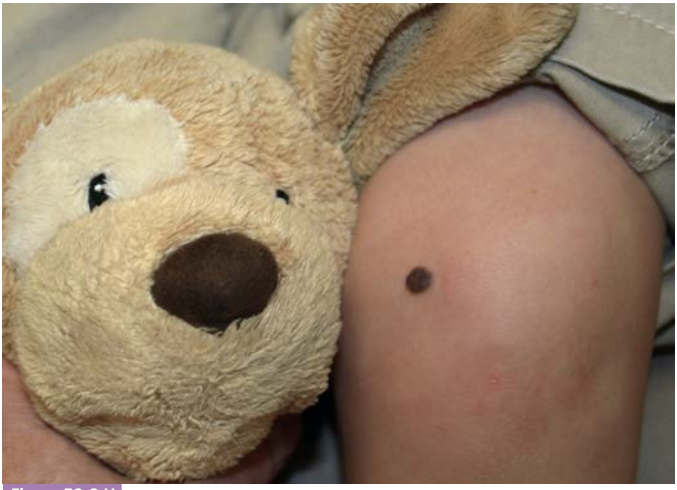

Figure EC 8.V
Pigmented spitz nevus. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

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).

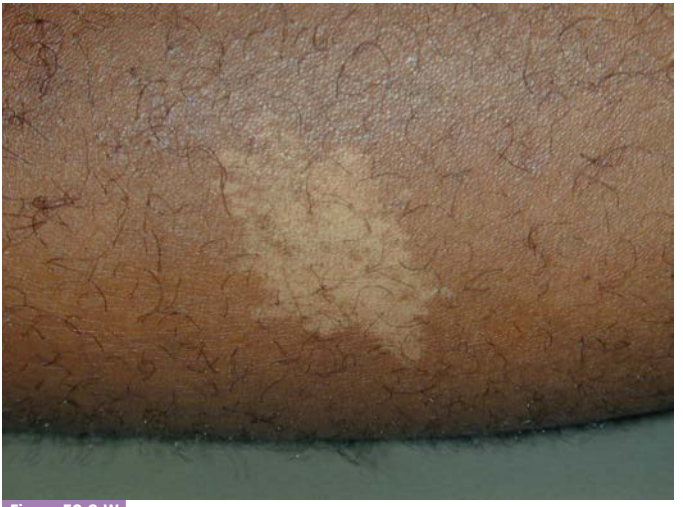

Figure EC 8.W

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.

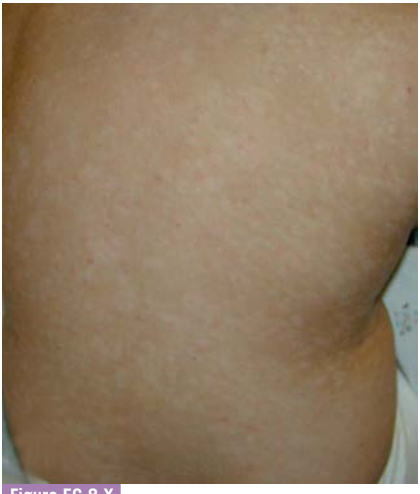

Figure EC 8.X

Postinflammatory hypopigmentation. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

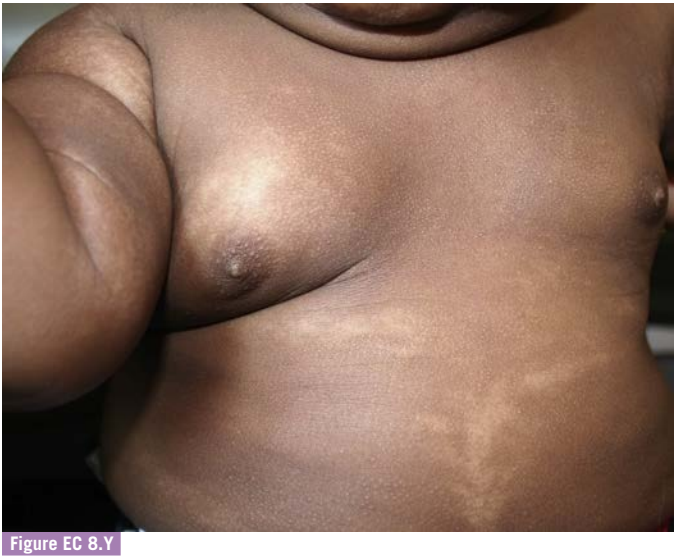

Figure EC 8.Y

Blaschkoid dyspigmentation. (From Cohen BA. Disorders in pigmentation. In: *Pediatric Dermatology*. 4th ed. China: Saunders Elsevier; 2013:48–68.)

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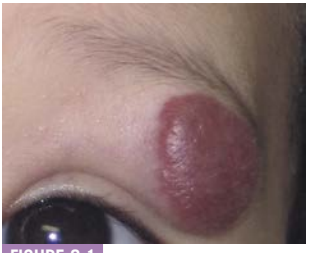

FIGURE 8.1
Infantile hemangioma. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005:126.)

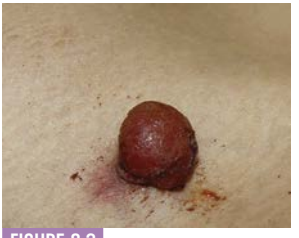

FIGURE 8.2
Pyogenic granuloma. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

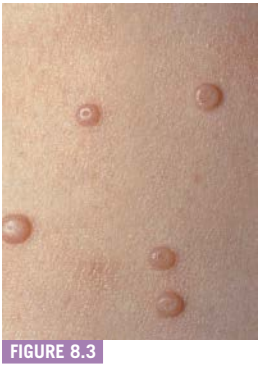

FIGURE 8.3
Molluscum contagiosum. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:131.)

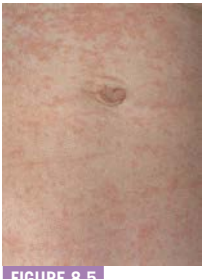

FIGURE 8.5
Roseola. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:177.)

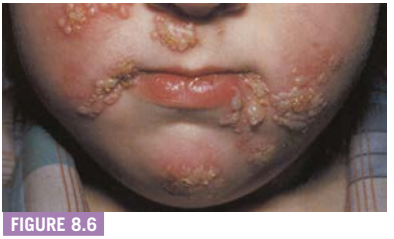

FIGURE 8.6
Herpetic gingivostomatitis. (Modified from Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:106.)

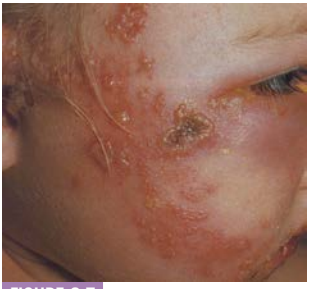

FIGURE 8.7
Herpes zoster. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:110.)

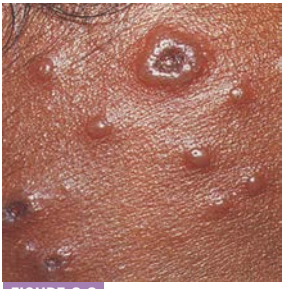

FIGURE 8.8
Varicella. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:108.)

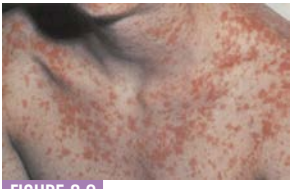

FIGURE 8.9
Measles. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:175.)

FIGURE 8.10
Fifth disease. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:176.)

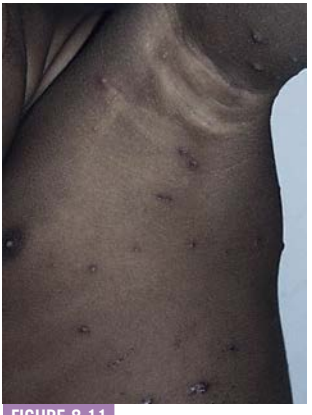

FIGURE 8.11
Scabies. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005:126.)

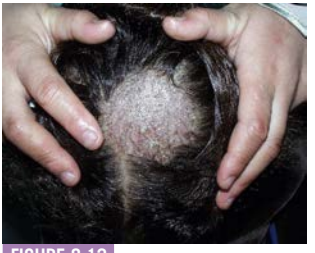

FIGURE 8.12
Tinea capitis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 1993.)

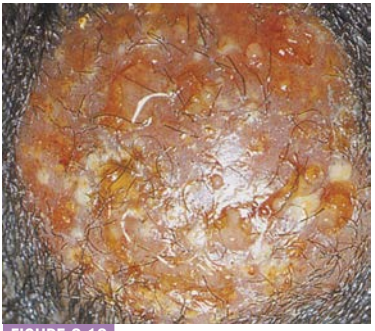

FIGURE 8.13
Kerion. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:218c.)

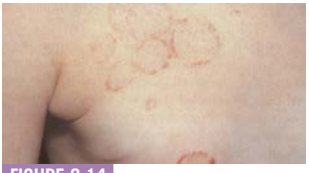

FIGURE 8.14
Tinea corporis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:96.)

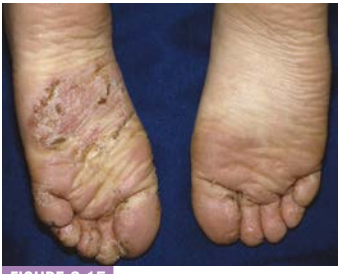

FIGURE 8.15
Tinea pedis. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

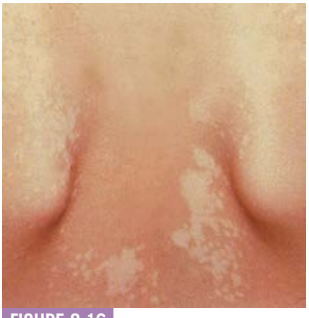

FIGURE 8.16
Tinea versicolor. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:99.)

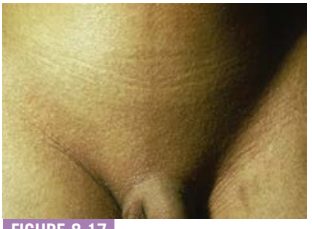

FIGURE 8.17
Scarlet fever. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

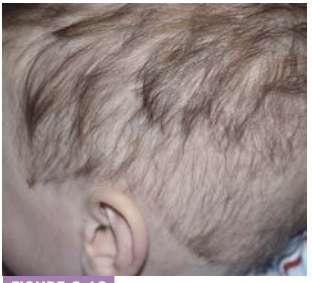

FIGURE 8.18
Telogen effluvium. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

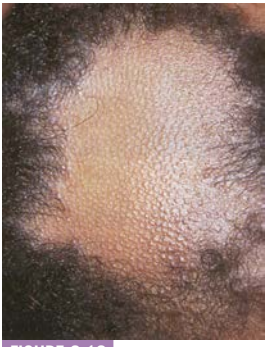

FIGURE 8.19
Alopecia areata. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:219.)

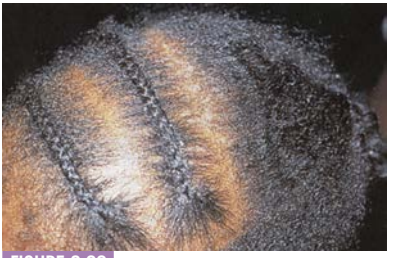

FIGURE 8.20
Traction alopecia. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:220.)

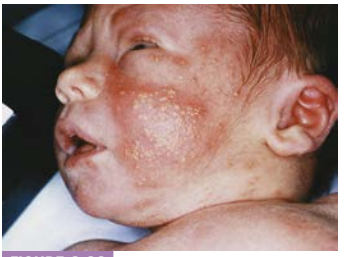

FIGURE 8.22
Erythema toxicum neonatorum. (From Cohen BA. *Pediatric Dermatology*. 2nd ed. St Louis: Mosby; 1999:18.)

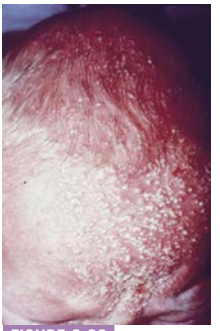

FIGURE 8.23
Transient neonatal pustular melanosis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:20.)

FIGURE 8.24
Hyperpigmentation from resolving transient neonatal pustular melanosis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:20.)

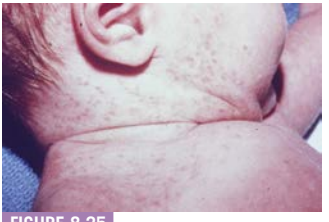

FIGURE 8.25
Miliaria rubra. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:21.)

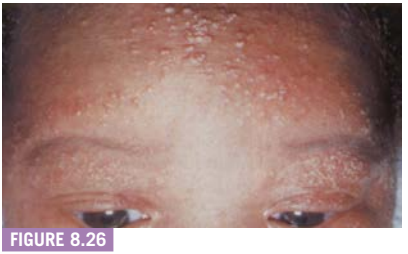

FIGURE 8.26
Milia. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:22.)

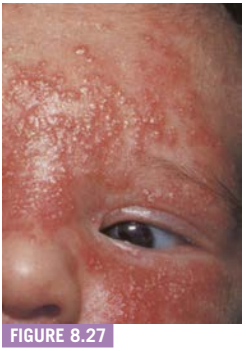

FIGURE 8.27
Neonatal acne. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:22.)

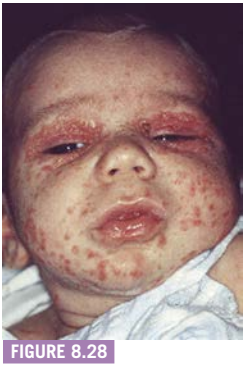

FIGURE 8.28
Seborrheic dermatitis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:32.)

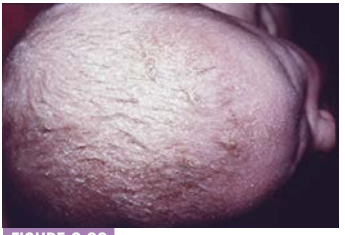

FIGURE 8.29
Seborrheic dermatitis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:32.)

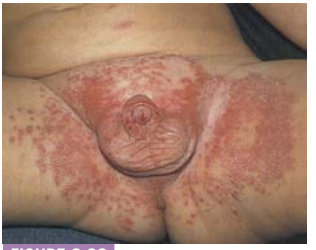

FIGURE 8.30
Diaper candidiasis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:33.)

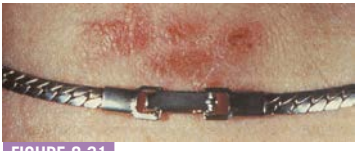

FIGURE 8.31
Allergic contact dermatitis. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:77.)

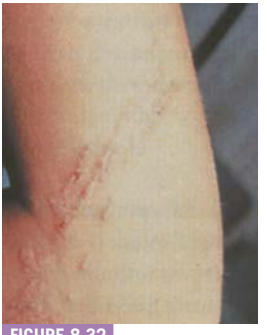

FIGURE 8.32
Poison ivy. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

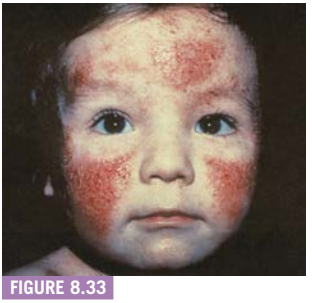

FIGURE 8.33
Infantile eczema. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005:79.)

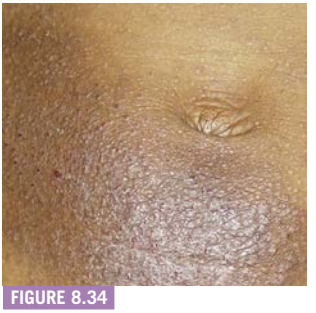

FIGURE 8.34
Childhood eczema. (From Cohen BA. *Dermatology Image Atlas*; 2001. http://www.dermatlas.org/.)

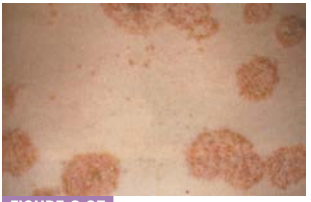

FIGURE 8.35
Nummular eczema. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005:80.)

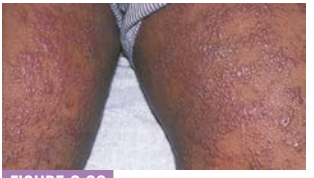

FIGURE 8.36
Follicular eczema. (From Cohen BA. *Atlas of Pediatric Dermatology*. 4th ed. China: Elsevier Limited; 2013:83.)

FIGURE 8.37
Childhood eczema with lesion in suprapubic area. (From Cohen BA. *Atlas of Pediatric Dermatology*. 3rd ed. St Louis: Mosby; 2005.)

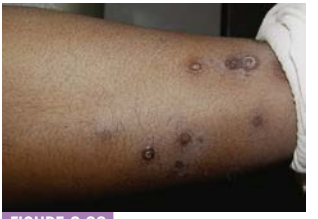

FIGURE 8.38

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

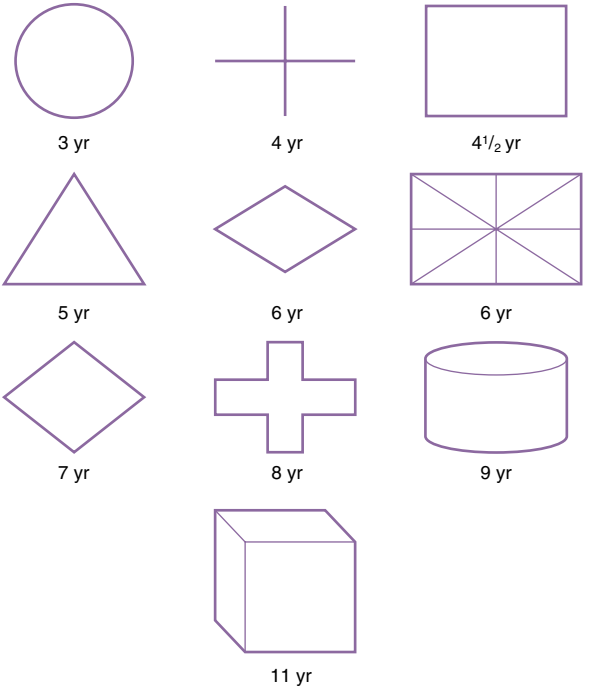

FIGURE EC 9.A

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.)

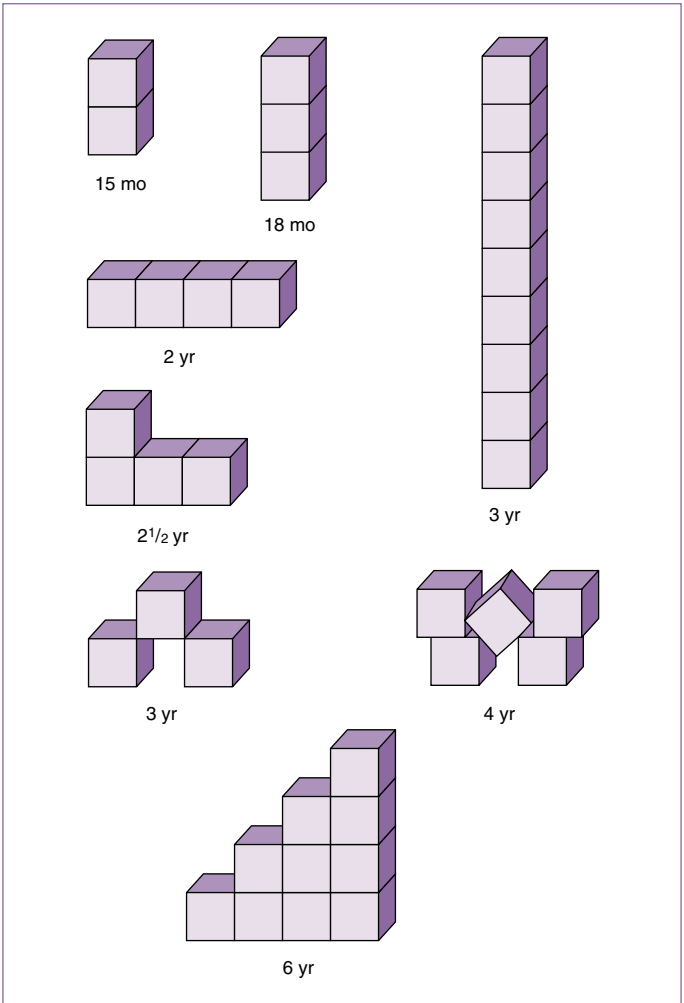

FIGURE EC 9.B

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

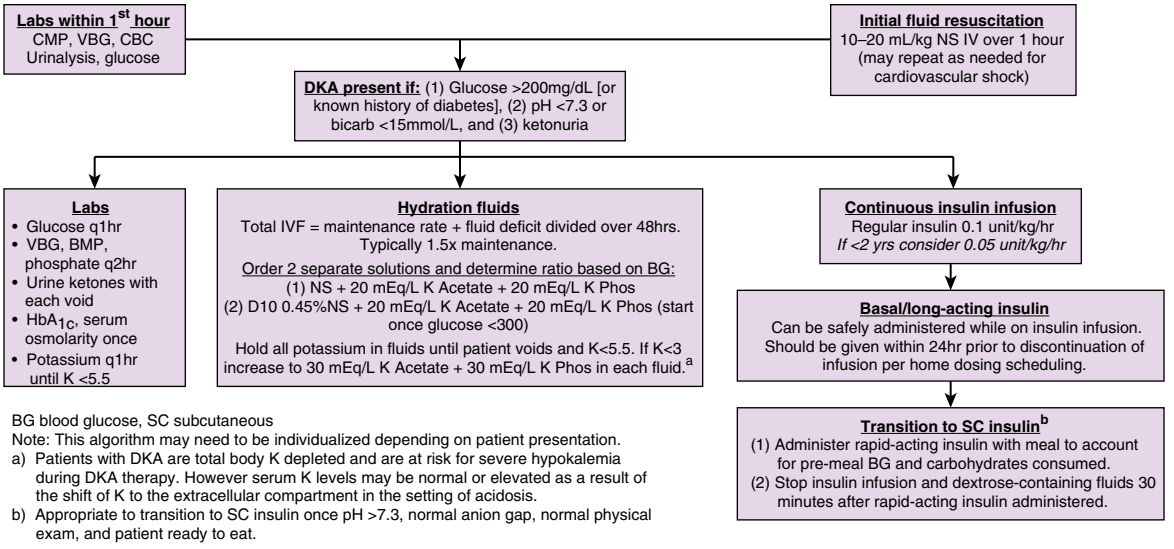
SCREENING FOR DIABETES-ASSOCIATED CONDITIONS AND COMPLICATIONS[6,11]

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.



BG blood glucose, SC subcutaneous

Note: This algorithm may need to be individualized depending on patient presentation.

a) Patients with DKA are total body K depleted and are at risk for severe hypokalemia during DKA therapy. However serum K levels may be normal or elevated as a result of the shift of K to the extracellular compartment in the setting of acidosis.

b) Appropriate to transition to SC insulin once pH >7.3, normal anion gap, normal physical exam, and patient ready to eat.

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.

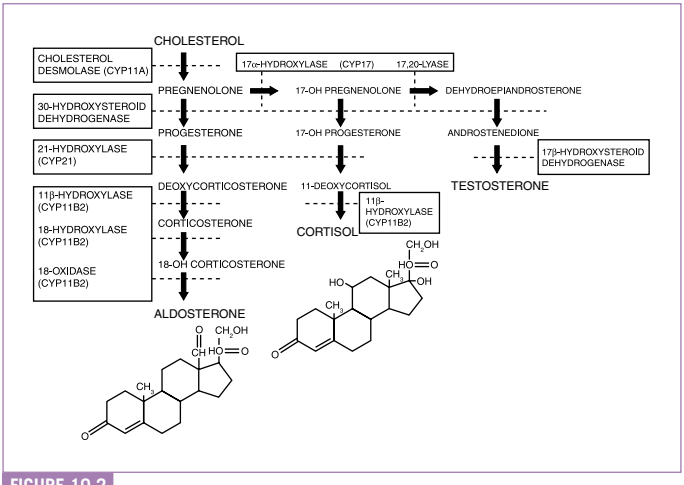


FIGURE 10.2
Biosynthetic Pathway for Steroid Hormones.

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.

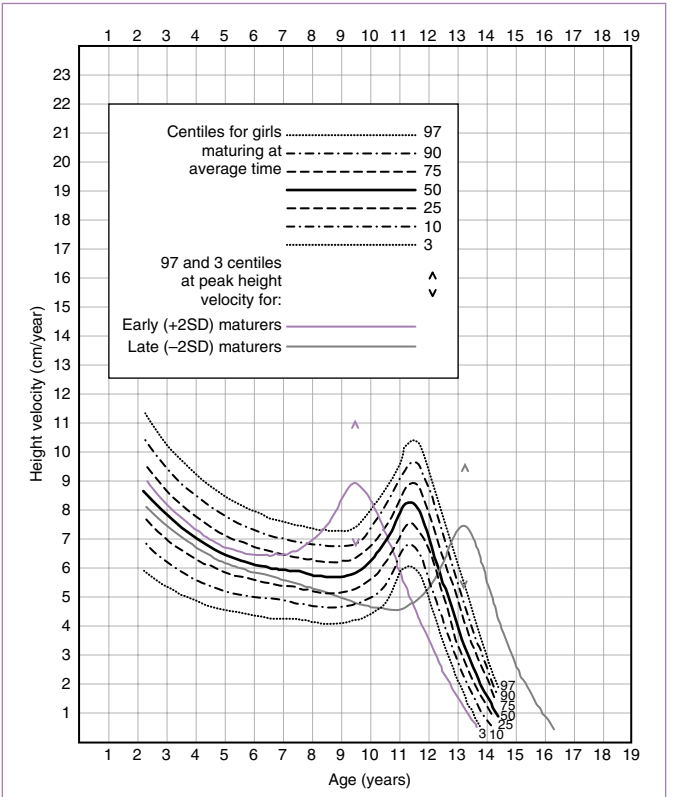


FIGURE EC 10.A

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.)

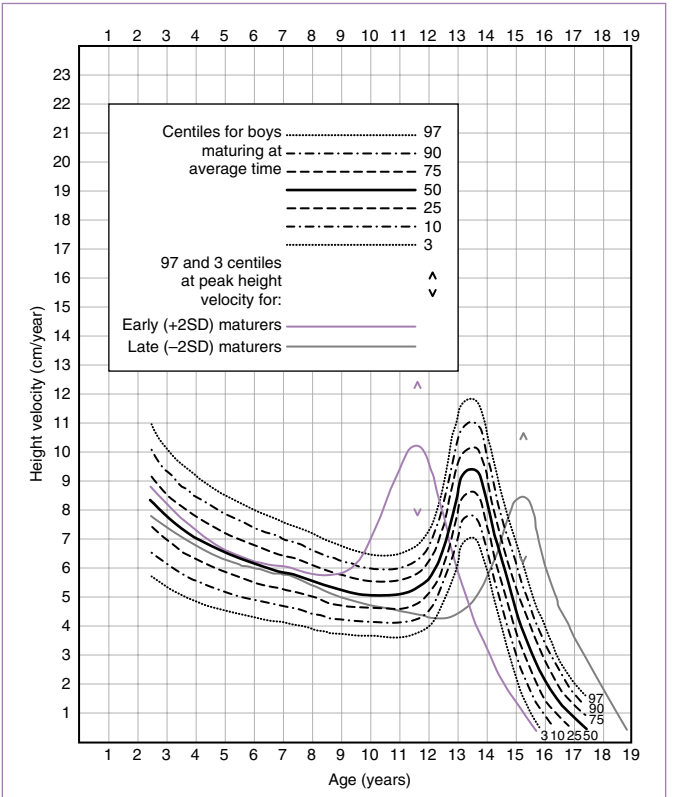


FIGURE EC 10.B

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

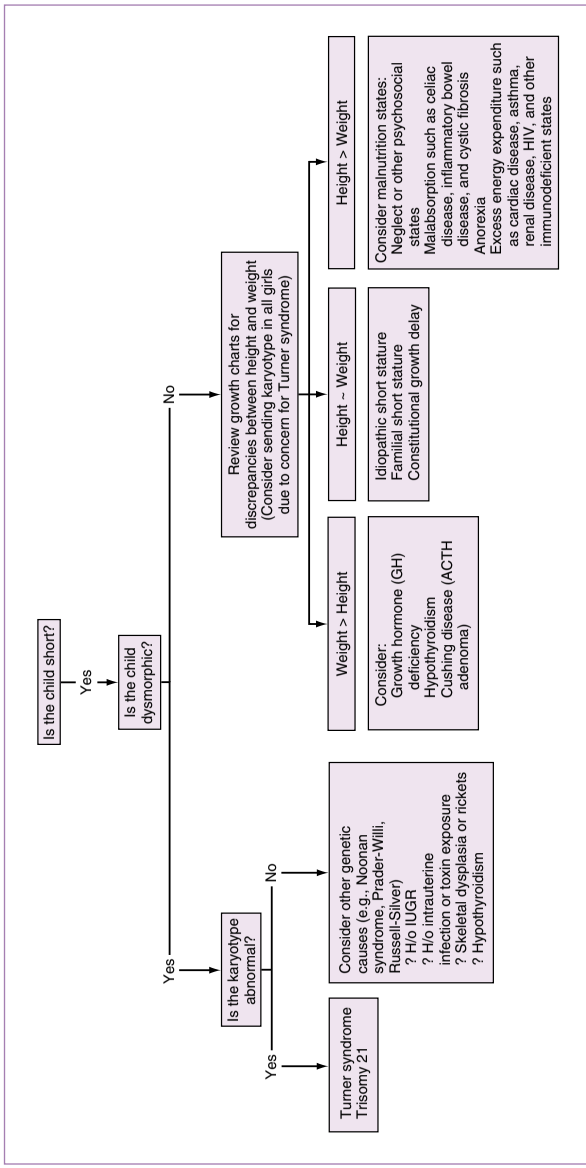


FIGURE 10.3
Differential Diagnosis of Short Stature.

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.

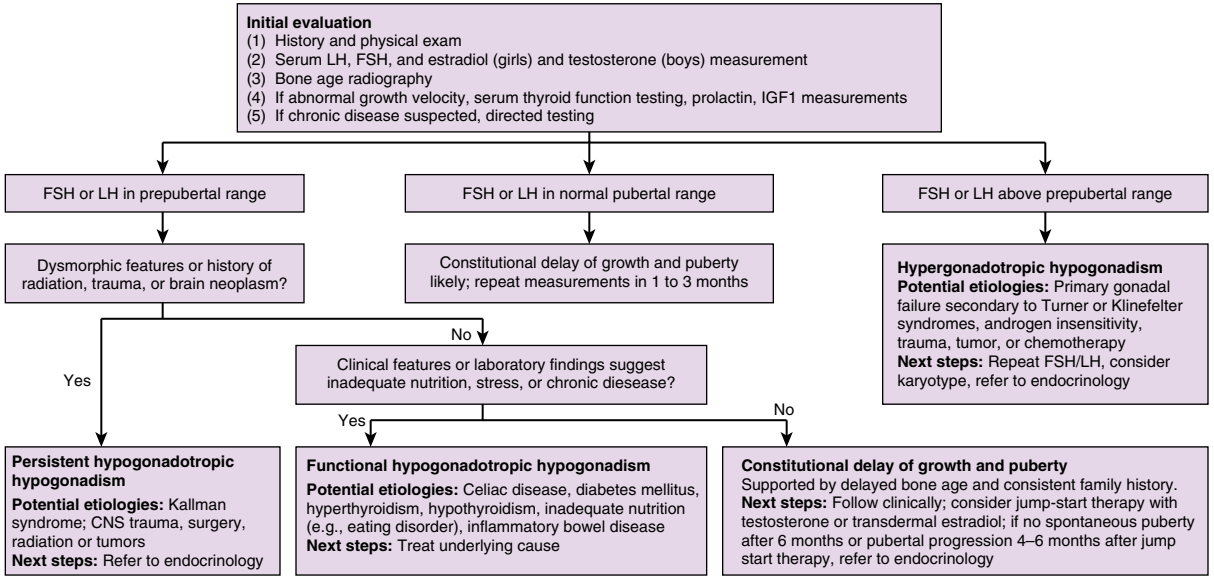


FIGURE 10.4

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.)

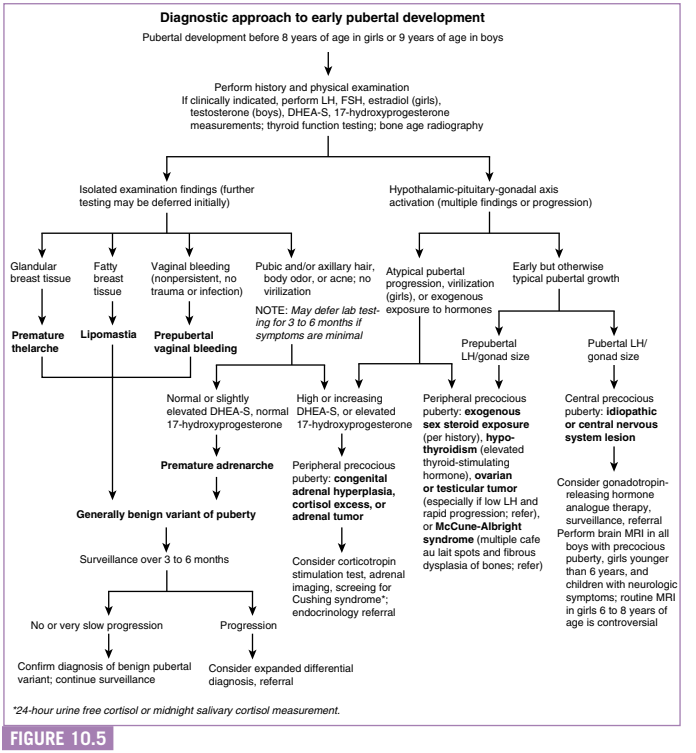


FIGURE 10.5

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

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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) Postobstructive diuresis CKD Diuretic use Polyuric phase of ATN	GI losses Skin losses Respiratory[a] Increased insensible losses Adipsia	Exogenous Na^+ (meds, infant formula) Mineralocorticoid excess (e.g., hyperaldosteronism)
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

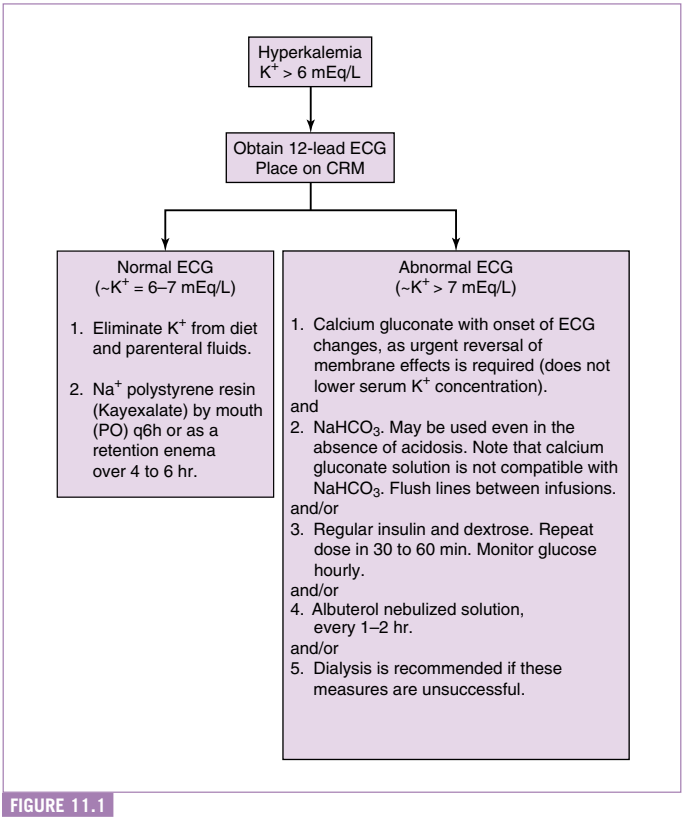

FIGURE 11.1

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)

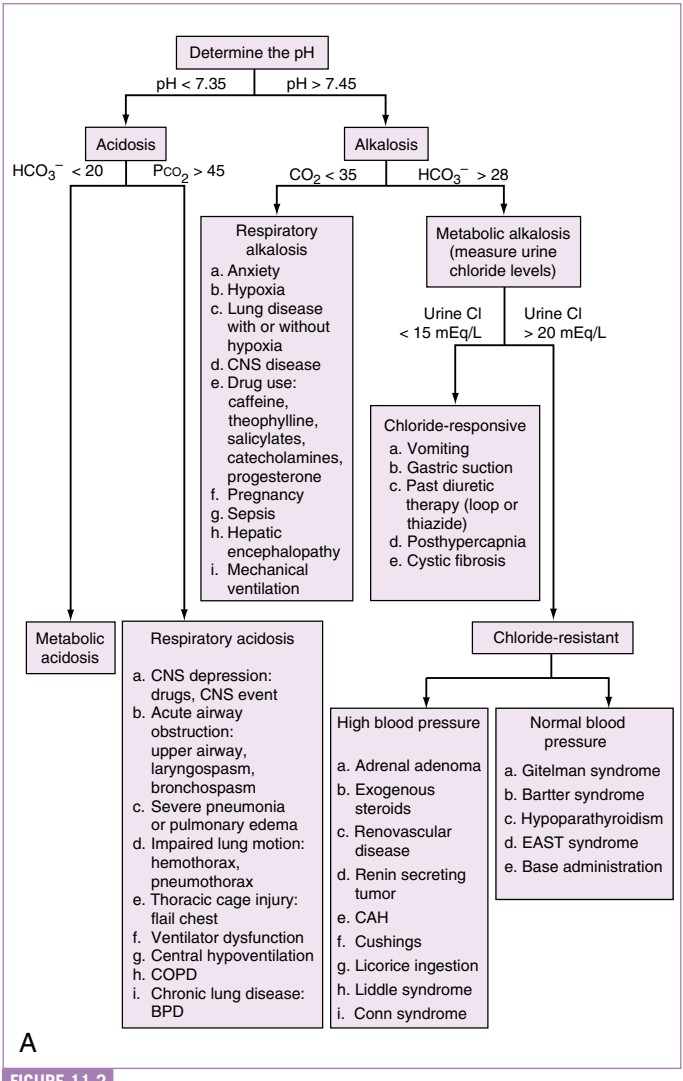

FIGURE 11.2

(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.

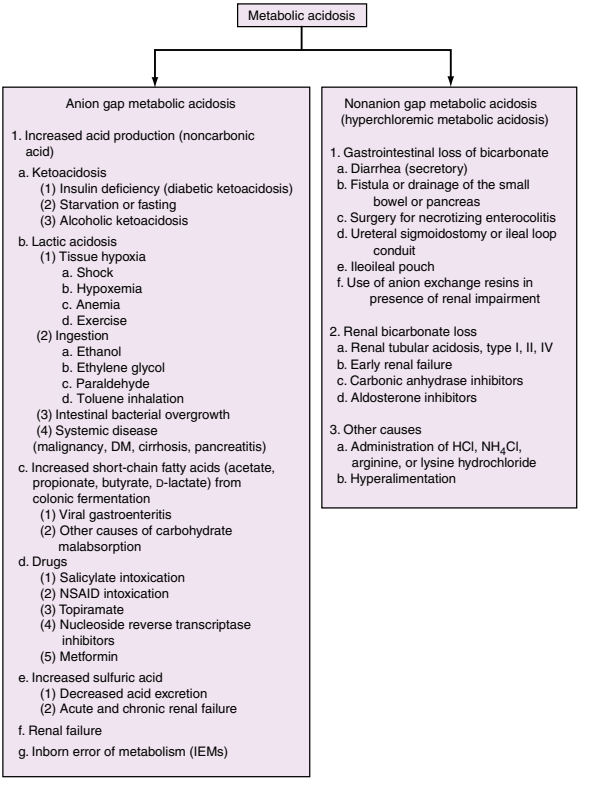

FIGURE 11.2, cont'd

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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.

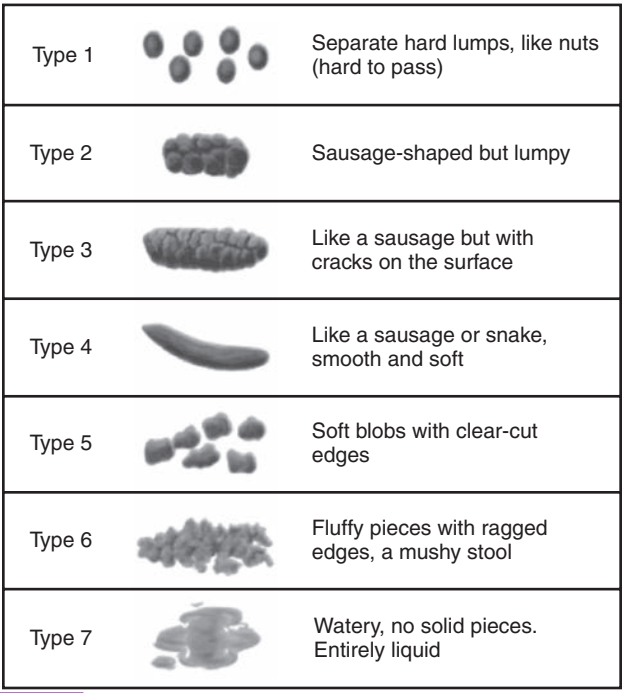

FIGURE 12.1

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

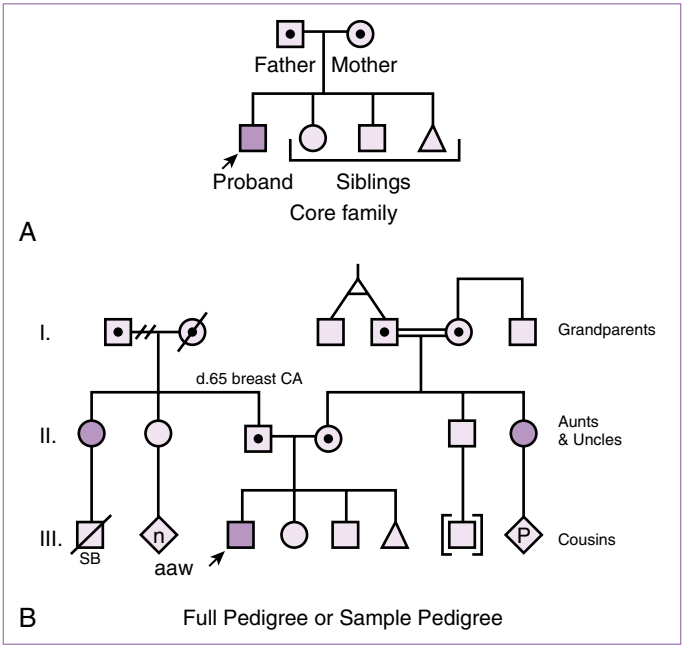

FIG. EC 13.A
Pedigree construction.

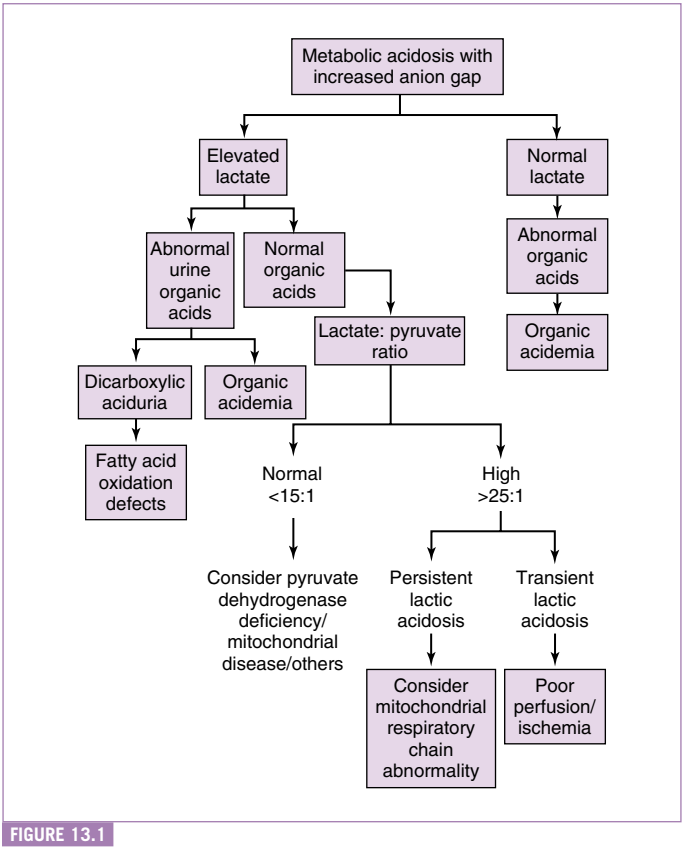

FIGURE 13.1

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.

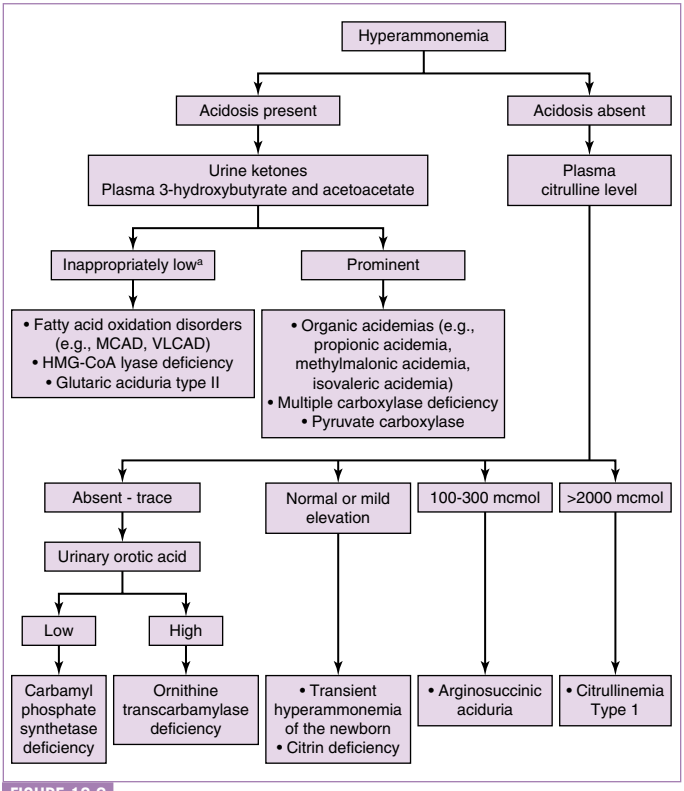

FIGURE 13.2

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.

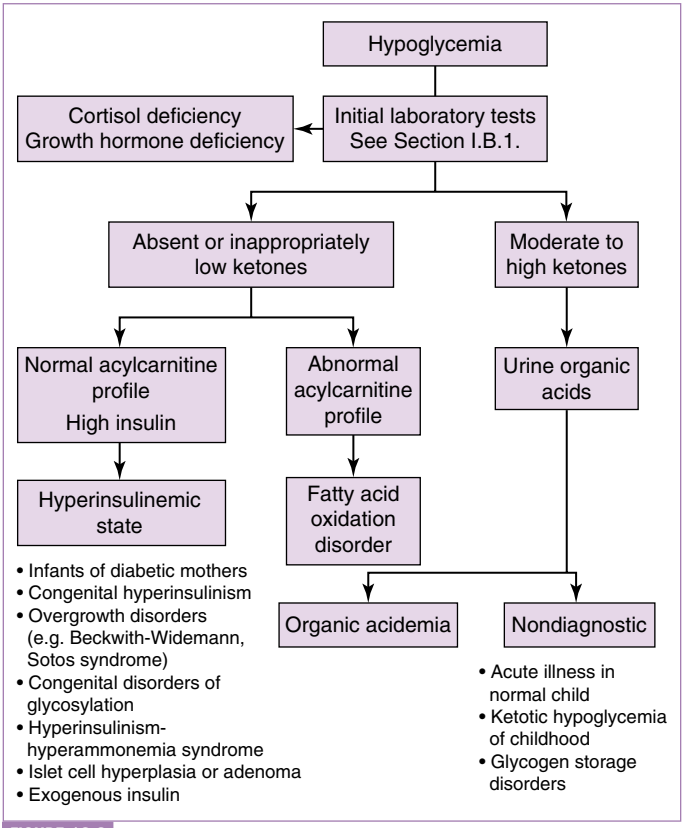

FIGURE 13.3

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

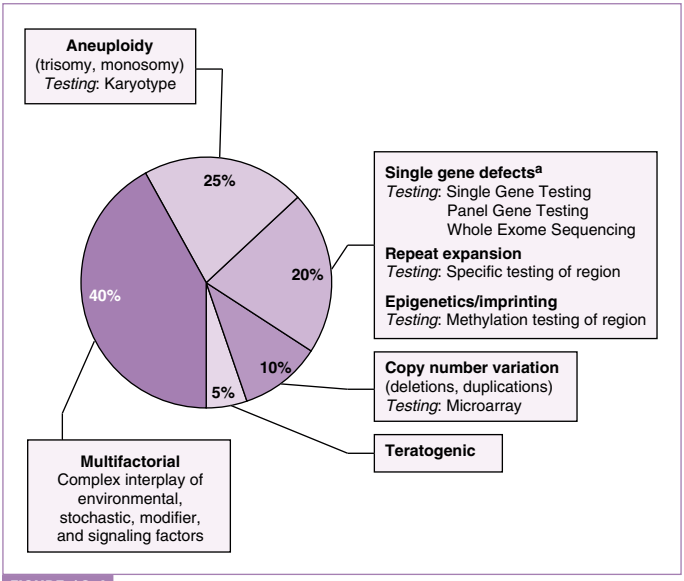

FIGURE 13.4

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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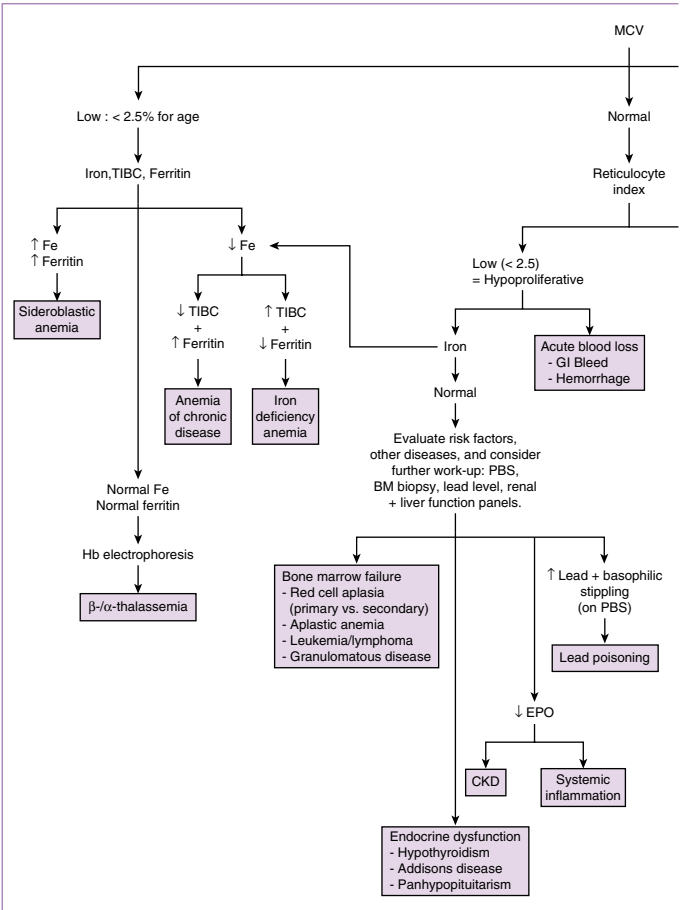


FIGURE 14.1

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.)

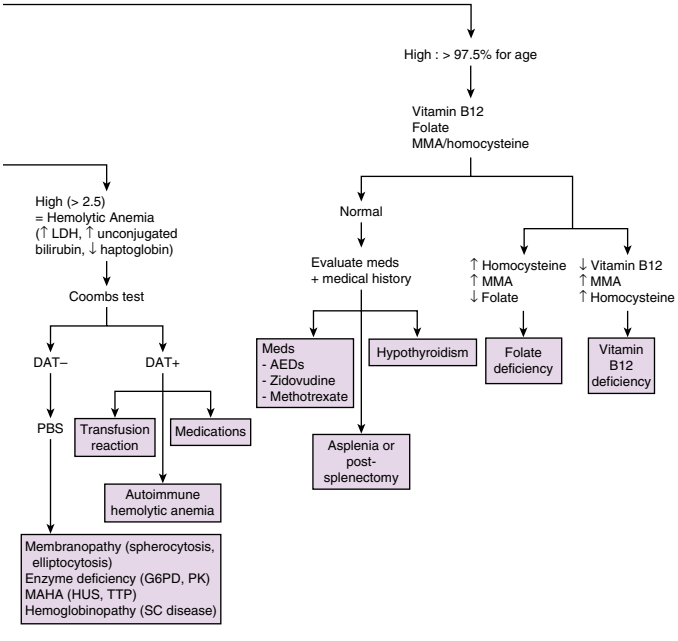


FIGURE 14.1–cont'd

(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.

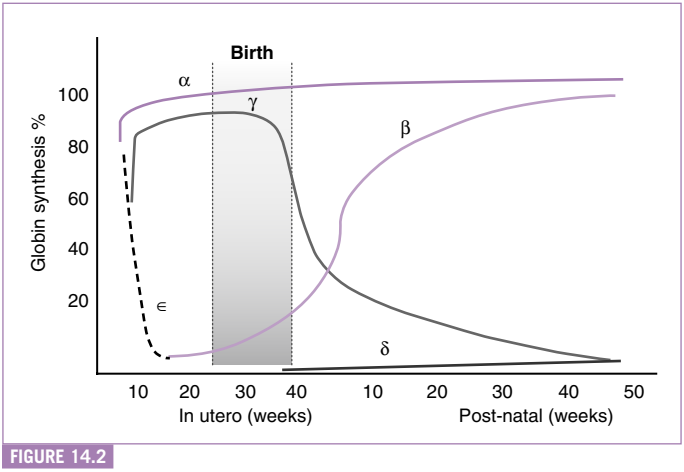


FIGURE 14.2

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.)

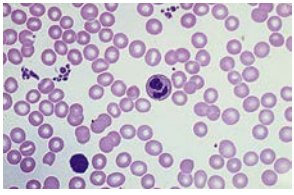


FIGURE EC 14.A
Normal smear. Round red blood cells with central pallor about one-third of the cell's diameter, scattered platelets, occasional white blood cells.

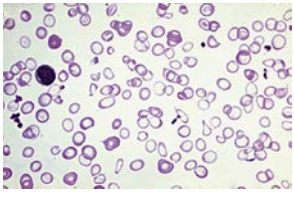


FIGURE EC 14.B
Iron deficiency. Hypochromic/microcytic red blood cells, poikilocytosis, plentiful platelets, occasional ovalocytes, and target cells.

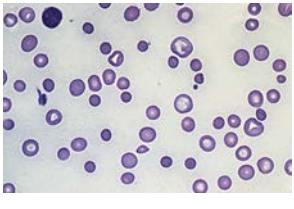


FIGURE EC 14.C
Spherocytosis. Microspherocytes (densely stained red blood cells with no central pallor) are a hallmark.

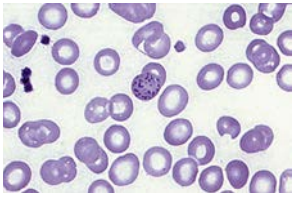


FIGURE EC 14.D
Basophilic stippling as a result of precipitated RNA throughout the cell; seen with heavy metal intoxication, thalassemia, iron deficiency, and other states of ineffective erythropoiesis.

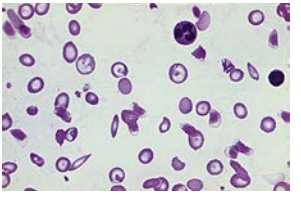


FIGURE EC 14.E
Sickle cell disease (hemoglobin SS) disease. Sickled cells, target cells, hypochromia, poikilocytosis, Howell–Jolly bodies; nucleated red blood cells common (not shown).

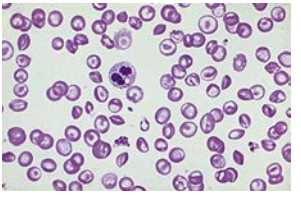


FIGURE EC 14.F
Sickle-hemoglobin C disease (hemoglobin SC) disease. Target cells, oat cells, poikilocytosis; sickle forms rarely seen.

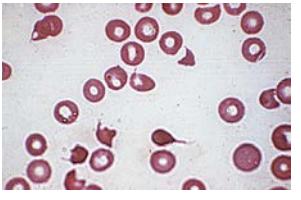


FIGURE EC 14.G
Microangiopathic hemolytic anemia. Red blood cell fragments, anisocytosis, polychromasia, decreased platelets.

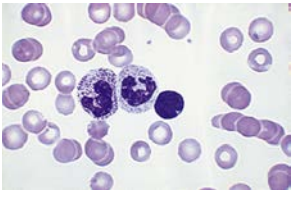


FIGURE EC 14.H
Toxic granulations. Prominent dark blue primary granules; commonly seen with infection and other toxic states (e.g., Kawasaki disease).

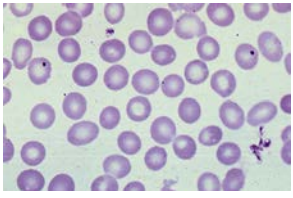


FIGURE EC 14.I
Howell–Jolly body. Small, dense nuclear remnant in a red blood cell; suggests splenic dysfunction or asplenia.

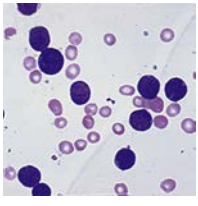


FIGURE EC 14.J
Leukemic blasts showing large nucleus-to-cytoplasm ratio.

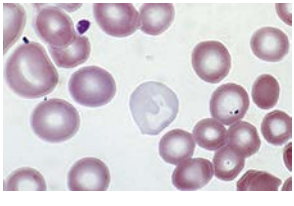


FIGURE EC 14.K
Polychromatophilia. Diffusely basophilic because of RNA staining; seen with early release of reticulocytes from the marrow.

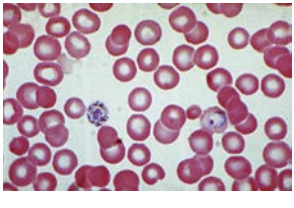


FIGURE EC 14.L
Malaria. Intraerythrocytic parasites.

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.

Segel GB, Halterman JS. Neutropenia in pediatric practice. *Pediat Rev.* 2008:29(1):12–24.

Moerdler S, LaTuga MS. Neonatal neutropenia. *NeoReviews.* 2018:19(1):e22–e28.

Orkin SH, Nathan DG, Ginsburg D, et al. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood.* 8th ed. Philadelphia: Saunders; 2015.

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.

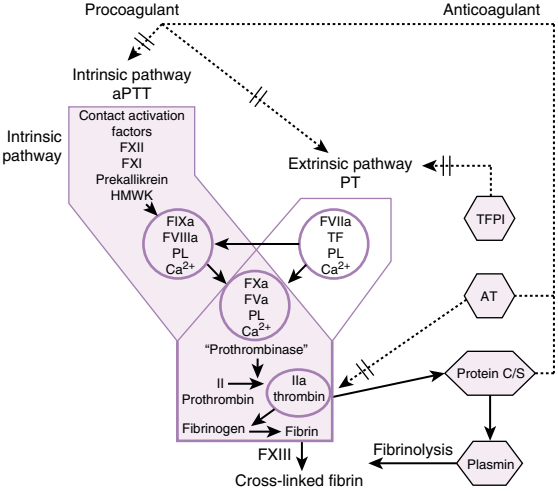
IV. COAGULATION

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.

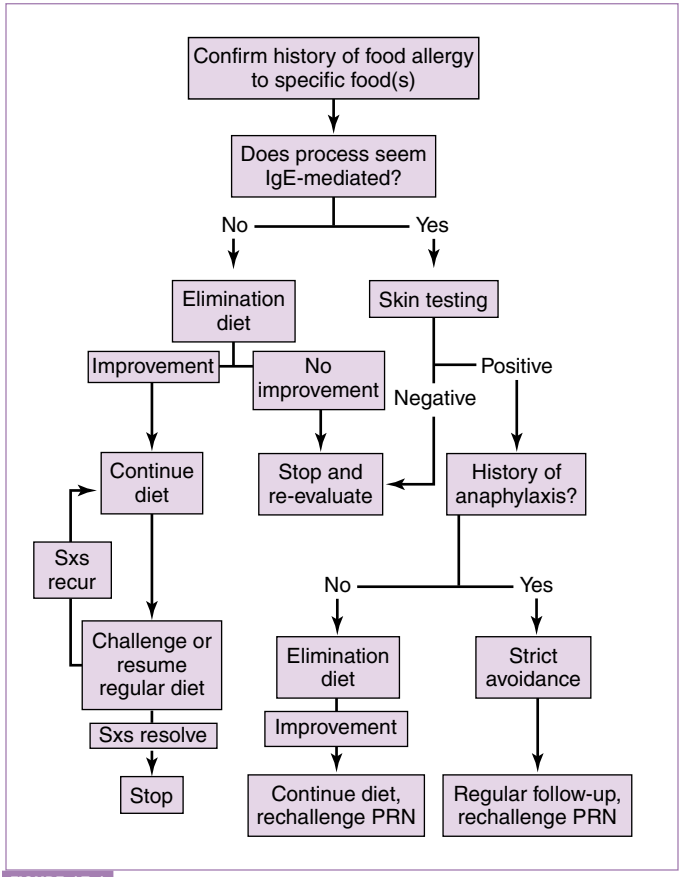

FIGURE 15.1

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.

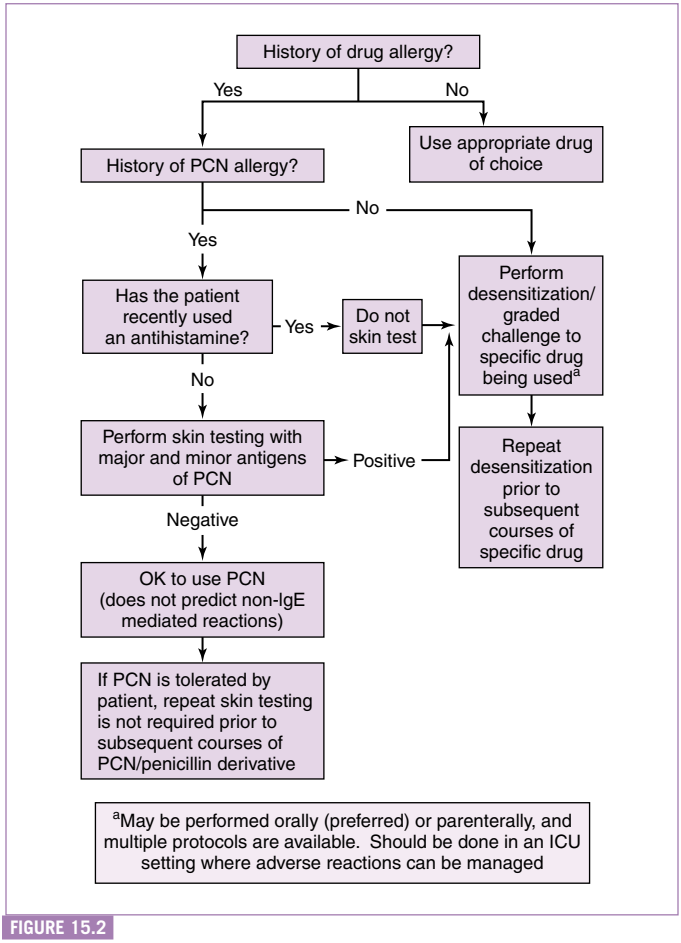

FIGURE 15.2

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/.

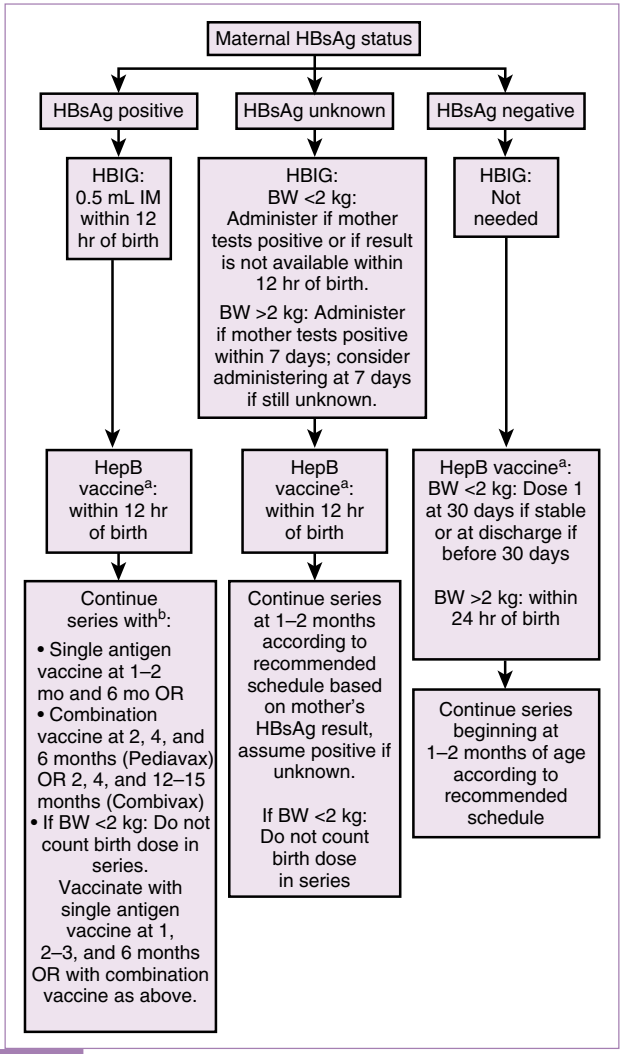

FIGURE 16.1

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.

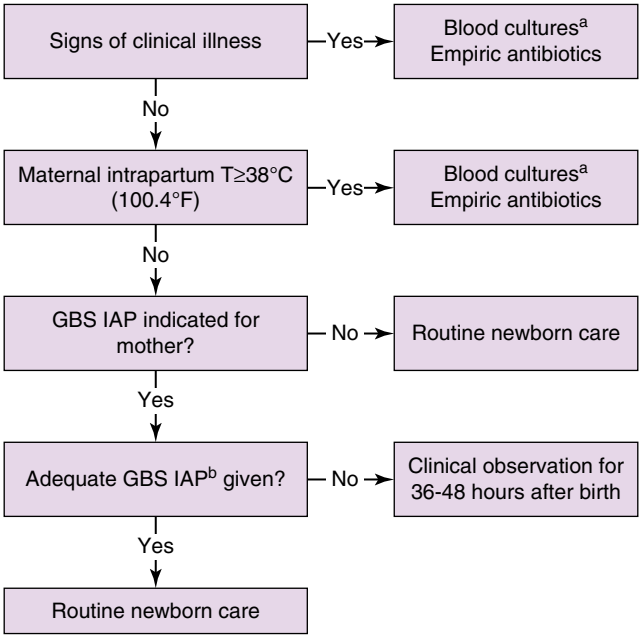
2. Treatment of latent TB infection (Cont'd from pg. 408)
   a. Rule out active TB.
   b. Treatment regimens
      (1) 12 weeks of weekly isoniazid and rifapentine if above 2 years.
      (2) 9 months of isoniazid daily.
      (3) Rifampin daily for 4 months (preferred regimen if isoniazid-resistant).
   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)

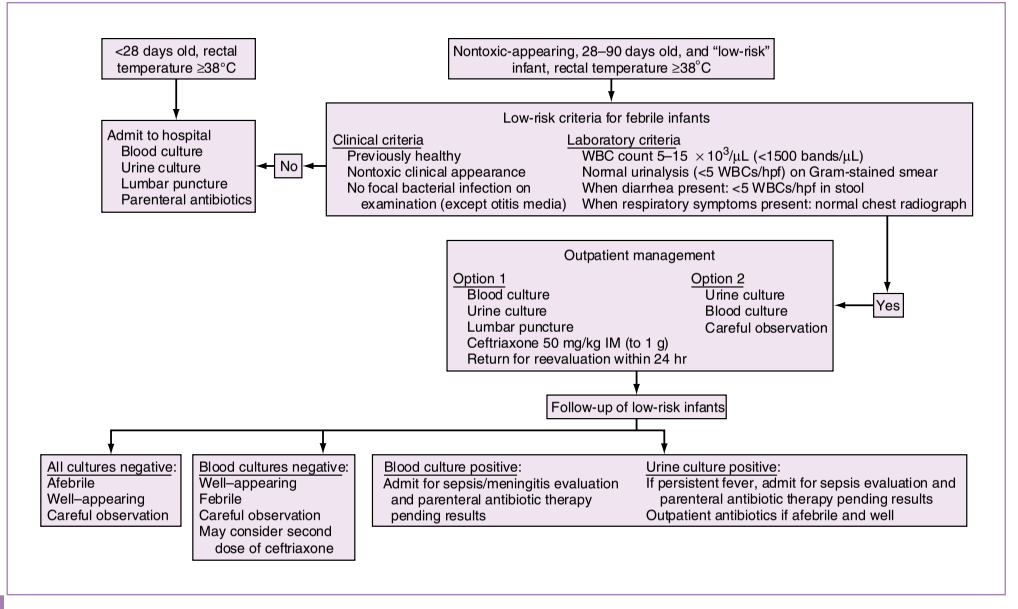


FIGURE 17.2

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.)

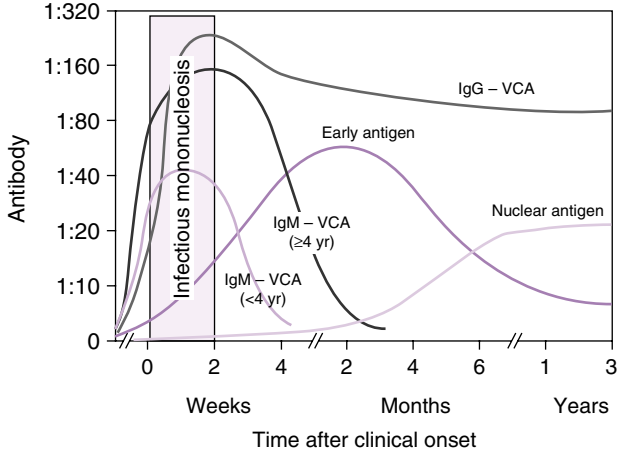


FIGURE 17.3

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.

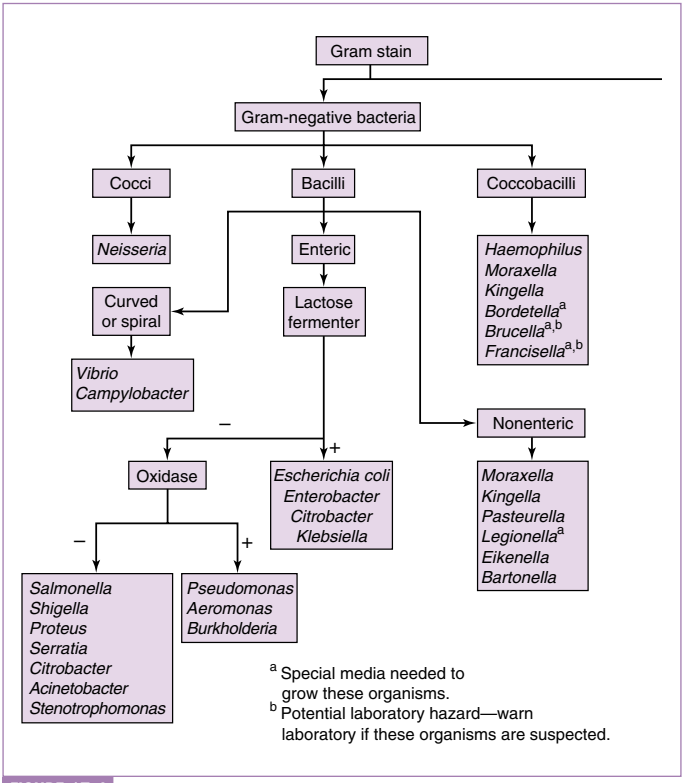
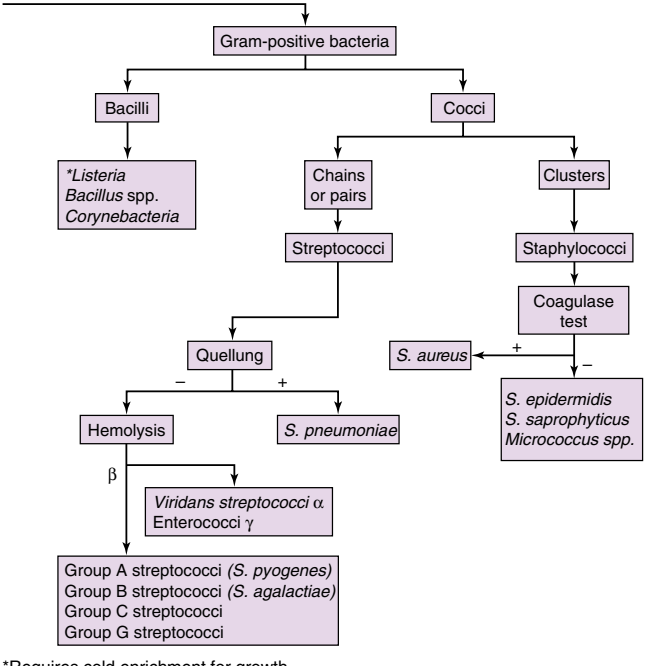


FIGURE 17.4
Algorithm demonstrating identification of aerobic bacteria.



*Requires cold enrichment for growth.

FIGURE 17.4, cont'd

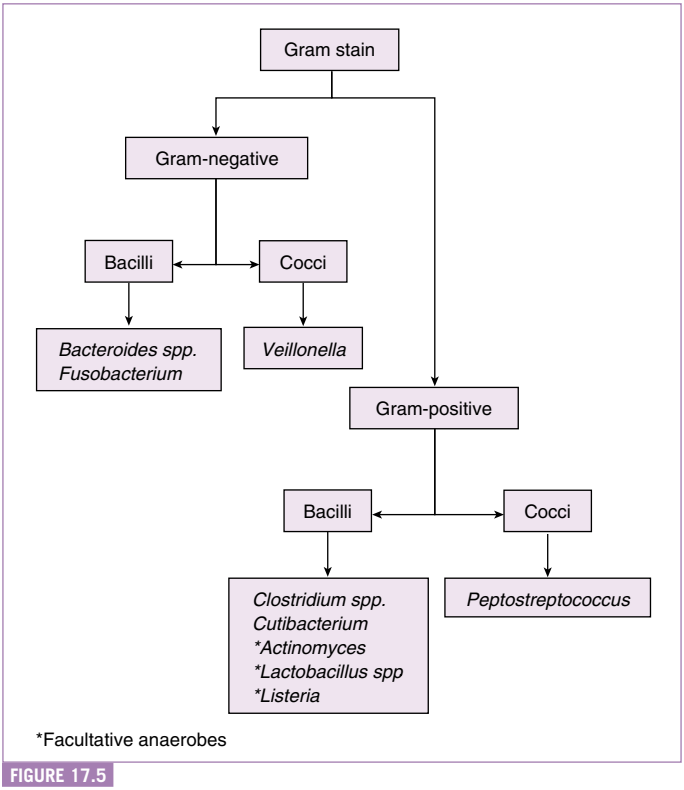


FIGURE 17.5
Algorithm demonstrating identification of anaerobic bacteria.

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.

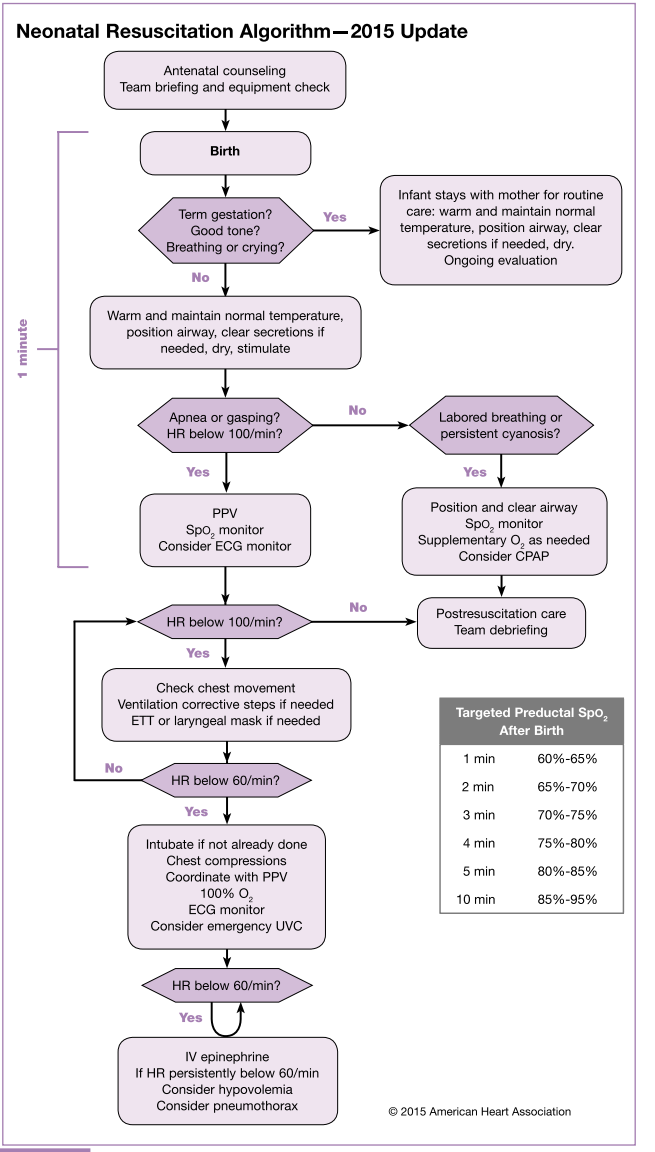


FIGURE 18.1

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.

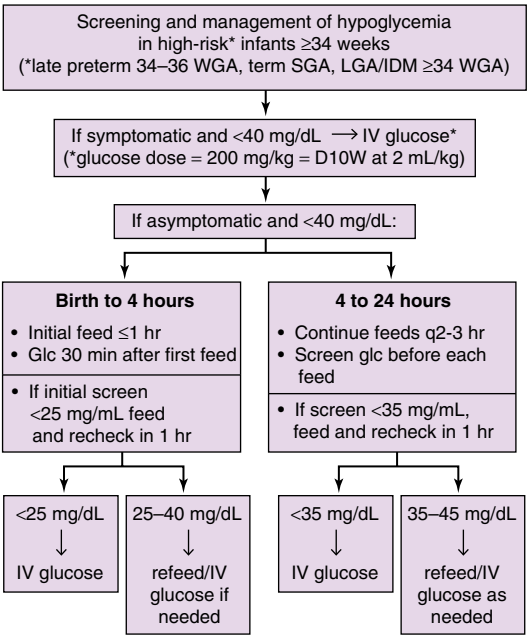


FIGURE 18.2

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.

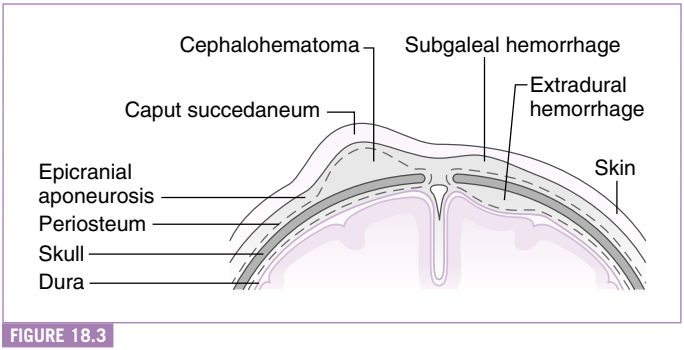


FIGURE 18.3

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.

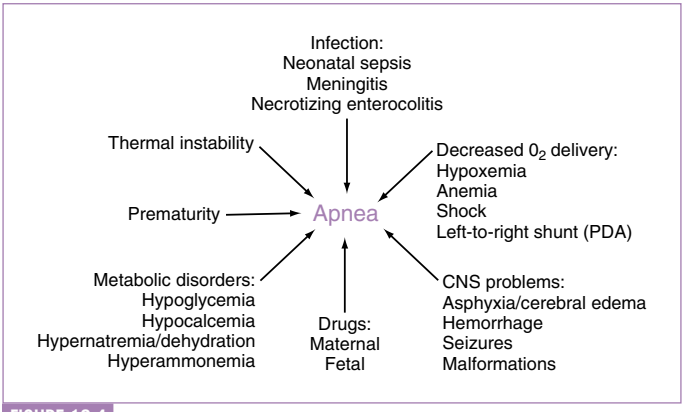


FIGURE 18.4

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.

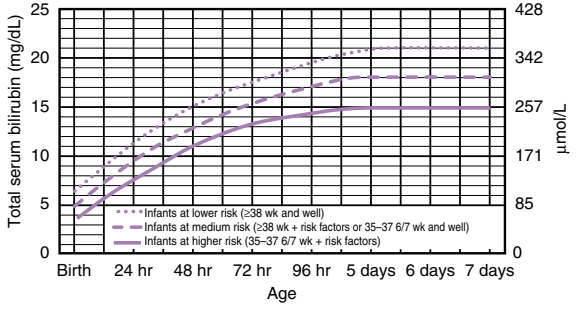
3. **Management:**
   a. Phototherapy: Ideally, intensive phototherapy should produce a TSB decline of 1 to 2 mg/dL within 4 to 6 hours, with further subsequent decline. Guidelines:
      (1) Preterm newborn (Table 18.9)
      (2) Term newborn (Fig. 18.5)
   b. Intravenous immunoglobulin (IVIG) (>35 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

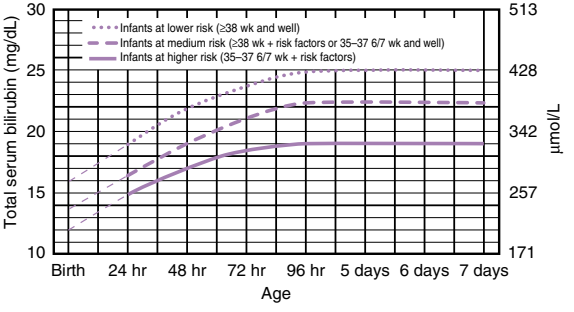
Data from Maisels MJ, Watchko JF, Bhutani V. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. *J Perinatol*. 2012;32(9):660–4.



- 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).

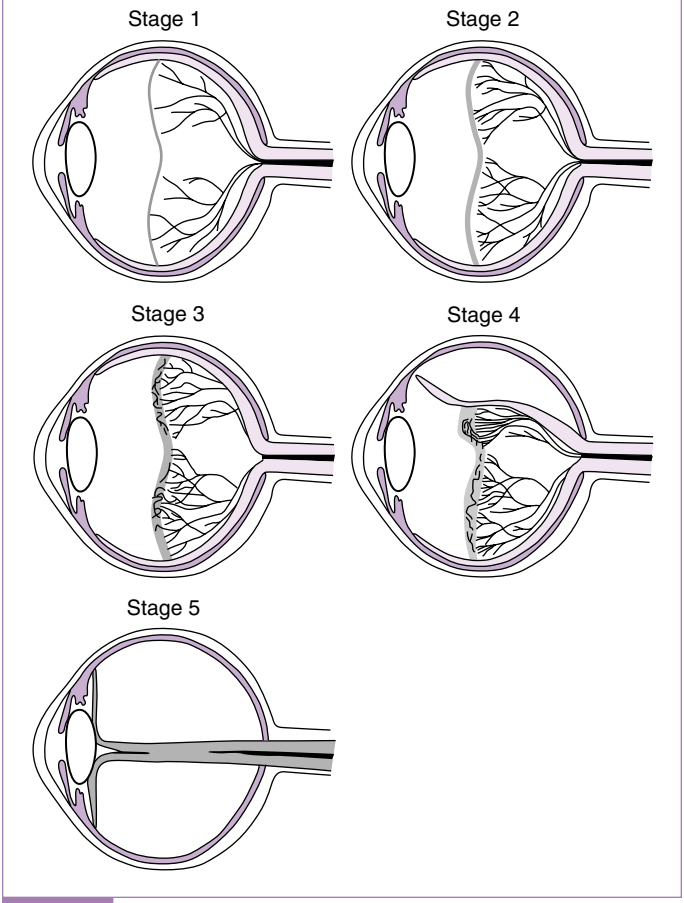


FIGURE 18.7

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).

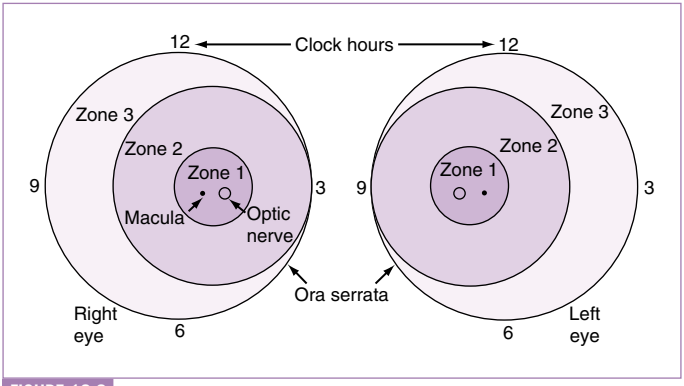


FIGURE 18.8

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.

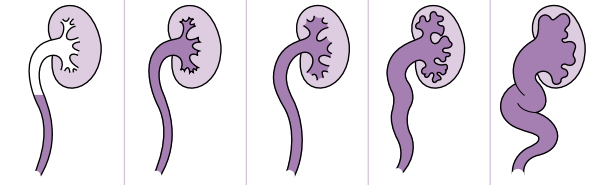
G. Imaging

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.

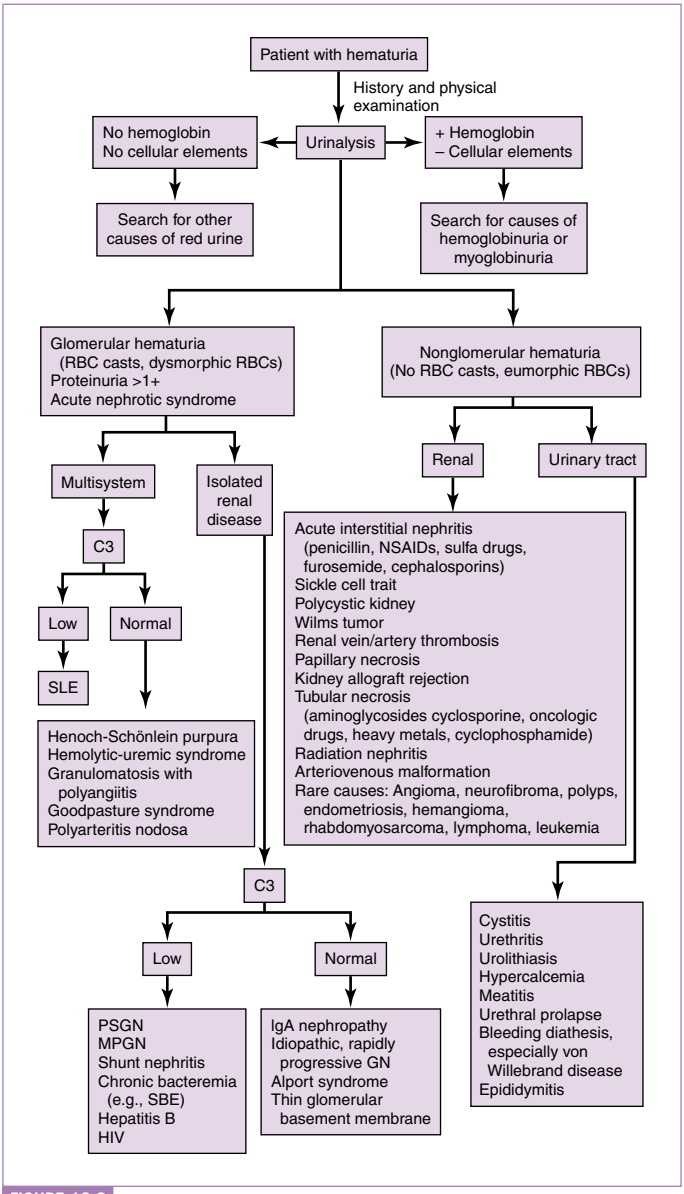


FIGURE 19.2

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.

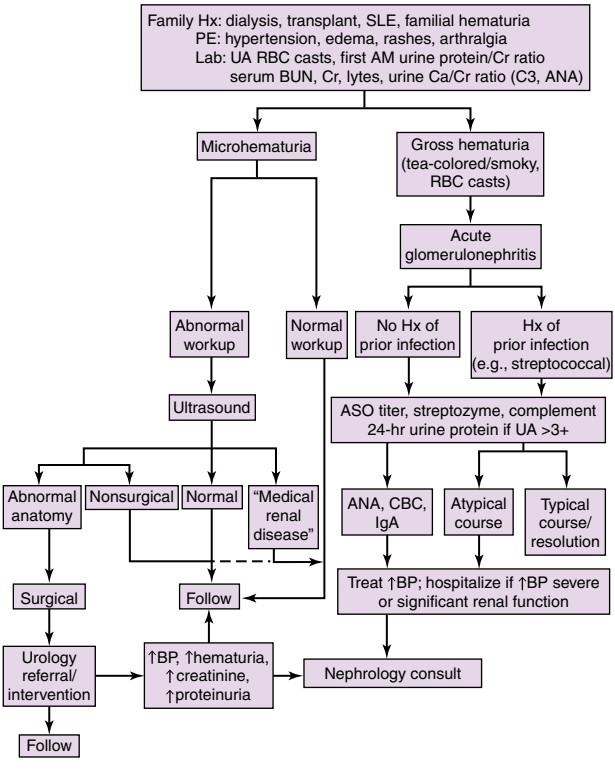


FIGURE 19.3

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)

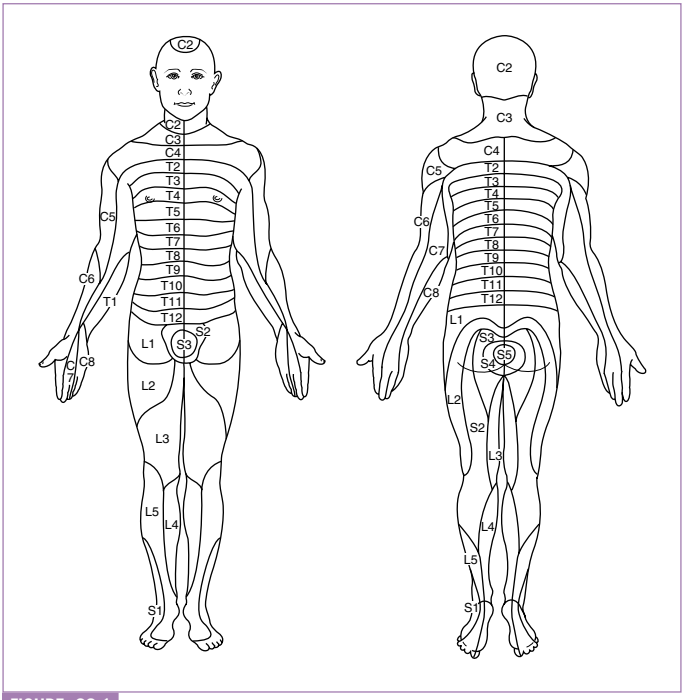

FIGURE. 20.1

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.

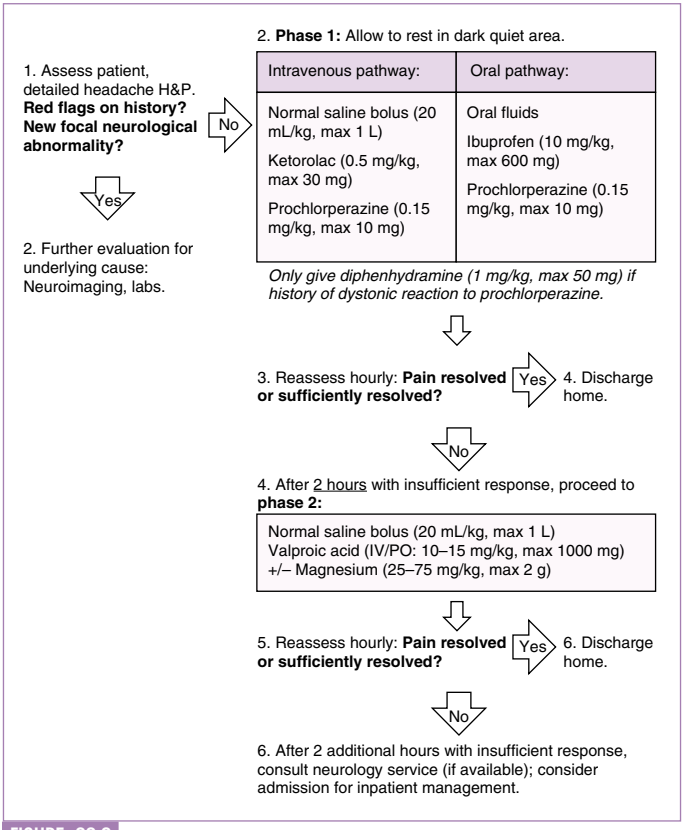

FIGURE. 20.2

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.

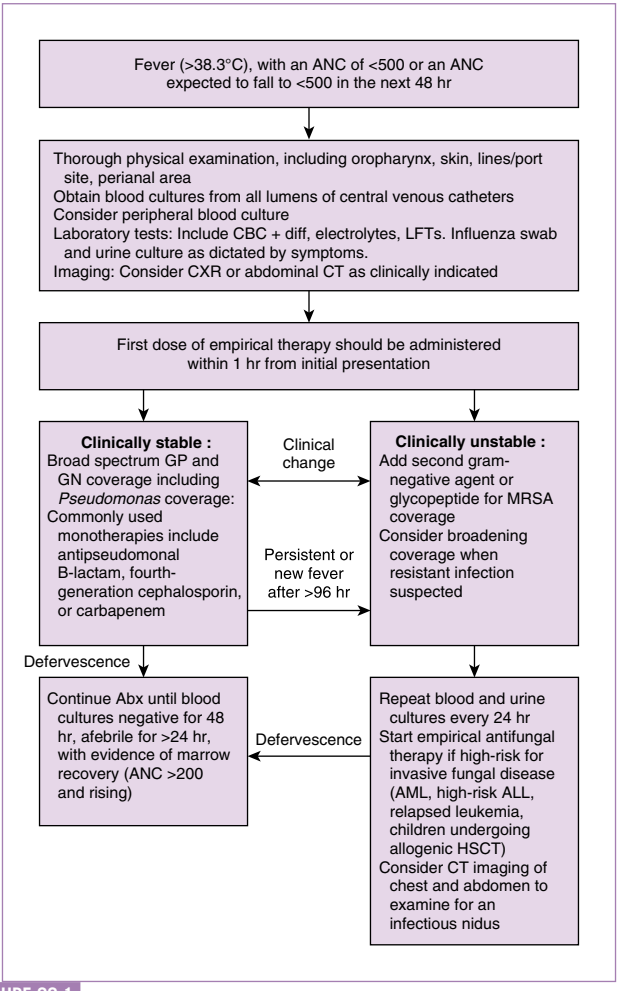

FIGURE 22.1

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.coca i.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.

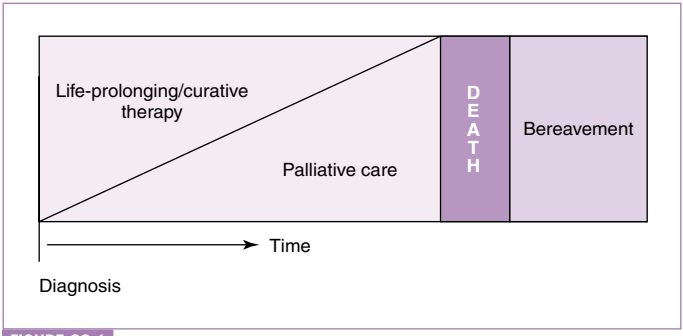

FIGURE 23.1
Current accepted model for palliative care.

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]

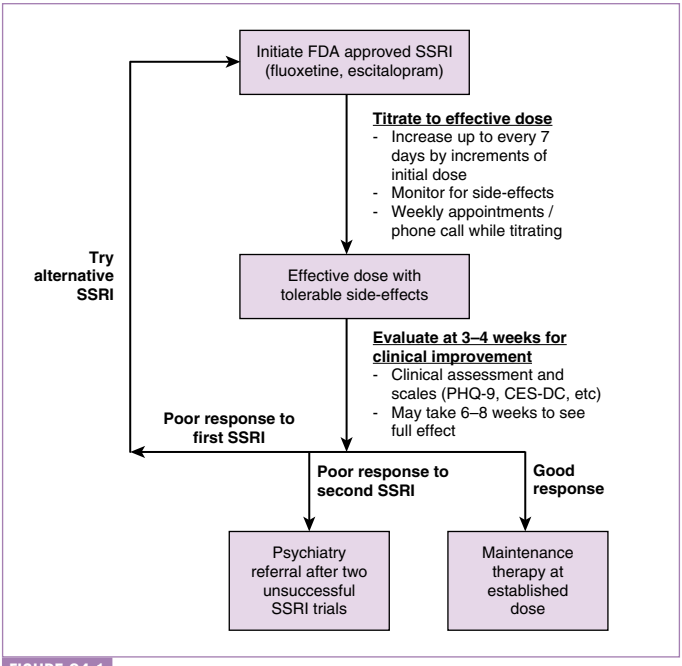

FIGURE 24.1
SSRI initiation algorithm. *CES-DC*, Center for Epidemiological Studies Depression Scale for Children; *FDA*, US Food and Drug Administration; *PHQ-9*, Patient Health Questionnaire-9; *SSRI*, selective serotonin reuptake inhibitor.

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.

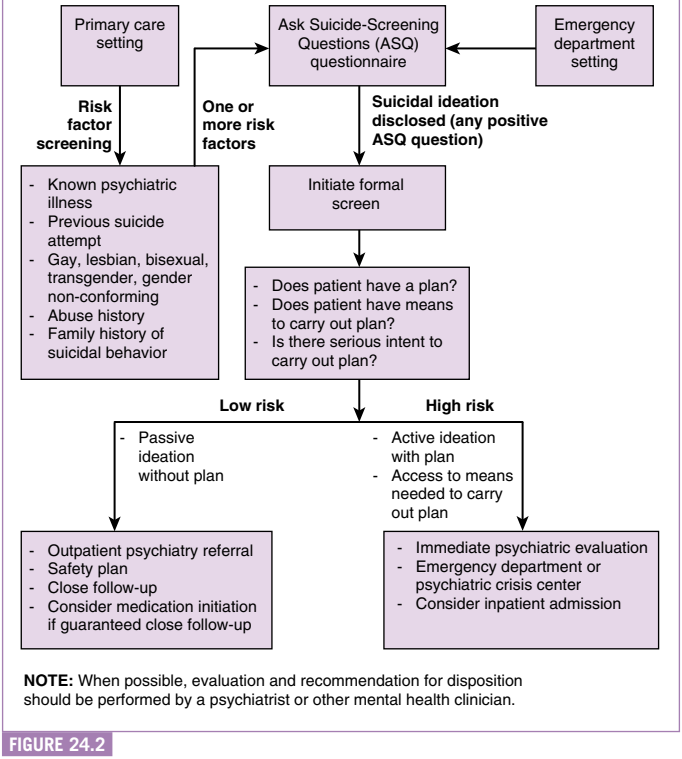

FIGURE 24.2
Suicide screening and assessment.

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

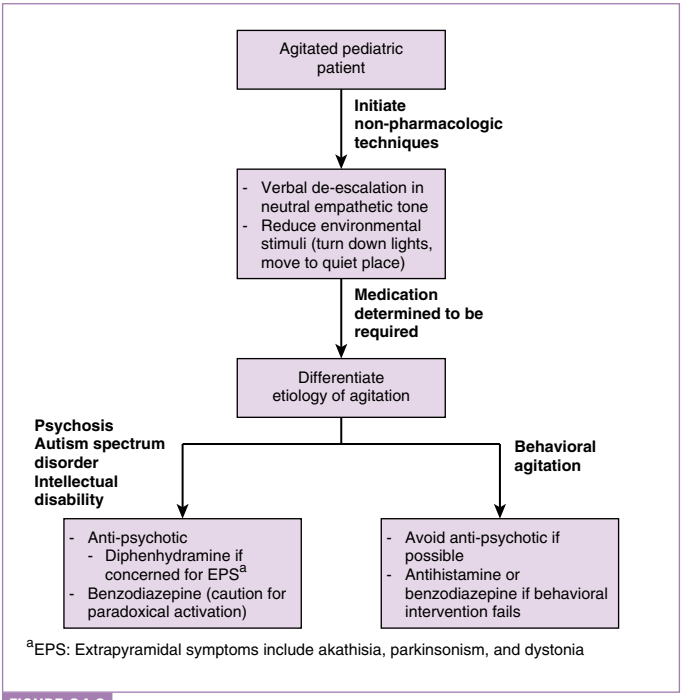

FIGURE 24.3
Agitation management algorithm.

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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.

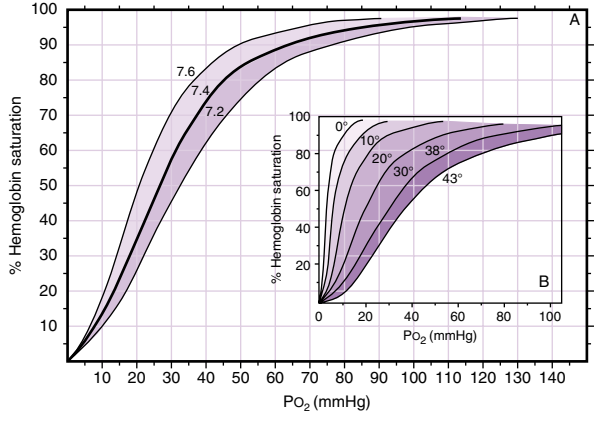


FIG. EC 25.A

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.

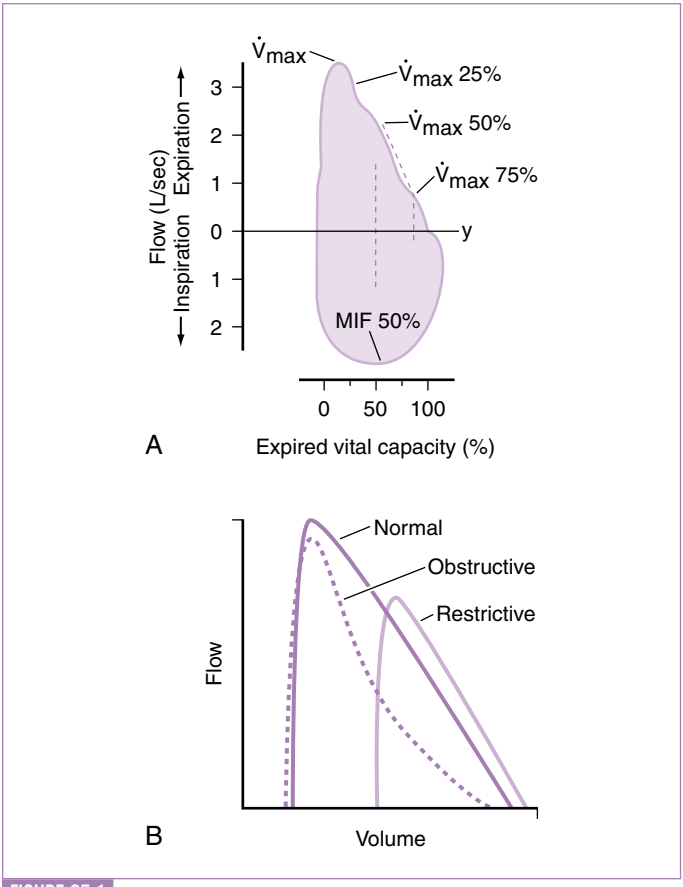


FIGURE 25.1

(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.

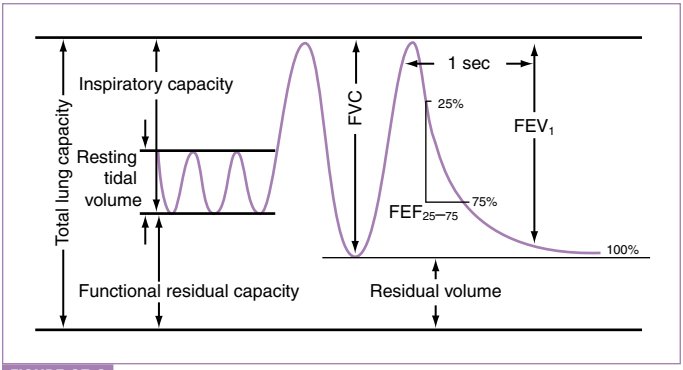


FIGURE 25.2

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.			

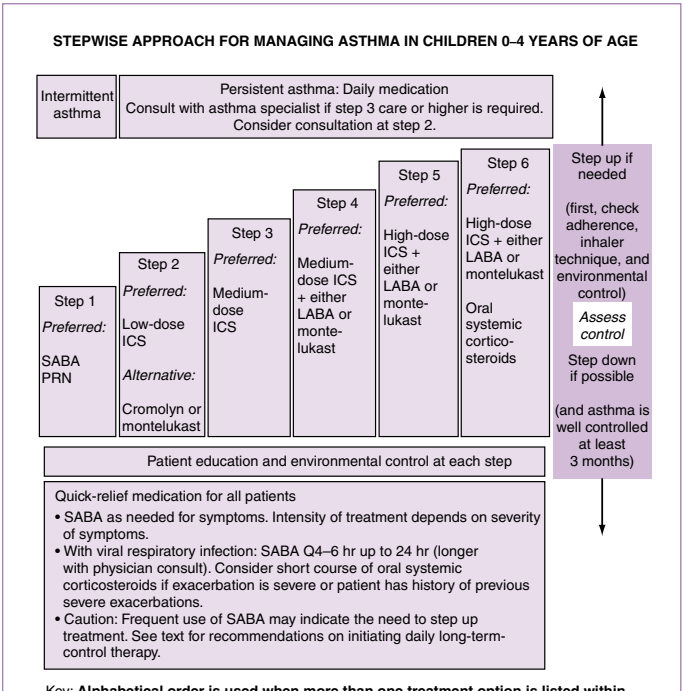
Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

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

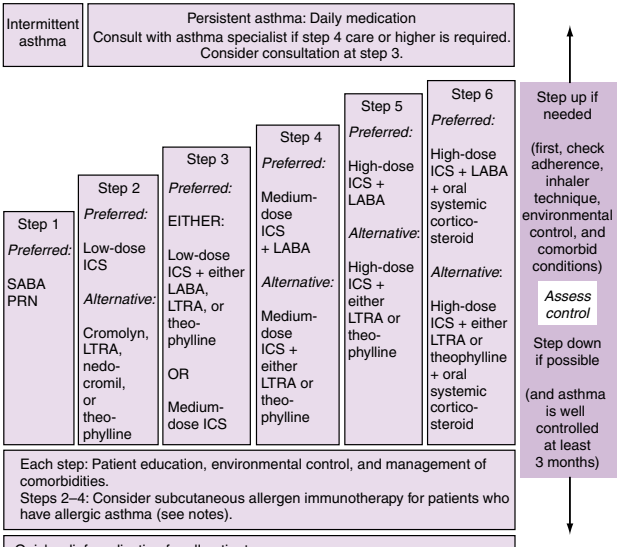
Notes:

- 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



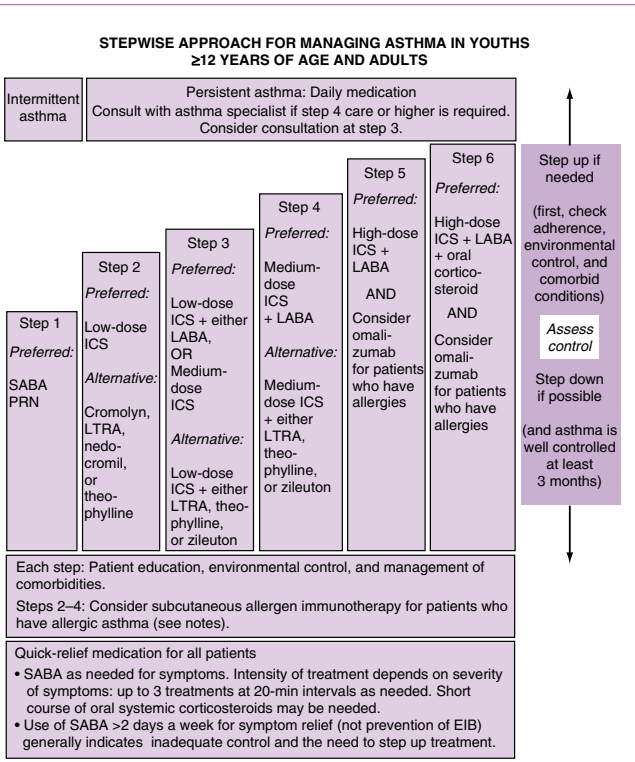
Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy**. ICS, inhaled corticosteroid; LABA, long-acting inhaled β_2-agonist; LTRA, leukotriene receptor antagonist; PRN, as needed; SABA, short-acting inhaled β_2-agonist

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.

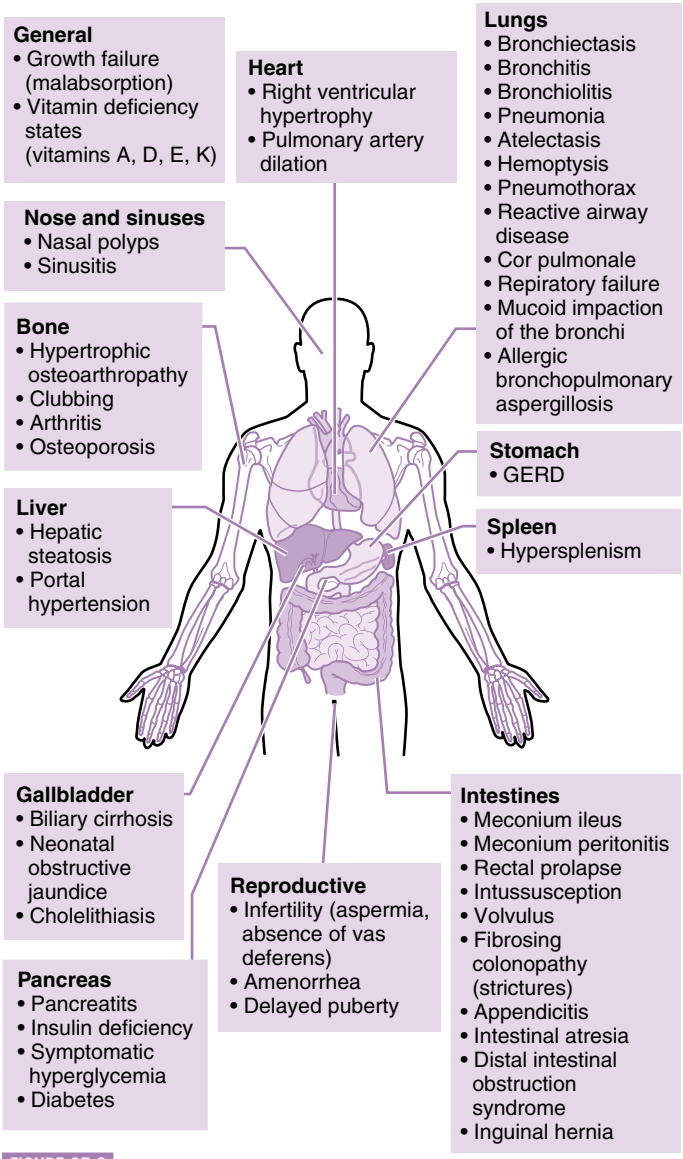


FIGURE 25.9

Clinical manifestations of cystic fibrosis. (Adapted from Kliegman R., Kliegman RM. *Nelson Essentials of Pediatrics.* St. Louis: Elsevier Saunders; 2019.)

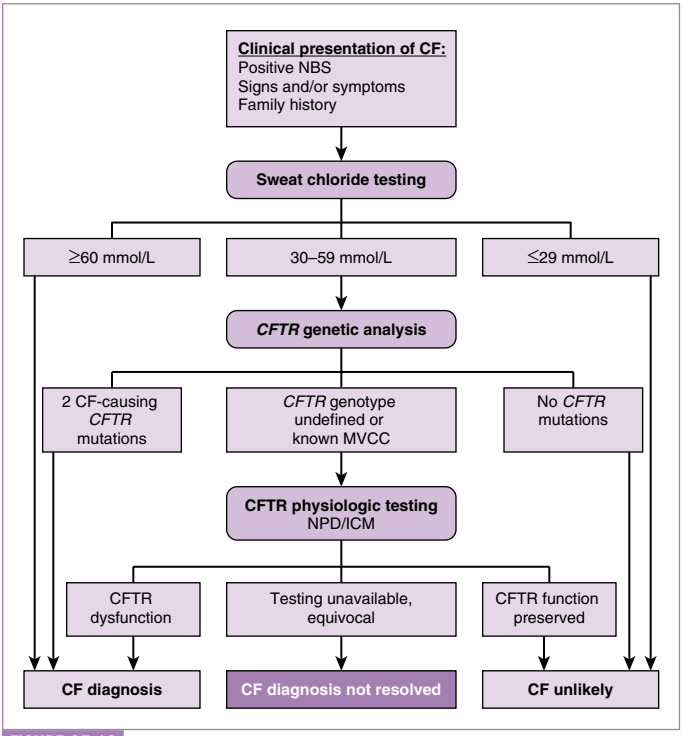


FIGURE 25.10

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.

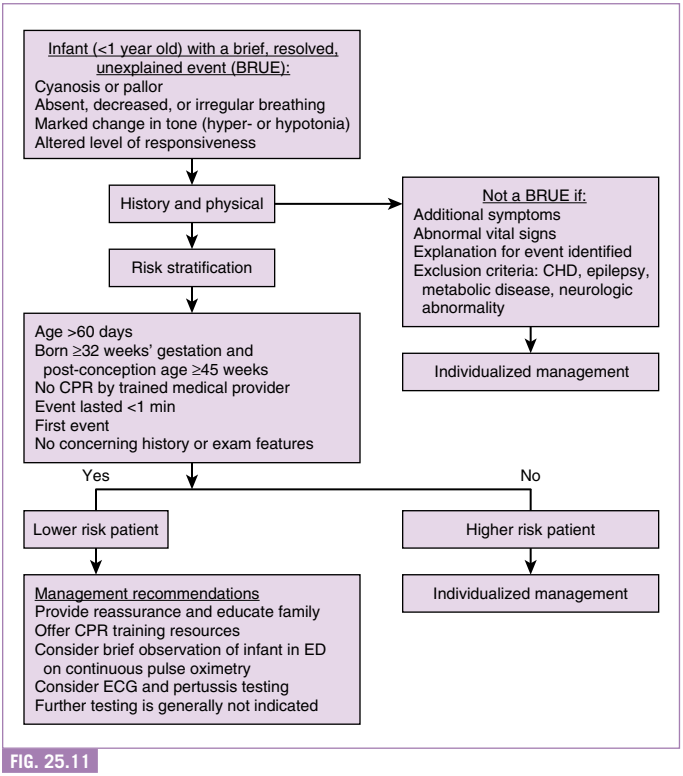


FIG. 25.11

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.

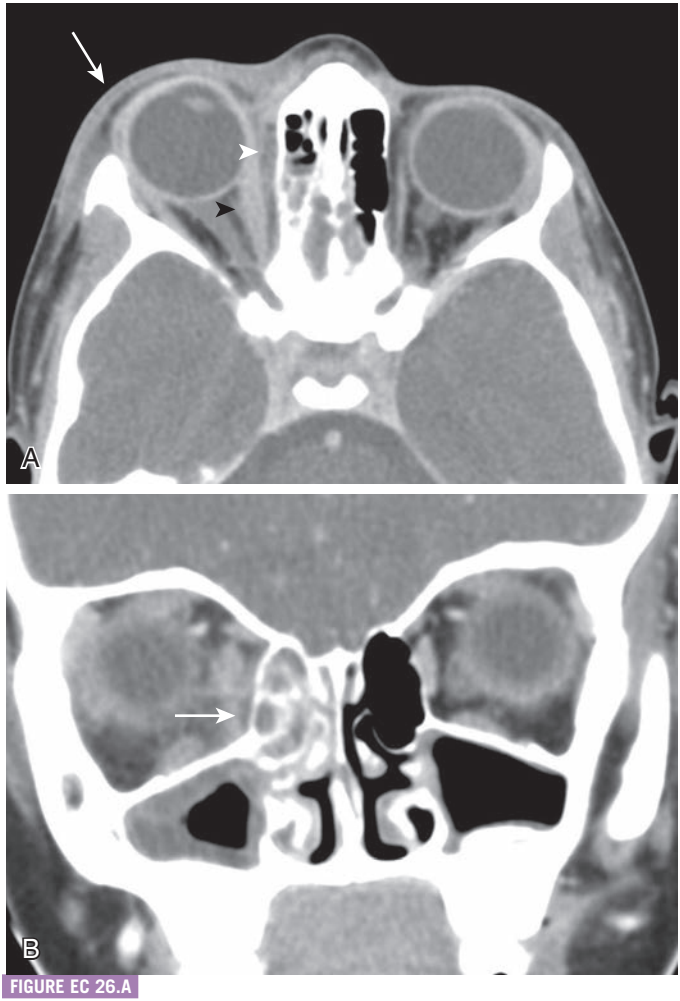


FIGURE EC 26.A

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.)

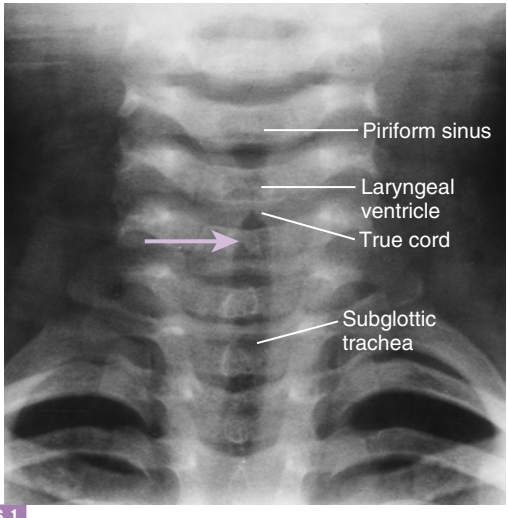


FIGURE 26.1
Anteroposterior neck film with normal anatomy. Note subglottic airway demonstrates rounded shoulders *(arrow)* that are convex outward. (Figure modified from Blickman JG, Van Die L. *Pediatric Radiology: The Requisites*. 3rd ed. Philadelphia: Elsevier; 2009, Fig. 2.17B.)

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]

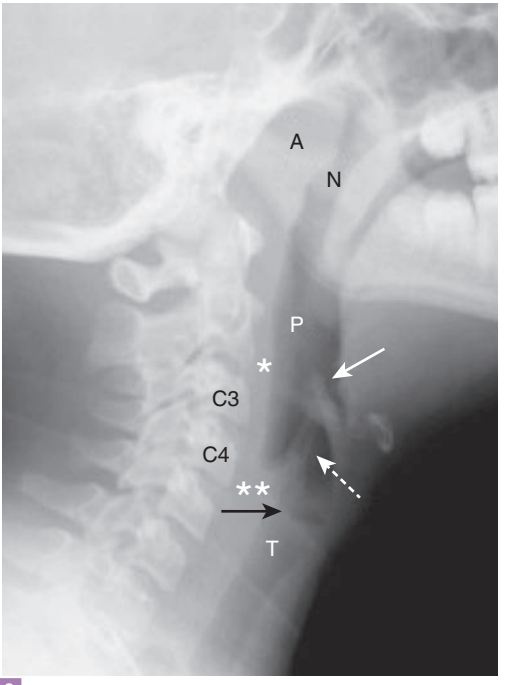


FIGURE 26.2

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]

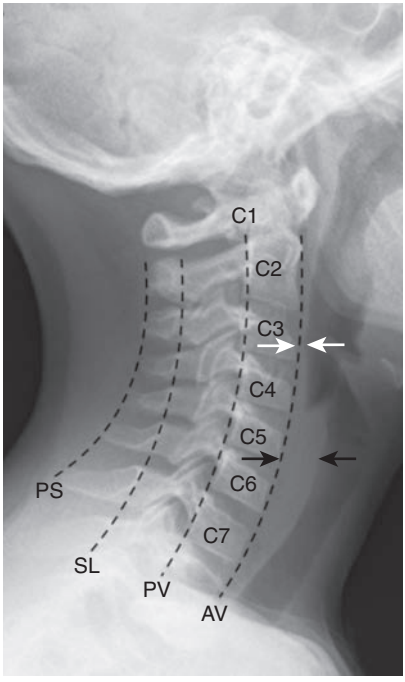


FIGURE 26.3
Normal lateral cervical spine radiograph. Four curvilinear lines can be used to help evaluate alignment: anterior vertebral line *(AV)*, posterior vertebral line *(PV)*, spinolaminar line *(SL)*, posterior spinous line *(PS)*. The retropharyngeal space should be less than one-half the width 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]

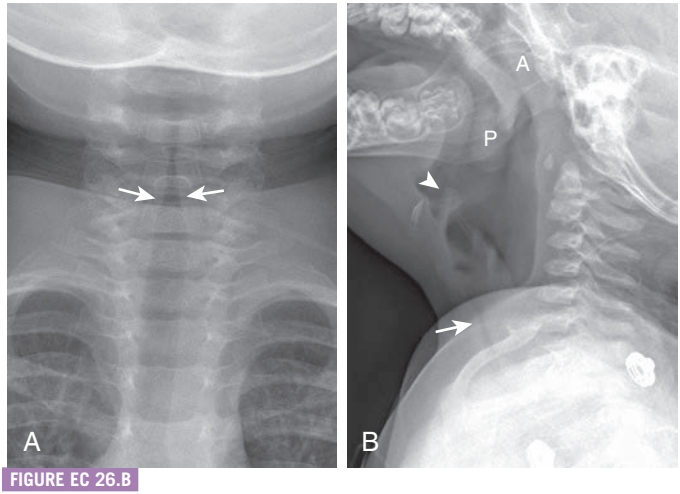


FIGURE EC 26.B

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.)

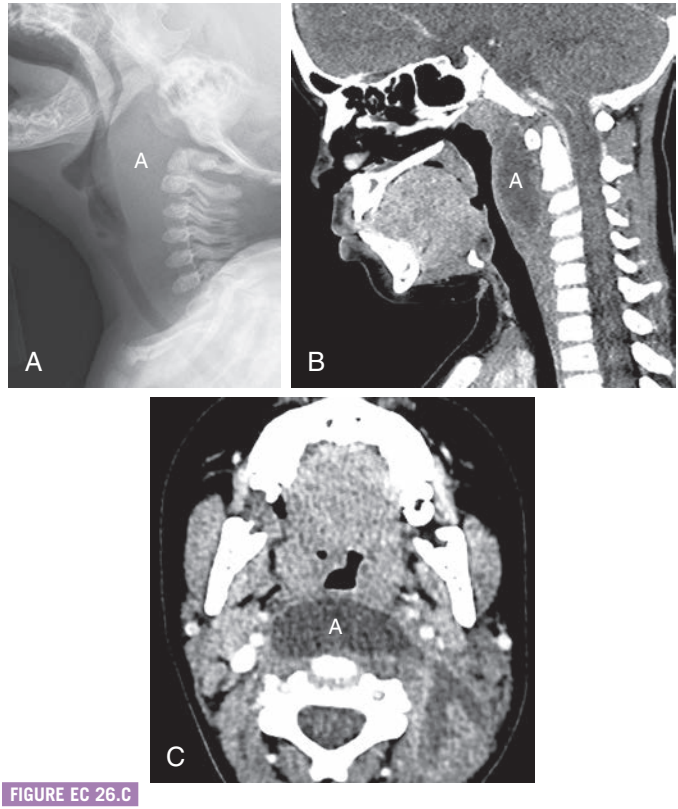
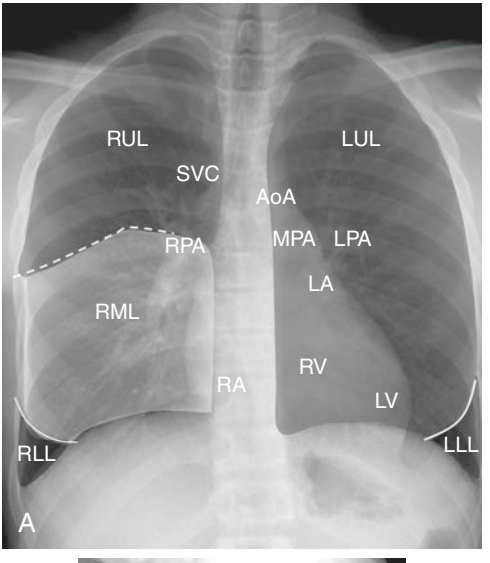


FIGURE EC 26.C

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.)



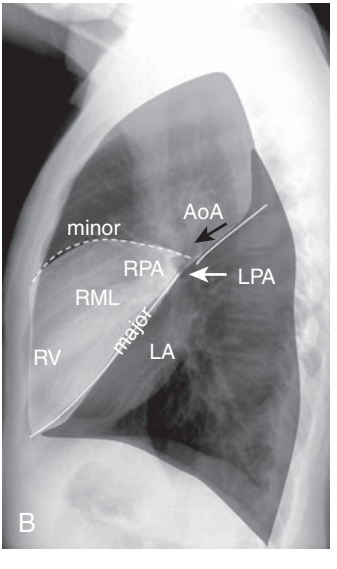


FIGURE 26.4

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

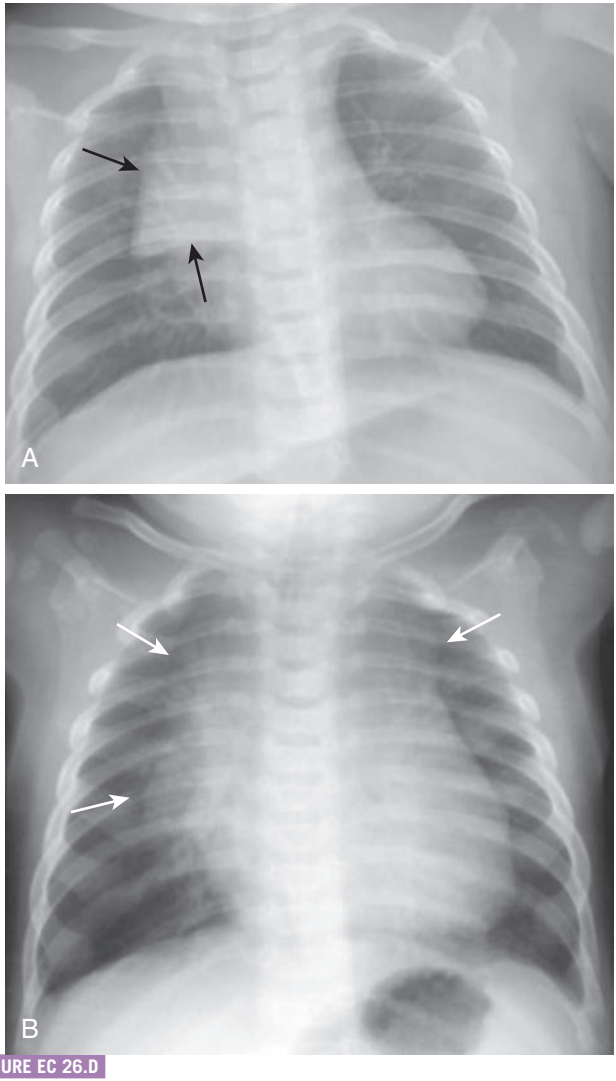


FIGURE EC 26.D

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]

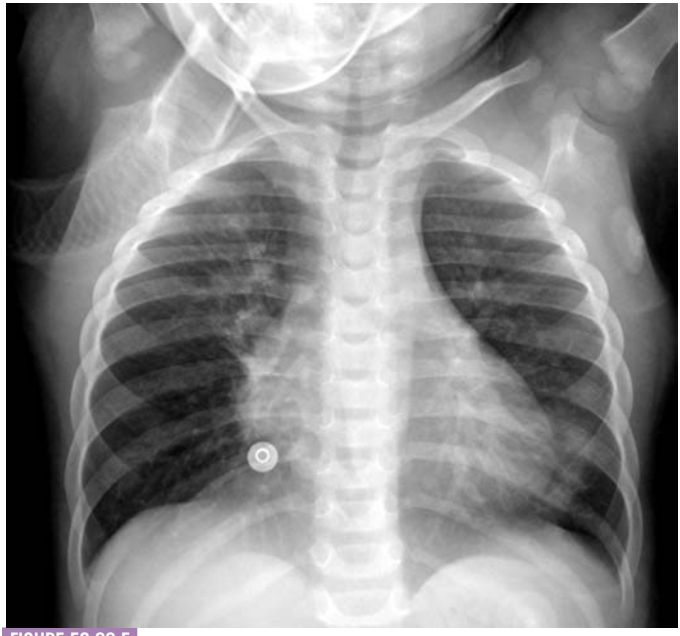


FIGURE EC 26.E

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.

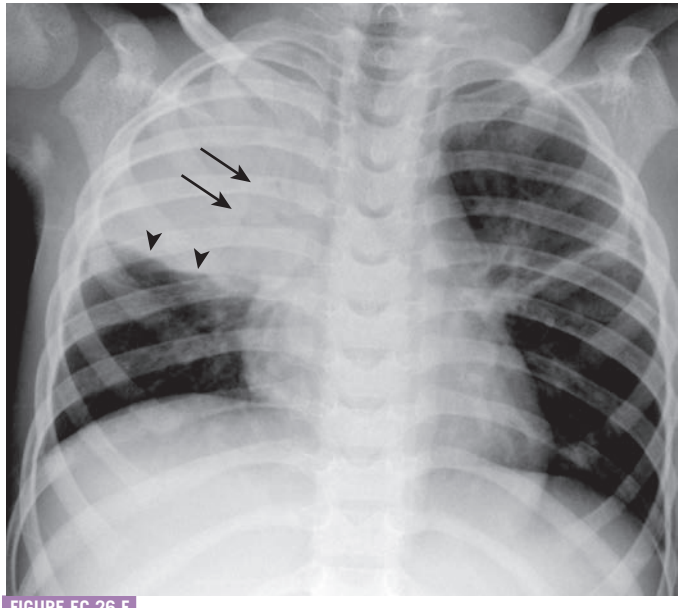


FIGURE EC 26.F

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

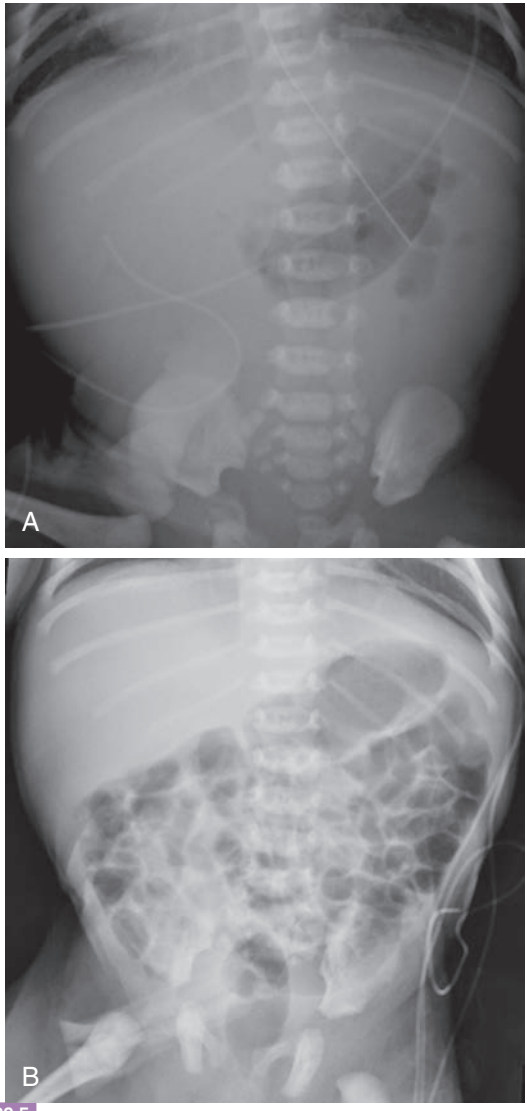


FIGURE 26.5

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]

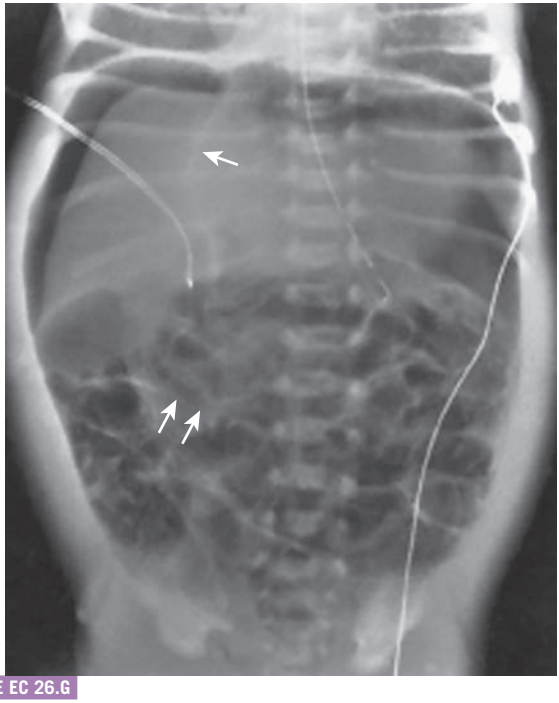


FIGURE EC 26.G

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.)

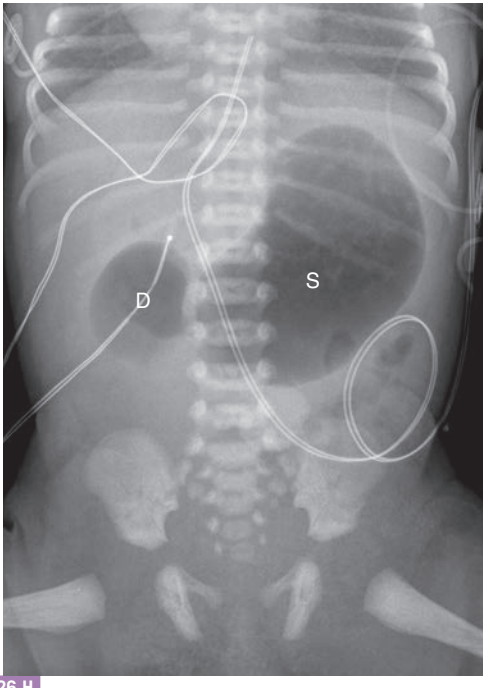


FIGURE EC 26.H

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.)

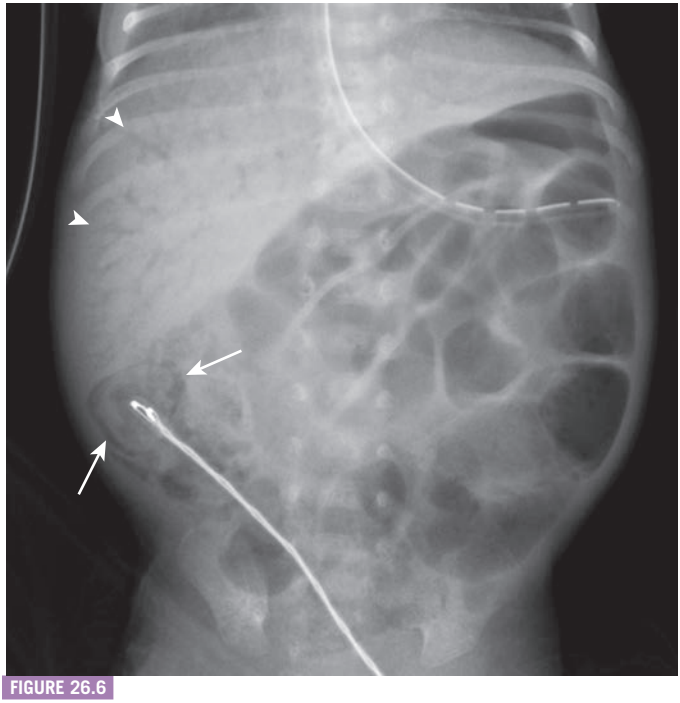


FIGURE 26.6
Necrotizing enterocolitis (NEC) in a premature infant. Radiography shows multiple dilatated bowel loops with multiple areas of linear lucency *(arrows)* along the bowel wall, consistent with pneumatosis. Note portal venous gas *(arrowheads)* as branching, tubular lucencies overlying the liver. (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.

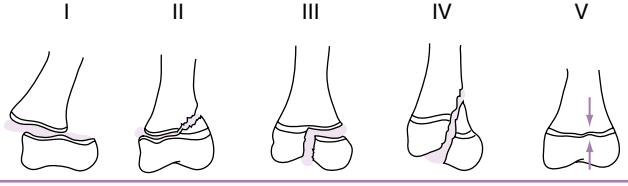
A. Fractures and Trauma

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]

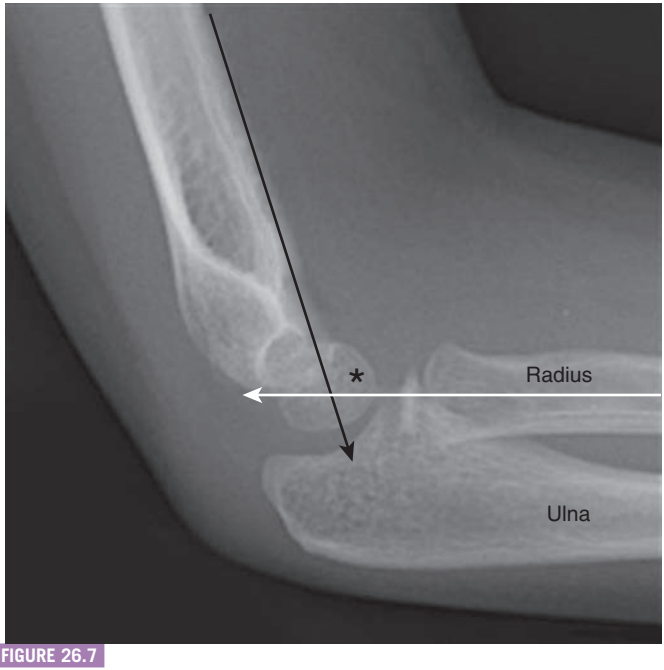


FIGURE 26.7
Normal elbow alignment on lateral radiograph. The anterior humeral line *(black arrow)* is drawn along the anterior cortex of the humerus and should intersect the middle third of the capitellum *(asterisk)*. The radiocapitellar line *(white arrow)* is drawn along the axis of the radius. (Modified 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]

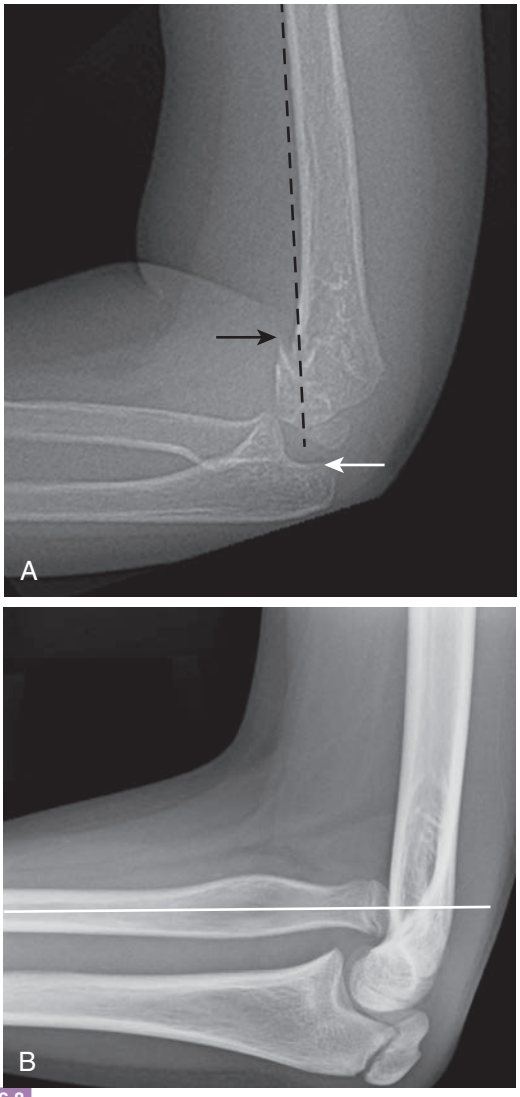


FIGURE 26.8

(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

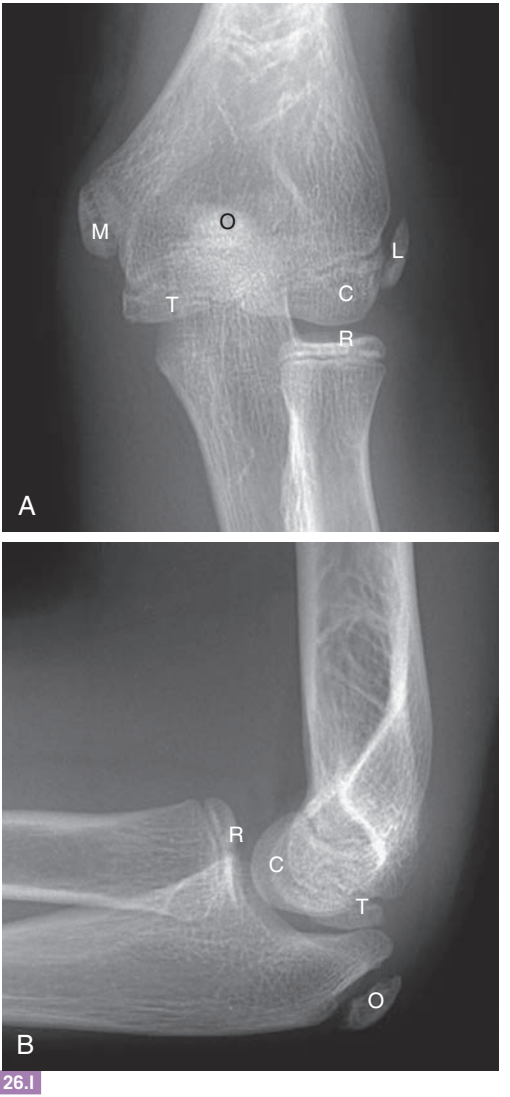


FIGURE EC 26.1

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.)

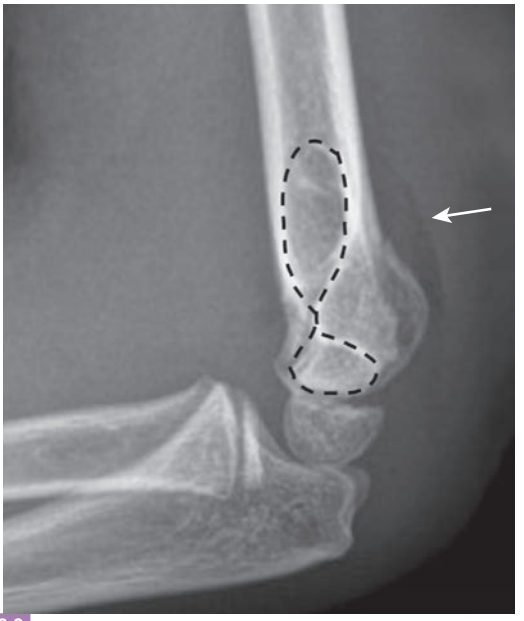


FIGURE 26.9
Lateral radiograph of elbow demonstrates visible posterior fat pad *(white arrow)*, "positive fat-pad sign." Note the "hourglass sign" *(dashed line)*.

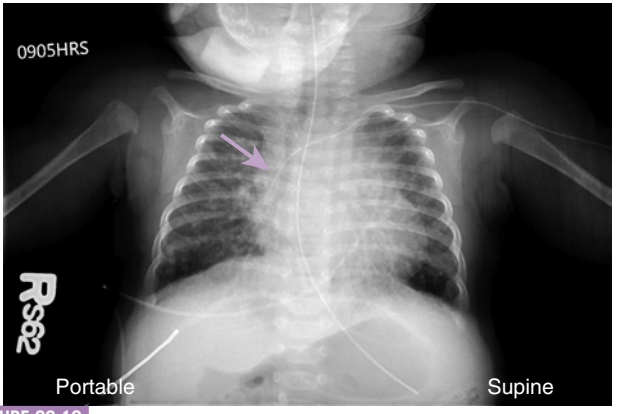


FIGURE 26.10
Central line placement on anteroposterior chest radiograph for line inserted in arm or neck. *Arrow* indicates termination of catheter at junction of superior vena cava and right atrium.

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.

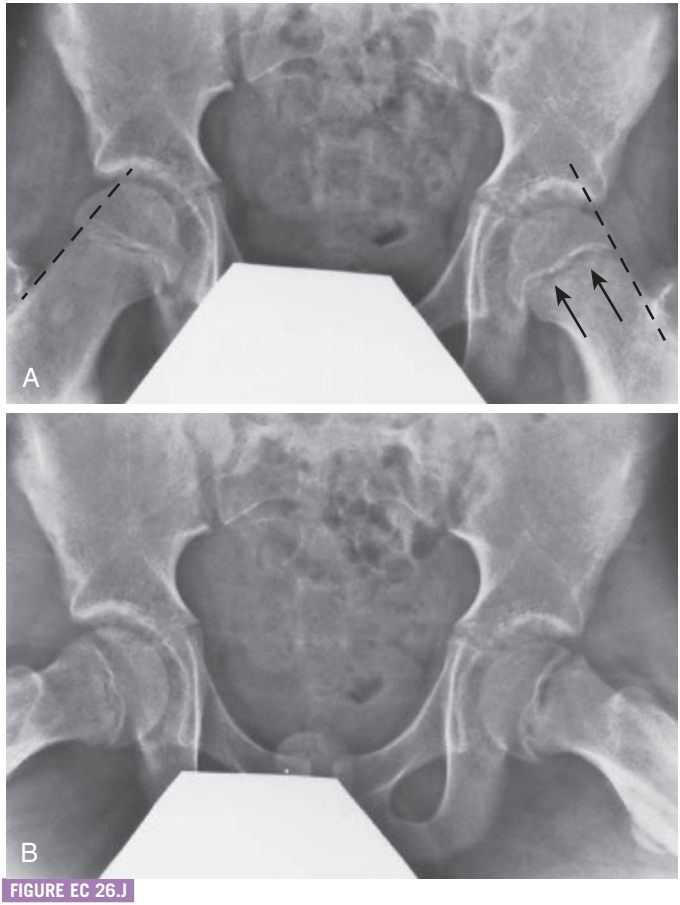


FIGURE EC 26.J

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.)

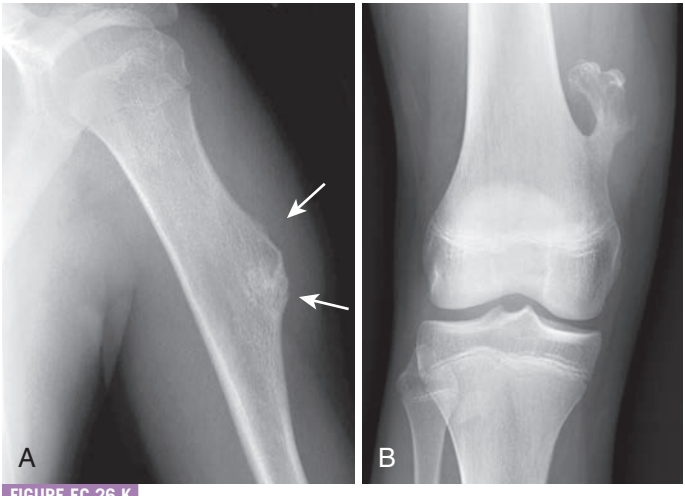


FIGURE EC 26.K

(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.)

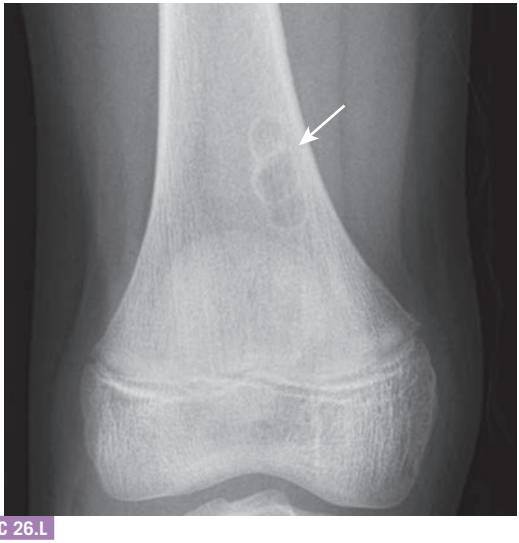


FIGURE EC 26.L

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.)

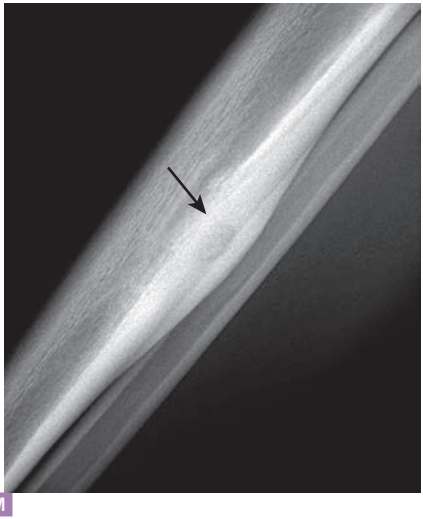


FIGURE EC 26.M

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.)

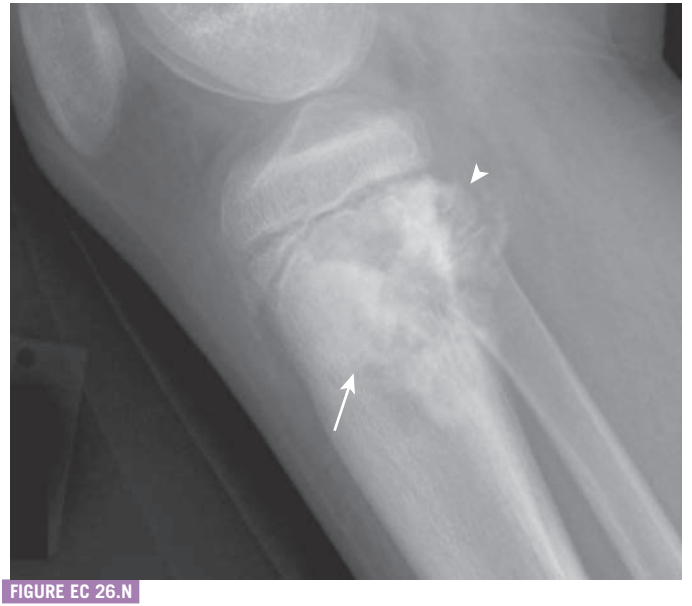


FIGURE EC 26.N

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.)

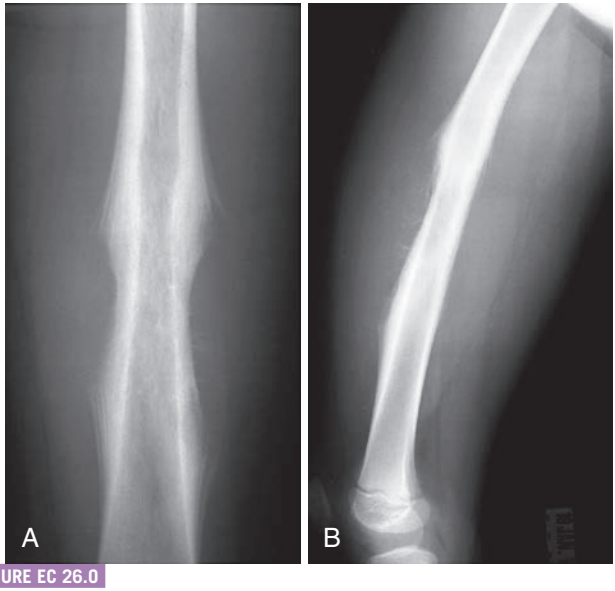


FIGURE EC 26.0

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.)

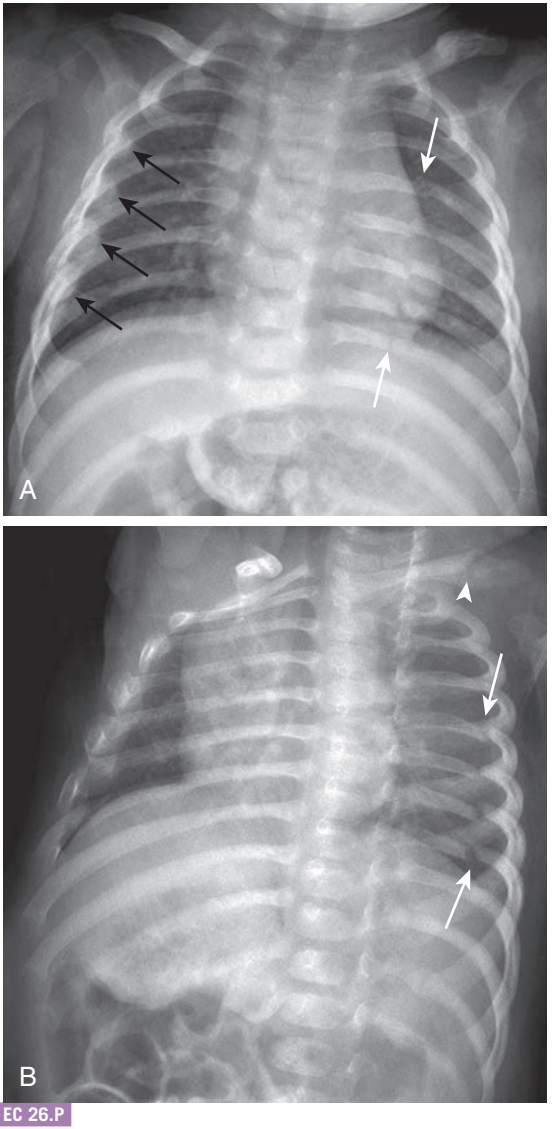


FIGURE EC 26.P

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.)

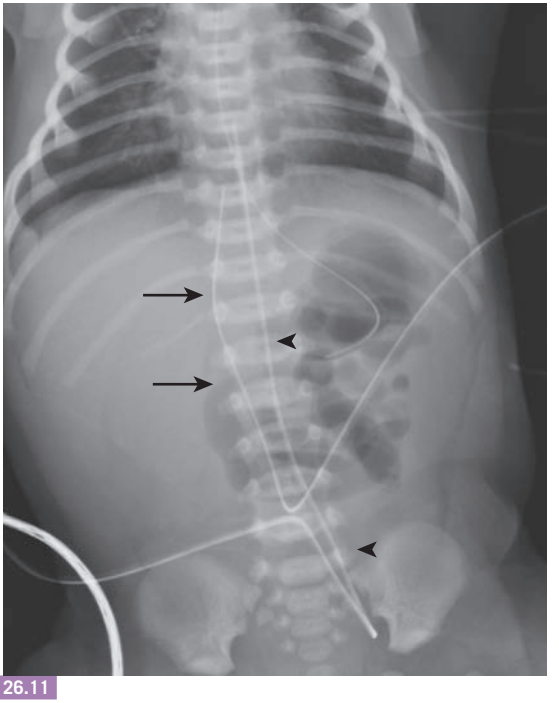


FIGURE 26.11
Umbilical catheters. Umbilical venous catheter (UVC) terminates at inferior cavoatrial junction *(arrows)*. The umbilical arterial catheter (UAC) first descends the iliac artery before it ascends the aorta and terminates in a typical "high" position, at T7 *(arrowheads)*.

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/

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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

Lauren McDaniel, MD

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).**

Special thanks to Lori Sokoll, PhD, and Stefani Thomas, PhD, for their guidance in preparing this chapter.

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[8]
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)

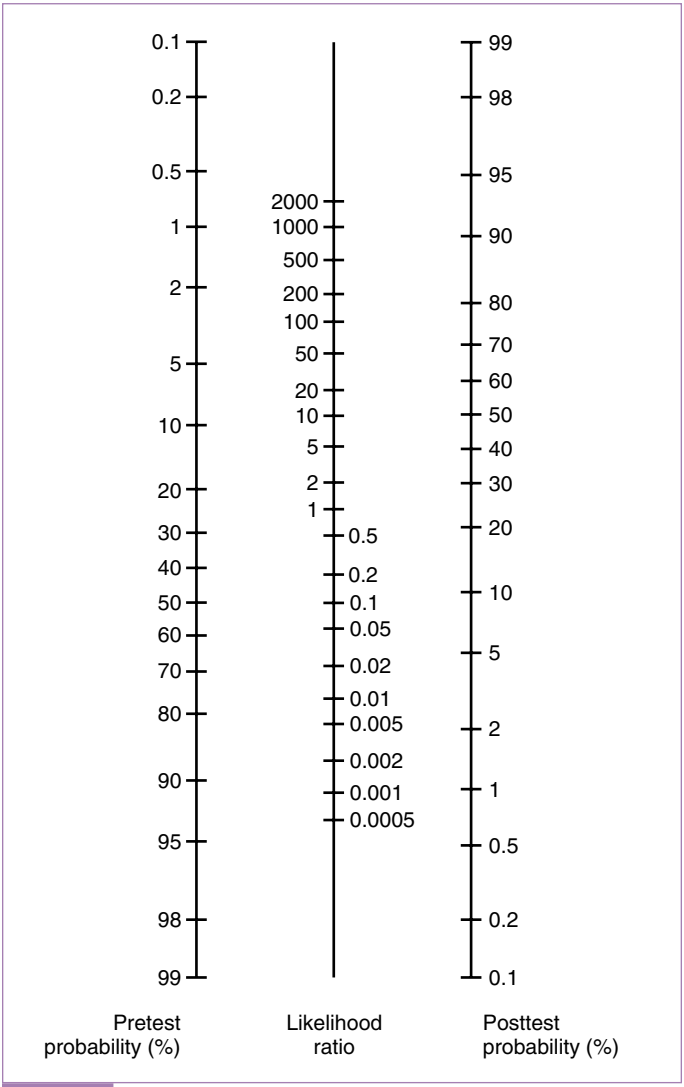

FIGURE 29.1

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 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 $t_{1/2}$ (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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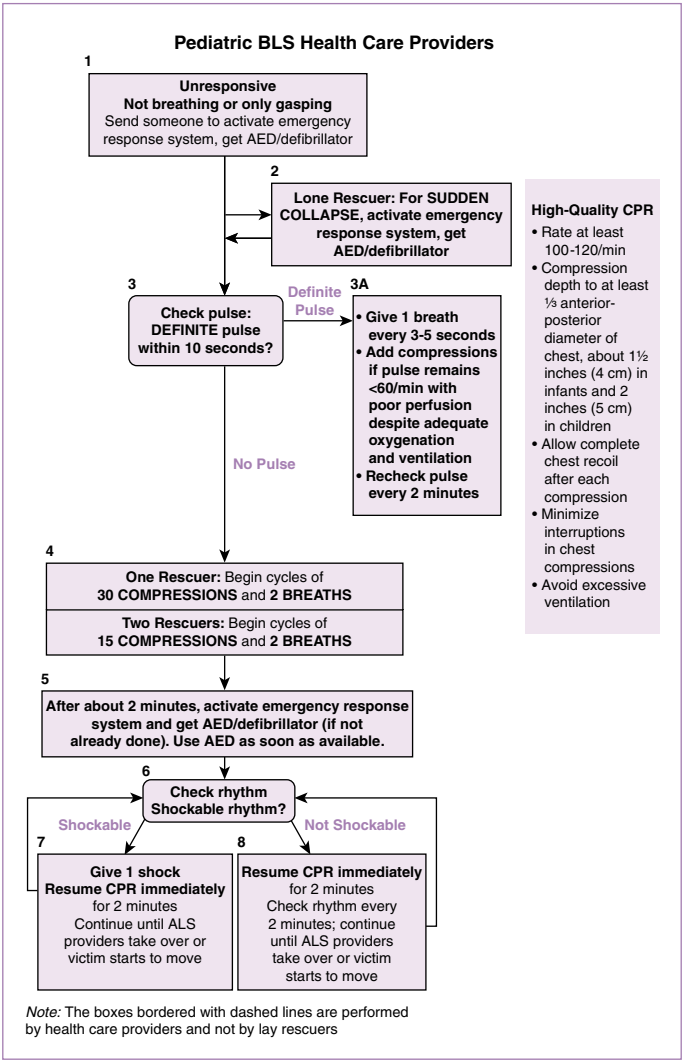
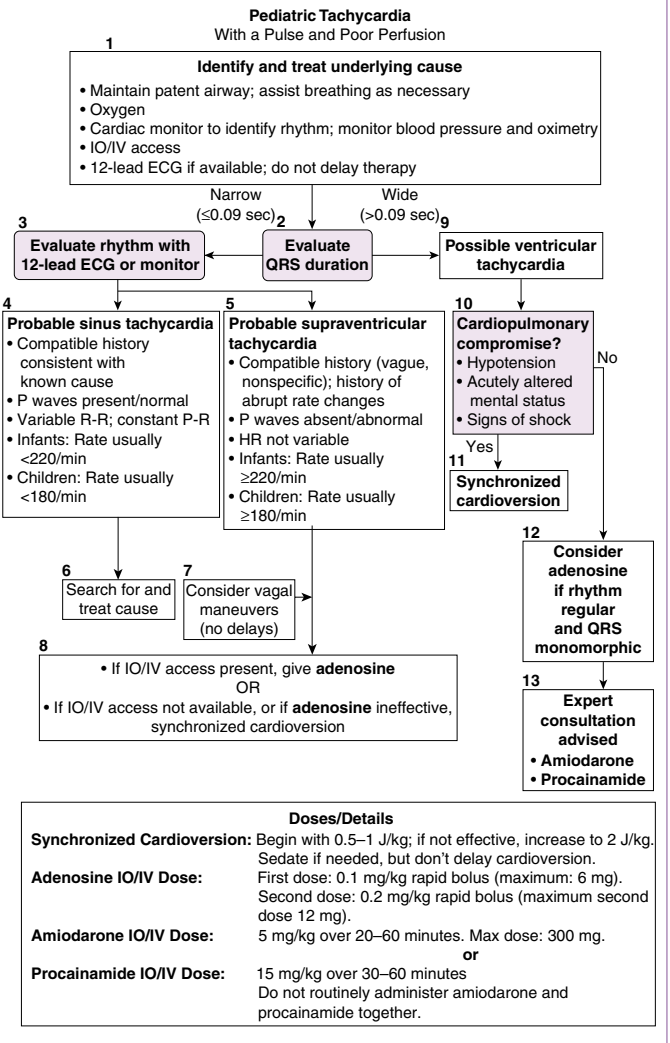
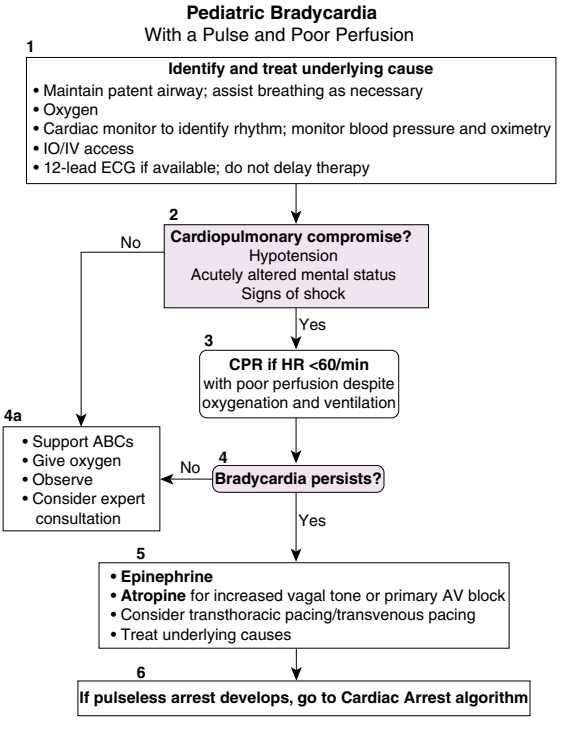


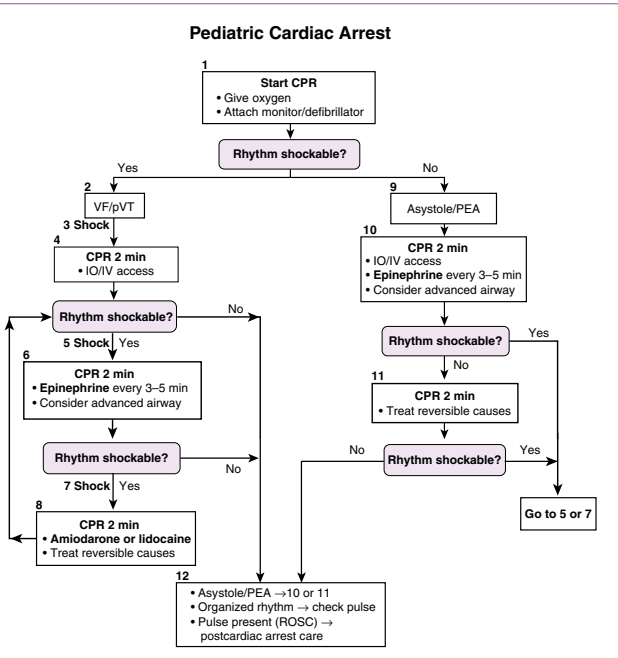
Pediatric BLS health care providers algorithm. (Reprinted with permission. Atkins DL, Berger S, Duff JP, et al. Part 11: pediatric basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Associated Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular 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.)