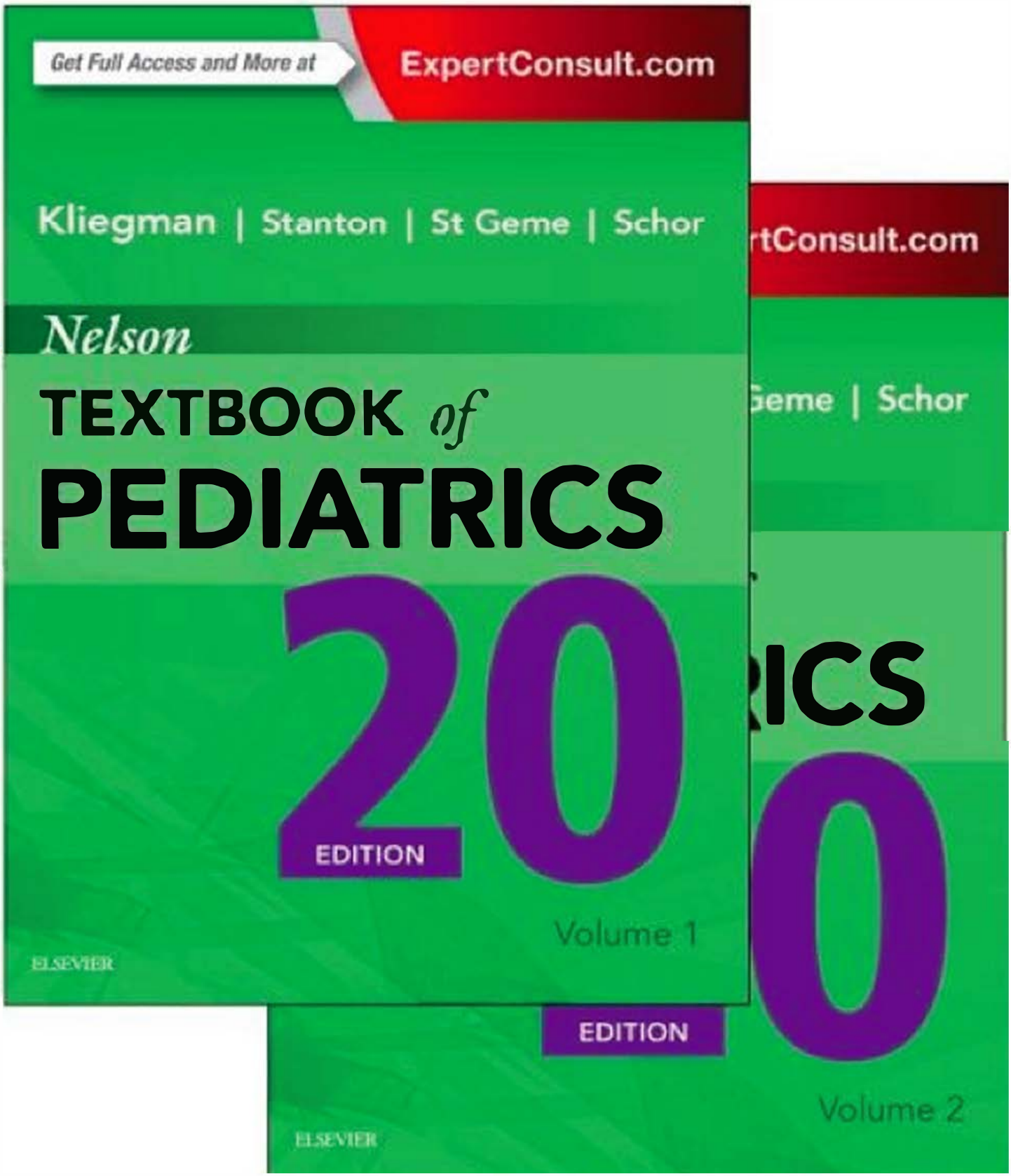

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PEDIATRICS Tables

Prepared and Edited By

Dr. Ahmed Mohammed Abd Elsattar
Al-Azhar University

نسألكم الدعاء

CONTENTS

Growth, Develoment and Behaviour

Table 1-6 Evidence-based Interventions to Address Newborn and Child Health and Undernutrition

NEWBORN	NUTRITION	DIARRHEA	PNEUMONIA
Breastfeeding promotion including initiation			
	Improved water source, sanitation, and hygiene Preventive vitamin A supplementation Preventive zinc supplementation		
Periconceptional folic acid supplementation or fortification Multiple micronutrient/iron-folate supplementation in pregnancy Maternal balanced energy protein supplementation Maternal calcium supplementation			
ORS Antibiotics for dysentery		ORS Antibiotics for dysentery	
Case management of pneumonia			Case management of pneumonia
IPTp case management, Syphilis detection and treatment Tetanus toxoid vaccination Diabetes case management Fetal growth restriction detection Hypertensive disease prevention and case management Induction of labor for pregnancies after 41 weeks Active management of the third stage of labor Clean birth practices Labor and delivery management ANS for preterm labor Antibiotics for preterm premature rupture of membranes Immediate assessment and stimulation Neonatal resuscitation Thermal care Chlorhexidine cord application Clean postnatal practices Hospital care of preterm babies including Kangaroo mother care	Appropriate complementary feeding Management of moderate acute malnutrition Management of severe acute malnutrition	Zinc for treatment of diarrhea Rotavirus vaccine	Hib vaccine Pneumococcal vaccine

ANS, antenatal corticosteroid treatment; Hib, *Haemophilus influenzae* type b; IPTp, intermittent preventive treatment of malaria for pregnant women.

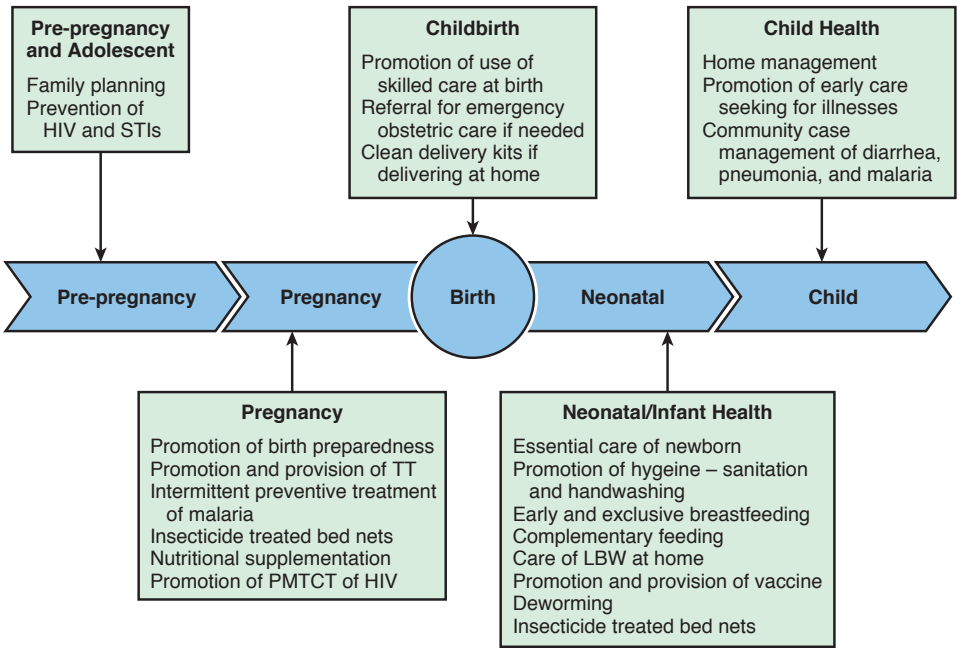
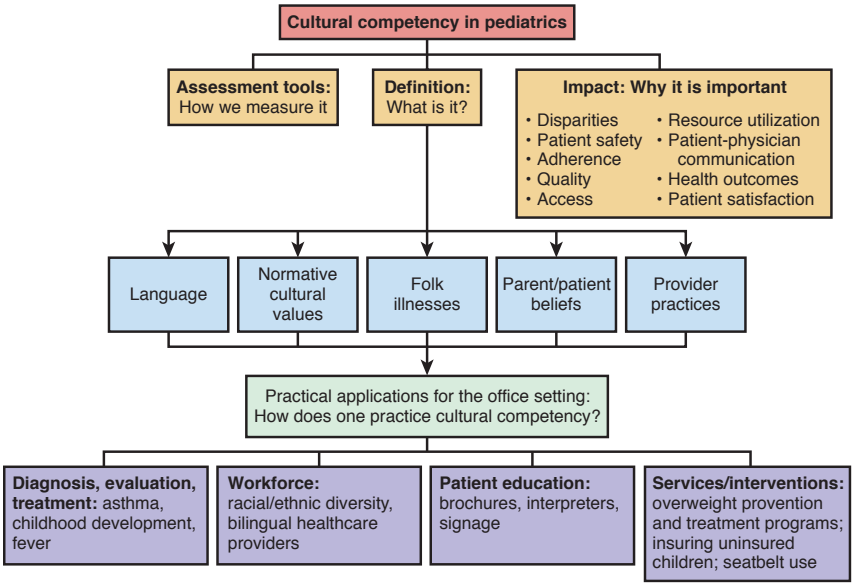


Figure 1-13 Neonatal and child health interventions: delivered by community health workers.



Conceptual framework for cultural competency in pediatrics: (1) what is known about the impact of cultural competency on general pediatric care; (2) the domains of cultural competency; and (3) practical applications of cultural competency for general pediatricians

Figure 4-1 Components of cultural competency in pediatric practice. *(From Brotanek JM, Seeley CE, Flores G: The importance of cultural competency in general pediatrics,* Curr Opin Pediatr *20:711–718, 2008, Fig. 1, p. 712.)*

Table 4-3 Home Remedies for Fever, Colic, and Teething Among African-Americans

CONDITION	REMEDY	KNOWLEDGE, % (*N* = 107)	USE, % (*N* = 107)
Fever	Acetaminophen*	98	77.6
	Cool bath*	85	48.3
	Isopropyl alcohol*	71	38.3
	Cool drinks/popsicles†	11.2	0
	Undress child†	10.3	0
	Ibuprofen†	10.3	0
	Warm feet†	8.4	0
	Potatoes or onions in socks†	6.5	0
Colic	Catnip*	34.6	8.4
	Senna extract*	25.2	4.7
	Other (asafetida, paregoric, or bicarbonate)†	13.1	0
	Chamomile*	7.5	0
	Walk†	6.5	0
	Cigarette smoke†	5.6	0
	Simethicone drops†	4.7	0
	Vacuum/steam†	3.7	0
	Cover head†	3.7	0
	Massage†	2.8	0
	Gripe water*	1.9	0
Teething	Nonprescription benzocaine gel*	97.2	57
	Teething object†	35.2	7.5
	Whiskey*	34.6	1.9
	Penny*	16.8	0
	Ice cubes/popsicles†	13.3	0
	Egg†	11.4	0
	Spices (asafetida, cloves, or vanilla)†	4.8	0

*Responses given in closed-ended questions.
†Responses given in open-ended questions.
From Smitherman LC, Janisse J, Mathur A: The use of folk remedies among children in an urban black community: remedies for fever, colic and teething, Pediatrics 115:297–304, 2005, Table 2.

Table 10-1 Developmental Milestones in the 1st 2 Yr of Life

MILESTONE	AVERAGE AGE OF ATTAINMENT (MO)	DEVELOPMENTAL IMPLICATIONS
GROSS MOTOR		
Holds head steady while sitting	2	Allows more visual interaction
Pulls to sit, with no head lag	3	Muscle tone
Brings hands together in midline	3	Self-discovery of hands
Asymmetric tonic neck reflex gone	4	Can inspect hands in midline
Sits without support	6	Increasing exploration
Rolls back to stomach	6.5	Truncal flexion, risk of falls
Walks alone	12	Exploration, control of proximity to parents
Runs	16	Supervision more difficult
FINE MOTOR		
Grasps rattle	3.5	Object use
Reaches for objects	4	Visuomotor coordination
Palmar grasp gone	4	Voluntary release
Transfers object hand to hand	5.5	Comparison of objects
Thumb-finger grasp	8	Able to explore small objects
Turns pages of book	12	Increasing autonomy during book time
Scribbles	13	Visual–motor coordination
Builds tower of 2 cubes	15	Uses objects in combination
Builds tower of 6 cubes	22	Requires visual, gross, and fine motor coordination
COMMUNICATION AND LANGUAGE		
Smiles in response to face, voice	1.5	More active social participant
Monosyllabic babble	6	Experimentation with sound, tactile sense
Inhibits to "no"	7	Response to tone (nonverbal)
Follows one-step command with gesture	7	Nonverbal communication
Follows one-step command without gesture	10	Verbal receptive language (e.g., "Give it to me")
Says "mama" or "dada"	10	Expressive language
Points to objects	10	Interactive communication
Speaks first real word	12	Beginning of labeling
Speaks 4-6 words	15	Acquisition of object and personal names
Speaks 10-15 words	18	Acquisition of object and personal names
Speaks 2-word sentences (e.g., "Mommy shoe")	19	Beginning grammatization, corresponds with 50 word vocabulary
COGNITIVE		
Stares momentarily at spot where object disappeared	2	Lack of object permanence (out of sight, out of mind [e.g., yarn ball dropped])
Stares at own hand	4	Self-discovery, cause and effect
Bangs 2 cubes	8	Active comparison of objects
Uncovers toy (after seeing it hidden)	8	Object permanence
Egocentric symbolic play (e.g., pretends to drink from cup)	12	Beginning symbolic thought
Uses stick to reach toy	17	Able to link actions to solve problems
Pretend play with doll (e.g., gives doll bottle)	17	Symbolic thought

Table 10-2 Emerging Patterns of Behavior During the 1st Yr of Life*

NEONATAL PERIOD (1ST 4 WK)	
Prone:	Lies in flexed attitude; turns head from side to side; head sags on ventral suspension
Supine:	Generally flexed and a little stiff
Visual:	May fixate face on light in line of vision; "doll's-eye" movement of eyes on turning of the body
Reflex:	Moro response active; stepping and placing reflexes; grasp reflex active
Social:	Visual preference for human face
AT 1 MO	
Prone:	Legs more extended; holds chin up; turns head; head lifted momentarily to plane of body on ventral suspension
Supine:	Tonic neck posture predominates; supple and relaxed; head lags when pulled to sitting position
Visual:	Watches person; follows moving object
Social:	Body movements in cadence with voice of other in social contact; beginning to smile
AT 2 MO	
Prone:	Raises head slightly farther; head sustained in plane of body on ventral suspension
Supine:	Tonic neck posture predominates; head lags when pulled to sitting position
Visual:	Follows moving object 180 degrees
Social:	Smiles on social contact; listens to voice and coos
AT 3 MO	
Prone:	Lifts head and chest with arms extended; head above plane of body on ventral suspension
Supine:	Tonic neck posture predominates; reaches toward and misses objects; waves at toy
Sitting:	Head lag partially compensated when pulled to sitting position; early head control with bobbing motion; back rounded
Reflex:	Typical Moro response has not persisted; makes defensive movements or selective withdrawal reactions
Social:	Sustained social contact; listens to music; says "aah, ngah"
AT 4 MO	
Prone:	Lifts head and chest, with head in approximately vertical axis; legs extended
Supine:	Symmetric posture predominates, hands in midline; reaches and grasps objects and brings them to mouth
Sitting:	No head lag when pulled to sitting position; head steady, tipped forward; enjoys sitting with full truncal support
Standing:	When held erect, pushes with feet
Adaptive:	Sees raisin, but makes no move to reach for it
Social:	Laughs out loud; may show displeasure if social contact is broken; excited at sight of food
AT 7 MO	
Prone:	Rolls over; pivots; crawls or creep-crawls (Knobloch)
Supine:	Lifts head; rolls over; squirms
Sitting:	Sits briefly, with support of pelvis; leans forward on hands; back rounded
Standing:	May support most of weight; bounces actively
Adaptive:	Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; rakes at raisin
Language:	Forms polysyllabic vowel sounds
Social:	Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact
AT 10 MO	
Sitting:	Sits up alone and indefinitely without support, with back straight
Standing:	Pulls to standing position; "cruises" or walks holding on to furniture
Motor:	Creeps or crawls
Adaptive:	Grasps objects with thumb and forefinger; pokes at things with forefinger; picks up pellet with assisted pincer movement; uncovers hidden toy; attempts to retrieve dropped object; releases object grasped by other person
Language:	Repetitive consonant sounds ("mama," "dada")
Social:	Responds to sound of name; plays peek-a-boo or pat-a-cake; waves bye-bye
AT 1 YR	
Motor:	Walks with one hand held; rises independently, takes several steps (Knobloch)
Adaptive:	Picks up raisin with unassisted pincer movement of forefinger and thumb; releases object to other person on request or gesture
Language:	Says a few words besides "mama," "dada"
Social:	Plays simple ball game; makes postural adjustment to dressing

*Data are derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others.
Data from Knobloch H, Stevens F, Malone AF: Manual of developmental diagnosis, *Hagerstown, MD, 1980, Harper & Row.*

Table 10-3 Time of Appearance in X-Rays of Centers of Ossification in Infancy and Childhood

BOYS—AGE AT APPEARANCE*	BONES AND EPIPHYSEAL CENTERS	GIRLS—AGE AT APPEARANCE*
HUMERUS, HEAD		
3 wk		3 wk
CARPAL BONES		
2 mo ± 2 mo	Capitate	2 mo ± 2 mo
3 mo ± 2 mo	Hamate	2 mo ± 2 mo
30 mo ± 16 mo	Triangular†	21 mo ± 14 mo
42 mo ± 19 mo	Lunate†	34 mo ± 13 mo
67 mo ± 19 mo	Trapezium†	47 mo ± 14 mo
69 mo ± 15 mo	Trapezoid†	49 mo ± 12 mo
66 mo ± 15 mo	Scaphoid†	51 mo ± 12 mo
No standards available	Pisiform†	No standards available
METACARPAL BONES		
18 mo ± 5 mo	II	12 mo ± 3 mo
20 mo ± 5 mo	III	13 mo ± 3 mo
23 mo ± 6 mo	IV	15 mo ± 4 mo
26 mo ± 7 mo	V	16 mo ± 5 mo
32 mo ± 9 mo	I	18 mo ± 5 mo
FINGERS (EPIPHYSES)		
16 mo ± 4 mo	Proximal phalanx, 3rd finger	10 mo ± 3 mo
16 mo ± 4 mo	Proximal phalanx, 2nd finger	11 mo ± 3 mo
17 mo ± 5 mo	Proximal phalanx, 4th finger	11 mo ± 3 mo
19 mo ± 7 mo	Distal phalanx, 1st finger	12 mo ± 4 mo
21 mo ± 5 mo	Proximal phalanx, 5th finger	14 mo ± 4 mo
24 mo ± 6 mo	Middle phalanx, 3rd finger	15 mo ± 5 mo
24 mo ± 6 mo	Middle phalanx, 4th finger	15 mo ± 5 mo
26 mo ± 6 mo	Middle phalanx, 2nd finger	16 mo ± 5 mo
28 mo ± 6 mo	Distal phalanx, 3rd finger	18 mo ± 4 mo
28 mo ± 6 mo	Distal phalanx, 4th finger	18 mo ± 5 mo
32 mo ± 7 mo	Proximal phalanx, 1st finger	20 mo ± 5 mo
37 mo ± 9 mo	Distal phalanx, 5th finger	23 mo ± 6 mo
37 mo ± 8 mo	Distal phalanx, 2nd finger	23 mo ± 6 mo
39 mo ± 10 mo	Middle phalanx, 5th finger	22 mo ± 7 mo
152 mo ± 18 mo	Sesamoid (adductor pollicis)	121 mo ± 13 mo
HIP AND KNEE		
Usually present at birth	Femur, distal	Usually present at birth
Usually present at birth	Tibia, proximal	Usually present at birth
4 mo ± 2 mo	Femur, head	4 mo ± 2 mo
46 mo ± 11 mo	Patella	29 mo ± 7 mo
FOOT AND ANKLE‡		

Values represent mean ± standard deviation, when applicable.
*To nearest month.
†Except for the capitate and hamate bones, the variability of carpal centers is too great to make them very useful clinically.
‡Standards for the foot are available, but normal variation is wide, including some familial variants, so this area is of little clinical use.
The norms present a composite of published data from the Fels Research Institute, Yellow Springs, OH (Pyle SI, Sontag L: AJR Am J Roentgenol 49:102, 1943), and unpublished data from the Brush Foundation, Case Western Reserve University, Cleveland, OH, and the Harvard School of Public Health, Boston, MA. Compiled by Lieb, Buehl, and Pyle.

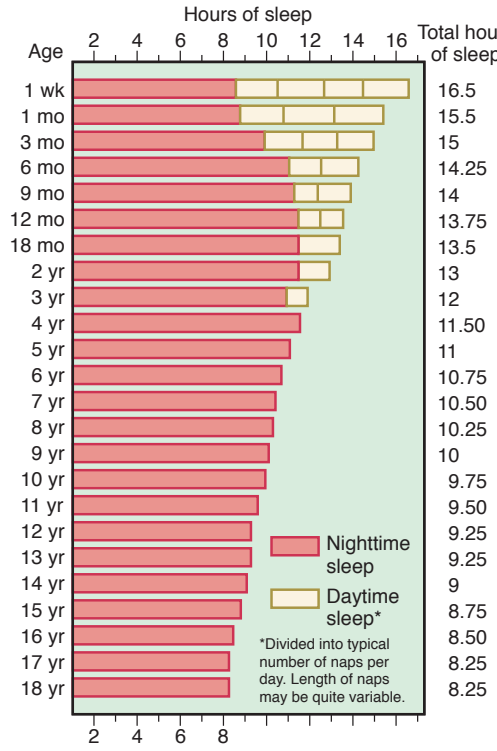


Figure 10-2 Typical sleep requirements in children. *(From Ferber R: Solve your child's sleep problems, New York, 1985, Simon & Schuster.)*

Table 15-1 Growth and Caloric Requirements

AGE	APPROXIMATE DAILY WEIGHT GAIN (g)	APPROXIMATE MONTHLY WEIGHT GAIN	GROWTH IN LENGTH (cm/mo)	GROWTH IN HEAD CIRCUMFERENCE (cm/mo)	RECOMMENDED DAILY ALLOWANCE (kcal/kg/day)
0-3 mo	30	2 lb	3.5	2.00	115
3-6 mo	20	1.25 lb	2.0	1.00	110
6-9 mo	15	1 lb	1.5	0.50	100
9-12 mo	12	13 oz	1.2	0.50	100
1-3 yr	8	8 oz	1.0	0.25	100
4-6 yr	6	6 oz	3 cm/yr	1 cm/yr	90-100

Adapted from National Research Council, Food and Nutrition Board: Recommended daily allowances, *Washington, DC, 1989, National Academy of Sciences; Frank D, Silva M, Needlman R: Failure to thrive: myth and method,* Contemp Pediatr *10:114, 1993.*

Table 15-3 Chronology of Human Dentition of Primary or Deciduous and Secondary or Permanent Teeth

	Calcification		Age at Eruption		Age at Shedding	
	BEGINS AT	COMPLETE AT	MAXILLARY	MANDIBULAR	MAXILLARY	MANDIBULAR
PRIMARY TEETH						
Central incisors	5th fetal mo	18-24 mo	6-8 mo	5-7 mo	7-8 yr	6-7 yr
Lateral incisors	5th fetal mo	18-24 mo	8-11 mo	7-10 mo	8-9 yr	7-8 yr
Cuspids (canines)	6th fetal mo	30-36 mo	16-20 mo	16-20 mo	11-12 yr	9-11 yr
First molars	5th fetal mo	24-30 mo	10-16 mo	10-16 mo	10-12 yr	10-12 yr
Second molars	6th fetal mo	36 mo	20-30 mo	20-30 mo	10-12 yr	11-13 yr
SECONDARY TEETH						
Central incisors	3-4 mo	9-10 yr	7-8 yr	6-7 yr		
Lateral incisors	Max, 10-12 mo Mand, 3-4 mo	10-11 yr	8-9 yr	7-8 yr		
Cuspids (canines)	4-5 mo	12-15 yr	11-12 yr	9-11 yr		
First premolars (bicuspids)	18-21 mo	12-13 yr	10-11 yr	10-12 yr		
Second premolars (bicuspids)	24-30 mo	12-14 yr	10-12 yr	11-13 yr		
First molars	Birth	9-10 yr	6-7 yr	6-7 yr		
Second molars	30-36 mo	14-16 yr	12-13 yr	12-13 yr		
Third molars	Max, 7-9 yr Mand, 8-10 yr	18-25 yr	17-22 yr	17-22 yr		

Mand, Mandibular; Max, maxillary.

Adapted from a chart prepared by P.K. Losch, Harvard School of Dental Medicine, who provided the data for this table.

Table 16-3 Red Flags in Developmental Screening and Surveillance

These indicators suggest that development is seriously disordered and that the child should be promptly referred to a developmental or community pediatrician.
Note: Most children do not have "red flags" and thus require quality screening to detect any problems.

POSITIVE INDICATORS (THE PRESENCE OF ANY OF THE FOLLOWING)
Loss of developmental skills at any age
Parental or professional concerns about vision, fixing, or following an object or a confirmed visual impairment at any age (simultaneous referral to pediatric ophthalmology)
Hearing loss at any age (simultaneous referral for expert audiologic or ear, nose, and throat assessment)
Persistently low muscle tone or floppiness
No speech by 18 mo, especially if the child does not try to communicate by other means such as gestures (simultaneous referral for urgent hearing test)
Asymmetry of movements or other features suggestive of cerebral palsy, such as increased muscle tone
Persistent toe walking
Complex disabilities
Head circumference above the 99.6th centile or below 0.4th centile. Also, if circumference has crossed 2 centiles (up or down) on the appropriate chart or is disproportionate to parental head circumference
An assessing clinician who is uncertain about any aspect of assessment but thinks that development may be disordered

NEGATIVE INDICATORS (ACTIVITIES THAT THE CHILD CANNOT DO)
Sit unsupported by 12 mo
Walk by 18 mo (boys) or 2 yr (girls) (check creatine kinase urgently)
Walk other than on tiptoes
Run by 2.5 yr
Hold object placed in hand by 5 mo (corrected for gestation)
Reach for objects by 6 mo (corrected for gestation)
Point at objects to share interest with others by 2 yr

From Bellman M, Byrne O, Sege R: Developmental assessment of children. BMJ *346:31–36, 2013.*

Table 16-4 Resources for Developmental–Behavioral Screening/Surveillance in Primary Care

DEVELOPMENTAL–BEHAVIORAL PROMOTION AND PARENT TRAINING
Kids' Health
From the Nemours Foundation, this site has a well-visit guide for each age, anticipatory guidance information, and an easily searchable database for handouts (in English and Spanish) on health and safety, emotional and social development and positive parenting for babies through adolescence.
Reach Out and Read
Offers parenting handouts on how to share books, literacy milestones, and guidance for professionals. Tabs within the site include: Parents and Educators Home, Importance of Reading Aloud, Literacy Milestones, Reading Tips, Books for Children, and Books for Parents.
American Academy of Pediatrics (Information for Families)
The AAP has numerous handouts that can be downloaded for free and available in multiple languages. Provides information on a variety of topics including health conditions, safety and prevention, mental health issues from birth through adolescence.
American Academy of Child and Adolescent Psychiatry
AACAP was one of the first professional organizations to develop handouts for families. These are freely downloadable and cover a wide range of topics as divorce, sleep problems, specific mental health diagnoses, help for military families, and how and where to find a psychiatrist. Handouts are written in many different languages including Spanish, Malaysian, Urdu, Arabic, Icelandic, Polish, and Hebrew. Other site research reviews for professionals, video clips, and links to other resources.

REFERRAL LINKS
American Academy of Pediatrics: Find a Pediatrician
Helps locate developmental–behavioral, neurodevelopmental, general and other subspecialty pediatricians.
Individuals with Disabilities Education Act
Provides links to state, regional and local early intervention programs under the Individuals with Disabilities Education Act, and testing services for young children with suspected or known to have disabilities go to
Early Head Start and Head Start
Provides links to local programs including services for migrant workers, tribal councils, etc.

INTERVENTION SERVICES FOR OLDER CHILDREN
To refer children 3 yr of age and older for evaluations, contact the school district's department of psychology or special education.
For after school/tutoring programs, check with the child's school of zone, and see the websites of the **Boys and Girls Club** and the **YWCA.**

TRAINING AND IMPLEMENTATION PLANNING
Medical Home Initiative
From the AAP and focused on coordinated care for children with special healthcare needs, the site has training materials, rating scales, an e-mail announcement list for providers, how-to information, etc. Medical Home also sponsors several conferences each year.
Harvard University
Includes a helpful video showing providers who, although reluctant to try quality screening, found use of tools far more sensitive and less than time-consuming. The site also provides a helpful implementation guide.
PEDStest.org
Includes downloadable implementation planning forms, workflow charts, two-way consent forms, longitudinal problem checklists, age-specific encounter forms, training guides, slide shows, freely downloadable risk and resilience measures, mental health and academic screens for older children, videos offering a rationale for screening, information about tools, guidance on billing and coding, and links to parenting resources in multiple languages.

Table 17-1 Conditions That Do and Do Not Require Exclusion from Group Childcare Settings

CONDITIONS THAT REQUIRE EXCLUSION	COMMENTS
If any of these 3 key criteria for exclusion of children who are ill are met, the child should be temporarily excluded, regardless of the type of illness:	
Illness preventing the child from participating comfortably in activities as determined by the childcare provider	Providers should specify in their policies, approved by the facilities' healthcare consultant, what severity level of illness the facility can manage, and how much and what types of illness will be addressed: • Severity level 1 consists of children whose health condition is accompanied by high interest and complete involvement in activity associated with an absence of symptoms of illness (such as children recovering from pinkeye, rash, or chickenpox), but who need further recuperation time • Severity level 2 encompasses children whose health condition is accompanied by a medium activity level because of symptoms (such as children with low-grade fever, children at the beginning of an illness, and children in the early recovery period of an illness) • Severity level 3 is composed of children whose health condition is accompanied by a low activity level because of symptoms that preclude much involvement
Illness resulting in a greater need for care than the childcare staff can provide without compromising the health and safety of the other children as determined by the childcare provider	
Illness that poses a risk of spread of harmful diseases to others	
In addition to the above key criteria, temporary exclusion is recommended when the child has any of the following conditions:	
Fever (temperature above 38°C [101°F] orally, above 38.9°C [102°F] rectally, or above 37.8°C [100°F] or higher taken axillary [armpit] or measured by an equivalent method) and behavior change or other signs and symptoms (e.g., sore throat, rash, vomiting, diarrhea)	Accompanied by behavior changes or other signs or symptoms of illness until medical professional evaluation finds the child able to be included at the facility
Acute change in behavior including lethargy/lack of responsiveness, inexplicable irritability or persistent crying, difficult breathing, or having a quickly spreading rash	Until evaluation by a medical professional finds the child able to be included at the facility
Diarrhea (defined by watery stools or decreased form of stool that is not associated with changes of diet). Exclusion is required for all diapered children whose stool is not contained in the diaper and toilet-trained children if the diarrhea is causing soiled pants or clothing	Readmission after diarrhea can occur when diapered children have their stool contained by the diaper (even if the stools remain loose) and when toilet-trained children are continent. Special circumstances that require specific exclusion criteria include the following: • Toxin-producing *Escherichia coli* or *Shigella* infection, until stools are formed and test results of 2 stool cultures obtained from stools produced 24-hr apart do not detect these organisms • *Salmonella* serotype Typhi infection, until diarrhea resolves and, in children younger than age 5 yr, 3 negative stool cultures obtained with 24-hr-intervals are obtained
Blood or mucus in stool	Not explained by dietary change, medication, or hard stools
Vomiting illness	More than 2 times in the previous 24 hr, unless the vomiting is determined to be caused by a noninfectious condition and the child remains adequately hydrated
Abdominal pain	Persistent (continues more than 2 hr) or intermittent associated with fever or other signs or symptoms
Mouth sores with drooling	Unless the child's primary care provider or local health department authority states that the child is noninfectious
Rash with fever or behavior changes	Until the primary care provider has determined that the illness is not an infectious disease
Active tuberculosis	Until the child's primary care provider or local health department states child is on appropriate treatment and can return
Impetigo	Until treatment has been started
Streptococcal pharyngitis (i.e., strep throat or other streptococcal infection)	Until 24 hr after treatment has been started
Purulent conjunctivitis	Defined as pink or red conjunctiva with white or yellow eye discharge, until after treatment has been initiated
Pediculosis (head lice)	Until after the first treatment *Note:* Exclusion is not necessary before the end of the program day
Scabies	Until after treatment has been given

Continued

Table 17-1 Conditions That Do and Do Not Require Exclusion from Group Childcare Settings—cont'd

CONDITIONS THAT REQUIRE EXCLUSION	COMMENTS
Varicella-zoster (chickenpox)	Until all lesions have dried or crusted (usually 6 days after onset of rash)
Rubella	Until 6 days after onset of rash
Pertussis	Until 5 days of appropriate antibiotic treatment
Mumps	Until 5 days after onset of parotid gland swelling
Measles	Until 4 days after onset of rash
Hepatitis A virus	Until 1 wk after onset of illness or jaundice if the child's symptoms are mild or as directed by the health department
Any child determined by the local health department to be contributing to the transmission of illness during an outbreak	
CONDITIONS THAT DO NOT REQUIRE EXCLUSION	**COMMENTS**
Common colds, runny noses	Regardless of color or consistency of nasal discharge
A cough not associated with an infectious disease or a fever	
Watery, yellow or white discharge or crusting eye discharge without fever, eye pain, or eyelid redness	
Presence of bacteria or viruses in urine or feces in the absence of illness symptoms, like diarrhea	Exceptions include children infected with highly contagious organisms capable of causing serious illness
Pink eye (bacterial conjunctivitis) indicated by pink or red eyelids after sleep	If 2 unrelated children in the same program have conjunctivitis, the organism causing the conjunctivitis may have a higher risk for transmission and a child healthcare professional should be consulted.
Fever without any signs or symptoms of illness in children who are older than 6 mo regardless of whether acetaminophen or ibuprofen was given	If the child is behaving normally but has a fever of below 38.9°C (102°F) rectally or the equivalent, the child should be monitored, but does not need to be excluded for fever alone
Rash without fever and without behavioral changes	
Lice or nits	Exclusion for treatment of an active lice infestation may be delayed until the end of the day
Ringworm	Exclusion for treatment may be delayed until the end of the day
Molluscum contagiosum	Do not require exclusion or covering of lesions
Thrush (i.e., white spots or patches in the mouth or on the cheeks or gums)	
Fifth disease	Once the rash has appeared
Methicillin-resistant *Staphylococcus aureus* (MRSA) without an infection or illness that would otherwise require exclusion	Known MRSA carriers or colonized individuals should not be excluded
Cytomegalovirus infection	
Chronic hepatitis B infection	
HIV infection	
Asymptomatic children who have been previously evaluated and found to be shedding potentially infectious organisms in the stool	Children who are continent of stool or who are diapered with formed stools that can be contained in the diaper may return to care
Children with chronic infections conditions that can be accommodated in the program according to the legal requirement of federal law in the Americans with Disabilities Act	The act requires that childcare programs make reasonable accommodations for children with disabilities and/or chronic illnesses, considering each child individually

Adapted from American Academy of Pediatrics, American Public Health Association, National Resource Center for Health and Safety in Child Care and Early Education: Stepping stones to caring for our children: national health and safety performance standards: guidelines for early care and education programs, third edition, *Elk Grove Village, IL, 2013, Authors, pp 46–52, available at:* http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/

Table 19-1 Normal Developmental Changes in Children's Sleep

AGE CATEGORY	SLEEP DURATION AND SLEEP PATTERNS	ADDITIONAL SLEEP ISSUES	SLEEP DISORDERS
Newborn (0-2 mo)	Total sleep: 10-19 hr per 24 hr (average = 13-14.5 hr), may be higher in premature babies Bottlefed babies generally sleep for longer periods (2-5 hr bouts) than breastfed babies (1-3 hr) Sleep periods are separated by 1-2 hr awake No established nocturnal–diurnal pattern in the 1st few wk; sleep is evenly distributed throughout the day and night, averaging 8.5 hr at night and 5.75 hr during the day	The American Academy of Pediatrics issued a formal recommendation in 2005 advocating against bed sharing in the 1st yr of life, instead encouraging proximate but separate sleeping surfaces for mother and infant. Safe sleep practices for infants: • Place the baby on his or her back to sleep at night and during nap times • Place the baby on a firm mattress with a well-fitting sheet in a safety-approved crib • Do not use pillows or comforters • Cribs should not have corner posts over 1/16 in high or decorative cutouts • Make sure the baby's face and head stay uncovered and clear of blankets and other coverings during sleep	Most sleep issues that are perceived as problematic at this stage represent a discrepancy between parental expectations and developmentally appropriate sleep behaviors Newborns who are noted by parents to be extremely fussy and persistently difficult to console are more likely to have underlying medical issues, such as colic, gastroesophageal reflux, and formula intolerance
Infant (2-12 mo)	Total sleep: average is 12-13 hr (note that there is great individual variability in sleep times during infancy) Nighttime: average is 9-10 hr Naps: average is 3-4 hr	Sleep regulation or self-soothing involves the infant's ability to negotiate the sleep–wake transition, both at sleep onset and following normal awakenings throughout the night. The capacity to self-soothe begins to develop in the 1st 12 wk of life, and is a reflection of both neurodevelopmental maturation and learning Sleep consolidation, or "sleeping through the night," is usually defined by parents as a continuous sleep episode without the need for parental intervention (e.g., feeding, soothing) from the child's bedtime through the early morning. Infants develop the ability to consolidate sleep between 6 wk and 3 mo	Behavioral insomnia of childhood; sleep onset association type Sleep-related rhythmic movements (head banging, body rocking)
Toddler (1-3 yr)	Total sleep: average is 11-13 hr Nighttime: average is 9.5-10.5 hr Naps: average is 2-3 hr; decrease from 2 naps to 1 at average age of 18 mo	Cognitive, motor, social, language developmental issues impact on sleep Nighttime fears develop; transitional objects, bedtime routines important	Behavioral insomnia of childhood, sleep onset association type Behavioral insomnia of childhood, limit setting type
Preschool (3-5 yr)	Nighttime: average is 9-10 hr Naps decrease from 1 nap to no nap Overall, 26% of 4 yr olds and just 15% of 5 yr olds nap	Persistent cosleeping tends to be highly associated with sleep problems in this age group Sleep problems may become chronic	Behavioral insomnia of childhood, limit setting type Sleepwalking Sleep terrors Nighttime fears/nightmares Obstructive sleep apnea
Middle childhood (6-12 hr)	9-11 hr	School and behavior problems may be related to sleep problems Media and electronics, such as television, computer, video games, and the Internet increasingly compete for sleep time Irregularity of sleep–wake schedules reflects increasing discrepancy between school and non–school night bedtimes and wake times	Nightmares Obstructive sleep apnea Insufficient sleep
Adolescence (>12 yr)	Average sleep duration 7-7.5 hr; only 20% of adolescents overall get the recommended 9-9.25 hr of sleep Later bedtimes; increased discrepancy sleep patterns weekdays/weekends	Puberty-mediated phase delay (later sleep onset and wake times), relative to sleep-wake cycles in middle childhood Earlier required wake times Environmental competing priorities for sleep	Insufficient sleep Delayed sleep phase disorder Narcolepsy Restless legs syndrome/periodic limb movement disorder

Table 19-3 Basic Principles of Healthy Sleep for Adolescents

1. **Wake up and go to bed at about the same time** every night. Bedtime and wake-up time should not differ from school to non–school nights by more than approximately 1 hr.
2. **Avoid sleeping in on weekends** to "catch up" on sleep. This makes it more likely that you will have problems falling asleep.
3. If you take **naps**, they should be **short** (no more than 1 hr) and **scheduled in the early to midafternoon**. However, if you have a problem with falling asleep at night, **napping** during the day may make it worse and should be avoided.
4. **Spend time outside** every day. Exposure to sunlight helps to keep your body's internal clock on track.
5. **Exercise regularly.** Exercise may help you fall asleep and sleep more deeply.
6. **Use your bed for sleeping only.** Don't study, read, listen to music, watch television, etc., on your bed.
7. Make the 30-60 minutes before a **quiet or wind-down time**. Relaxing, calm, enjoyable activities, such as reading a book or listening to calm music, help your body and mind slow down enough to let you get to sleep. Don't study, watch exciting/scary movies, exercise, or get involved in "energizing" activities just before bed.
8. Eat regular meals and **don't go to bed hungry**. A light snack before bed is a good idea; eating a full meal in the hour before bed is not.
9. **Avoid** eating or drinking products containing **caffeine** from dinner time on. These include caffeinated sodas, coffee, tea, and chocolate.
10. **Do not use alcohol.** Alcohol disrupts sleep and may cause you to awaken throughout the night.
11. **Smoking disturbs sleep.** Don't smoke at least 1 hr before bed (and preferably, not at all!).
12. Don't use **sleeping pills, melatonin**, or other **nonprescription sleep aids** to help you sleep unless specifically recommended by your doctor. These can be dangerous, and the sleep problems often return when you stop taking the medicine.

Table 19-4 Anatomic Factors That Predispose to Obstructive Sleep Apnea and Hypoventilation in Children

NOSE
Anterior nasal stenosis
Choanal stenosis/atresia
Deviated nasal septum
Seasonal or perennial rhinitis
Nasal polyps, foreign body, hematoma, mass lesion
NASOPHARYNGEAL AND OROPHARYNGEAL
Adenotonsillar hypertrophy
Macroglossia
Cystic hygroma
Velopharyngeal flap repair
Cleft palate repair
Pharyngeal mass lesion
CRANIOFACIAL
Micrognathia/retrognathia
Midface hypoplasia (e.g., trisomy 21, Crouzon, Apert syndrome)
Mandibular hypoplasia (Pierre Robin sequence, Treacher Collins, Cornelia de Lange)
Craniofacial trauma
Skeletal and storage diseases
Achondroplasia
Storage diseases (e.g., glycogen, Hunter, Hurler syndrome)

Table 19-5 American Academy of Pediatrics Clinical Practice Guideline: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome (September 2012)

Key Action Statement 1: Screening for OSAS As part of routine health maintenance visits, clinicians should inquire whether the child or adolescent snores. If the answer is affirmative or if a child or adolescent presents with signs or symptoms of OSAS, clinicians should perform a more focused evaluation. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 2A: Polysomnography If a child or adolescent snores on a regular basis and has any of the complaints or findings of OSAS, clinicians should either (1) obtain a polysomnogram (Evidence Quality A; Key Action strength: Recommendation) *or* (2) refer the patient to a sleep specialist or otolaryngologist for a more extensive evaluation (Evidence quality D; Key Action strength: Option). (Evidence Quality: Grade A for polysomnography, Grade D for specialist referral; Recommendation Strength: Recommendation.)
Key Action Statement 2B: Alternative Testing If polysomnography is not available, then clinicians may order alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap polysomnography, or ambulatory polysomnography. (Evidence Quality: Grade C; Recommendation Strength: Option.)
Key Action Statement 3: Adenotonsillectomy If a child is determined to have OSAS, has a clinical examination consistent with adenotonsillar hypertrophy, and does not have a contraindication to surgery, the clinician should recommend adenotonsillectomy as the first line of treatment. If the child has OSAS but does not have adenotonsillar hypertrophy, other treatment should be considered (see Key Action Statement 6). Clinical judgment is required to determine the benefits of adenotonsillectomy compared with other treatments in obese children with varying degrees of adenotonsillar hypertrophy. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 4: High-Risk Patients Undergoing Adenotonsillectomy Clinicians should monitor high-risk patients undergoing adenotonsillectomy as inpatients postoperatively. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 5: Reevaluation Clinicians should clinically reassess all patients with OSAS for persisting signs and symptoms after therapy to determine whether further treatment is required. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 5B: Reevaluation of High-Risk Patients Clinicians should reevaluate high-risk patients for persistent OSAS after adenotonsillectomy, including those who had a significantly abnormal baseline polysomnogram, have sequelae of OSAS, are obese, or remain symptomatic after treatment, with an objective test (see Key Action Statement 2) or refer such patients to a sleep specialist. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 6: CPAP Clinicians should refer patients for CPAP management if symptoms/signs or objective evidence of OSAS persists after adenotonsillectomy or if adenotonsillectomy is not performed. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 7: Weight Loss Clinicians should recommend weight loss in addition to other therapy if a child/adolescent with OSAS is overweight or obese. (Evidence Quality: Grade C; Recommendation Strength: Recommendation.)
Key Action Statement 8: Intranasal Corticosteroids Clinicians may prescribe topical intranasal corticosteroids for children with mild OSAS in whom adenotonsillectomy is contraindicated or for children with mild postoperative OSAS. (Evidence Quality: Grade B; Recommendation Strength: Option.)

Adapted from Marcus CL, Brooks LJ, Draper KA, et al: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 130:576-584, 2012.

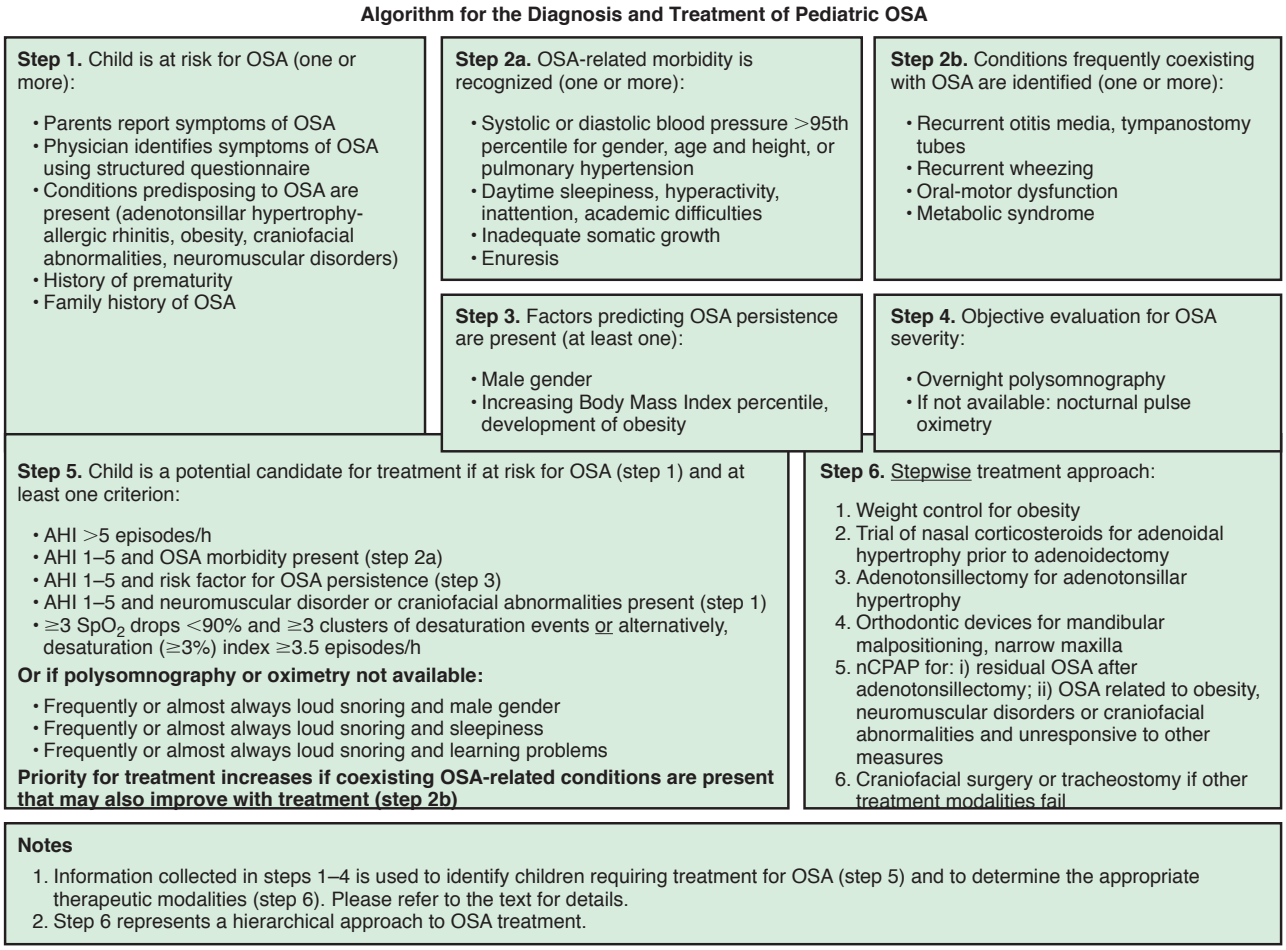


Figure 19-1 Algorithm for the diagnosis and treatment of pediatric OSA. *(From Kaditis A, Kheirandish-Gozal L, Gozal D: Algorithm for the diagnosis and treatment of pediatric OSA: a proposal of two pediatric sleep centers,* Sleep Med *13(3):217–227, 2012, Figure 1.)*

Table 21-3 Medications for ADHD Symptoms

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE RANGE
STIMULANTS				
Long Acting				
Methylphenidate (Concerta)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	6-12: 18-54 mg >12: 18-72 mg	6-12: 54 mg >12: 72 mg
Dexmethylphenidate (Focalin XR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	Child: 5-30 mg	Child: 30 mg
Amphetamine combination (Adderall XR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	6-12: 5-10 mg >12: 10-20 mg	6-12: 30 mg >12: 40 mg
Dextroamphetamine (Dexedrine Spansule)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	5-40 mg	40 mg
Intermediate Acting				
Methylphenidate (Metadate CD, Metadate ER, Ritalin LA, Ritalin SR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	10-60 mg	60 mg
Short Acting				
Dexmethylphenidate (Focalin)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	2.5-20 mg	20 mg
Methylphenidate (Ritalin, Methylin)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	5-30 mg	60 mg
Amphetamine combination (Adderall)	ADHD (3 and up)	Inattention Hyperactivity Impulsivity	3-5: 2.5-40 mg >6: 5-40 mg	40 mg
Dextroamphetamine (Dexedrine)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	2.5-40 mg	40 mg
SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR				
Atomoxetine (Strattera)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	<70 kg: 0.5-1.2 mg/kg >70 kg: 40-80 mg	<70 kg: 1.4 mg/kg >70 kg: 100 mg
α-AGONISTS				
Clonidine (Catapres)	Not approved for ADHD in children & adolescents	Inattention Hyperactivity Impulsivity	27-40.5 kg: 0.05-0.2 mg 40.5-45 kg: 0.05-0.3 mg >45 kg: 0.05-0.4 mg	27-40.5 kg: 0.2 mg 40.5-45 kg: 0.3 mg >45 kg: 0.4 mg
Clonidine (Kapvay)	ADHD (6-17)	Inattention Hyperactivity Impulsivity	0.1-0.4 mg/day	0.4 mg
Guanfacine (Tenex)	Not approved for ADHD in children & adolescents	Inattention Hyperactivity Impulsivity	27-40.5 kg: 0.5-2 mg 40.5-45 kg: 0.5-3 mg >45 kg: 0.5-4 mg	27-40.5 kg: 2 mg 40.5-45 kg: 3 mg >45 kg: 4 mg
Guanfacine (Intuniv)	ADHD (6-17)	Inattention Hyperactivity Impulsivity	1-4 mg	4 mg

ADHD, attention-deficit/hyperactivity disorder.

Table 21-4 Medications for Depression and Anxiety Symptoms

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
SELECTIVE SEROTONIN REUPTAKE INHIBITORS				
Citalopram (Celexa)	Not approved for anxiety & depression in children & adolescents	Depression Anxiety Obsessions/compulsions	20-40 mg	40 mg
Escitalopram (Lexapro)	Depression (12-17)	Depression Anxiety Obsessions/compulsions	10-20 mg	20 mg
Fluoxetine (Prozac)	Depression (8-17) OCD (7-17)	Depression Anxiety Obsessions/compulsions	10-60 mg	60 mg
Sertraline (Zoloft)	OCD (6-17)	Depression Anxiety Obsessions/compulsions	25-200 mg	200 mg
TRICYCLIC ANTIDEPRESSANTS				
Clomipramine (Anafranil)	OCD (10-17)	Obsessions/compulsions	25-100 mg	Lesser of 200 mg or 3 mg/kg
ATYPICAL ANTIDEPRESSANTS				
Bupropion (Wellbutrin XL)	Not approved for depression in children & adolescents	Depression	150-300 mg	450 mg
Venlafaxine (Effexor XR)	Not approved for anxiety & depression in children & adolescents	Depression Anxiety	75-225 mg	225 mg
ANXIOLYTIC AGENTS				
Lorazepam (Ativan)	Not approved for anxiety	Anxiety	0.5-6 mg	10 mg
Clonazepam (Klonopin)	Not approved for panic in children & adolescents	Panic	0.5-1 mg	4 mg
Buspirone (BuSpar)	Not approved for anxiety & depression in children & adolescents	Anxiety	15-30 mg	60 mg
Hydroxyzine (Atarax, Vistaril)	Anxiety	Anxiety	50 mg >6: 50-100 mg	<6: 2 mg/kg 50 mg >6: 100 mg

ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder.

Table 21-6 Medications for Mania

	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
MOOD STABILIZERS				
Lithium carbonate (Eskalith, Eskalith CR, Lithobid)	Bipolar disorder (12-17)	Mania Depression	<22 kg: 600 mg 22-41 kg: 900 mg >41 kg: 1200 mg	1800 mg
Divalproex (Depakote, Depakote ER)	Not approved for mania in children & adolescents	Mania	Teen: 10-60 mg/kg *(Blood valproic acid level 50-100 μg/mL)*	60 mg/kg
ATYPICAL ANTIPSYCHOTICS				
Aripiprazole (Abilify)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (6-17)	Irritability Psychosis Mania Aggression Agitation	2-30 mg	30 mg Autism: 15 mg
Risperidone (Risperdal)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (5-17)	Psychosis Mania Aggression Agitation Irritability	0.5-6 mg Autism: 15-20 kg: 0.25 mg-0.5 mg >20 kg: 0.5-1 mg	Bipolar & Schizophrenia: 6 mg Autism: 3 mg

Table 21-5 Medications for Psychosis and Agitation

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
ATYPICAL ANTIPSYCHOTICS				
Aripiprazole (Abilify)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (6-17)	Psychosis Mania Irritability Aggression Agitation	2-30 mg qd	30 mg Autism: 15 mg
Olanzapine (Zyprexa)	Bipolar disorder (13-17) Schizophrenia (13-17)	Psychosis Mania Agitation	2.5-10 mg qd	20 mg
Quetiapine (Seroquel)	Bipolar disorder (10-17) Schizophrenia (13-17)	Psychosis Mania Agitation	Bipolar: 400-600 mg Schizophrenia: 400-800 mg	Bipolar: 600 mg Schizophrenia: 800 mg
Risperidone (Risperdal)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (5-17)	Psychosis Mania Aggression Agitation Irritability	0.5-6 mg Autism: 15-20 kg: 0.25 mg-0.5 mg >20 kg: 0.5-1 mg	Bipolar & Schizophrenia: 6 mg Autism: 3 mg
Ziprasidone (Geodon)	Not approved for psychosis, mania, aggression, or agitation in children & adolescents	Psychosis Mania Agitation	40-160 mg	200 mg
TYPICAL ANTIPSYCHOTICS				
Haloperidol (Haldol)	Psychosis (3-17) Tourette (3-17) Severe behavioral disorders (3-17) Agitation (3-17)	Psychosis Mania Aggression Agitation	3-12: 0.05-0.15 mg/kg >12: 0.5-5 mg Agitation: 3-12: 0.01-0.03 mg/kg >12: 0.5-10 mg	3-12: 0.15 mg/kg/day >12: maximum 100 mg for severe refractory cases

Table 22-4 DSM-5 Diagnostic Criteria for Factitious Disorders

Factitious Disorder Imposed on Self

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.
B. The individual presents himself or herself to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Factitious Disorder Imposed on Another (Previously Factitious Disorder by Proxy)

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, in another, associated with identified deception.
B. The individual presents another individual (victim) to others as ill, impaired or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Note: The perpetrator, not the victim, receives this diagnosis

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 324.

Table 22-1 DSM-5 Diagnostic Criteria for Conversion Disorder or Functional Neurologic Symptom Disorder

A. One or more symptoms or deficits affecting voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurologic or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify symptom type: weakness or paralysis, abnormal movements, swallowing symptoms, speech symptom, attacks/seizures, or anesthesia/sensory loss, special sensory symptom (visual, olfactory, or hearing), or mixed symptoms.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 318.

Table 22-2 DSM-5 Diagnostic Criteria for Somatic Symptom Disorder

A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.
B. Excessive thoughts, feelings or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
   1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
   2. Persistent high level of anxiety about health and symptoms.
   3. Excessive time and energy devoted to these symptoms or health concerns.
C. Although any 1 somatic symptom may not be continuously present, the state of being symptomatic is persistent.

Specify if:

With predominant pain (previously known as pain disorder in DSM IV-TR): for individuals whose somatic symptoms predominantly involve pain.

Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 mo).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 311.

Table 22-5 DSM-5 Diagnostic Criteria for Other Specified/Unspecified Somatic Symptom and Related Disorders

Other Specified
This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet full criteria for any of the disorders in the somatic symptom and related disorders diagnostic class.
Examples of presentations that can be specified using the "other specified" designation include the following:
1. Brief somatic symptom disorder: Duration of symptoms is <6 mo.
2. Brief illness anxiety disorder: Duration of symptoms is <6 mo.
3. Illness anxiety disorder without excessive health-related behaviors: Criterion D for illness anxiety disorder is not met.
4. Pseudocyesis: A false belief of being pregnant that is associated with objective signs and reported symptoms of pregnancy.

Unspecified
This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in functioning predominate but do not meet criteria for any of the other disorders in the somatic symptom and related disorders diagnostic class.

Table 22-3 DSM-5 Diagnostic Criterial for Psychological Factors Affecting Other Medical Conditions

A. A medical symptom or condition (other than a mental disorder) is present.
B. Psychological or behavioral factors adversely affect the medical condition in 1 of the following ways:
   1. The factors have influenced the course of the medical condition as shown by a close temporal association between the psychological factors and the development or exacerbation of, or delayed recovery from, the medical condition.
   2. The factors interfere with the treatment of the medical condition (e.g., poor adherence).
   3. The factors constitute additional well-established health risks for the individual.
   4. The factors influence the underlying pathophysiology, precipitating or exacerbating symptoms or necessitating medical attention.
C. The psychological and behavioral factors in Criterion B are not better explained by another mental disorder (e.g., panic disorder, major depressive disorder, posttraumatic stress disorder).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 322.

Table 24-1 DSM-5 Diagnostic Criteria for Tic Disorders

Note: A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization.

TOURETTE'S DISORDER
A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).

PERSISTENT (CHRONIC) MOTOR OR VOCAL TIC DISORDER
A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).
E. Criteria have never been met for Tourette's disorder.
Specify if:
With motor tics only
With vocal tics only

PROVISIONAL TIC DISORDER
A. Single or multiple motor and/or vocal tics.
B. The tics have been present for less than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).
E. Criteria have never been met for Tourette's disorder or persistent (chronic) motor or vocal tic disorder.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 81.

Table 24-3 Diagnostic Criteria Proposed for Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

CRITERION	DESCRIPTION
I.	Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
II.	Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least 2 of the following 7 categories (see text for full description): 1. Anxiety 2. Emotional lability and/or depression 3. Irritability, aggression and/or severely oppositional behaviors 4. Behavioral (developmental) regression 5. Deterioration in school performance 6. Sensory or motor abnormalities 7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency
III.	Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others. *Note:* The diagnostic work-up of patients suspected of PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.

Table 24-2 Repetitive Movements of Childhood

	DESCRIPTION	TYPICAL DISORDERS WHERE PRESENT
Tics	Sudden rapid, recurrent, nonrhythmic, stereotyped, vocalization or motor movement	Transient tics, Tourette disorder, persistent tic disorder
Dystonia	Involuntary, sustained, or intermittent muscle contractions that cause twisting and repetitive movements, abnormal postures, or both	DYT1 Gene, Wilson, myoclonic dystonia, extrapyramidal symptoms caused by dopamine blocking agents
Chorea	Involuntary, random, quick, jerking movements, most often of the proximal extremities, that flow from joint to joint. Movements are abrupt, nonrepetitive, and arrhythmic and have variable frequency and intensity	Sydenham chorea, Huntington chorea
Stereotypies	Stereotyped, rhythmic, repetitive movements or patterns of speech, with lack of variation over time	Autism, stereotypic movement disorder, intellectual disability
Compulsions	A repetitive, excessive, meaningless activity or mental exercise that a person performs in an attempt to avoid distress or worry	Obsessive-compulsive disorder, anorexia, body dysmorphic disorder, trichotillomania, excoriation disorder
Myoclonus	Shock-like involuntary muscle jerk that may affect a single body region, one side of the body, or the entire body; may occur as a single jerk or repetitive jerks	Hiccups, hypnic jerks, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, mitochondrial encephalopathies, metabolic disorders
Akathisia	Unpleasant sensations of "inner" restlessness, often prompting movements in an effort to reduce the sensations	Extrapyramidal adverse effects from dopamine blocking agents; anxiety
Volitional behaviors	Behavior that may be impulsive or due to boredom like tapping peers, making sounds (animal noises)	Attention-deficit/hyperactivity disorder, oppositional defiant disorder, sensory integration disorders

Adapted from Murphy TK, Lewin AB, Storch EA, et al: Practice parameter for the assessment and treatment of children and adolescents with chronic tic disorders, J Am Acad Child Adolesc Psychiatry *52(12):1341–1359, 2013.*

Table 26-1 DSM-5 Diagnostic Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   1. Depressed most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gain.
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Table 26-2 DSM-5 Diagnostic Criteria for Persistent Depressive Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 yr.

Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr.

B. Presence, while depressed, of 2 (or more) of the following:
   1. Poor appetite or overeating.
   2. Insomnia or hypersomnia.
   3. Low energy or fatigue.
   4. Low self-esteem.
   5. Poor concentration or difficulty making decisions.
   6. Feelings of hopelessness.

C. During the 2 yr period (1 yr for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 mo at a time.

D. Criteria for a major depressive disorder may be continuously present for 2 yr.

E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

G. The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: Because the criteria for a major depressive episode include 4 symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 yr but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.

Table 28-1 DSM-5 Diagnostic Criteria for Anorexia Nervosa

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Specify whether:

Restricting type (ICD-10-CM code F50.01): During the last 3 mo, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

Binge-eating/purging type (ICD-10-CM code F50.02): During the last 3 mo, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Specify if:

In partial remission: After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.

In full remission: After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based, for adults, on current body mass index (BMI) (see below) or, for children and adolescents, on BMI percentile. **The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used.** The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

Mild: BMI ≥ 17 kg/m^2
Moderate: BMI 16–16.99 kg/m^2
Severe: BMI 15–15.99 kg/m^2
Extreme: BMI < 15 kg/m^2

Table 28-2 DSM-5 Diagnostic Criteria for Bulimia Nervosa

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   1. Eating, in a discrete period of time (e.g., within any 2 hr period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
   2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.
C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specify if:

In partial remission: After full criteria for bulimia nervosa were previously met, some, but not all, of the criteria have been met for a sustained period of time.

In full remission: After full criteria for bulimia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based on the frequency of inappropriate compensatory behaviors (see below). The level of severity may be increased to reflect other symptoms and the degree of functional disability.

Mild: An average of 1-3 episodes of inappropriate compensatory behaviors per week.
Moderate: An average of 4-7 episodes of inappropriate compensatory behaviors per week.
Severe: An average of 8-13 episodes of inappropriate compensatory behaviors per week.
Extreme: An average of 14 or more episodes of inappropriate compensatory behaviors per week.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 345.

Table 28-3 DSM-5 Diagnostic Criteria for Avoidant/Restrictive Food Intake Disorder

A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:
   1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children).
   2. Significant nutritional deficiency.
   3. Dependence on enteral feeding or oral nutritional supplements.
   4. Marked interference with psychosocial functioning.
B. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.
C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.
D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

Specify if:

In remission: After full criteria for avoidant/restrictive food intake disorder were previously met, the criteria have not been met for a sustained period of time.

Table 28-4 Eating and Weight Control Habits Commonly Found in Children and Adolescents with an Eating Disorder

	Prominent Feature		Clinical Comments Regarding Eating Disorder Habits	
HABIT	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**
Overall intake	Inadequate energy (calories), although volume of food and beverages may be high because of very low caloric density of intake as a result of "diet" and nonfat choices	Variable, but calories normal to high; intake in binges often "forbidden" food or drink that differs from intake at meals	Consistent inadequate caloric intake leading to wasting of the body is an essential feature of diagnosis	Inconsistent balance of intake, exercise and vomiting, but severe caloric restriction is short-lived
Food	Counts and limits calories, especially from fat; Emphasis on "healthy food choices" with reduced caloric density Monotonous, limited "good" food choices, often leading to vegetarian or vegan diet Strong feelings of guilt after eating more than planned leads to exercise and renewed dieting	Aware of calories and fat, but less regimented in avoidance than AN Frequent dieting interspersed with overeating, often triggered by depression, isolation, or anger	Obsessive-compulsive attention to nutritional data on food labels and may have "logical" reasons for food choices in highly regimented pattern, such as sports participation or family history of lipid disorder	Choices less structured, with more frequent diets
Beverages	Water or other low- or no-calorie drinks; nonfat milk	Variable, diet soda common; may drink alcohol to excess	Fluids often restricted to avoid weight gain	Fluids ingested to aid vomiting or replace losses
Meals	Consistent schedule and structure to meal plan Reduced or eliminated caloric content, often starting with breakfast, then lunch, then dinner Volume can increase with fresh fruits, vegetables, and salads as primary food sources	Meals less regimented and planned than in AN; more likely impulsive and unregulated, often eliminated following a binge-purge episode	Rigid adherence to "rules" governing eating leads to sense of control, confidence, and mastery	Elimination of a meal following a binge-purge only reinforces the drive for binge later in the day
Snacks	Reduced or eliminated from meal plan	Often avoided in meal plans, but then impulsively eaten	Snack foods removed early because "unhealthy"	Snack "comfort foods" can trigger a binge
Dieting	Initial habit that becomes progressively restrictive, although often appearing superficially "healthy" Beliefs and "rules" about the patient's idiosyncratic nutritional requirements and response to foods are strongly held	Initial dieting gives way to chaotic eating, often interpreted by the patient as evidence of being "weak" or "lazy"	Distinguishing between healthy meal planning with reduced calories and dieting in ED may be difficult	Dieting tends to be impulsive and short-lived, with "diets" often resulting in unintended weight gain
Binge eating	None in restrictive subtype, but an essential feature in binge-purge subtype	Essential feature, often secretive Shame and guilt prominent afterward	Often "subjective" (more than planned but not large)	Relieves emotional distress, may be planned
Exercise	Characteristically obsessive-compulsive, ritualistic, and progressive May excel in dance, long-distance running	Less predictable May be athletic, or may avoid exercise entirely	May be difficult to distinguish active thin vs. ED	Males often use exercise as means of "purging"
Vomiting	Characteristic of binge-purge subtype May chew, then spit out, rather than swallow, food as a variant	Most common habit intended to reduce effects of overeating Can occur after meal as well as a binge	Physiologic and emotional instability prominent	Strongly "addictive" and self-punishing, but does not eliminate calories ingested—many still absorbed
Laxatives	If used, generally to relieve constipation in restrictive subtype, but as a cathartic in binge-purge subtype	Second most common habit used to reduce or avoid weight gain, often used in increasing doses for cathartic effect	Physiologic and emotional instability prominent	Strongly "addictive," self-punishing, but ineffective means to reduce weight (calories are absorbed in the small intestine, but laxatives work in the colon)
Diet pills	Very rare, if used; more common in binge-purge subtype	Used to either reduce appetite or increase metabolism	Use of diet pills implies inability to control eating	Control over eating may be sought by any means

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder.

Table 28-5 Symptoms Commonly Reported by Patients with an Eating Disorder

SYMPTOMS	Diagnosis		CLINICAL COMMENTS REGARDING ED SYMPTOMS
	ANOREXIA NERVOSA	BULIMIA NERVOSA	
Body image	Feels fat, even with extreme emaciation, often with specific body distortions (e.g., stomach, thighs); Strong drive for thinness, with self-efficacy closely tied to appraisal of body shape, size, and/or weight	Variable body image distortion and dissatisfaction, but drive for thinness is less than the desire to avoid gaining weight	Challenging a patient's body image is both ineffective and counter-therapeutic clinically Accepting the patient's expressed body image but noting its discrepancy with symptoms and signs reinforces concept that patient can "feel" fat but also "be" too thin and unhealthy
Metabolism	Hypometabolic symptoms include feeling cold, tired, and weak and lacking energy May be both bothersome and reinforcing	Variable, depending on balance of intake and output and hydration	Symptoms are evidence of body's "shutting down" in an attempt to conserve calories with an inadequate diet Emphasizing reversibility of symptoms with healthy eating and weight gain can motivate patients to cooperate with treatment
Skin	Dry skin, delayed healing, easy bruising, goose flesh Orange-yellow skin on hands	No characteristic symptom, self-injurious behavior may be seen	Skin lacks good blood flow and the ability to heal in low weight Carotenemia with large intake of β-carotene foods; reversible
Hair	Lanugo-type hair growth on face and upper body Slow growth and increased loss of scalp hair	No characteristic symptom	Body hair growth conserves energy Scalp hair loss can worsen during refeeding "telogen effluvium" (resting hair is replaced by growing hair) Reversible with continued healthy eating
Eyes	No characteristic symptom	Subconjunctival hemorrhage	Caused by increased intrathoracic pressure during vomiting
Teeth	No characteristic symptom	Erosion of dental enamel erosion Decay, fracture, and loss of teeth	Intraoral stomach acid resulting from vomiting etches dental enamel, exposing softer dental elements
Salivary glands	No characteristic symptom	Enlargement (no to mild tenderness)	Caused by chronic binge eating and induced vomiting, with parotid enlargement more prominent than submandibular; reversible
Heart	Dizziness, fainting in restrictive subtype Palpitations more common in binge-purge subtype	Dizziness, fainting, palpitations	Dizziness and fainting due to postural orthostatic tachycardia and dysregulation at hypothalamic and cardiac level with weight loss, as a result of hypovolemia with binge-purge Palpitations and arrhythmias often caused by electrolyte disturbance Symptoms reverse with weight gain and/or cessation of binge-purge
Abdomen	Early fullness and discomfort with eating Constipation Perceives contour as "fat," often preferring well-defined abdominal musculature	Discomfort after a binge Cramps and diarrhea with laxative abuse	Weight loss is associated with reduced volume and tone of GI tract musculature, especially the stomach Laxatives may be used to relieve constipation or as a cathartic Symptom reduction with healthy eating can take weeks to occur
Extremities and musculoskeletal	Cold, blue hands and feet	No characteristic symptoms Self-cutting or burning on wrists or arms	Energy-conserving low body temperature with slow blood flow most notable peripherally Quickly reversed with healthy eating
Nervous system	No characteristic symptom	No characteristic symptom	Neurologic symptoms suggest a diagnosis other than an ED
Mental status	Depression, anxiety, obsessive-compulsive symptoms, alone or in combination	Depression; PTSD; borderline personality disorder traits	Underlying mood disturbances can worsen with dysfunctional weight control practices and can improve with healthy eating AN patients might report emotional "numbness" with starvation, preferable to emotionality associated with healthy eating

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder; GI, gastrointestinal; PTSD, posttraumatic stress disorder.

Table 28-6 Signs Commonly Found in Patients with Eating Disorders Relative to Prominent Feature of Weight Control

PHYSICAL SIGN	Prominent Feature: RESTRICTIVE INTAKE	Prominent Feature: BINGE EATING/PURGING	CLINICAL COMMENTS RELATED TO EATING DISORDER SIGNS
General appearance	Thin to cachetic, depending on balance of intake and output Might wear bulky clothing to hide thinness and might resist being examined	Thin to overweight, depending on the balance of intake and output through various means	Examine in hospital gown Weight loss more rapid with reduced intake and excessive exercise Binge eating can result in large weight gain, regardless of purging behavior Appearance depends on balance of intake and output and overall weight control habits
Weight	Low and falling (if previously overweight may be normal or high); may be falsely elevated if patient drinks fluids or adds weights to body before being weighed	Highly variable, depending on balance of intake and output and state of hydration Falsification of weight is unusual	Weigh in hospital gown with no underwear, after voiding (measure urine SG) Remain in gown until physical exam completed to identify possible fluid loading (low urine SG, palpable bladder) or adding weights to body
Metabolism	Hypothermia: temp < 35.5°C (95.9°F), pulse < 60 beats/min Slowed psychomotor response with very low core temperature	Variable, but hypometabolic state is less common than in AN	Hypometabolism related to disruption of hypothalamic control mechanisms as a result of weight loss Signs of hypometabolism (cold skin, slow capillary refill, acrocyanosis) most evident in hands and feet, where energy conservation is most active
Skin	Dry Increased prominence of hair follicles Orange or yellow hands	Calluses over proximal knuckle joints of hand (Russell's sign)	Carotenemia with large intake of β-carotene foods Russell's sign: maxillary incisors abrasion develops into callus with chronic digital pharyngeal stimulation, usually on dominant hand
Hair	Lanugo-type hair growth on face and upper body Scalp hair loss, especially prominent in parietal region	No characteristic sign	Body hair growth conserves energy Scalp hair loss "telogen effluvium" can worsen weeks after refeeding begins, as hair in resting phase is replaced by growing hair
Eyes	No characteristic sign	Subconjunctival hemorrhage	Increased intrathoracic pressure during vomiting
Teeth	No characteristic sign	Eroded dental enamel and decayed, fractured, missing teeth	Perimolysis, worse on lingual surfaces of maxillary teeth, is intensified by brushing teeth without preceding water rinse
Salivary glands	No characteristic sign	Enlargement, relatively nontender	Parotid > submandibular involvement with frequent and chronic binge eating and induced vomiting
Throat	No characteristic sign	Absent gag reflex	Extinction of gag response with repeated pharyngeal stimulation
Heart	Bradycardia, hypotension, and orthostatic pulse differential > 25 beats/min	Hypovolemia if dehydrated	Changes in AN resulting from central hypothalamic and intrinsic cardiac function Orthostatic changes less prominent if athletic, more prominent if associated with purging
Abdomen	Scaphoid, organs may be palpable but not enlarged, stool-filled left lower quadrant	Increased bowel sounds if recent laxative use	Presence of organomegaly requires investigation to determine cause Constipation prominent with weight loss
Extremities and musculoskeletal system	Cold, acrocyanosis, slow capillary refill Edema of feet Loss of muscle, subcutaneous, and fat tissue	No characteristic sign, but may have rebound edema after stopping chronic laxative use	Signs of hypometabolism (cold) and cardiovascular dysfunction (slow capillary refill and acrocyanosis) in hands and feet Edema, caused by capillary fragility more than hypoproteinemia in AN, can worsen in early phase of refeeding
Nervous system	No characteristic sign	No characteristic sign	Water loading before weigh-ins can cause acute hyponatremia
Mental status	Anxiety about body image, irritability, depressed mood, oppositional to change	Depression, evidence of PTSD, more likely suicidal than AN	Mental status often improves with healthier eating and weight; SSRIs only shown to be effective for BN

AN, anorexia nervosa; BN, bulimia nervosa; PTSD, posttraumatic stress disorder; SG, specific gravity; SSRI, selective serotonin reuptake inhibitor.

Table 30-1 DSM-5 Diagnostic Criteria for Autism Spectrum Disorder

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity.
   2. Deficits in nonverbal communicative behaviors used for social interaction.
   3. Deficits in developing, maintaining, and understanding relationships.
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:
   1. Stereotyped or repetitive motor movements, use of objects, or speech.
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior.
   3. Highly restricted, fixated interests that are abnormal in intensity or focus.
   4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.
C. Symptoms must be present in the early developmental period (may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

Table 30-4 Medical and Genetic Evaluation of Children with Autism Spectrum Disorder

Recommended evaluations
Careful physical examination to identify dysmorphic physical features
Macrocephaly
Wood's lamp examination for tuberous sclerosis
Formal audiologic evaluation
Lead test; repeat periodically in children with pica
Chromosomal microarray

Consider if results of above evaluation are normal and if accompanying intellectual impairment
FISH test for region 15q11q13 to rule out duplications in Prader-Willi/Angelman syndrome
Fluorescence in situ hybridization (FISH) test for telomeric abnormalities
Test for mutations in *MECP2* gene (Rett syndrome) in females
DNA testing for fragile X syndrome

Metabolic testing to consider based on clinical features (emesis, hypotonia, lethargy, ataxia, coarse facial features of a storage disease, multiple organs involved)
Fasting blood glucose
Plasma amino acids
Ammonia and lactate
Fatty acid profile, paroxysmal
Carnitine
Acylcarnitine, quantitative
Homocysteine
Urine amino acids
Urine organic acids
Urine purine/pyrimidines
Urine acylglycine, random
Plasma 7-dehydrocholesterol (Smith-Lemli-Opitz disease screening)

Medical testing to consider based on clinical features
Complete blood cell count
Liver enzymes
Biotinidase
Thyroxine, thyroid-stimulating hormone
Ceruloplasmin/serum copper

EEG if the following clinical features are noted
Clinically observable seizures
History of significant regression in social or communication functioning

Table 30-5 Level of Evidence for Pharmacologic Treatment of Target Symptoms in Autism Spectrum Disorder

CLASS	AGENT	PRIMARY TARGET SYMPTOM(S)	LEVEL OF EVIDENCE
α_2-Agonist	Clonidine	Hyperactivity	Insufficient
	Guanfacine	Hyperactivity	Insufficient
Antipsychotics	Aripiprazole	Irritability, hyperactivity, stereotypy	Established
	Haloperidol	Behavioral symptoms	Established
	Risperidone	Irritability, hyperactivity	Established
	Risperidone	Repetitive behavior, stereotypy	Preliminary
	Olanzapine	Global functioning	Insufficient
Mood stabilizers	Divalproex sodium/Valproic acid	Irritability, repetitive behavior	Insufficient
	Lamotrigine	Irritability, social behavior	Insufficient
	Levetiracetam	Irritability	Insufficient
Norepinephrine reuptake inhibitors	Atomoxetine	Hyperactivity	Preliminary
Serotonin reuptake inhibitors	Citalopram	Repetitive behavior	Insufficient
	Fluoxetine	Repetitive behavior	Insufficient
	Clomipramine	Repetitive behavior, stereotypy, irritability, hyperactivity	Insufficient
Stimulants	Methylphenidate	Hyperactivity	Promising
Miscellaneous	Amantadine	Hyperactivity, irritability	Insufficient
	Naltrexone	Social behavior, communication, Indiscriminant learning, SIB	Insufficient
	Naltrexone	Hyperactivity	Preliminary
	Pentoxifylline	Irritability, social withdrawal	Preliminary

Established, >2 strong studies or >4 adequate studies in separate settings; Insufficient, lack of research or mixed outcomes; Preliminary, >1 adequate study; Promising, >2 adequate studies.

Adapted from Siegel M, Beaulieu AA. Psychotropic medications in child with autism spectrum disorders: A systematic review and synthesis for evidenced based practice. J Autism Dev Disord *42(8):1592–1605, 2012.*

Table 30-2 Signs and Symptoms of Possible Autism in Preschool Children (or Equivalent Mental Age)

Social interaction and reciprocal communication behaviors

Spoken language
- Language delay (in babble or words—for example, using fewer than 10 words by the age of 2 yr)
- Regression in or loss of use of speech
- Spoken language (if present) may include unusual features, such as: vocalizations that are not speech-like; odd or flat intonation; frequent repetition of set words and phrases (echolalia); reference to self by name or "you" or "she" or "he" beyond age 3 yr
- Reduced and/or infrequent use of language for communication—for example, use of single words, although able to speak in sentences

Responding to others
- Absent or delayed response to name being called, despite normal hearing
- Reduced or absent responsive social smiling
- Reduced or absent responsiveness to other people's facial expressions or feelings
- Unusually negative response to the requests of others ("demand avoidance" behavior)
- Rejection of cuddles initiated by parent or carer, although the child himself or herself may initiate cuddles

Interacting with others
- Reduced or absent awareness of personal space, or unusually intolerant of people entering their personal space
- Reduced or absent social interest in others, including children of his or her own age—may reject others; if interested in others, he or she may approach others inappropriately, seeming to be aggressive or disruptive
- Reduced or absent imitation of others' actions
- Reduced or absent initiation of social play with others, plays alone
- Reduced or absent enjoyment of situations that most children like—for example, birthday parties
- Reduced or absent sharing of enjoyment

Eye contact, pointing, and other gestures
- Reduced or absent use of gestures and facial expressions to communicate (although may place an adult's hand on objects)
- Reduced and poorly integrated gestures, facial expressions, body orientation, eye contact (looking at people's eyes when speaking), and speech used in social communication
- Reduced or absent social use of eye contact (assuming adequate vision)
- Reduced or absent "joint attention" (when 1 person alerts another to something by means of gazing, finger pointing, or other verbal or nonverbal indication for the purpose of sharing interest). This would be evident in the child from lack of:
  - Gaze switching
  - Following a point (looking where the other person points to—may look at hand)
  - Using pointing at or showing objects to share interest

Ideas and imagination
- Reduced or absent imagination and variety of pretend play

Unusual or restricted interests and/or rigid and repetitive behaviors
- Repetitive "stereotypical" movements such as hand flapping; body rocking while standing; spinning; finger flicking
- Repetitive or stereotyped play—for example, opening and closing doors
- Over focused or unusual interests
- Excessive insistence on following own agenda
- Extremes of emotional reactivity to change or new situations; insistence on things being "the same"
- Over-reaction or under-reaction to sensory stimuli, such as textures, sounds, smells
- Excessive reaction to the taste, smell, texture, or appearance of food, or having extreme food fads

From Baird G, Douglas HR, Murphy MS: Recognizing and diagnosing autism in children and young people: summary of NICE guidance. BMJ 343:d6360, 2011, Box 1, p. 901.

Table 30-3 DSM-5 Severity Levels for Autism Spectrum Disorder

SEVERITY LEVEL	SOCIAL COMMUNICATION	RESTRICTED, REPETITIVE BEHAVIORS
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. *For example,* a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. *For example,* a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication	Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. *For example,* a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 52.

Table 33-1 DSM-5 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder

DIAGNOSTIC CRITERIA

1. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):
   1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      - **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

      1. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
      2. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
      3. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
      4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
      5. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
      6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
      7. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
      8. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
      9. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

   2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      - **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.

      1. Often fidgets with or taps hands or feet or squirms in seat.
      2. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
      3. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
      4. Often unable to play or engage in leisure activities quietly.
      5. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
      6. Often talks excessively.
      7. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
      8. Often has difficulty waiting his or her turn (e.g., while waiting in line).
      9. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

2. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
3. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
4. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
5. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

- **Combined presentation:** If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
- **Predominantly inattentive presentation:** If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
- **Predominantly hyperactive/impulsive presentation:** If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

- **In partial remission:** When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

- **Mild:** Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.
- **Moderate:** Symptoms or functional impairment between "mild" and "severe" are present.
- **Severe:** Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

Table 33-2 Differences Between U.S. and European Criteria for ADHD or HKD

DSM-5 ADHD	ICD-10 HKD
SYMPTOMS	
Either or both of following: At least 6 of 9 inattentive symptoms At least 6 of 9 hyperactive or impulsive symptoms	All of following: At least 6 of 8 inattentive symptoms At least 3 of 5 hyperactive symptoms At least 1 of 4 impulsive symptoms
PERVASIVENESS	
Some impairment from symptoms is present in >1 setting	Criteria are met for >1 setting

ADHD, attention-deficit/hyperactivity disorder; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; HKD, hyperkinetic disorder; ICD-10, *International Classification of Diseases, 10th edition.*

Adapted from Biederman J, Faraone S: Attention-deficit hyperactivity disorder, Lancet *366:237–248, 2005.*

Table 33-3 Differential Diagnosis of Attention-Deficit/Hyperactivity Disorder

PSYCHOSOCIAL FACTORS
Response to physical or sexual abuse
Response to inappropriate parenting practices
Response to parental psychopathology
Response to acculturation
Response to inappropriate classroom setting
DIAGNOSES ASSOCIATED WITH ADHD BEHAVIORS
Fragile X syndrome
Fetal alcohol syndrome
Pervasive developmental disorders
Obsessive-compulsive disorder
Gilles de la Tourette syndrome
Attachment disorder with mixed emotions and conduct
MEDICAL AND NEUROLOGIC CONDITIONS
Thyroid disorders (including general resistance to thyroid hormone)
Heavy metal poisoning (including lead)
Adverse effects of medications
Effects of abused substances
Sensory deficits (hearing and vision)
Auditory and visual processing disorders
Neurodegenerative disorder, especially leukodystrophies
Posttraumatic head injury
Postencephalitic disorder

Note: Coexisting conditions with possible ADHD presentation include oppositional defiant disorder, anxiety disorders, conduct disorder, depressive disorders, learning disorders, and language disorders. Presence of 1 or more of the symptoms of these disorders can fall within the spectrum of normal behavior, whereas a range of these symptoms may be problematic but fall short of meeting the full criteria for the disorder.

From Reiff MI, Stein MT: Attention-deficit/hyperactivity disorder evaluation and diagnosis: a practical approach in office practice, Pediatr Clin North Am *50:1019–1048, 2003. Adapted from Reiff MI: Attention-deficit/hyperactivity disorders. In Bergman AB, editor:* 20 Common problems in pediatrics, *New York, 2001, McGraw-Hill, p 273.*

Table 36-1 Identification of Cause in Children with Severe Intellectual Disability

CAUSE	EXAMPLES	PERCENT OF TOTAL
Chromosomal disorder	Trisomies 21, 18, 13, Deletion 1p36 Klinefelter syndrome Wolf Hirschhorn syndrome	~20
Genetic syndrome	Fragile X syndrome Prader-Willi syndrome Rett syndrome	~20
Nonsyndromic autosomal mutations	Variations in copy number, de novo mutations in *SYNGAP1*, *GRIK2*, *TUSC3*, oligosaccharyl transferase, and others	~10
Developmental brain abnormality	Hydrocephalus ± meningomyelocele, lissencephaly	~8
Inborn errors of metabolism or neurodegenerative disorder	PKU, Tay-Sachs, various storage diseases	~7
Congenital infections	HIV, toxoplasmosis, rubella, CMV, syphilis, herpes simplex	~3
Familial intellectual disability	Environment, syndromic, or genetic	~5
Perinatal causes	HIE, meningitis, IVH, PVL, fetal alcohol syndrome	4
Postnatal causes	Trauma (abuse), meningitis, hypothyroidism	~4
Unknown	Cerebral palsy	20

CMV, Cytomegalovirus; HIE, hypoxic ischemic encephalopathy; HIV, human immunodeficiency virus; IVH, intraventricular hemorrhage; PKU, phenylketonuria; PVL, periventricular leukomalacia.

Modified from Stromme P, Hayberg G: Aetiology in severe and mild mental retardation: a population based study of Norwegian children, Dev Med Child Neurol *42:76–86, 2000.*

Table 33-4 Medications Used in the Treatment of Attention-Deficit/Hyperactivity Disorder

GENERIC NAME	BRAND NAME	DURATION	DOSAGE RANGE	SIDE EFFECTS
METHYLPHENIDATE				
Immediate-release	Ritalin, Methylin	3-4 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
Extended-release	Metadate ER, Methylin ER,	4-6 hr	10, 20 mg extended-release tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
	Metadate-CD	8-10 hr	10, 20, 30 mg extended-release caps	
	Ritalin LA	8-10 hr	20, 30, 40 mg caps	
	Concerta	10-12 hr	18, 27, 36, 54 mg caps	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Sustained-release	Ritalin SR, Methylphenidate SR	4-6 hr	20 mg sustained-release tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
Transdermal system	Daytrana	≥12 hr	Patch	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
DEXMETHYLPHENIDATE				
	Focalin	4-6 hr	2.5, 5, 10 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Extended-release	Focalin XR	6-8 hr		Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
DEXTROAMPHETAMINE				
Short-acting	Dexedrine, DextroStat	4-6 hr	5, 10, 15 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Intermediate-acting	Dexedrine, Spansule	6-8 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Lisdexamfetamine	Vyvanse	≤12 hr	30 mg, 50 mg, 70 mg tablets	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
MIXED AMPHETAMINE SALTS				
Intermediate-acting	Adderall	4-6 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Extended-release	Adderall XR	8-12 hr	5, 10, 15, 20, 25, 30 mg caps	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
ATOMOXETINE				
Extended-release	Strattera	12 hr	10, 18, 25, 40, 60 mg caps	Nervousness, sleep problems, fatigue, stomach upset, dizziness, dry mouth Can lead in rare cases to severe liver injury or to suicidal ideation
Bupropion	Wellbutrin	4-5 hr	100, 150 mg tabs	Difficulty sleeping, headache, seizures
Bupropion	Wellbutrin SR, Wellbutrin XL		100, 150, 200 mg tabs	
TRICYCLIC ANTIDEPRESSANTS				
Imipramine	Tofranil	Variable	See Table 21-4	Nervousness, sleep problems, fatigue, stomach upset, dizziness, dry mouth, accelerated heart rate
Desipramine*	Norpramin			
Nortriptyline	Aventyl, Pamelor			
α-AGONISTS				
Clonidine	Catapres, Kapvay	6-12 hr	3-10 µg/kg/day bid-qid	Sedation, depression, dry mouth, rebound hypertension on discontinuing, confusion
Guanfacine	Tenex, Intuniv	6-12 hr	1, 2, 3 mg tabs	Hypotension, lightheadedness

cap, capsule; tab, tablet.
*Associated with deaths from cardiac problems. Not recommended for children.

Table 36-2 Common Presentations of Intellectual Disability By Age

AGE	AREA OF CONCERN
Newborn	Dysmorphic syndromes, (multiple congenital anomalies), microcephaly Major organ system dysfunction (e.g., feeding and breathing)
Early infancy (2-4 mo)	Failure to interact with the environment Concerns about vision and hearing impairments
Later infancy (6-18 mo)	Gross motor delay
Toddlers (2-3 yr)	Language delays or difficulties
Preschool (3-5 yr)	Language difficulties or delays Behavior difficulties, including play Delays in fine motor skills: cutting, coloring, drawing
School age (>5 yr)	Academic underachievement Behavior difficulties (attention, anxiety, mood, conduct, etc.)

Table 35-1 Normal Language Milestones

HEARING AND UNDERSTANDING	TALKING
BIRTH TO 3 MONTHS	
Startles to loud sounds Quiets or smiles when spoken to Seems to recognize your voice and quiets if crying Increases or decreases sucking behavior in response to sound	Makes pleasure sounds (cooing, gooing) Cries differently for different needs Smiles when sees you
4-6 MO	
Moves eyes in direction of sounds Responds to changes in tone of your voice Notices toys that make sounds Pays attention to music	Babbling sounds more speech-like, with many different sounds, including *p, b,* and *m* Vocalizes excitement and displeasure Makes gurgling sounds when left alone and when playing with you
7 MO-1 YEAR	
Enjoys games such as peekaboo and pat-a-cake Turns and looks in direction of sounds Listens when spoken to Recognizes words for common items, such as *cup, shoe,* and *juice* Begins to respond to requests *(Come here. Want more?)*	Babbling has both long and short groups of sounds, such as *tata upup bibibibi.* Uses speech or noncrying sounds to get and keep attention Imitates different speech sounds Has 1 or 2 words *(bye-bye, Dada, Mama),* although they might not be clear
1-2 YR	
Points to a few body parts when asked Follows simple commands and understands simple questions *(Roll the ball. Kiss the baby. Where's your shoe?)* Listens to simple stories, songs, and rhymes Points to pictures in a book when named	Says more words every month Uses some 1-2 word questions *(Where kitty? Go bye-bye? What's that?)* Puts 2 words together *(more cookie, no juice, mommy book)* Uses many different consonant sounds at the beginning of words
2-3 YR	
Understands differences in meaning (e.g., go–stop, in–on, big–little, up–down) Follows 2-step requests *(Get the book and put it on the table.)*	Has a word for almost everything Uses 2-3 word "sentences" to talk about and ask for things Speech is understood by familiar listeners most of the time Often asks for or directs attention to objects by naming them
3-4 YR	
Hears you when you call from another room Hears television or radio at the same loudness level as other family members Understands simple *who, what, where, why* questions	Talks about activities at school or at friends' homes Usually understood by people outside the family Uses a lot of sentences that have ≥4 words Usually talks easily without repeating syllables or words
4-5 YR	
Pays attention to a short story and answers simple questions about it Hears and understands most of what is said at home and in school	Voice sounds as clear as other children's Uses sentences that include details *(I like to read my books.)* Tells stories that stick to a topic Communicates easily with other children and adults Says most sounds correctly except a few, such as *l, s, r, v, z, ch, sh,* and *th* Uses the same grammar as the rest of the family

Adapted from American Speech-Language-Hearing Association, 2005. http://www.asha.org/public/speech/development/chart.htm.

Table 35-3 Speech and Language Screening

REFER FOR SPEECH–LANGUAGE EVALUATION IF:

AT AGE	RECEPTIVE	EXPRESSIVE
15 mo	Does not look/point at 5-10 objects	Is not using 3 words
18 mo	Does not follow simple directions ("get your shoes")	Is not using Mama, Dad, or other names
24 mo	Does not point to pictures or body parts when they are named	Is not using 25 words
30 mo	Does not verbally respond or nod/shake head to questions	Is not using unique 2-word phrases, including noun–verb combinations
36 mo	Does not understand prepositions or action words; does not follow 2-step directions	Has a vocabulary of <200 words; does not ask for things; echolalia to questions; language regression after attaining 2-word phrases

Table 36-3 Suggested Evaluation of the Child with Intellectual Disability/Global Developmental Delay

TEST	COMMENT
In-depth history	Includes pre-, peri-, and postnatal events (including seizures); developmental attainments; and 3-generation pedigree in family history
Physical examination	Particular attention to minor or subtle abnormalities; neurologic examination for focality and skull abnormalities Behavioral phenotype
Vision and hearing evaluation	Essential to detect and treat; can mask as developmental delay
Gene microarray analysis	A 7.8% yield overall (10% in syndromic and 6.5% in nonsyndromic intellectual disability) Better resolution than Karyotype. May identify up to twice as many abnormalities as karyotyping. Excellent in detecting de novo microdeletions or microduplications
Karyotype	Yield 4% in global developmental delay/intellectual disability Best for inversions and balanced insertions, reciprocal translocations, and polyploidy
Fragile X screen	Combined yield 2% Preselection on clinical grounds can increase yield to 7.6%
X-linked candidate intellectual disability genes	May explain up to 10% of intellectual disability Yield may be as high as 42% if there is a definite family history and as high as 17% from a possibly linked kindred
Exomic gene sequencing	Detects inherited and de novo point mutations especially in nonsyndromic severe intellectual disability
Neuroimaging	MRI preferred. Positives increased by abnormalities of skull contour or microcephaly and macrocephaly, or focal neurologic examination. Overall has a higher yield Identification of specific etiologies is rare. Most conditions that are found do not alter the treatment plan. Need to weigh risk of sedation against possible yield
Thyroid (T_4, TSH)	Near 0% in settings with universal newborn screening program
Serum lead	If there are identifiable risk factors for excessive environmental lead exposure
Metabolic testing	Yield 0.2-4.6% based on clinical indicators and tests performed Urine organic acids, plasma amino acids, ammonia, lactate, and a capillary blood gas. Focused testing based on clinical findings is warranted Tandem mass spectrometry newborn screening has allowed for identification of many disorders in perinatal period and have decreased yield in older children. Other disorders have emerged; e.g., congenital disorders of glycosylation and disorders of creatine synthesis and transport
MECP2 for Rett syndrome	1.5% of females with severe intellectual disability 0.5% of males
EEG	May be deferred in absence of history of seizures
Repeated history and physical examination	Can give time for maturation of physical and behavioral phenotype. New technology may be available for evaluation

EEG, Electroencephalogram; CGH, comparative genomic hybridization; MECP2, methyl CpG binding protein 2; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Based on Michelson DJ, Shevell MI, Sherr EH, et al: Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of Child Neurology. Neurology 77:1629-35, 2011; Curry CJ, Stevenson RE, Aughton D, et al: Evaluation of mental retardation: recommendations of a Consensus Conference: American College of Medical Genetics. Am J Med Genet 12:72:468-477, 1997. Shapiro BK, Batshaw ML: Mental retardation. In Burg FD, Ingelfinger JR, Polin RA, et al: Gellis and Kagan's current pediatric therapy, *ed 18, Philadelphia, 2005, WB Saunders, used with permission; and Shevell M, Ashwal S, Donley D, et al: Practice parameter: evaluation of the child with global developmental delay,* Neurology *60:367–380, 2003.*

Table 41-1 Historical Factors About the Period After the Neonatal Period to Be Considered in an Evaluation of Growth Failure Using a Biopsychosocial Model

BIOLOGICAL SPHERE	PSYCHOSOCIAL SPHERES
Frequency and source of routine medical care	Provision of baby care, especially feeding
Growth measurements	Maternal sleep deprivation
Immunization status	Postnatal depression or other mental illness
Medical illnesses	Type and amount of social support
Hospitalizations	Availability of respite for mother
Medications	Involvement of father and/or other intimate partner
Allergies—medications, food, other	Intimate partner violence
Surgeries	Financial resources, including money for baby supplies
Injuries, including bruises on infants	Enrollment in governmental aid programs
Feeding issues—vigorous or difficult feeder	Parental reaction to fussing/crying
Breastfeeding:	Who lives with baby
• Milk letdown	Reactions of others in the home to the baby
• Sense of fullness/emptying	Parental employment
• Frequency and duration of feedings	Use of daycare or babysitting
• Maternal observation of baby swallowing	Caregiver perception of weight gain and general appearance
• Maternal diet and medical problems while breastfeeding	
Formula feeding:	
• Type	
• Method of mixing (concentration)	
• Frequency and quantity of feedings	
Other intake in first few months of life, such as:	
• Water	
• Juice	
• Tea	
• Soda	
• Cereal	
Sleep schedule	
Baby's temperament	
Developmental milestones	
Use of alternative or complementary medicines	

From Jenny C: Child abuse and neglect: diagnosis, treatment, and evidence, *Philadelphia, 2011, Elsevier/Saunders, p. 554, Table 57-5.*

Table 41-2 Diagnostic Classification of Causes and Selected Examples of Failure to Thrive

INADEQUATE INTAKE	MALABSORPTION
Inadequate food offered	Cystic fibrosis
• Food insecurity	Celiac disease
• Poor knowledge of child's needs	Hepatobiliary disease
• Formula dilution or excessive juice	Food protein allergy, insensitivity, or intolerance
• Breastfeeding difficulties	Infection (giardiasis)
• Medical child abuse/caregiver fabricated illness (Munchausen by proxy)	Short gut syndrome
• Medical neglect	INCREASED METABOLIC DEMAND
• Food fads including "rice" milk as substitute for formula or cow milk	Insulin resistance (intrauterine growth restriction)
Child not taking enough food	Congenital infections (human immunodeficiency virus, TORCHES)
• Oromotor dysfunction, neurologic disease	Syndromes (Russell-Silver, Turner, Down)
• Developmental delay	Malignancy
• Behavioral feeding problem (altered oromotor sensitivity, pain and conditioned aversion)	Chronic disease (cardiac, pulmonary, renal)
• Anorexia from systemic causes	Metabolic disorders
Emesis	Immunodeficiency/autoinflammatory disorders
• Pyloric stenosis	Endocrine (diabetes mellitus, diabetes insipidus, hyperthyroidism)
• Gastroesophageal reflux	
• Eosinophilic esophagitis	
• Vascular rings	
• Malrotation with intermittent volvulus	
• Increased intracranial pressure and other neurologic disorders	
• Inborn errors of metabolism	
• Rumination	
• Cyclic vomiting	

TORCHES, toxoplasma, other agents, rubella, cytomegalovirus, herpes simplex.
Data from Jaffe A: Failure to thrive: current clinical concepts, Pediatr Rev *32:100-108, 2011.*

Table 41-3 Failure to Thrive: Differential Diagnosis by System

PSYCHOSOCIAL/BEHAVIORAL
Inadequate diet because of poverty/food insufficiency, errors in food preparation
Poor parenting skills (lack of knowledge of sufficient diet)
Child/parent interaction problems (autonomy struggles, coercive feeding, maternal depression)
Food refusal
Rumination
Parental cognitive or mental health problems
Child abuse or neglect; emotional deprivation

NEUROLOGIC
Cerebral palsy
Hypothalamic and other central nervous system tumors (diencephalic syndrome)
Neuromuscular disorders
Neurodegenerative disorders

RENAL
Recurrent urinary tract infection
Renal tubular acidosis
Renal failure

ENDOCRINE
Diabetes mellitus
Diabetes insipidus
Hypothyroidism/hyperthyroidism
Growth hormone deficiency
Adrenal insufficiency

GENETIC/METABOLIC/CONGENITAL
Sickle cell disease
Inborn errors of metabolism (organic acidosis, hyperammonemia, storage disease)
Fetal alcohol syndrome
Skeletal dysplasias
Chromosomal disorders
Multiple congenital anomaly syndromes (VATER, CHARGE)

GASTROINTESTINAL
Pyloric stenosis
Gastroesophageal reflux
Repair of tracheoesophageal fistula
Malrotation
Malabsorption syndromes
Celiac disease
Milk intolerance: lactose, protein
Pancreatic insufficiency syndromes (cystic fibrosis)
Chronic cholestasis
Inflammatory bowel disease
Chronic congenital diarrhea states
Short bowel syndrome
Pseudoobstruction
Hirschsprung disease
Food allergy

CARDIAC
Cyanotic heart lesions
Congestive heart failure
Vascular rings

PULMONARY/RESPIRATORY
Severe asthma
Cystic fibrosis; bronchiectasis
Chronic respiratory failure
Bronchopulmonary dysplasia
Adenoid/tonsillar hypertrophy
Obstructive sleep apnea

MISCELLANEOUS
Collagen-vascular disease
Malignancy
Primary immunodeficiency
Transplantation

INFECTIONS
Perinatal infection (TORCHES)
Occult/chronic infections
Parasitic infestation
Tuberculosis
HIV

CHARGE, coloboma, heart disease, atresia choanae, retarded growth and retarded development and/or central nervous system anomalies, genital hypoplasia, and ear anomalies and/or deafness; TORCHES, toxoplasma, other agents, rubella, cytomegalovirus, herpes simplex; VATER, vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.

Table 41-4 Approach to Failure to Thrive Based on Signs and Symptoms

HISTORY/PHYSICAL EXAMINATION	DIAGNOSTIC CONSIDERATION
Spitting, vomiting, food refusal	Gastroesophageal reflux, chronic tonsillitis, food allergies, eosinophilic esophagitis
Diarrhea, fatty stools	Malabsorption, intestinal parasites, milk protein intolerance, pancreatic insufficiency, celiac disease, immunodeficiency, inflammatory bowel disease
Snoring, mouth breathing, enlarged tonsils	Adenoid hypertrophy, obstructive sleep apnea
Recurrent wheezing, pulmonary infections	Asthma, aspiration, food allergy, cystic fibrosis, immunodeficiency
Recurrent infections	HIV or congenital immunodeficiency diseases, anatomic defects
Travel to/from developing countries	Parasitic or bacterial infections of the gastrointestinal tract

Table 41-5	Approach to Physical Examination
Vital signs	Blood pressure, if over 2 yr, temperature, pulse, respirations, oxygen saturation, anthropometry (growth percentiles, body mass index)
General appearance	Activity, affect, posture
Skin	Hygiene, rashes, trauma (bruises, burns, scars)
Head	Hair whorls, color and pluckability of hair, occipital alopecia, fontanel size and patency, frontal bossing, sutures, shape, facial dysmorphisms, philtrum
Eyes	Ptosis, strabismus, fundoscopic examination where possible, palpebral fissures, conjunctival pallor, icterus, cataracts
Ears	External form, rotation, tympanic membranes
Mouth, nose, throat	Thinness of lip, hydration, dental eruption and hygiene caries, glossitis, cheilosis, gum bleeding, marked tonsillar enlargement
Neck	Hairline, masses, lymphadenopathy
Cardiovascular	Evidence of congestive heart failure, cyanosis
Abdomen	Protuberance, hepatosplenomegaly, masses
Genitalia	Malformations, hygiene, trauma
Rectum	Fissures, trauma, hemorrhoids
Extremities	Edema, dysmorphisms, rachitic changes, nails and nail beds
Neurologic	Cranial nerves, reflexes, tone, retention of primitive reflexes, quality of voluntary movement

Table 43-4	Key Elements of Effective Symptom Management

Establish and periodically revisit goals of care and ensure that goals are communicated to entire care team.
Anticipate and plan for symptoms before they occur.
Assess the child for symptoms regularly, using consistent and developmentally appropriate assessment tools.
- Utilize self-report, if the child is able to reliably report symptoms.
- Evaluate all aspects of the symptom, including quality, frequency, duration, and intensity.

Consider the holistic nature of symptoms.
- Explore the meaning that symptoms may have for families in their social, cultural, religious context.
- Assess distress caused by the symptom.
- Evaluate the degree of functional impairment from the symptom.

Understand the pathophysiology of the symptom and establish a complete differential diagnosis.
Treat the underlying cause if possible, weighing benefits and risks, in the context of goals of care.
Choose the least-invasive route for medications—by mouth whenever possible.
Prescribe regular medications for constant symptoms, and consider prn doses for breakthrough or uncontrolled symptoms.
Consider both pharmacologic and nonpharmacologic approaches.
Reassess the symptom and response to interventions regularly.
- For refractory symptoms, revisit the differential diagnosis and review potentially contributing factors.
- Effective interventions relieve the symptom and reduce distress and functional impairment.

Partner with families to identify and address any barriers to optimal control of symptoms.
Address spiritual, emotional, and existential suffering in addition to physical suffering as these are often interrelated.

Table 43-5	Guidelines for Pain Management

Utilize nonopioid analgesics as monotherapy for mild pain and together with opioids for more severe pain.
- Nonopioid analgesics include acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), salicylates, and selective cyclooxygenase (COX-2) inhibitors.

For moderate or severe pain, start with a short-acting opioid at regular intervals.
- When dose requirements have stabilized, consider converting opioid to a long-acting formulation with doses available for breakthrough or uncontrolled pain, as needed.
- For uncontrolled pain, increase opioid dose by 30-50%; for severe pain increase by 50-100%.
- Avoid codeine and opioids with mixed agonist activity (e.g., butorphanol, pentazocine).

Administer medications via the simplest, most effective, and least-distressing route.
Dispel the myth that strong medications should be saved for extreme situations or the very end of life.
- Opioids do not have a "ceiling effect," and escalating symptoms may be treated with an increase in dose.

Clarify for families the differences between tolerance, physical dependence, and addiction.
Anticipate and treat/prevent common analgesic side effects (gastritis with NSAIDs; constipation, pruritus, nausea, sedation with opioids).
- Always initiate a bowel regimen to prevent constipation when starting opioids.
- Consider a stimulant for opioid-induced somnolence.
- Pruritus rarely indicates a true allergy. If not responsive to an antihistamine, consider low-dose naloxone or switching opioids.
- Consider switching to a different opioid for intolerable side effects or neurotoxicity (e.g., myoclonus).
- Use an equianalgesic conversion table when switching opioids, and account for incomplete cross-tolerance.

Consider the use of adjuvant drugs for specific pain syndromes, and for their opioid-sparing effect:
- Antidepressants (e.g., amitriptyline, nortriptyline) and anticonvulsants (e.g., gabapentin, carbamazepine, topiramate) for neuropathic pain.
- Steroids or NSAIDs for bone pain.
- Sedatives and hypnotics for anxiety and muscle spasm.
- To enhance analgesia from opioids, consider clonidine or ketamine.
  - Use topical local anesthetics (lidocaine, prilocaine, bupivacaine) when possible.
  - Consider anesthetic blocks for regional pain.
  - Consider palliative radiation therapy.
  - Consider psychological approaches (e.g., cognitive or behavioral therapy) and integrative therapies (e.g., acupuncture, massage).

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pain—mild	Acetaminophen	15 mg/kg po q 4 hr, max 4 g/day	Available po (including liquid), pr, IV
	Ibuprofen	10 mg/kg po q 6 hr	PO (including liquid) only; avoid if risk of bleeding; use only in infants ≥6 mo. Use with caution in congestive heart failure. Chewable tablets contain phenylalanine
	Trilisate	10-15 mg/kg po tid	Trilisate may have less antiplatelet activity and therefore pose less risk for bleeding than other salicylates. Salicylates, however, have been associated with Reye syndrome in children <2 yr
Pain—moderate/ severe	Morphine immediate release (i.e., MSIR)	0.3 mg/kg po q 4 hr if <50 kg; 5-10 mg po q 4 hr*†	Also available in IV/SQ formulation‡§
	Oxycodone	0.1 mg/kg po q 4 hr if <50 kg; 5-10 mg po q 4 hr if >50 kg*†	No injectable formulation‡§
	Hydromorphone	0.05 mg/kg po q 4 hr if <50 kg; 1-2 mg po q 4 hr if >50 kg*†	Also available in IV/SQ formulation. Injectable form very concentrated, facilitating subcutaneous delivery‡§
	Fentanyl	0.5-1.5 µg/kg IV/SQ q 30 min*†	Rapid infusion may cause chest wall rigidity‡§
	Methadone	Starting dose 0.1-0.2 mg/kg po bid. May give tid if needed. Recommend consultation with experienced clinician for equivalence dosing from other opioids.*†	Only opioid with immediate and prolonged effect available as a liquid; do not adjust dose more often than every 72 hr as prolonged biologic half-life > than therapeutic half-life. Knowledge of the pharmacokinetics of methadone is needed for converting to and from doses of other opioids. Also available IV/SQ. May cause QT interval prolongation (consider ECG), especially in adults on >200 mg/day or in those at risk for QT prolongation. Interacts with several antiretrovirals§
Pain—sustained release	MS Contin Kadian (contains sustained-release pellets), Avinza (contains immediate and extended release beads) Oramorph	Total daily dose of MSIR divided bid-tid	Do not crush MS Contin. For those unable to swallow pills, Kadian and Avinza capsules may be opened and contents mixed with food but *cannot be chewed*. Kadian contents may be mixed in 10 mL water and given via 16-French G-tube. Avoid alcohol with Avinza. Larger dose formulation may not be suitable for small children§
	OxyContin	Total daily dose of oxycodone divided bid-tid	Do not crush§
	Transdermal fentanyl patch	Divide 24-hr po morphine dose by 2 to determine starting dose of transdermal fentanyl. There is no data on the equianalgesic conversion from transdermal fentanyl to any oral opioid	Smallest patch size may be too high for small children. For children >2 yr. Apply to upper back in young children. Patch may not be cut. Typically for patients on at least 60 mg morphine/day or its equivalent. Not appropriate when dosage changes are frequent or for opioid-naïve patients. Fever >40°C results in higher serum concentrations§
Pain—neuropathic	Nortriptyline	0.5 mg/kg po at bedtime to maximum of 150 mg/day	Fewer anticholinergic side effects than amitriptyline. May cause constipation, sedation, postural hypotension, dry mouth. May cause QT interval prolongation (consider ECG). At higher doses monitor ECG and plasma levels
	Gabapentin	Start at 5 mg/kg/day at bedtime and gradually increase to 10-15 mg/kg/day divided tid; titrate up by 5 mg/kg/day every 3-4 days as needed but not to exceed 50-75 mg/kg/day (3600 mg/day)	May cause neuropsychiatric events in children (aggression, emotional lability, hyperkinesia), usually mild but may require discontinuation of gabapentin. May cause dizziness, drowsiness, tremor, nystagmus, ataxia, swelling
	Pregabalin	Start at 1 mg/kg/dose po at bedtime for 3 days, then increase to 1 mg/kg/dose bid. Increase every 3 days to 3 mg/kg/dose po bid (maximum: 6 mg/kg/dose)	
	Methadone	See previous listing	See previous listing
Dyspnea	Morphine, immediate release (i.e., MSIR)	0.1 mg/kg po q 4 hr prn*†	All opioids may relieve dyspnea. For dyspnea, the starting dose is 30% of the dose that would be administered for pain§
	Lorazepam	0.025-0.05 mg/kg IV/po q 6 hr, up to 2 mg/dose	See previous listing

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Respiratory secretions	Scopolamine patch	1.5 mg patch, change q 72 hr	Excessive drying of secretions can cause mucus plugging of airways. Good for motion-induced nausea and vomiting. Handling patch and contacting eye may cause anisocoria and blurry vision. May fold patches but do not cut them. Anticholinergic side effects possible
	Glycopyrrolate	0.04-0.1 mg/kg po q 4-8 hr	Powerful antisialagogue. Excessive drying of secretions can cause mucus plugging of airways. Anticholinergic side effects possible. Quaternary ammonium structure limits its ability to cross lipid membranes, such as the blood–brain barrier (in contrast to atropine, scopolamine and hyoscyamine sulfate), so may exert fewer central anticholinergic effects
	Hyoscyamine sulfate	4 gtt po q 4 hr prn if <2 yr; 8 gtt po q 4 hr prn if 2-12 yr; do not exceed 24 gtt/24 hr	Anticholinergic side effects possible, including sedation. May be given sublingually
	Atropine	1-2 gtt SL q 4-6 hr prn	Give 0.5% ophthalmic drops sublingually
Nausea	Metoclopramide	0.1-0.2 mg/kg/dose q 6 hr, up to 10 mg/dose (prokinetic and mild nausea dosing). For chemotherapy-associated nausea 0.5-1 mg/kg q 6 hr prn po/IV/SC, give with diphenhydramine and continue diphenhydramine for 24 hr after last dose of high-dose metoclopramide to prevent extrapyramidal reaction	Helpful when dysmotility is an issue; may cause extrapyramidal reactions, particularly in children following IV administration of high doses. Contraindicated in complete bowel obstruction or pheochromocytoma
	Ondansetron	0.15 mg/kg dose IV/po q 8 hr prn. No single intravenous dose should exceed 16 mg because of risk of QT prolongation	Significant experience in pediatrics. Good empiric therapy for nausea in palliative care population. Oral dissolving tablet contains phenylalanine. Higher doses used with chemotherapy although single 32 mg IV dose is no longer available (risk for QT prolongation). Consider ECG monitoring in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or in patients on other medications with the potential to cause QT prolongation
	Dexamethasone	0.1 mg/kg/dose tid po/IV; max dose 10 mg/day	Also helpful with hepatic capsular distention, bowel wall edema, anorexia, increased intracranial pressure. May cause mood swings or psychosis
	Lorazepam	See previous listing	See previous listing
	Dronabinol	2.5-5 mg/m^2/dose q 3-4 hr	Available in 2.5- and 5-mg capsules. May remove liquid contents from capsules for children who cannot swallow capsules. Avoid in patients with sesame oil hypersensitivity or history of schizophrenia. May cause euphoria, dysphoria or other mood changes. Tolerance to central nervous system side effects usually develops in 1-3 days of continuous use. Avoid in patients with depression or mania
	Scopolamine patch	See previous listing	See previous listing
Anxiety	Lorazepam	See previous listing	See previous listing
Agitation	Haloperidol	0.01 mg/kg po tid prn for acute onset: 0.025-0.050 mg/kg po, may repeat 0.025 mg/kg in 1 hr prn	May cause extrapyramidal reactions, which can be reversed with diphenhydramine or Cogentin. Safety not established in children <3 yr
Sleep disturbance/ insomnia	Lorazepam	See previous listing	See previous listing
	Trazodone	Children 6-18 yr: 0.75-1 mg/kg/dose, given bid-tid if needed If >18 yr, start at 25-50 mg/dose, given bid-tid if needed	Potentially arrhythmogenic
Fatigue	Methylphenidate	0.3 mg/kg/dose titrated as needed, up to 60 mg/day	Rapid antidepressant effect; also improves cognition. Administer before meals to avoid appetite suppression. Use with caution in children at risk for cardiac arrhythmia. Available as liquid and chewable tablet

Continued

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pruritus	Diphenhydramine	0.5-1 mg/kg q 6 hr IV/po (100 mg max per day)	May reverse phenothiazine-induced dystonic reactions. Topical formulation on large areas of the skin or open area may cause toxic reactions. May cause paradoxical reaction in young children
	Hydroxyzine	0.5-1 mg/kg q 6 hr IV/po (600 mg maximum per day)	
Constipation	Docusate	40-150 mg/day po in 1-4 divided doses	Stool softener available as liquid or capsule
	MiraLAX	<5 yr: ½ scoop (8.5 g) in 4 oz of water daily >5 yr: 1 scoop (17 g) in 8 oz of water daily	Tasteless powder may be mixed in beverage of choice. Now available nonprescription
	Lactulose	5-10 mL po up to q 2 hr until bowel movement	Bowel stimulant; dosing q 2 hr may cause cramping
	Senna	2.5 mL po daily (for children weighing >27 kg)	Bowel stimulant; available as granules
	Dulcolax	3-12 yr: 5-10 mg po daily >12 yr 5-15 mg po daily	Available in oral or rectal formulation
	Pediatric Fleets Enema	2.5 oz pediatric enema for children 2-11 yr; adult enema for children ≥12 yr	May repeat ×1 if needed. Do not use in neutropenic patients
	Methylnaltrexone	10-20 kg: 2 mg SC 21-33 kg: 4 mg SC 34-46 kg: 6 mg SC 47-62 kg: 8 mg SC 63-114 kg: 12 mg SC ≥155 kg: 0.15 mg/kg SC Administer 1 dose every other day as needed; maximum of 1 dose per 24 hr	A peripherally acting opioid antagonist for opioid-induced constipation. Usually works within 30-60 minutes of administration
Muscle spasm	Diazepam	0.5 mg/kg/dose IV/po q 6 hr prn; initial dose for children <5 yr is 5 mg dose; for children ≥5 yr dose is 10 mg/dose	May be irritating if given by peripheral IV
	Baclofen	5 mg po tid, increase by 5 mg/dose as needed	Helpful with neuropathic pain and spasticity; abrupt withdrawal may result in hallucinations and seizures; not for children <10 yr
Seizures	Lorazepam	0.1 mg/kg IV/po/SL/PR; repeat q 10 min ×2	
	Diazepam	0.1 mg/kg q 6 hr (max 5 mg/dose if <5 yr; max 10 mg/dose if >5 yr)	May be given pr as Diastat (0.2 mg/kg/dose q 15 minutes ×3 doses)
Neuroirritability	Gabapentin	See previous listing	
	Clonidine	Starting dose: 0.05 mg/day. May increase every 3-5 days by 0.05 mg/day to 3-5 μg/kg/day given in divided doses 3-4 times/day; maximum dose is 0.3 mg/day May switch from oral to transdermal route once optimal oral dose is established; Transdermal dose is equivalent to the total oral daily dose (e.g., if total oral dose is 0.1 mg/day, apply 1 patch (delivers 0.1 mg/day). Change patch every 7 days.	Transdermal patch may contain metal (e.g., aluminum) that may cause burns if worn during MRI scan. Remove patch prior to MRI. Patch may be cut into quarter or half fractions based on dose needed
	Clonazepam	<10 yr or <30 kg Initial dose: 0.01-0.03 mg/kg/day divided tid; ≥10 yr (≥30 kg) Initial dose: up to 0.25 mg po tid; may increase by 0.5-1 mg/day every 3 days Maintenance dose: 0.05-0.2 mg/kg/day up to 20 mg/day	
Anorexia	Megestrol acetate	10 mg/kg/day in 1-4 divided doses, may titrate up to 15 mg/kg/day or 800 mg/day	For children >10 yr. Acute adrenal insufficiency may occur with abrupt withdrawal after long-term use. Use with caution in patients with diabetes mellitus or history of thromboembolism. May cause photosensitivity
	Dronabinol	See previous listing	See previous listing
	Cyproheptadine	Children ≥2 yr and adolescents: 0.08 mg/kg po q 8 hr; if no benefit in 5 days, increase dose by 0.04-0.08 mg/kg/dose maximum daily dose: ≤6 yr: 12 mg/day; 7-14 yr: 16 mg/day; ≥15 yr: 32 mg/day	Potent antihistamine and serotonin antagonist

*Infants <6 mo should receive 25-30% of the usual opioid starting dose.
†Although the usual opioid starting dose is presented, dose may be titrated as needed. There is no ceiling/maximum dose for opioids.
‡Breakthrough dose is 10% of 24 hr dose. See Chapter 62 for information regarding titration of opioids.
§Side effects from opioids include constipation, respiratory depression, pruritus, nausea, urinary retention, physical dependence.
ECG, electrocardiogram; gtt, drops; hr, hr; IV, intravenously; po, by mouth; pr, rectally; prn, as needed; SC, subcutaneously; SL, sublingually.
Adapted from Ullrich C, Wolfe J: Pediatric pain and symptom control. In Walsh TD, Caraceni AT, Fainsinger R, et al: *Palliative medicine*, Philadelphia, 2008, Saunders, pp. 1101-1102, Table 198.3.

Table 43-7 Nonpharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

SYMPTOM	APPROACH TO MANAGEMENT
Pain	Prevent pain when possible by limiting unnecessary painful procedures, providing sedation, and giving pre-emptive analgesia prior to a procedure (e.g., including sucrose for procedures in neonates) Address coincident depression, anxiety, sense of fear or lack of control Consider guided imagery, relaxation, hypnosis, art/pet/play therapy, acupuncture/acupressure, biofeedback, massage, heat/cold, yoga, transcutaneous electric nerve stimulation, distraction
Dyspnea or air hunger	Suction secretions if present, positioning, comfortable loose clothing, fan to provide cool, blowing air Limit volume of IV fluids, consider diuretics if fluid overload/pulmonary edema present Behavioral strategies including breathing exercises, guided imagery, relaxation, music, distraction
Fatigue	Sleep hygiene (establish a routine, promote habits for restorative sleep) Regular, gentle exercise; Prioritize or modify activities Address potentially contributing factors (e.g., anemia, depression, side effects of medications) Aromatherapy*: peppermint, rosemary, basil
Nausea/vomiting	Consider dietary modifications (bland, soft, adjust timing/volume of foods or feeds) Aromatherapy*: ginger, peppermint, lavender acupuncture/acupressure
Constipation	Increase fiber in diet, encourage fluids, ambulation (if possible)
Oral lesions/dysphagia	Oral hygiene and appropriate liquid, solid and oral medication formulation (texture, taste, fluidity). Treat infections, complications (mucositis, pharyngitis, dental abscess, esophagitis) Oropharyngeal motility study and speech (feeding team) consultation
Anorexia/cachexia	Manage treatable lesions causing oral pain, dysphagia, or anorexia. Support caloric intake during phase of illness when anorexia is reversible. Acknowledge that anorexia/cachexia is intrinsic to the dying process and may not be reversible Prevent/treat coexisting constipation
Pruritus	Moisturize skin Trim child's nails to prevent excoriation Try specialized antiitch lotions Apply cold packs Counterstimulation, distraction, relaxation
Diarrhea	Evaluate/treat if due to obstipation Assess and treat infection Dietary modification
Depression	Psychotherapy, behavioral techniques, setting attainable daily goals Aromatherapy*: bergamot, lavender
Anxiety	Psychotherapy (individual and family), behavioral techniques Aromatherapy*: clary sage, angelica, mandarin, lavender
Agitation/terminal restlessness	Evaluate for organic or drug causes Educate family Orient and reassure child; provide calm, nonstimulating environment, use familiar music, verse, voice, touch Aromatherapy*: frankincense, ylang ylang

*Best if aromatherapy is administered by a practitioner trained in aromatherapy.

From Sourkes B, Frankel L, Brown M, et al: Food, toys, and love: pediatric palliative care, *Curr Probl Pediatr Adolesc Health Care* 35:345-392, 2005.

Nutrition

Table 45-2 Conditions for Which Human Milk Has Been Suggested to Possibly Have a Protective Effect

Acute disorders	Crohn disease
Diarrhea	Childhood cancer
Otitis media	Lymphoma
Urinary tract infection	Leukemia
Necrotizing enterocolitis	Recurrent otitis media
Septicemia	Allergy
Infant botulism	Obesity and overweight
Insulin-dependent diabetes mellitus	Hospitalizations
Celiac disease	Infant mortality

Table 45-1 Selected Beneficial Properties of Human Milk Compared to Infant Formula

Secretory IgA	Specific antigen-targeted antiinfective action
Lactoferrin	Immunomodulation, iron chelation, antimicrobial action, antiadhesive, trophic for intestinal growth
κ-Casein	Antiadhesive, bacterial flora
Oligosaccharides	Prevention of bacterial attachment
Cytokines	Antiinflammatory, epithelial barrier function
Growth factors	
Epidermal growth factor	Luminal surveillance, repair of intestine
Transforming growth factor (TGF)	Promotes epithelial cell growth (TGF-β) Suppresses lymphocyte function (TGF-β)
Nerve growth factor	Promotes neural growth
Enzymes	
Platelet-activating factor-acetylhydrolase	Blocks action of platelet-activating factor
Glutathione peroxidase	Prevents lipid oxidation
Nucleotides	Enhance antibody responses, bacterial flora

Adapted from Hamosh M: Bioactive factors in human milk, Pediatr Clin North Am *48:69–86, 2001.*

Table 45-3 Absolute and Relative Contraindications to Breastfeeding Because of Maternal Health Conditions

MATERNAL HEALTH CONDITION	DEGREE OF RISK
HIV and HTLV infection	In the United States, breastfeeding is contraindicated In other settings, health risks of not breastfeeding must be weighed against the risk of transmitting virus to the infant
Tuberculosis infection	Breastfeeding is contraindicated until completion of approximately 2 wk of appropriate maternal therapy
Varicella-zoster infection	Infant should not have direct contact to active lesions Infant should receive immune globulin
Herpes simplex infection	Breastfeeding is contraindicated with active herpetic lesions of the breast
CMV infection	May be found in milk of mothers who are CMV seropositive Transmission through human milk causing symptomatic illness in term infants is uncommon
Hepatitis B infection	Infants routinely receive hepatitis B immune globulin and hepatitis B vaccine if mother is HbsAg positive No delay in initiation of breastfeeding is required
Hepatitis C infection	Breast-feeding is not contraindicated
Alcohol intake	Limit maternal alcohol intake to <0.5 g/kg/day (for a woman of average weight, this is the equivalent of 2 cans of beer, 2 glasses of wine, or 2 oz of liquor)
Cigarette smoking	Discourage cigarette smoking, but smoking is not a contraindication to breastfeeding
Chemotherapy, radiopharmaceuticals	Breastfeeding is generally contraindicated

Table 45-4 Recommendations on Breastfeeding Management for Healthy Term Infants

1. Exclusive breastfeeding for about 6 months
   - Breastfeeding preferred; alternatively expressed mother's milk, or donor breast milk
   - To continue for at least the first year and beyond as long as mutually desired by mother and child
   - Complementary foods rich in iron and other micronutrients should be introduced at about 6 mo of age
2. Peripartum policies and practices that optimize breastfeeding initiation and maintenance should be compatible with the AAP and Academy of Breastfeeding Medicine Model Hospital Policy and include the following:
   - Direct skin-to-skin contact with mothers immediately after delivery until the first feeding is accomplished and encouraged throughout the postpartum period
   - Delay in routine procedures (weighing, measuring, bathing, blood tests, vaccines, and eye prophylaxis) until after the first feeding is completed
   - Delay in administration of intramuscular vitamin K until after the first feeding is completed but within 6 hr of birth
   - Ensure 8-12 feedings at the breast every 24 hr
   - Ensure formal evaluation and documentation of breastfeeding by trained caregivers (including position, latch, milk transfer, examination) at least once for each nursing shift
   - Give no supplements (water, glucose water, commercial infant formula, or other fluids) to breastfeeding newborn infants unless medically indicated using standard evidence-based guidelines for the management of hyperbilirubinemia and hypoglycemia
   - Avoid routine pacifier use in the postpartum period
   - Begin daily oral vitamin D drops (400 IU) at hospital discharge
3. All breastfeeding infants should be seen by a pediatrician within 48 to 72 hr after discharge from the hospital
   - Evaluate hydration (elimination patterns)
   - Evaluate body weight gain (body weight loss no more than 7% from birth and no further weight loss by day 5: assess feeding and consider more frequent follow-up)
   - Discuss maternal/infant issues
   - Observe feeding
4. Mother and infant should sleep in proximity to each other to facilitate breastfeeding
5. Pacifier should be offered, while placing infant in back-to-sleep-position, no earlier than 3 to 4 weeks of age and after breastfeeding has been established

Table 46-2 Classification of Undernutrition

CLASSIFICATION	INDEX	GRADING
Gomez (underweight)	90-75% of median weight-for-age	Grade 1 (mild)
	75-60%	Grade 2 (moderate)
	<60%	Grade 3 (severe)
Waterlow (wasting)	90-80% of median weight-for-height	Mild
	<70%	Severe
Waterlow (stunting)	95-90% of median height-for-age	Mild
	90-85%	Moderate
	<85%	Severe
WHO (wasting)	<–2 to >–3 SD weight-for-height	Moderate
	<–3	Severe
WHO (stunting)	<–2 to >–3 SD height-for-age	Moderate
	<–3	Severe
WHO (wasting) (for age group 6-59 mo)	115-125 mm mid-upper arm circumference	Moderate
	<115 mm	Severe

Table 46-6 Clinical Signs of Malnutrition

SITE	SIGNS
Face	Moon face (kwashiorkor), simian facies (marasmus)
Eye	Dry eyes, pale conjunctiva, Bitot spots (vitamin A), periorbital edema
Mouth	Angular stomatitis, cheilitis, glossitis, spongy bleeding gums (vitamin C), parotid enlargement
Teeth	Enamel mottling, delayed eruption
Hair	Dull, sparse, brittle hair, hypopigmentation, flag sign (alternating bands of light and normal color), broomstick eyelashes, alopecia
Skin	Loose and wrinkled (marasmus), shiny and edematous (kwashiorkor), dry, follicular hyperkeratosis, patchy hyper- and hypopigmentation (crazy paving or flaky paint dermatoses), erosions, poor wound healing
Nails	Koilonychia, thin and soft nail plates, fissures, or ridges
Musculature	Muscle wasting, particularly buttocks and thighs; Chvostek or Trousseau sign (hypocalcemia)
Skeletal	Deformities, usually as a result of calcium, vitamin D, or vitamin C deficiencies
Abdomen	Distended: hepatomegaly with fatty liver; ascites may be present
Cardiovascular	Bradycardia, hypotension, reduced cardiac output, small vessel vasculopathy
Neurologic	Global developmental delay, loss of knee and ankle reflexes, impaired memory
Hematologic	Pallor, petechiae, bleeding diathesis
Behavior	Lethargic, apathetic, irritable on handling

From Grover Z, Ee LC: Protein energy malnutrition, Pediatr Clin N Am *56:1055–1068, 2009.*

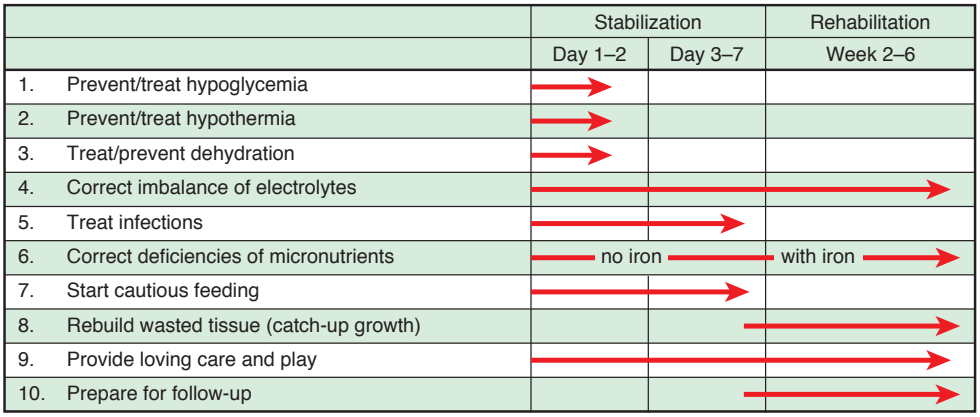


Figure 46-6 The 10 steps of treatment for severe acute malnutrition and their approximate time frames.

Table 46-7 Emergency Treatment in Severe Malnutrition

CONDITION	IMMEDIATE ACTION
Shock • lethargic or unconscious and • cold hands Plus either: • slow capillary refill (longer than 3 sec) or • weak fast pulse	1. Give oxygen 2. Give sterile 10% glucose (5 mL/kg) by IV 3. Give IV fluid at 15 mL/kg over 1 hr, using: • Ringers lactate with 5% dextrose or • half-normal saline with 5% dextrose or • half-strength Darrow solution with 5% dextrose • if all of the above are unavailable, Ringer lactate 4. Measure and record pulse and respirations at the start and every 10 minutes If there are signs of improvement (pulse and respiration rates fall) repeat IV 15 mL/kg for 1 more hr. Then switch to oral or nasogastric rehydration with ReSoMal, 5-10 mL/kg in alternate hr (see Table 46-8 step 3) If there are no signs of improvement assume septic shock and: 1. Give maintenance fluid IV (4 mL/kg/hr) while waiting for blood 2. Order 10 mL/kg fresh whole blood and transfuse slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood 3. Give furosemide 1 mL/kg IV at the start of the transfusion
Hypoglycemia Blood glucose less than 3 mmol/L	See Table 46-8 step 1 for treatment
Severe dehydration	Do *not* give IV fluids except in shock See Table 46-8 step 3 for treatment
Very severe anemia Hb less than 4 g/dL	If very severe anemia (or Hb 4-6 g/dL AND respiratory distress): 1. Give whole blood 10 mL/kg slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood 2. Give furosemide 1 mL/kg IV at the start of the transfusion
Emergency eye care Corneal ulceration	If corneal ulceration: 1. Give vitamin A immediately (age <6 mo 50,000 IU, 6-12 mo 100,000 IU, >12 mo 200,000 IU) 2. Instill 1 drop atropine (1%) into affected eye to relax the eye and prevent the lens from pushing out

Table 46-8 Therapeutic Directives for Stabilization

STEP	PREVENTION	TREATMENT
1. Prevent/treat hypoglycemia blood glucose <3 mmol/L	Avoid long gaps without food and minimize need for glucose: 1. Feed immediately 2. Feed every 3 hr day and night (2 hr if ill) 3. Feed on time 4. Keep warm 5. Treat infections (they compete for glucose) *Note:* Hypoglycemia and hypothermia often coexist, and are signs of severe infection	If conscious: 1. 10% glucose (50 mL), or a feed (see step 7), or 1 teaspoon sugar under the tongue-whichever is quickest 2. Feed every 2 hr for at least the first day. Initially give ¼ of feed every 30 min 3. Keep warm 4. Start broad-spectrum antibiotics If unconscious: 1. Immediately give sterile 10% glucose (5 mL/kg) by IV 2. Feed every 2 hr for at least first day. Initially give ¼ of feed every 30 min. Use nasogastric (NG) tube if unable to drink 3. Keep warm. 4. Start broad-spectrum antibiotics
2. Prevent/treat hypothermia axillary <35°C (95°F); rectal <35.5°C (95.9°F)	Keep warm and dry and feed frequently 1. Avoid exposure 2. Dress warmly, including head and cover with blanket 3. Keep room hot; avoid draughts 4. Change wet clothes and bedding 5. Do not bathe if very ill 6. Feed frequently day and night 7. Treat infections	Actively rewarm 1. Feed 2. Skin-to-skin contact with carer ("kangaroo technique") or dress in warmed clothes, cover head, wrap in warmed blanket and provide indirect heat (e.g. heater; transwarmer mattress; incandescent lamp) 3. Monitor temperature hourly (or every 30 min if using heater) 4. Stop rewarming when rectal temperature is 36.5°C (97.7°F)
3. Prevent/treat dehydration	Replace stool losses 1. Give ReSoMal after each watery stool. ReSoMal (37.5 mmol Na/L) is a low-sodium rehydration solution for malnutrition	Do *not* give IV fluids unless the child is in shock 1. Give ReSoMal 5 mL/kg every 30 min for first 2 hr orally or NG tube 2. Then give 5-10 mL/kg in alternate hours for up to 10 hr. Amount depends on stool loss and eagerness to drink. Feed in the other alternate hour 3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins) 4. Stop when rehydrated (3 or more signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate).

Continued

Table 46-8 Therapeutic Directives for Stabilization—cont'd

STEP	PREVENTION	TREATMENT
4. Correct electrolyte imbalance—deficit of potassium and magnesium, excess sodium		1. Give extra potassium (4 mmol/kg/day) and magnesium (0.6 mmol/kg/day) for at least 2 wk (see Table 46-12) *Note:* Potassium and magnesium are already added in Nutriset F75 and F100 packets
5. Prevent/treat infections	Minimize risk of cross-infection 1. Avoid overcrowding 2. Wash hands 3. Give measles vaccine to unimmunized children age >6 mo	Infections are often silent. Starting on the first day, give broad-spectrum antibiotics to all children. 1. For antibiotic choices/schedule see Table 46-9 2. Ensure all doses are given, and given on time 3. Cover skin lesions so they do not become infected *Note:* Avoid steroids as they depress immune function
6. Correct micronutrient deficiencies	*Note:* Folic acid, multivitamins, zinc, copper, and other trace minerals are already added in Nutriset F75 and F100 packets	Do *not* give iron in the stabilization phase 1. Give vitamin A on day 1 (under 6 mo 50,000 units; 6-12 mo 100,000 units; >12 mo 200,000 units) if child has any eye signs of vitamin A deficiency or has had recent measles. Repeat this dose on days 2 and 14 2. Folic acid 1 mg (5 mg on day 1) 3. Zinc (2 mg/kg/day) and copper (0.3 mg/kg/day).These are in the electrolyte/mineral solution and Combined Mineral Vitamin mix (CMV) and can be added to feeds and ReSoMal 4. Multivitamin syrup or CMV
7. Start cautious feeding		1. Give 8-12 small feeds of F75 to provide 130 mL/kg/day,100 kcal/kg/day and 1-1.5 g protein/kg/day 2. If gross edema, reduce volume to 100 ml/kg/day 3. Keep a 24-hr intake chart. Measure feeds carefully. Record leftovers 4. If child has poor appetite, coax and encourage to finish the feed. If unfinished, reoffer later. Use NG tube if eating 80% or less of the amount offered 5. If breastfed, encourage continued breastfeeding but also give F75 6. Transfer to F100 when appetite returns (usually within 1 wk) and edema has been lost or is reduced 7. Weigh daily and plot weight.

Table 46-9 Recommended Antibiotics*

	GIVE
If no complications	Amoxicillin oral 25 mg/kg twice daily for 5 days
If complications (shock, hypoglycemia, hypothermia, skin lesions, respiratory or urinary tract infections, or lethargy/sickly)	Gentamicin (7.5 mg/kg IV or IM) once daily for 7 days *and* Ampicillin (50 mg/kg IV or IM) every 6 hr for 2 days, then oral amoxicillin (25-40 mg/kg) every 8 hr for 5 days

*Local resistance patterns may require these to be adjusted: Ensure that there is Gram-negative cover.
If specific infections are identified, add appropriate antibiotics.
For persistent diarrhea/small bowel overgrowth, add metronidazole (7.5 mg/kg oral) every 8 hr for 7 days.

Table 46-10 Recipes for Milk Formulas F75 and F100

	F75[b] (STARTER)	F75[c] (STARTER) (CEREAL-BASED)	F100[d] (CATCH-UP)
Dried skimmed milk (g)	25	25	80
Sugar (g)	100	70	50
Cereal flour (g)	—	35	—
Vegetable oil (g)	30	30	60
Electrolyte/mineral solution (mL)[a]	20	20	20
Water: make up to (mL)	1000	1000	1000
Content/100 mL			
Energy (kcal)	75	75	100
Protein (g)	0.9	1.1	2.9
Lactose (g)	1.3	1.3	4.2
Potassium (mmol)	4.0	4.2	6.3
Sodium (mmol)	0.6	0.6	1.9
Magnesium (mmol)	0.43	0.46	0.73
Zinc (mg)	2.0	2.0	2.3
Copper (mg)	0.25	0.25	0.25
% Energy from protein	5	6	12
% Energy from fat	32	32	53
Osmolality (mOsm/L)	413	334	419

Whisk at high speed to prevent oil from separating out.
[a]See Table 46-12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).
[b]A comparable F75 can be made from 35 g dried whole milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 300 mL full cream cow's milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.
[c]This lower-osmolality formula may be helpful for children with dysentery or persistent diarrhea. Cook for 4 min.
[d]A comparable F100 can be made from 110 g dried whole milk, 50 g sugar, 30 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 880 mL full cream cow's milk, 75 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.

Table 46-11 Recipe for Rehydration Solution for Malnutrition (ReSoMal)

INGREDIENT	AMOUNT
Water	2 L
WHO-ORS	One 1-L sachet*
Sucrose	50 g
Electrolyte/mineral solution†	mL

ReSoMal contains 37.5 mmol sodium and 40 mmol potassium/L
*Sachet contains 2.6 g sodium chloride, 2.9 g trisodium citrate, 1.5 g potassium chloride, 13.5 g glucose.
†See Table 46-12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).

Table 46-12 Recipe for Concentrated Electrolyte/Mineral Solution*

INGREDIENT	g	mol/20 mL
Potassium chloride: KCl	224.0	24 mmol
Tripotassium citrate	81.0	2 mmol
Magnesium chloride: $MgCl_2$. $6H_2O$	76.0	3 mmol
Zinc acetate: Zn acetate.$2H_2O$	8.2	300 µmol
Copper sulfate: $CuSO_4$. $5H_2O$	1.4	45 µmol
Water: make up to	2500 mL	

Add 20 mL when preparing 1 L of feed or ReSoMal.
*Make fresh each month. Use cooled boiled water.

Table 46-13 Clinical Signs and Symptoms of Refeeding Syndrome

HYPOPHOSPHATEMIA	HYPOKALEMIA	HYPOMAGNESEMIA	VITAMIN/THIAMINE DEFICIENCY	SODIUM RETENTION	HYPERGLYCEMIA
Cardiac Hypotension Decreased stroke volume **Respiratory** Impaired diaphragm contractility Dyspnea Respiratory failure **Neurologic** Paresthesia Weakness Confusion Disorientation Lethargy Areflexic paralysis Seizures Coma **Hematologic** Leukocyte dysfunction Hemolysis Thrombocytopenia **Other** Death	**Cardiac** Arrhythmias **Respiratory** Failure **Neurologic** Weakness Paralysis **Gastrointestinal** Nausea Vomiting Constipation **Muscular** Rhabdomyolysis Muscle necrosis **Other** Death	**Cardiac** Arrhythmias **Neurologic** Weakness Tremor Tetany Seizures Altered mental status Coma **Gastrointestinal** Nausea Vomiting Diarrhea **Other** Refractory hypokalemia and hypocalcemia Death	Encephalopathy Lactic acidosis Death	Fluid overload Pulmonary edema Cardiac compromise	**Cardiac** Hypotension **Respiratory** Hypercapnia Failure **Other** Ketoacidosis Coma Dehydration Impaired immune function

Data from Kraft MD, Btaiche IF, Sacks GS: Review of RFS, Nutr Clin Pract *20:625–633, 2005. From Fuentebella J, Kerner JA: Refeeding syndrome,* Pediatr Clin North Am *56:1201–1210, 2009.*

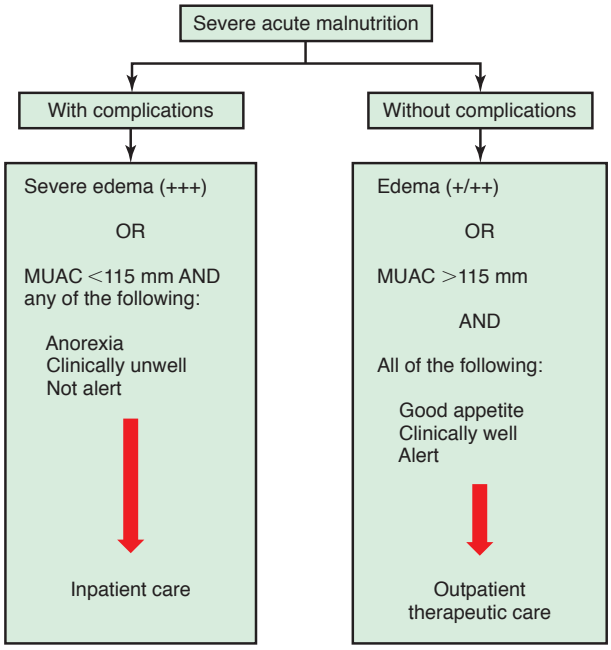


Figure 46-7 Flow diagram for inpatient and outpatient care in the child with severe acute malnutrition. MUAC, Mid upper arm circumference.

Table 47-1 Endocrine and Genetic Causes of Obesity

DISEASE	SYMPTOMS	LABORATORY
ENDOCRINE		
Cushing syndrome	Central obesity, hirsutism, moon face, hypertension	Dexamethasone suppression test
GH deficiency	Short stature, slow linear growth	Evoked GH response, IGF-1
Hyperinsulinism	Nesidioblastosis, pancreatic adenoma, hypoglycemia, Mauriac syndrome	Insulin level
Hypothyroidism	Short stature, weight gain, fatigue, constipation, cold intolerance, myxedema	TSH, FT_4
Pseudohypoparathyroidism	Short metacarpals, subcutaneous calcifications, dysmorphic facies, mental retardation, short stature, hypocalcemia, hyperphosphatemia	Urine cAMP after synthetic PTH infusion
GENETIC		
Alstrom syndrome	Cognitive impairment, retinitis pigmentosa, diabetes mellitus, hearing loss, hypogonadism, retinal degeneration	*ALMS1* gene
Bardet-Biedl syndrome	Retinitis pigmentosa, renal abnormalities, polydactyly, hypogonadism	*BBS1* gene
Biemond syndrome	Cognitive impairment, iris coloboma, hypogonadism, polydactyly	
Carpenter syndrome	Polydactyly, syndactyly, cranial synostosis, mental retardation	Mutations in the *RAB23* gene, located on chromosome 6 in humans
Cohen syndrome	Mid-childhood-onset obesity, short stature, prominent maxillary incisors, hypotonia, mental retardation, microcephaly, decreased visual activity	Mutations in the *VPS13B* gene (often called the *COH1* gene) at locus 8q22
Deletion 9q34	Early-onset obesity, mental retardation, brachycephaly, synophrys, prognathism, behavior and sleep disturbances	Deletion 9q34
Down syndrome	Short stature, dysmorphic facies, mental retardation	Trisomy 21
ENPP1 gene mutations	Insulin resistance, childhood obesity	Gene mutation on chromosome 6q
Fröhlich syndrome	Hypothalamic tumor	
FTO gene polymorphism	Dysregulation of orexigenic hormone acyl-ghrelin, poor postprandial appetite suppression	Homozygous for *FTO* AA allele
Leptin or leptin receptor gene deficiency	Early-onset severe obesity, infertility (hypogonadotropic hypogonadism)	Leptin
Melanocortin 4 receptor gene mutation	Early-onset severe obesity, increased linear growth, hyperphagia, hyperinsulinemia Most common known genetic cause of obesity Homozygous worse than heterozygous	*MC4R* mutation
Prader-Willi Syndrome	Neonatal hypotonia, slow infant growth, small hands and feet, mental retardation, hypogonadism, hyperphagia leading to severe obesity, paradoxically elevated ghrelin	Partial deletion of chromosome 15 or loss of paternally expressed genes
Proopiomelanocortin deficiency	Obesity, red hair, adrenal insufficiency, hyperproinsulinemia	Loss-of-function mutations of the *POMC* gene
Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD)	Often confused with congenital central hypoventilation syndrome (CCHS), presentation ≥1.5 yr with weight gain, hyperphagia, hypoventilation, cardiac arrest, central diabetes insipidus, hypothyroidism, growth hormone deficiency, pain insensitivity, hypothermia, precocious puberty, neural crest tumors	Unknown genes May be a paraneoplastic disorder
Turner syndrome	Ovarian dysgenesis, lymphedema, web neck, short stature, cognitive impairment	XO chromosome

cAMP, cyclic adenosine monophosphate; FT_4, free thyroxine; GH, growth hormone; IGF, insulin-like growth factor; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

Table 47-2 Obesity-Associated Comorbidities

DISEASE	POSSIBLE SYMPTOMS	LABORATORY CRITERIA
CARDIOVASCULAR		
Dyslipidemia	HDL <40, LDL >130, total cholesterol >200	Fasting total cholesterol, HDL, LDL, triglycerides
Hypertension	SBP >95% for sex, age, height	Serial testing, urinalysis, electrolytes, blood urea nitrogen, creatinine
ENDOCRINE		
Type 2 diabetes mellitus	Acanthosis nigrans, polyuria, polydipsia	Fasting blood glucose >110, hemoglobin A_{1c}, insulin level, C-peptide, oral glucose tolerance test
Metabolic syndrome	Central adiposity, insulin resistance, dyslipidemia, hypertension, glucose intolerance	Fasting glucose, LDL and HDL cholesterol
Polycystic ovary syndrome	Irregular menses, hirsutism, acne, insulin resistance, hyperandrogenemia	Pelvic ultrasound, free testosterone, LH, FSH
GASTROINTESTINAL		
Gallbladder disease	Abdominal pain, vomiting, jaundice	Ultrasound
Nonalcoholic fatty liver disease (NAFLD)	Hepatomegaly, abdominal pain, dependent edema, ↑ transaminases Can progress to fibrosis, cirrhosis	AST, ALT, ultrasound, CT, or MRI
NEUROLOGIC		
Pseudotumor cerebri	Headaches, vision changes, papilledema	Cerebrospinal fluid opening pressure, CT, MRI
Migraines	Hemicrania, headaches	None
ORTHOPEDIC		
Blount disease (tibia vara)	Severe bowing of tibia, knee pain, limp	Knee x-rays
Musculoskeletal problems	Back pain, joint pain, frequent strains or sprains, limp, hip pain, groin pain, leg bowing	X-rays
Slipped capital femoral epiphysis	Hip pain, knee pain, limp, decreased mobility of hip	Hip x-rays
PSYCHOLOGICAL		
Behavioral complications	Anxiety, depression, low self-esteem, disordered eating, signs of depression, worsening school performance, social isolation, problems with bullying or being bullied	Child Behavior Checklist, Children's Depression Inventory, Peds QL, Eating Disorder Inventory 2, subjective ratings of stress and depression, Behavior Assessment System for Children, Pediatric Symptom Checklist
PULMONARY		
Asthma	Shortness of breath, wheezing, coughing, exercise intolerance	Pulmonary function tests, peak flow
Obstructive sleep apnea	Snoring, apnea, restless sleep, behavioral problems	Polysomnography, hypoxia, electrolytes (respiratory acidosis with metabolic alkalosis)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; MRI, magnetic resonance imaging; Peds QL, Pediatric Quality of Life Inventory; SBP, systolic blood pressure.

Table 47-6 Proposed Suggestions for Preventing Obesity

PREGNANCY
Normalize body mass index before pregnancy.
Do not smoke.
Maintain moderate exercise as tolerated.
In gestational diabetics, provide meticulous glucose control.
Gestational weight gain within the Institute of Medicine (IOM) recommendations.
POSTPARTUM AND INFANCY
Breastfeeding: exclusive for 4-6 mo, continue with other foods for 12 mo.
Postpone the introduction of baby foods to 4-6 mo and juices to 12 mo.
FAMILIES
Eat meals as a family in a fixed place and time.
Do not skip meals, especially breakfast.
No television during meals.
Use small plates, and keep serving dishes away from the table.
Avoid unnecessary sweet or fatty foods and sugar-sweetened drinks.
Remove televisions from children's bedrooms; restrict times for television viewing and video games.
Do not use food as a reward.
SCHOOLS
Eliminate candy and cookie sales as fundraisers.
Review the contents of vending machines and replace with healthier choices; eliminate sodas.
Avoid financial support for sports teams from beverage and food industries.
Install water fountains and hydration stations.
Educate teachers, especially physical education and science faculty, about basic nutrition and the benefits of physical activity.
Educate children from preschool through high school on appropriate diet and lifestyle.
Mandate minimum standards for physical education, including 60 min of strenuous exercise 5 times weekly.
Encourage "the walking school bus": groups of children walking to school with adult supervision.
COMMUNITIES
Increase family-friendly exercise and safe play facilities for children of all ages.
Develop more mixed residential-commercial developments for walkable and bicyclable communities.
Discourage the use of elevators and moving walkways.
Provide information on how to shop and prepare healthier versions of culture-specific foods.
HEALTHCARE PROVIDERS
Explain the biologic and genetic contributions to obesity.
Give age-appropriate expectations for body weight in children.
Work toward classifying obesity as a disease to promote recognition, reimbursement for care, and willingness and ability to provide treatment.
INDUSTRY
Mandate age-appropriate nutrition labeling for products aimed at children (e.g., red light/green light foods, with portion sizes).
Encourage marketing of interactive video games in which children must exercise in order to play.
Use celebrity advertising directed at children for healthful foods to promote breakfast and regular meals.
Reduce portion size (drinks and meals).
GOVERNMENT AND REGULATORY AGENCIES
Classify childhood obesity as a legitimate disease.
Find novel ways to fund healthy lifestyle programs (e.g., with revenues from food and drink taxes).
Subsidize government-sponsored programs to promote the consumption of fresh fruits and vegetables.
Provide financial incentives to industry to develop more healthful products and to educate the consumer on product content.
Provide financial incentives to schools that initiate innovative physical activity and nutrition programs.
Allow tax deductions for the cost of weight loss and exercise programs.
Provide urban planners with funding to establish bicycle, jogging, and walking paths.
Ban advertising of fast foods, nonnutritious foods, and sugar-sweetened beverages directed at preschool children, and restrict advertising to school-age children.
Ban toys as gifts to children for purchasing fast foods.

Adapted from Speiser PW, Rudolf MCJ, Anhalt H, et al: Consensus statement: childhood obesity, J Clin Endocrinol Metab *90:1871–1887, 2005.*

Table 47-7 Anticipatory Guidance: Establishing Healthy Eating Habits in Children

Do not punish a child during mealtimes with regard to eating. The emotional atmosphere of a meal is very important. Interactions during meals should be pleasant and happy.
Do not use foods as rewards.
Parents, siblings, and peers should model healthy eating, tasting new foods, and eating a well-balanced meal.
Children should be exposed to a wide range of foods, tastes, and textures.
New foods should be offered multiple times. Repeated exposure leads to acceptance and liking.
Forcing a child to eat a certain food will decrease the child's preference for that food. Children's wariness of new foods is normal and should be expected. Offering a variety of foods with low-energy density helps children balance energy intake.
Parents should control what foods are in the home. Restricting access to foods in the home will increase rather than decrease a child's desire for that food.
Children tend to be more aware of satiety than adults, so allow children to respond to satiety, and stop eating. Do not force children to "clean their plate."

Adapted from Benton D: Role of parents in the determination of food preferences of children and the development of obesity, Int J Obes Relat Metab Disord *28:858–869, 2004. Copyright 2004. Reprinted by permission from Macmillan Publishers Ltd.*

Table 49-1 Water-Soluble Vitamins

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETARY SOURCES	RDA* BY AGE
Thiamine (vitamin B_1)	Coenzyme in carbohydrate metabolism Nucleic acid synthesis Neurotransmitter synthesis	Neurologic (dry beriberi): irritability, peripheral neuritis, muscle tenderness, ataxia Cardiac (wet beriberi): tachycardia, edema, cardiomegaly, cardiac failure	3-5 mg/day PO thiamine for 6 wk	Polished rice–based diets Malabsorptive states Severe malnutrition Malignancies Alcoholism	Meat, especially pork; fish; liver Rice (unmilled), wheat germ; enriched cereals; legumes	0-6 mo: 0.2 mg/day 7-12 mo: 0.3 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 0.9 mg/day 14-18 yr: Girls: 1.0 mg/day Boys: 1.2 mg/day
Riboflavin (vitamin B_2)	Constituent of flavoprotein enzymes important in oxidation-reduction reactions: amino acid, fatty acid, and carbohydrate metabolism and cellular respiration	Glossitis, photophobia, lacrimation, corneal vascularization, poor growth, cheilosis	3-10 mg/day PO riboflavin	Severe malnutrition Malabsorptive states Prolonged treatment with phenothiazines, probenecid, or OCPs	Milk, milk products, eggs, fortified cereals, green vegetables	0-6 mo: 0.3 mg/day 7-12 mo: 0.4 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 0.9 mg/day 14-18 yr: Girls: 1.0 mg/day Boys: 1.3 mg/day
Niacin (vitamin B_3)	Constituent of NAD and NADP, important in respiratory chain, fatty acid synthesis, cell differentiation, and DNA processing	Pellagra manifesting as diarrhea, symmetric scaly dermatitis in sun-exposed areas, and neurologic symptoms of disorientation and delirium	50-300 mg/day PO niacin	Predominantly maize-based diets Anorexia nervosa Carcinoid syndrome	Meat, fish, poultry Cereals, legumes, green vegetables	0-6 mo: 2 mg/day 7-12 mo: 4 mg/day 1-3 yr: 6 mg/day 4-8 yr: 8 mg/day 9-13 yr: 12 mg/day 14-18 yr: Girls: 14 mg/day Boys: 16 mg/day
Pyridoxine (vitamin B_6)	Constituent of coenzymes for amino acid and glycogen metabolism, heme synthesis, steroid action, neurotransmitter synthesis	Irritability, convulsions, hypochromic anemia Failure to thrive Oxaluria	5-25 mg/day PO for deficiency states 100 mg IM or IV for pyridoxine-dependent seizures	Prolonged treatment with INH, penicillamine, OCPs	Fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, potatoes	0-6 mo: 0.1 mg/day 7-12 mo: 0.3 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 1.0 mg/day 14-18 yr: Girls: 1.2 mg/day Boys: 1.3 mg/day

Continued

Table 51-4 Laboratory Findings in Various Disorders Causing Rickets

DISORDER	Ca	Pi	PTH	25-(OH)D	1,25-$(OH)_2$D	Alk Phos	URINE Ca	URINE Pi
Vitamin D deficiency	N, ↓	↓	↑	↓	↓, N, ↑	↑	↓	↑
Chronic kidney disease	N, ↓	↑	↑	N	↓	↑	N, ↓	↓
Dietary Pi deficiency	N	↓	N, ↓	N	↑	↑	↑	↓
Tumor-induced rickets	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dietary Ca deficiency	N, ↓	↓	↑	N	↑	↑	↓	↑

↓, decreased; ↑, increased; ↑↑, extremely increased; 1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ADHR, autosomal dominant hypophosphatemic rickets; Alk Phos, alkaline phosphatase; ARHR, autosomal recessive hypophosphatemic rickets; Ca, calcium; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; N, normal; Pi, inorganic phosphorus; PTH, parathyroid hormone; RD, relatively decreased (because it should be increased given the concurrent hypophosphatemia); VDDR, vitamin D–dependent rickets; XLH, X-linked hypophosphatemic rickets.

Table 49-1 Water-Soluble Vitamins—cont'd

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETARY SOURCES	RDA* BY AGE
Biotin	Cofactor for carboxylases, important in gluconeogenesis, fatty acid and amino acid metabolism	Scaly periorificial dermatitis, conjunctivitis, alopecia, lethargy, hypotonia, and withdrawn behavior	1-10 mg/day PO biotin	Consumption of raw eggs for prolonged periods Parenteral nutrition with infusates lacking biotin Valproate therapy	Liver, organ meats, fruits	0-6 mo: 5 µg/day 7-12 mo: 6 µg/day 1-3 yr: 8 µg/day 4-8 yr: 12 µg/day 9-13 yr: 20 µg/day 14-18 yr: 25 µg/day
Pantothenic acid (vitamin B_5)	Component of coenzyme A and acyl carrier protein involved in fatty acid metabolism	Experimentally produced deficiency in humans: irritability, fatigue, numbness, paresthesias (burning feet syndrome), muscle cramps		Isolated deficiency extremely rare in humans	Beef, organ meats, poultry, seafood, egg yolk Yeast, soybeans, mushrooms	0-6 mo: 1.7 mg/day 7-12 mo: 1.8 mg/day 1-3 yr: 2 mg/day 4-8 yr: 3 mg/day 9-13 yr: 4 mg/day 14-18 yr: 5 mg/day
Folic acid	Coenzymes in amino acid and nucleotide metabolism as an acceptor and donor of one-carbon units	Megaloblastic anemia Growth retardation, glossitis Neural tube defects in progeny	0.5-1 mg/day PO folic acid	Malnutrition Malabsorptive states Malignancies Hemolytic anemias Anticonvulsant therapy	Enriched cereals, beans, leafy vegetables, citrus fruits, papaya	0-6 mo: 65 µg/day 7-12 mo: 80 µg/day 1-3 yr: 150 µg/day 4-8 yr: 200 µg/day 9-13 yr: 300 µg/day 14-18 yr: 400 µg/day
Cobalamin (vitamin B_{12})	As deoxyadenosylcobalamin, acts as cofactor for lipid and carbohydrate metabolism As methylcobalamin, important for conversion of homocysteine to methionine and folic acid metabolism	Megaloblastic anemia, irritability, developmental delay, developmental regression, involuntary movements, hyperpigmentation	1,000 µg IM vitamin B_{12}	Vegan diets Malabsorptive states Crohn disease Intrinsic factor deficiency (pernicious anemia)	Organ meats, sea foods poultry, egg yolk, milk, fortified ready-to-eat cereals	0-6 mo: 0.4 µg/day 7-12 mo: 0.5 µg/day 1-3 yr: 0.9 µg/day 4-8 yr: 1.2 µg/day 9-13 yr: 1.8 µg/day 14-18 yr: 2.4 µg/day
Ascorbic acid (vitamin C)	Important for collagen synthesis, metabolism of cholesterol and neurotransmitters Antioxidant functions and nonheme iron absorption	Scurvy manifesting as irritability, tenderness and swelling of legs, bleeding gums, petechiae, ecchymoses, follicular hyperkeratosis, and poor wound healing	100-200 mg/day PO ascorbic acid for up to 3 mo	Predominantly milk-based (non–human milk) diets Severe malnutrition	Citrus fruits and fruit juices, peppers, berries, melons, tomatoes, cauliflower, leafy green vegetables	0-6 mo: 40 mg/day 7-12 mo: 50 mg/day 1-3 yr: 15 mg/day 4-8 yr: 25 mg/day 9-13 yr: 45 mg/day 14-18 yr: Girls: 65 mg/day Boys: 75 mg/day

*For healthy breastfed infants, the values represent adequate intakes, that is, the mean intake of apparently "normal" infants.

INH, isoniazid; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; OCP, oral contraceptive pill; RDA, recommended dietary allowance.

Source: Dietary Reference Intakes (DRIs): Recommended dietary allowances and adequate intakes, vitamins. *Food and Nutrition Board, Institute of Medicine, National Academies. Available from:* http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables.

Table 51-5 Biochemical Changes in Genetic Causes of Rickets

	SERUM BIOCHEMISTRY							URINE BIOCHEMISTRY		
	Phosphate	**Calcium**	**PTH**	**250HD**	**1,250H$_2$D**	**FGF23**	**Alk Phos**	**Phosphate**	**Calcium**	**OTHER FEATURES**
HYPOCALCEMIC VITAMIN D PATHWAY DEFECTS										
Vitamin D deficiency	Low	Variable	High	Low	Might be increased	NA	Increased	Increased	Low	Variable aminoaciduria
VDDR1B	Low	Low	High	Very low	Variable	NA	Increased	Increased	Low	250HD does not increase after vitamin D dosing
VDDR1A	Low	Low	High	Normal or high	Very low or ND	NA	Increased	Increased	Low	250HD does increase after vitamin D dosing
VDDR2A	Low	Low	High	Normal or high	High	NA	Increased	Increased	Low	—
VDDR2B	Low	Low	High	Normal or high	High	NA	Increased	Increased	Low	—
HYPOPHOSPHATEMIC RICKETS WITH RAISED FGF23										
XLH	Low	Normal	Normal or slightly high	Normal	Low	High	Increased	Increased	Variable	Urine calcium : creatinine used in monitoring therapy
ADHR	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
ARHR1	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
ARHR2	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
HYPOPHOSPHATEMIC RICKETS WITHOUT RAISED FGF23										
Dent's disease*	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	High	Low molecular weight proteinuria
HHRH	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	High	No loss of low molecular weight protein
αKlotho mutation	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	Variable	—
OTHER INHERITED RACHITIC DISORDERS										
HPP (severe)	High	High	Low	Normal	Normal	Normal	Very low	Normal or high	High	Raised concentrations of mineralization inhibitors
HPP (mild)	Normal or high	Normal or high	Low or normal	Normal	Normal	Normal	Low	Normal	Variable	Raised concentrations of mineralization inhibitors

From Elder CJ, Bishop NJ: Rickets. Lancet *383:1665-1674, 2014.*

PTH, parathyroid hormone; 250HD, calcidiol; 1,2SOH$_2$D, calcitriol; FGF23, fibroblast growth factor 23; Alk phos, alkaline phosphatase; NA, data not available; VDDR1B, vitamin D–dependent rickets due to defects in CYP2R1 encoding vitamin D 25-hydroxylase; VDDR1A, vitamin D–dependent rickets due to defects in CYP27BI encoding 25-hydroxyvitamin D-1alpha hydroxylase; ND, not detected; VDDR2A, vitamin D–dependent rickets due to defects in VDR encoding the vitamin D receptor; VDDR2B, vitamin D–dependent rickets due to defects in *HNRNPC* encoding hnRNPC1 and hnRNPC2; XLH, X-linked hypophosphatemic rickets due to mutations in *PHEX*; ADHR, autosomal dominant hypophosphatemic rickets due to mutations in *FGF23*; ARHR1, autosomal recessive hypophosphatemic rickets due to mutations in DMP1; ARHR2, autosomal recessive hypophosphatemic rickets due to mutations in *ENPP1*; HHRH, hereditary hypophosphatemic rickets with hypercalciuria due to mutations in *SLC34A3*; HPP, hypophosphatasia.

*Dent's disease is due to mutations in CLCN$_5$.

Table 54-1 Trace Elements

ELEMENT	PHYSIOLOGY	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	DIETARY SOURCES
Chromium	Potentiates the action of insulin	Impaired glucose tolerance, peripheral neuropathy, and encephalopathy	Unknown	Meat, grains, fruits, and vegetables
Copper	Absorbed via specific intestinal transporter Circulates bound to ceruloplasmin Enzyme cofactor (superoxide dismutase, cytochrome oxidase, and enzymes involved in iron metabolism and connective tissue formation)	Microcytic anemia, osteoporosis, neutropenia, neurologic symptoms, depigmentation of hair and skin	Acute: nausea, emesis, abdominal pain, coma, and hepatic necrosis Chronic toxicity (liver and brain injury) occurs in Wilson disease (see Chapter 357.2) and secondary to excess intake (see Chapter 357.3)	Vegetables, grains, nuts, liver, margarine, legumes, corn oil
Fluoride	Incorporated into bone	Dental caries (see Chapter 312)	Chronic: dental fluorosis (see Chapter 307)	Toothpaste, fluoridated water
Iodine	Component of thyroid hormone (see Chapter 564)	Hypothyroidism (see Chapters 566 and 568)	Hypothyroidism and goiter (see Chapters 566 and 568); maternal excess can cause congenital hypothyroidism and goiter (see Chapter 568.1)	Saltwater fish, iodized salt
Iron	Component of hemoglobin, myoglobin, cytochromes, and other enzymes	Anemia (see Chapter 456), decreased alertness, impaired learning	Acute (see Chapter 63): nausea, vomiting, diarrhea, abdominal pain, and hypotension Chronic excess usually secondary to hereditary disorders (see Chapters 463.9 and 357.4); causes organ dysfunction	Meat, fortified foods Deficiency can also result from blood loss (hookworm infestation, menorrhagia)
Manganese	Enzyme cofactor	Hypercholesterolemia, weight loss, decreased clotting proteins*	Neurologic manifestations, cholestatic jaundice	Nuts, meat, grains, tea
Molybdenum	Enzyme cofactor (xanthine oxidase and others)	Tachycardia, tachypnea, night blindness, irritability, coma*	Hyperuricemia and increased risk of gout	Legumes, grains, liver
Selenium	Enzyme cofactor (prevents oxidative damage)	Cardiomyopathy (Keshan disease), myopathy	Nausea, diarrhea, neurologic manifestations, nail and hair changes, garlic odor	Meat, seafood, whole grains, garlic
Zinc	Enzyme cofactor Constituent of zinc-finger proteins, which regulate gene transcription	Decreased growth, dermatitis of extremities and around orifices, impaired immunity, poor wound healing, hypogonadism, diarrhea Supplements beneficial in diarrhea and improve neurodevelopmental outcomes	Abdominal pain, diarrhea, vomiting Can worsen copper deficiency	Meat, shellfish, whole grains, legumes, cheese

*These deficiency states have been reported only in case reports associated with parenteral nutrition or highly unusual diets.

Electrolyte and Acid-Base Disorders

Table 55-1 Causes of Hypernatremia

EXCESSIVE SODIUM
Improperly mixed formula
Excess sodium bicarbonate
Ingestion of seawater or sodium chloride
Intentional salt poisoning (child abuse or Munchausen syndrome by proxy)
Intravenous hypertonic saline
Hyperaldosteronism
WATER DEFICIT
Nephrogenic diabetes insipidus
Acquired
X-linked (OMIM 304800)
Autosomal recessive (OMIM 222000)
Autosomal dominant (OMIM 125800)
Central diabetes insipidus
Acquired
Autosomal recessive (OMIM 125700)
Autosomal dominant (OMIM 125700)
Wolfram syndrome (OMIM 222300/598500)
Increased insensible losses
Premature infants
Radiant warmers
Phototherapy
Inadequate intake:
Ineffective breastfeeding
Child neglect or abuse
Adipsia (lack of thirst)
WATER AND SODIUM DEFICITS
Gastrointestinal losses
Diarrhea
Emesis/nasogastric suction
Osmotic cathartics (lactulose)
Cutaneous losses
Burns
Excessive sweating
Renal losses
Osmotic diuretics (mannitol)
Diabetes mellitus
Chronic kidney disease (dysplasia and obstructive uropathy)
Polyuric phase of acute tubular necrosis
Postobstructive diuresis

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Table 55-2 Causes of Hyponatremia

PSEUDOHYPONATREMIA
Hyperlipidemia
Hyperproteinemia
HYPEROSMOLALITY
Hyperglycemia
Iatrogenic (mannitol, sucrose, glycine)
HYPOVOLEMIC HYPONATREMIA
EXTRARENAL LOSSES
Gastrointestinal (emesis, diarrhea)
Skin (sweating or burns)
Third space losses (bowel obstruction, peritonitis, sepsis)
RENAL LOSSES
Thiazide or loop diuretics
Osmotic diuresis
Postobstructive diuresis
Polyuric phase of acute tubular necrosis
Juvenile nephronophthisis (OMIM 256100/606966/602088/604387/611498)
Autosomal recessive polycystic kidney disease (OMIM 263200)
Tubulointerstitial nephritis
Obstructive uropathy
Cerebral salt wasting
Proximal (type II) renal tubular acidosis (OMIM 604278)*
Lack of aldosterone effect (high serum potassium):
Absence of aldosterone (e.g., 21-hydroxylase deficiency [OMIM 201910])
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Urinary tract obstruction and/or infection
EUVOLEMIC HYPONATREMIA
Syndrome of inappropriate antidiuretic hormone secretion
Nephrogenic syndrome of inappropriate antidiuresis (OMIM 304800)
Desmopressin acetate
Glucocorticoid deficiency
Hypothyroidism
Water intoxication:
Iatrogenic (excess hypotonic intravenous fluids)
Feeding infants excessive water products
Swimming lessons
Tap water enema
Child abuse
Psychogenic polydipsia
Diluted formula
Beer potomania
Exercise-induced hyponatremia
HYPERVOLEMIC HYPONATREMIA
Heart failure
Cirrhosis
Nephrotic syndrome
Acute, chronic kidney injury
Capillary leak caused by sepsis
Hypoalbuminemia caused by gastrointestinal disease (protein-losing enteropathy)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man

Table 55-5 Causes of Hypokalemia

SPURIOUS
High white blood cell count

TRANSCELLULAR SHIFTS
Alkalemia
Insulin
α-Adrenergic agonists
Drugs/toxins (theophylline, barium, toluene, cesium chloride, hydroxychloroquine)
Hypokalemic periodic paralysis (OMIM 170400)
Thyrotoxic period paralysis
Refeeding syndrome

DECREASED INTAKE
Anorexia nervosa

EXTRARENAL LOSSES
Diarrhea
Laxative abuse
Sweating
Sodium polystyrene sulfonate (Kayexalate) or clay ingestion

RENAL LOSSES
With metabolic acidosis
Distal rental tubular acidosis (OMIM 179800/602722/267300)
Proximal renal tubular acidosis (OMIM 604278)*
Ureterosigmoidostomy
Diabetic ketoacidosis
Without specific acid–base disturbance
Tubular toxins: amphotericin, cisplatin, aminoglycosides
Interstitial nephritis
Diuretic phase of acute tubular necrosis
Postobstructive diuresis
Hypomagnesemia
High urine anions (e.g., penicillin or penicillin derivatives)
With metabolic alkalosis
Low urine chloride
Emesis or nasogastric suction
Chloride-losing diarrhea (OMIM 214700)
Cystic fibrosis (OMIM 219700)
Low-chloride formula
Posthypercapnia
Previous loop or thiazide diuretic use
High urine chloride and normal blood pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/602522/241200/601678)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Loop and thiazide diuretics
High urine chloride and high blood pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism (OMIM 103900)
Renovascular disease
Renin-secreting tumor
17β-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Table 55-4 Causes of Hyperkalemia

SPURIOUS LABORATORY VALUE
Hemolysis
Tissue ischemia during blood drawing
Thrombocytosis
Leukocytosis
Familial pseudohyperkalemia (OMIM 609153/611184/612126)

INCREASED INTAKE
Intravenous or oral
Blood transfusions

TRANSCELLULAR SHIFTS
Acidosis
Rhabdomyolysis
Tumor lysis syndrome
Tissue necrosis
Hemolysis/hematomas/gastrointestinal bleeding
Succinylcholine
Digitalis intoxication
Fluoride intoxication
β-Adrenergic blockers
Exercise
Hyperosmolality
Insulin deficiency
Malignant hyperthermia (OMIM 145600/601887)
Hyperkalemic periodic paralysis (OMIM 170500)

DECREASED EXCRETION
Renal failure
Primary adrenal disease:
Acquired Addison disease
21-Hydroxylase deficiency (OMIM 201910)
3β-Hydroxysteroid dehydrogenase deficiency (OMIM 201810)
Lipoid congenital adrenal hyperplasia (OMIM 201710)
Adrenal hypoplasia congenita (OMIM 300200)
Aldosterone synthase deficiency (OMIM 203400/610600)
Adrenoleukodystrophy (OMIM 300100)
Hyporeninemic hypoaldosteronism:
Urinary tract obstruction
Sickle cell disease (OMIM 603903)
Kidney transplant
Lupus nephritis
Renal tubular disease:
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Pseudohypoaldosteronism type II (OMIM 145260)
Bartter syndrome, type 2 (OMIM 241200)
Urinary tract obstruction
Kidney transplant
Medications:
Angiotensin-converting enzyme inhibitors
Angiotensin II blockers
Potassium-sparing diuretics
Calcineurin inhibitors
Nonsteroidal antiinflammatory drugs
Trimethoprim
Heparin
Drospirenone (in some oral contraceptives)

Table 55-3 Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion

Absence of:
Renal, adrenal, or thyroid insufficiency
Heart failure, nephrotic syndrome, or cirrhosis
Diuretic ingestion
Dehydration
Urine osmolality >100 mOsm/kg (usually > plasma)
Serum osmolality <280 mOsm/kg and serum sodium <135 mEq/L
Urine sodium >30 mEq/L
Reversal of "sodium wasting" and correction of hyponatremia with water restriction

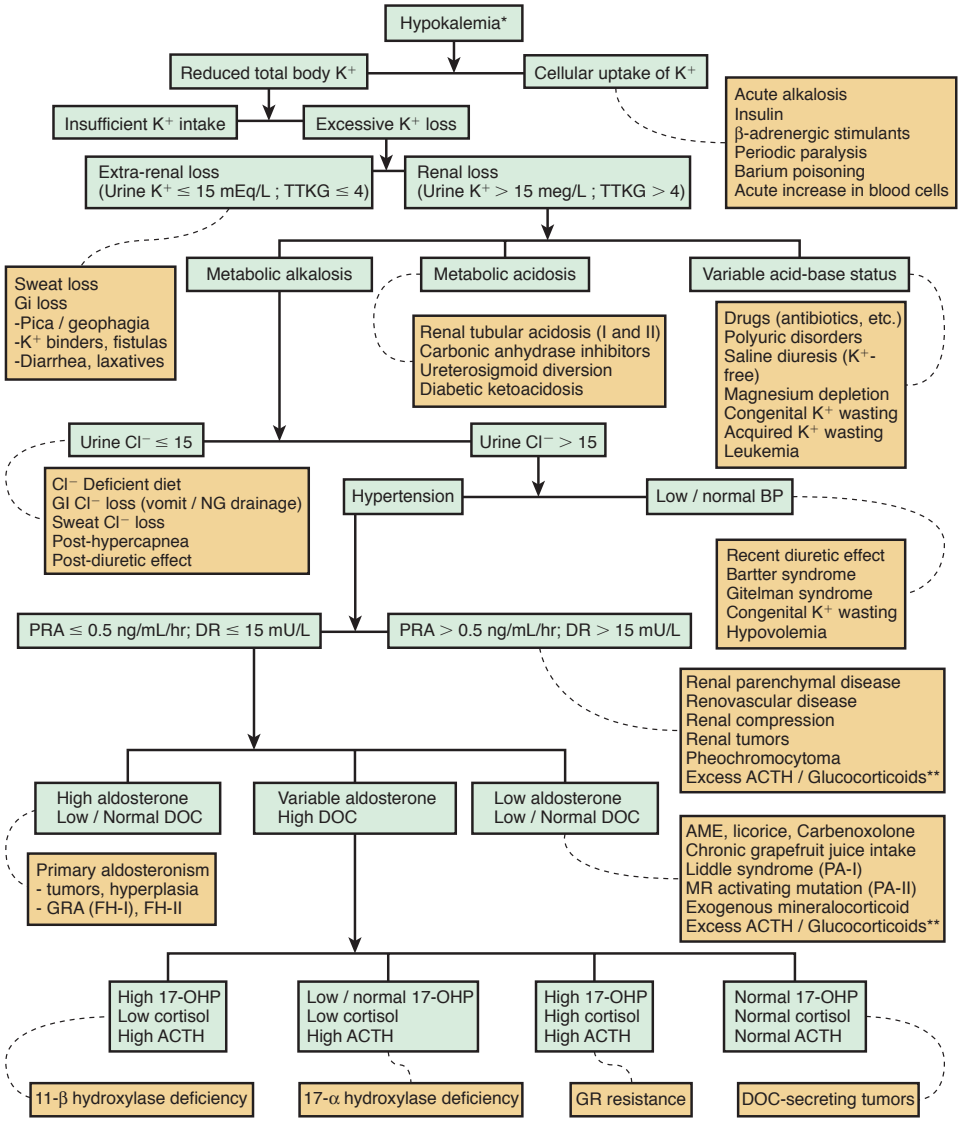


Figure 55-5 Diagnostic algorithm to evaluate persistent hypokalemia. *Spurious hypokalemia must be excluded. **Hypokalemia is uncommon in uncomplicated edematous disorders and in conditions associated with excessive glucocorticosteroids. Conditions associated with high circulating levels of glucocorticosteroids often have normal renin activity. 17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; BP, blood pressure; Cl^-, chloride; DOC, 11-deoxycorticosterone; DR, direct renin assay; GI, gastrointestinal; FH-II, familial hyperaldosteronism type II; GR, glucocorticoid receptor; GRA (FH-I), glucocorticoid remediable aldosteronism (familial hyperaldosteronism type I); K^+, potassium; MR, mineralocorticoid receptor; PA-I, pseudoaldosteronism type I; PA-II, pseudoaldosteronism type II; PRA, plasma renin activity; TTKG, transtubular potassium gradient. *(From Shoemaker LR, Eaton BV, Buchino JJ: A three-year-old with persistent hypokalemia, J Pediatr 151:696–699, 2007.)*

Table 55-7 Causes of Hypomagnesemia

GASTROINTESTINAL DISORDERS
Diarrhea
Nasogastric suction or emesis
Inflammatory bowel disease
Celiac disease
Cystic fibrosis
Intestinal lymphangiectasia
Small bowel resection or bypass
Pancreatitis
Protein-calorie malnutrition
Hypomagnesemia with secondary hypocalcemia (OMIM 602014)*
RENAL DISORDERS
Medications
Amphotericin
Cisplatin
Cyclosporin
Loop diuretics
Mannitol
Pentamidine
Proton pump inhibitors
Aminoglycosides
Thiazide diuretics
Epidermal growth factor receptor inhibitors
Diabetes
Acute tubular necrosis (recovery phase)
Postobstructive nephropathy
Chronic kidney diseases
Interstitial nephritis
Glomerulonephritis
Post–renal transplantation
Hypercalcemia
Intravenous fluids
Primary aldosteronism
Genetic diseases
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/601678)
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM 248250)
Familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement (OMIM 248190)
Autosomal recessive renal magnesium wasting with normocalciuria (OMIM 611718)
Renal cysts and diabetes syndrome (OMIM 137920)
Autosomal dominant hypomagnesemia (OMIM 160120/613882/154020)
EAST syndrome (OMIM 612780)
Autosomal dominant hypoparathyroidism (OMIM 146200)
Mitochondrial disorders (OMIM 500005)
MISCELLANEOUS CAUSES
Poor intake
Hungry bone syndrome
Insulin administration
Pancreatitis
Intrauterine growth retardation
Infants of diabetic mothers
Exchange transfusion

*This disorder is also associated with renal magnesium wasting.
EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Table 55-9 Causes of Hypophosphatemia

TRANSCELLULAR SHIFTS
Glucose infusion
Insulin
Refeeding
Total parenteral nutrition
Respiratory alkalosis
Tumor growth
Bone marrow transplantation
Hungry bone syndrome
DECREASED INTAKE
Nutritional
Premature infants
Low phosphorus formula
Antacids and other phosphate binders
RENAL LOSSES
Hyperparathyroidism
Parathyroid hormone–related peptide
X-linked hypophosphatemic rickets (OMIM 307800)
Overproduction of fibroblast growth factor-23
Tumor-induced rickets
McCune-Albright syndrome
Epidermal nevus syndrome
Neurofibromatosis
Autosomal dominant hypophosphatemic rickets (OMIM 193100)
Autosomal recessive hypophosphatemic rickets (OMIM 241520)
Fanconi syndrome
Dent disease (OMIM 300009/300555)
Hypophosphatemic rickets with hypercalciuria (OMIM 241530)
Hypophosphatemic nephrolithiasis/osteoporosis type 1 (OMIM 612286)
Hypophosphatemic nephrolithiasis/osteoporosis type 2 (OMIM 612287)
Volume expansion and intravenous fluids
Metabolic acidosis
Diuretics
Glycosuria
Glucocorticoids
Kidney transplantation
MULTIFACTORIAL
Vitamin D deficiency
Vitamin D–dependent rickets type 1 (OMIM 264700)
Vitamin D–dependent rickets type 2 (OMIM 277440)
Alcoholism
Sepsis
Dialysis

Table 55-10 Causes of Hyperphosphatemia

TRANSCELLULAR SHIFTS
Tumor lysis syndrome
Rhabdomyolysis
Acute hemolysis
Diabetic ketoacidosis and lactic acidosis
INCREASED INTAKE
Enemas and laxatives
Cow's milk in infants
Treatment of hypophosphatemia
Vitamin D intoxication
DECREASED EXCRETION
Renal failure
Hypoparathyroidism or pseudohypoparathyroidism (OMIM 146200/603233/103580/241410/203330)
Acromegaly
Hyperthyroidism
Tumoral calcinosis with hyperphosphatemia (OMIM 211900)

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Table 55-13 Causes of Metabolic Acidosis

NORMAL ANION GAP
Diarrhea
Renal tubular acidosis (RTA):
Distal (type I) RTA (OMIM 179800/602722/267300)*
Proximal (type II) RTA (OMIM 604278)†
Hyperkalemic (type IV) RTA (OMIM 201910/264350/177735/145260)‡
Urinary tract diversions
Posthypocapnia
Ammonium chloride intake
INCREASED ANION GAP
Lactic acidosis
Tissue hypoxia
Shock
Hypoxemia
Severe anemia
Liver failure
Malignancy
Intestinal bacterial overgrowth
Inborn errors of metabolism
Medications
Nucleoside reverse transcriptase inhibitors
Metformin
Propofol
Ketoacidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Alcoholic ketoacidosis
Kidney failure
Poisoning
Ethylene glycol
Methanol
Salicylate
Toluene
Paraldehyde

*Along with these genetic disorders, distal RTA may be secondary to renal disease or medications.

†Most cases of proximal RTA are not caused by this primary genetic disorder. Proximal RTA is usually part of Fanconi syndrome, which has multiple etiologies.

‡Hyperkalemic RTA can be secondary to a genetic disorder (some of the more common are listed) or other etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man

Table 55-11 Appropriate Compensation During Simple Acid–Base Disorders

DISORDER	EXPECTED COMPENSATION
Metabolic acidosis	$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in serum $[HCO_3^-]$
RESPIRATORY ACIDOSIS	
Acute	$[HCO_3^-]$ increases by 1 for each 10 mm Hg increase in P_{CO_2}
Chronic	$[HCO_3^-]$ increases by 3.5 for each 10 mm Hg increase in P_{CO_2}
RESPIRATORY ALKALOSIS	
Acute	$[HCO_3^-]$ falls by 2 for each 10 mm Hg decrease in P_{CO_2}
Chronic	$[HCO_3^-]$ falls by 4 for each 10 mm Hg decrease in P_{CO_2}

Table 55-12 Normal Values of Arterial Blood Gases

pH	7.35-7.45
$[HCO_3^-]$	20-28 mEq/L
P_{CO_2}	35-45 mm Hg

Table 55-14 Causes of Metabolic Alkalosis

CHLORIDE-RESPONSIVE (URINARY CHLORIDE <15 MEQ/L)
Gastric losses
Emesis
Nasogastric suction
Diuretics (loop or thiazide)
Chloride-losing diarrhea (OMIM 214700)
Chloride-deficient formula
Cystic fibrosis (OMIM 219700)
Post-hypercapnia
CHLORIDE-RESISTANT (URINARY CHLORIDE >20 MEQ/L)
High blood pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism (OMIM 103900)
Renovascular disease
Renin-secreting tumor
17β-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)
Normal blood pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/602522/241200/601678)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Base administration

EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man

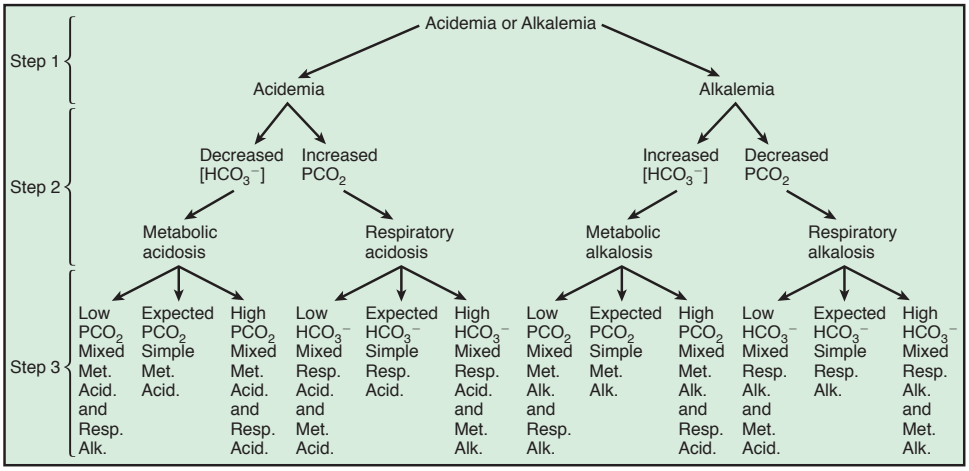


Figure 55-9 Three-step process for interpreting acid–base disturbances. In step 1, determine whether the pH is low (acidemia) or high (alkalemia). In step 2, establish an explanation for the acidemia or alkalemia. In step 3, calculate the expected compensation (see Table 55-11) and determine whether a mixed disturbance is present. Met. Acid., metabolic acidosis; Met. Alk., metabolic alkalosis; Resp. Acid., respiratory acidosis; Resp. Alk., respiratory alkalosis.

Table 55-15 Causes of Respiratory Acidosis

CENTRAL NERVOUS SYSTEM DEPRESSION
Encephalitis
Head trauma
Brain tumor
Central sleep apnea
Primary pulmonary hypoventilation (Ondine curse)
Stroke
Hypoxic brain damage
Obesity-hypoventilation (Pickwickian syndrome)
Increased intracranial pressure
Medications
  Narcotics
  Barbiturates
  Anesthesia
  Benzodiazepines
  Propofol
  Alcohols

DISORDERS OF THE SPINAL CORD, PERIPHERAL NERVES, OR NEUROMUSCULAR JUNCTION
Diaphragmatic paralysis
Guillain-Barré syndrome
Poliomyelitis
Spinal muscular atrophies
Tick paralysis
Botulism
Myasthenia
Multiple sclerosis
Spinal cord injury
Medications
  Vecuronium
  Aminoglycosides
  Organophosphates (pesticides)

RESPIRATORY MUSCLE WEAKNESS
Muscular dystrophy
Hypothyroidism
Malnutrition
Hypokalemia
Hypophosphatemia
Medications
  Succinylcholine
  Corticosteroids

PULMONARY DISEASE
Pneumonia
Pneumothorax
Asthma
Bronchiolitis
Pulmonary edema
Pulmonary hemorrhage
Acute respiratory distress syndrome
Neonatal respiratory distress syndrome
Cystic fibrosis
Bronchopulmonary dysplasia
Hypoplastic lungs
Meconium aspiration
Pulmonary thromboembolus
Interstitial fibrosis

UPPER AIRWAY DISEASE
Aspiration
Laryngospasm
Angioedema
Obstructive sleep apnea
Tonsillar hypertrophy
Vocal cord paralysis
Extrinsic tumor
Extrinsic or intrinsic hemangioma

MISCELLANEOUS
Flail chest
Cardiac arrest
Kyphoscoliosis
Decreased diaphragmatic movement due to ascites or peritoneal dialysis

Table 55-16 Causes of Respiratory Alkalosis

HYPOXEMIA OR TISSUE HYPOXIA
Pneumonia
Pulmonary edema
Cyanotic heart disease
Congestive heart failure
Asthma
Severe anemia
High altitude
Laryngospasm
Aspiration
Carbon monoxide poisoning
Pulmonary embolism
Interstitial lung disease
Hypotension

LUNG RECEPTOR STIMULATION
Pneumonia
Pulmonary edema
Asthma
Pulmonary embolism
Hemothorax
Pneumothorax
Respiratory distress syndrome (adult or infant)

CENTRAL STIMULATION
Central nervous system disease
  Subarachnoid hemorrhage
  Encephalitis or meningitis
  Trauma
  Brain tumor
  Stroke
Fever
Pain
Anxiety (panic attack)
Psychogenic hyperventilation or anxiety
Liver failure
Sepsis
Pregnancy
Mechanical ventilation
Hyperammonemia
Extracorporeal membrane oxygenation or hemodialysis
Medications
  Salicylate intoxication
  Theophylline
  Progesterone
  Exogenous catecholamines
  Caffeine

Table 57-4 Treatment of Hypernatremic Dehydration

Restore intravascular volume:
  Normal saline: 20 mL/kg over 20 min (repeat until intravascular volume restored)
  Determine time for correction on basis of initial sodium concentration:
    [Na] 145-157 mEq/L: 24 hr
    [Na] 158-170 mEq/L: 48 hr
    [Na] 171-183 mEq/L: 72 hr
    [Na] 184-196 mEq/L: 84 hr
Administer fluid at constant rate over time for correction:
  Typical fluid: 5% dextrose + half-normal saline (with 20 mEq/L KCl unless contraindicated)
  Typical rate: 1.25-1.5 times maintenance
Follow serum sodium concentration
Adjust fluid on basis of clinical status and serum sodium concentration:
  Signs of volume depletion: administer normal saline (20 mL/kg)
  Sodium decreases too rapidly; either:
    Increase sodium concentration of intravenous fluid
    Decrease rate of intravenous fluid
  Sodium decreases too slowly; either:
    Decrease sodium concentration of intravenous fluid
    Increase rate of intravenous fluid
Replace ongoing losses as they occur

Table 56-1 Goals of Maintenance Fluids

Prevent dehydration
Prevent electrolyte disorders
Prevent ketoacidosis
Prevent protein degradation

Table 57-1 Clinical Evaluation of Dehydration

Mild dehydration (<5% in an infant; <3% in an older child or adult): Normal or increased pulse; decreased urine output; thirsty; normal physical findings
Moderate dehydration (5-10% in an infant; 3-6% in an older child or adult): Tachycardia; little or no urine output; irritable/lethargic; sunken eyes and fontanel; decreased tears; dry mucous membranes; mild delay in elasticity (skin turgor); delayed capillary refill (>1.5 sec); cool and pale
Severe dehydration (>10% in an infant; >6% in an older child or adult): Peripheral pulses either rapid and weak or absent; decreased blood pressure; no urine output; very sunken eyes and fontanel; no tears; parched mucous membranes; delayed elasticity (poor skin turgor); very delayed capillary refill (>3 sec); cold and mottled; limp, depressed consciousness

Table 57-2 Fluid Management of Dehydration

Restore intravascular volume:
  Normal saline: 20 mL/kg over 20 min
  Repeat as needed
Calculate 24-hr fluid needs: maintenance + deficit volume
Subtract isotonic fluid already administered from 24 hr fluid needs
Administer remaining volume over 24 hr using 5% dextrose NS + 20 mEq/L KCl
Replace ongoing losses as they occur

Table 56-2 Body Weight Method for Calculating Daily Maintenance Fluid Volume

BODY WEIGHT	FLUID PER DAY
0-10 kg	100 mL/kg
11-20 kg	1,000 mL + 50 mL/kg for each kg >10 kg
>20 kg	1,500 mL + 20 mL/kg for each kg >20 kg*

*The maximum total fluid per day is normally 2,400 mL.

Table 56-3 Hourly Maintenance Water Rate

For body weight of 0-10 kg: 4 mL/kg/hr
For body weight of 10-20 kg: 40 mL/hr + 2 mL/kg/hr × (wt – 10 kg)
For body weight of >20 kg: 60 mL/hr + 1 mL/kg/hr × (wt – 20 kg)*

*The maximum fluid rate is normally 100 mL/hr.

Table 56-4 Composition of Intravenous Solutions

FLUID	[Na]	[Cl^-]	[K^+]	[Ca^{2+}]	[LACTATE–]
Normal saline (0.9% NaCl)	154	154	—	—	—
Half-normal saline (0.45% NaCl)	77	77	—	—	—
0.2 normal saline (0.2% NaCl)	34	34	—	—	—
Ringer lactate	130	109	4	3	28

Table 57-3 Monitoring Therapy

Vital signs:
  Pulse
  Blood pressure
Intake and output:
  Fluid balance
  Urine output
Physical examination:
  Weight
  Clinical signs of depletion or overload
Electrolytes

Pediatric Drug Therapy

Table 62-3 Commonly Used Nonopioid Medications

MEDICATION	DOSAGE	COMMENT(S)
Acetaminophen	10-15 mg/kg PO q4h 10 mg/kg IV q4h 15 mg/kg IV q6h 10 mg/kg IV q6h (<2 yr) 20-30 mg/kg/PR q4h 40 mg/kg/PR q6-8h Maximum daily dosing: 90 mg/kg/24 hr (children) 60 mg/kg/24 hr (<2 yr) 30-45 mg/kg/24 hr (neonates)	Little antiinflammatory action; no antiplatelet or adverse gastric effects; overdosing can produce fulminant hepatic failure
Aspirin	10-15 mg/kg PO q4h Maximum daily dosing: 120 mg/kg/24 hr (children)	Antiinflammatory; prolonged antiplatelet effects; may cause gastritis; associated with Reye syndrome
Ibuprofen	8-10 mg/kg PO q6h	Antiinflammatory; transient antiplatelet effects; may cause gastritis; extensive pediatric safety experience
Naprosyn	5-7 mg/kg PO q8-12h	Antiinflammatory; transient antiplatelet effects; may cause gastritis; more prolonged duration than that of ibuprofen
Ketorolac	Loading dose 0.5 mg/kg, then 0.25-0.3 mg/kg IV q6h to a maximum of 5 days; maximum dose 30 mg loading with maximum dosing of 15 mg q6h	Antiinflammatory; reversible antiplatelet effects; may cause gastritis; useful for short-term situations in which oral dosing is not feasible
Celecoxib	3-6 mg/kg PO q12-24h	Antiinflammatory; no antiplatelet or gastric effects; cross-reactivity with sulfa allergies
Choline magnesium salicylate	10-20 mg/kg PO q8-12h	Weak antiinflammatory; lower risk of bleeding and gastritis than with conventional NSAIDs
Nortriptyline, amitriptyline, desipramine	0.1-0.5 mg/kg PO qhs	For neuropathic pain; facilitates sleep; may enhance opioid effect; may be useful in sickle cell pain; risk of dysrhythmia in prolonged QTc syndrome; may cause fatal dysrhythmia in overdose; FDA says agents may enhance suicidal ideation
Gabapentin	100 mg bid or tid titrated to up to 3,600 mg/24 hr	For neuropathic pain; associated with sedation, dizziness, ataxia, headache, and behavioral changes
Quetiapine, risperidone, chlorpromazine, haloperidol	Quetiapine: 6.25 or 12.5 mg PO qd (hs); may use q6h prn acute agitation with pain. Escalate dose to 25 mg/dose if needed. Risperidone: useful for PDD spectrum or tic disorder and chronic pain; 0.25-1 mg (in 0.25-mg increments) qd or bid; see PDR for other dosing.	Useful when arousal is amplifying pain; often used when patient first starting SSRI and then weaned after at least 2 wk; check for normal QTc before initiating; side effects include extrapyramidal reactions (diphenhydramine may be used to treat) and sedation; in high doses, can lower the seizure threshold
Fluoxetine	10-20 mg PO qd (usually in morning)	SSRI for children with anxiety disorders in which arousal amplifies sensory signaling; useful in PDD spectrum disorders in very low doses; best to use in conjunction with psychiatric evaluation
Sucrose solution via pacifier or gloved finger	*Preterm infants (gestational age):* 28 wk: 0.2 mL swabbed into mouth 28-32 wk: 0.2-2 mL, depending on suck/swallow >32 wk: 2 mL *Term infants:* 1.5-2 mL PO over 2 min	Allow 2 min before starting procedure; analgesia may last up to 8 min; the dose may be repeated once

FDA, U.S. Food and Drug Administration; IV, intravenous(ly): NSAIDs, nonsteroidal antiinflammatory drugs; PDD, pervasive developmental disorder; PDR, *Physicians' Desk Reference;* PR, per rectum; QTc, corrected QT interval on an electrocardiogram; SSRI, selective serotonin reuptake inhibitor.

Table 62-4 Pediatric Dosage Guidelines for Opioid Analgesics

DRUG	EQUIANALGESIC DOSES		PARENTERAL DOSING (WEIGHT)		IV:PO DOSE RATIO	ORAL DOSING (WEIGHT)		COMMENTS
	IV	ORAL	<50 kg	>50 kg		<50 kg	>50 kg	
Fentanyl	10 µg	100 µg	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	Oral transmucosal: 1:10 Transdermal: 1:1	Oral transmucosal: 10 µg/kg Transdermal: 12.5-50 µg/hr	Transdermal patches available; patch reaches steady state at 24 hr and should be changed q72h	70-100 times as potent as morphine with rapid onset and shorter duration With high doses and rapid administration, can cause chest-wall rigidity Useful for short procedures; transdermal form should be used only in opioid-tolerant patients with chronic pain
Hydrocodone	N/A	1.5 mg	N/A	N/A	N/A	0.15 mg/kg	10 mg	Weak opioid; only available in form with acetaminophen
Hydromorphone	0.2 mg	0.6 mg	0.01 mg q2-4h 0.002 mg/kg/hr	0.01 mg q2-4h 0.002 mg/kg/hr	1:3	0.04-0.08 mg/kg q3-4h	2-4 mg q3-4h	5× the potency of morphine; no histamine release and fewer adverse events than morphine
Meperidine	10 mg	30 mg	0.5 mg/kg q2-4h	0.5 mg/kg q2-4h	1:4	2-3 mg/kg q3-4h	100-150 mg q3-4h	Primary use in low doses is for treatment of rigors and shivering after anesthesia or with amphotericin or blood products Not appropriate for repeated dosing
Methadone	1 mg	2 mg	0.1 mg/kg q8-24h	0.1 mg/kg q8-24h	1:2	0.2 mg/kg q8-12h PO; available as liquid or tablet	2.5 mg tid	Duration 12-24 hr; useful in certain types of chronic pain; requires additional vigilance, because it will accumulate over 72 hr and produce delayed sedation When patients who are tolerant to opioids are switched to methadone, they show incomplete cross-tolerance and improved efficacy; because it is associated with prolonged QTc, monitoring is needed for children on high and extended dosing
Morphine	1 mg	3 mg	0.05 mg/kg q2-4h 0.01-0.03 mg/kg/hr	*Bolus:* 5-8 mg q2-4h	1:3	Immediate release: 0.3 mg/kg q3-4h Sustained release: 20-35 kg: 10-15 mg q8-12h 35-50 kg: 15-30 mg q8-12h	Immediate release: 15-20 mg q3-4h Sustained release: 30-90 mg q8-12h	Potent opioid for moderate/severe pain; may cause histamine release Sustained-release form must be swallowed whole; if crushed, becomes immediate-acting, leading to acute overdose
Oxycodone	N/A	3 mg	N/A	N/A	N/A	0.1-0.2 mg q3-4h; available in liquid (1 mg/mL)	Immediate release: 5-10 mg q4h Sustained release: 10-120 mg q8-12h	Strong opioid only available as an oral agent in North America; more potent than and preferable to hydrocodone Sustained-release form must be swallowed whole; if crushed, becomes immediate-acting, leading to acute overdose

N/A, not available.

Table 63-2 Selected Historical and Physical Findings in Poisoning

SIGN	TOXIN
ODOR	
Bitter almonds	Cyanide
Acetone	Isopropyl alcohol, methanol, paraldehyde, salicylates
Alcohol	Ethanol
Wintergreen	Methyl salicylate
Garlic	Arsenic, thallium, organophosphates, selenium
OCULAR SIGNS	
Miosis	Opioids (except propoxyphene, meperidine, and pentazocine), organophosphates and other cholinergics, clonidine, phenothiazines, sedative–hypnotics, olanzapine
Mydriasis	Anticholinergics (e.g., antihistamines, TCAs, atropine), sympathomimetics (cocaine, amphetamines, PCP) postanoxic encephalopathy, opiate withdrawal
Nystagmus	Anticonvulsants, sedative–hypnotics, alcohols, PCP, ketamine, dextromethorphan
Lacrimation	Organophosphates, irritant gas or vapors
Retinal hyperemia	Methanol
CUTANEOUS SIGNS	
Diaphoresis	Cholinergics (organophosphates), sympathomimetics, withdrawal syndromes
Alopecia	Thallium, arsenic
Erythema	Boric acid, elemental mercury, cyanide, carbon monoxide, disulfiram, scombroid, anticholinergics, vancomycin
Cyanosis (unresponsive to oxygen)	Methemoglobinemia (e.g., benzocaine, dapsone, nitrites, phenazopyridine), amiodarone, silver
ORAL SIGNS	
Salivation	Organophosphates, salicylates, corrosives, ketamine, PCP, strychnine
Oral burns	Corrosives, oxalate-containing plants
Gum lines	Lead, mercury, arsenic, bismuth
GASTROINTESTINAL SIGNS	
Diarrhea	Antimicrobials, arsenic, iron, boric acid, cholinergics, colchicine, opioid withdrawal
Hematemesis	Arsenic, iron, caustics, NSAIDs, salicylates
Constipation	Lead
CARDIAC SIGNS	
Tachycardia	Sympathomimetics, anticholinergics, antidepressants, antipsychotics, methylxanthines (theophylline, caffeine), salicylates, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), withdrawal (ethanol, sedatives, clonidine, opioids), serotonin syndrome, neuroleptic malignant syndrome
Bradycardia	β Blockers, calcium channel blockers, digoxin, clonidine, organophosphates, opioids, sedative–hypnotics
Hypertension	Sympathomimetics, anticholinergics, monoamine oxidase inhibitors, serotonin syndrome, neuroleptic malignant syndrome, clonidine withdrawal
Hypotension	β Blockers, calcium channel blockers, cyclic antidepressants, iron, antipsychotics, barbiturates, clonidine, opioids, arsenic, amatoxin mushrooms, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), snake envenomation
RESPIRATORY SIGNS	
Depressed respirations	Opioids, sedative-hypnotics, alcohol, clonidine, barbiturates
Tachypnea	Salicylates, sympathomimetics, caffeine, metabolic acidosis, carbon monoxide, hydrocarbon aspiration
CENTRAL NERVOUS SYSTEM SIGNS	
Ataxia	Alcohols, anticonvulsants, sedative–hypnotics, lithium, dextromethorphan, carbon monoxide, inhalants
Coma	Opioids, sedative–hypnotics, anticonvulsants, antidepressants, antipsychotics, ethanol, anticholinergics, clonidine, GHB, alcohols, salicylates, barbiturates
Seizures	Sympathomimetics, anticholinergics, antidepressants (especially TCAs, bupropion, venlafaxine), cholinergics (organophosphates), isoniazid, camphor, lindane, salicylates, lead, nicotine, tramadol, water hemlock, withdrawal
Delirium/psychosis	Sympathomimetics, anticholinergics, LSD, PCP, hallucinogens, lithium, dextromethorphan, steroids, withdrawal
Peripheral neuropathy	Lead, arsenic, mercury, organophosphates

GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; NSAID, nonsteroidal antiinflammatory drug; PCP, phencyclidine; TCA, tricyclic antidepressant.

Table 63-4 Mini-Toxidromes

TOXIDROMES	SYMPTOMS AND SIGNS	EXAMPLES
α_1 Antagonists	CNS depression, tachycardia, miosis	Chlorpromazine, quetiapine, clozapine, olanzapine, risperidone
α_2 Agonist	CNS depression, bradycardia, hypertension (early), hypotension (late), miosis	Clonidine, oxymetazoline, tetrahydrozoline, tizanidine
Clonus/myoclonus	CNS depression, myoclonic jerks, clonus, hyperreflexia	Carisoprodol, lithium, serotonergic agents, bismuth, organic lead, organic mercury
Sodium channel blockers	CNS toxicity, wide QRS	Cyclic antidepressants and structurally related agents, propoxyphene, quinidine/quinine, amantadine, antihistamines, bupropion, cocaine
Potassium channel blockers	CNS toxicity, long QT	Butyrophenones, methadone, phenothiazines, ziprasidone

CNS, central nervous system.
From Ruha AM, Levine M: Central nervous system toxicity. Emerg Med Clin North Am *32(1):205–221, 2014, Table 2, p. 208.*

Table 63-5 Screening Laboratory Clues in Toxicologic Diagnosis

ANION GAP METABOLIC ACIDOSIS (MNEMONIC = MUDPILES CAT)
Methanol, metformin
Uremia
Diabetic ketoacidosis
Propylene glycol
Isoniazid, iron, massive ibuprofen
Lactic acidosis
Ethylene glycol
Salicylates
Cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide)
Alcoholic ketoacidosis
Tylenol
ELEVATED OSMOLAR GAP
Alcohols: ethanol, isopropyl, methanol, ethylene glycol
HYPOGLYCEMIA (MNEMONIC = HOBBIES)
Hypoglycemics, oral: sulfonylureas, meglitinides
Other: quinine, unripe ackee fruit
Beta **B**lockers
Insulin
Ethanol
Salicylates (late)
HYPERGLYCEMIA
Salicylates (early)
Calcium channel blockers
Caffeine
HYPOCALCEMIA
Ethylene glycol
Fluoride
RHABDOMYOLYSIS
Neuroleptic malignant syndrome, serotonin syndrome
Statins
Mushrooms (*Tricholoma equestre*)
Any toxin causing prolonged immobilization (e.g., opioids, antipsychotics) or excessive muscle activity or seizures (e.g., sympathomimetics)
RADIOPAQUE SUBSTANCE ON KUB (MNEMONIC = CHIPPED)
Chloral hydrate, calcium carbonate
Heavy metals (lead, zinc, barium, arsenic, lithium, bismuth)
Iron
Phenothiazines
Play-Doh, potassium chloride
Enteric-coated pills
Dental amalgam, drug packets

KUB, kidney-ureter-bladder radiograph.

Table 63-6 Electrocardiographic Findings in Poisoning

PR INTERVAL PROLONGATION
Digoxin
Lithium
QRS PROLONGATION
Tricyclic antidepressants
Diphenhydramine
Carbamazepine
Cardiac glycosides
Chloroquine, hydroxychloroquine
Cocaine
Lamotrigine
Quinidine, quinine, procainamide, disopyramide
Phenothiazines
Propoxyphene
Propranolol
Bupropion, venlafaxine (rare)
QTc PROLONGATION*
Amiodarone
Antipsychotics (typical and atypical)
Arsenic
Cisapride
Citalopram and other SSRIs
Clarithromycin, erythromycin
Disopyramide, dofetilide, ibutilide
Fluconazole, ketoconazole, itraconazole
Methadone
Pentamidine
Phenothiazines
Sotalol

*This is a select list of important toxins, other medications are also associated with QTc prolongation.
SSRI, selective serotonin reuptake inhibitor.

Table 63-7 Common Antidotes for Poisoning

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Acetaminophen	*N*-Acetylcysteine (Mucomyst)	140 mg/kg loading, followed by 70 mg/kg q4h	PO	Vomiting (patient-tailored regimens are the norm)
	N-Acetylcysteine (Acetadote)	150 mg/kg over 1 hr, followed by 50 mg/kg over 4 hr, followed by 100 mg/kg over 16 hr	IV	Anaphylactoid reactions (most commonly seen with loading dose) (Higher doses of the infusion are often recommended depending upon the acetaminophen level and the degree of injury)
Anticholinergics	Physostigmine	0.02 mg/kg over 5 min; may repeat q5-10min to 2 mg max	IV/IM	Bradycardia, seizures, bronchospasm *Note:* Do not use if conduction delays on ECG
Benzodiazepines	Flumazenil	0.2 mg over 30 sec; if response is inadequate, repeat q1min to 1 mg max	IV	Agitation, seizures; **do not use for unknown ingestions**
β Blockers	Glucagon	0.15 mg/kg bolus followed by infusion of 0.05-0.15 mg/kg/hr	IV	Hyperglycemia, vomiting
Calcium channel blockers	Insulin	1 unit/kg bolus followed by infusion of 0.5-1 unit/kg/hr	IV	Hypoglycemia Follow serum potassium and glucose closely
	Calcium salts	Dose depends on the specific calcium salt	IV	
Carbon monoxide	Oxygen	100% FIO_2 via non–rebreather mask (or ET if intubated)	Inhalational	Some patients may benefit from hyperbaric oxygen (see text)
Cyanide	Cyanide kit:			
	Amyl nitrate	1 crushable ampule; inhale 30 sec of each min	Inhalation	Methemoglobinemia
	Sodium nitrate	0.33 mL/kg of 3% solution if hemoglobin level is not known; otherwise, based on tables with product	IV	Methemoglobinemia Hypotension
	Sodium thiosulfate	1.6 mL/kg of 25% solution; may be repeated q30-60min to max of 50 mL	IV	If inducing methemoglobinemia is contraindicated; consider only using the thiosulfate component of the kit
	Hydroxocobalamin (Cyanokit)	70 mg/kg (adults: 5 g) given over 15 min	IV	Flushing/erythema, nausea, rash, chromaturia, hypertension, headache
Digitalis	Digoxin-specific Fab antibodies (Digibind; DigiFab)	1 vial binds 0.6 mg of digitalis glycoside; #vials = digitalis level × weight in kg/100	IV	Allergic reactions (rare), return of condition being treated with digitalis glycoside
Ethylene glycol, methanol	Fomepizole	15 mg/kg load; 10 mg/kg q12h × 4 doses; 15 mg/kg q12h until EG level is <20 mg/dL	IV	Infuse slowly over 30 min; If fomepizole is not available, can treat with oral ethanol (80 proof)
Iron	Deferoxamine	Infusion of 5-15 mg/kg/hr (max: 6 g/24 hr)	IV	Hypotension (minimized by avoiding rapid infusion rates)
Isoniazid (INH)	Pyridoxine	Empirical dosing: 70 mg/kg (max dose = 5 g) If ingested dose is known: 1 g per gram of INH	IV	May also be used for *Gyromitra* mushroom ingestions
Lead and other heavy metals (e.g., arsenic, inorganic mercury)	BAL (dimercaprol)	3-5 mg/kg/dose q4hr, for the 1st day; subsequent dosing depends on the toxin	Deep IM	Local injection site pain and sterile abscess, vomiting, fever, salivation, nephrotoxicity *Caution:* prepared in peanut oil; contraindicated in patients with peanut allergy
	Calcium disodium EDTA	35-50 mg/kg/day × 5 days; may be given as a continuous infusion or 2 divided doses/day	IV	Vomiting, fever, hypertension, arthralgias, allergic reactions, local inflammation, nephrotoxicity (maintain adequate hydration, follow UA and renal function)
	Dimercaptosuccinic acid (succimer, DMSA, Chemet)	10 mg/kg/dose q8h × 5 days, then 10 mg/kg q12h × 14 days	PO	Vomiting, hepatic transaminase elevation, rash

Continued

Table 63-7 Common Antidotes for Poisoning—cont'd

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Methemoglobinemia	Methylene blue, 1% solution	0.1-0.2 mL/kg (1-2 mg/kg) over 5-10 min; may be repeated q30-60min	IV	Vomiting, headache, dizziness, blue discoloration of urine
Opioids	Naloxone	0.01-0.1 mg/kg; adolescents/adults: 0.04-2 mg, repeated as needed; may give continuous infusion	IV	Acute withdrawal symptoms if given to addicted patients May also be useful for clonidine ingestions (inconsistent response)
Organophosphates	Atropine	0.05-0.1 mg/kg repeated q5-10min as needed	IV/ET	Tachycardia, dry mouth, blurred vision, urinary retention
	Pralidoxime (2-PAM)	25-50 mg/kg over 5-10 min (max: 200 mg/min); can be repeated after 1-2 hr, then q10-12hr as needed	IV/IM	Nausea, dizziness, headache, tachycardia, muscle rigidity, bronchospasm (rapid administration)
Salicylates	Sodium bicarbonate	Bolus 1-2 mEq/kg followed by a continuous infusion	IV	Follow potassium closely and replete as necessary Goal urine pH 7.5-8.0
Sulfonylureas	Octreotide and dextrose	1-2 μg/kg/dose (adults 50-100 μg) q6-8hr	IV/SC	
Tricyclic antidepressants	Sodium bicarbonate	Bolus 1-2 mEq/kg; repeated bolus dosing as needed to keep QRS <110 msec	IV	Indications: QRS widening (≥110 ms), hemodynamic instability; follow potassium

BAL, British antilewisite; DMSA, dimercaptosuccinic acid; ECG, electrocardiogram; FIO2, fraction of inspired oxygen; EDTA, ethylenediaminetetraacetic acid; EG, ethylene glycol; ET, endotracheal tube; max, maximum; UA, urinalysis.

Table 63-1 Common Agents Potentially Toxic to Young Children (<6 yr) in Small Doses*

SUBSTANCE	TOXICITY
Aliphatic hydrocarbons (e.g., gasoline, kerosene, lamp oil)	Acute lung injury
Antimalarials (chloroquine, quinine)	Seizures, dysrhythmias
Benzocaine	Methemoglobinemia
β Blockers (lipid-soluble β blockers [e.g., propranolol] are more toxic than water-soluble β blockers [e.g., atenolol])	Bradycardia, hypotension
Calcium channel blockers	Bradycardia, hypotension, hyperglycemia
Camphor	Seizures
Caustics (pH <2 or >12)	Airway, esophageal and gastric burns
Clonidine	Lethargy, bradycardia, hypotension
Diphenoxylate and atropine (Lomotil)	CNS depression, respiratory depression
Hypoglycemics, oral (sulfonylureas and meglitinides)	Hypoglycemia, seizures
Laundry detergent packets (pods)	Airway issues, respiratory distress, altered mental status
Lindane	Seizures
Monoamine oxidase inhibitors	Hypertension followed by delayed cardiovascular collapse
Methyl salicylate	Tachypnea, metabolic acidosis, seizures
Opioids (especially methadone, buprenorphine)	CNS depression, respiratory depression
Organophosphate pesticides	Cholinergic crisis
Phenothiazines (especially chlorpromazine, thioridazine)	Seizures, dysrhythmias
Theophylline	Seizures, dysrhythmias
Tricyclic antidepressants	CNS depression, seizures, dysrhythmias, hypotension

*"Small dose" typically implies 1 or 2 pills or 5 mL.
CNS, central nervous system.

Table 63-8 Additional Antidotes

ANTIDOTES	TOXIN OR POISON
Latrodectus antivenin	Black widow spider
Botulinum antitoxin	Botulinum toxin
Insulin and glucose	Calcium channel antagonists
Diphenhydramine and/or benztropine	Dystonic reactions
Calcium salts	Fluoride, calcium channel blockers
Protamine	Heparin
Folinic acid	Methotrexate, trimethoprim, pyrimethamine
Crotalidae-specific Fab antibodies	Rattlesnake envenomation
Sodium bicarbonate	Sodium channel blockade (tricyclic antidepressants, type 1 antiarrhythmics)

The Acutely Ill Child

Table 67-2 AVPU Neurologic Assessment

A	The child is awake, alert, and interactive with parents and care providers
V	The child responds only if the care provider or parents call the child's name or speak loudly
P	The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger
U	The child is unresponsive to all stimuli

From Ralston M, Hazinski MF, Zaritsky AL, et al, editors: Pediatric advanced life support course guide and PALS provider manual: provider manual, *Dallas, 2007, American Heart Association.*

Table 67-1 Normal Vital Signs According to Age

AGE	HEART RATE (beats/min)	BLOOD PRESSURE (mm Hg)	RESPIRATORY RATE (breaths/min)
Premature	120-170*	55-75/35-45†	40-70‡
0-3 mo	100-150*	65-85/45-55	35-55
3-6 mo	90-120	70-90/50-65	30-45
6-12 mo	80-120	80-100/55-65	25-40
1-3 yr	70-110	90-105/55-70	20-30
3-6 yr	65-110	95-110/60-75	20-25
6-12 yr	60-95	100-120/60-75	14-22
12+ yr	55-85	110-135/65-85	12-18

*In sleep, infant heart rates may drop significantly lower, but if perfusion is maintained, no intervention is required.

†A blood pressure cuff should cover approximately two-thirds of the arm; too small a cuff yields spuriously high pressure readings, and too large a cuff yields spuriously low pressure readings.

‡Many premature infants require mechanical ventilatory support, making their blood pressure. In nonhospital settings, much of the important

Table 64-1 Most Commonly Used Dietary Supplements in Pediatrics

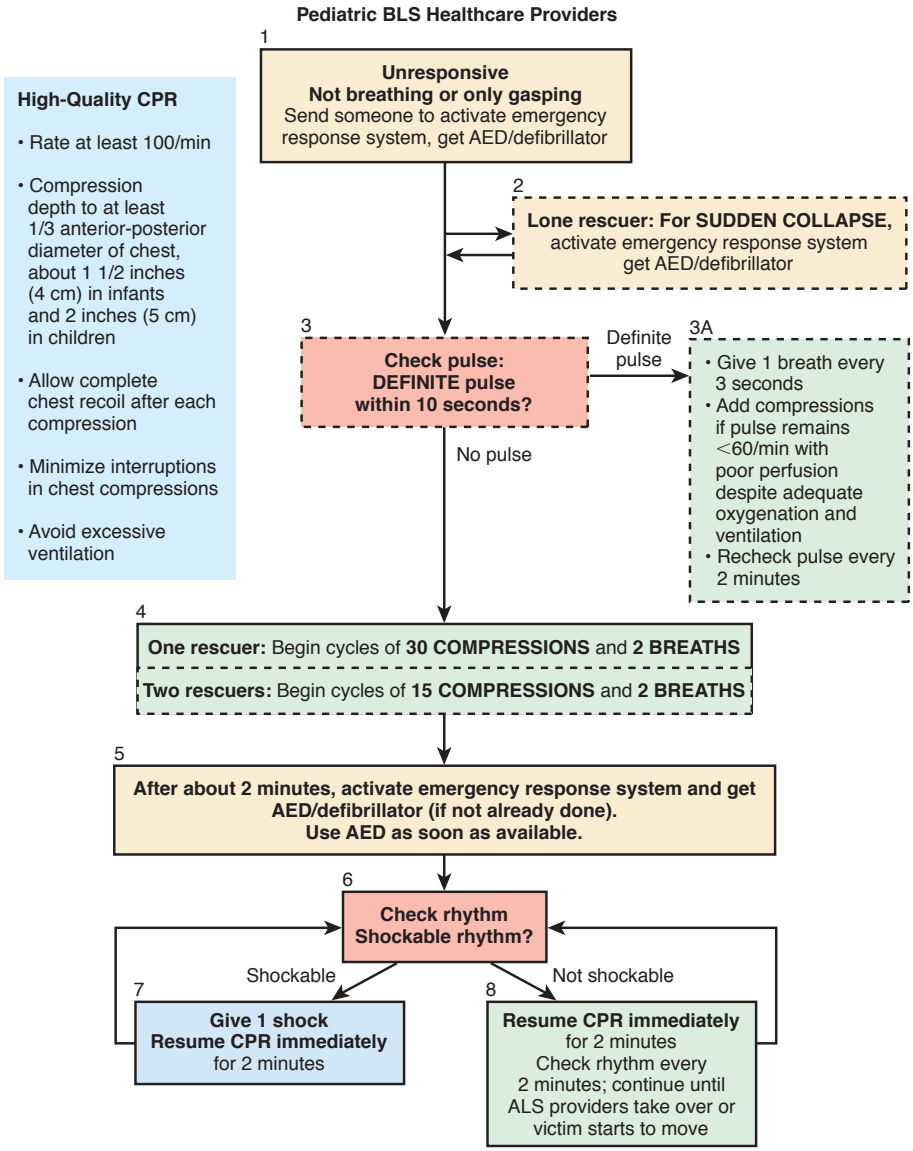
PRODUCT	USES
VITAMINS	
B_2 (riboflavin)	Migraine headache prophylaxis
B_6 (pyridoxine)	Pyridoxine-dependent epilepsy; neuropathy; nausea associated with pregnancy
B_9 (folate)	Prevention of neural tube defects
D	Prevention of rickets; treatment of deficiencies
Multivitamins	General health promotion, ADHD
MINERALS	
Iodine (salt)	Prevent goiter and mental retardation
Iron	Prevent and treat iron deficiency
Magnesium	Constipation, asthma, migraine prevention
Zinc	Diarrhea in nutrient-poor populations
HERBS	
Aloe vera	Mild burns
Chamomile	Mild sedative, dyspepsia
Echinacea	Prevention of upper respiratory infections
Ginger	Nausea
Lavender (aromatherapy)	Mild sedative
Peppermint	Irritable bowel syndrome
Tea tree oil	Anti-bacterial (acne remedies), pediculicide (lice)
OTHER	
Melatonin	Insomnia
Omega-3 fatty acids (fish oil)	ADHD, allergies, inflammation, anxiety and mood disorders
Probiotics	Antibiotic-associated diarrhea; *Clostridium difficile*–associated diarrhea; constipation; irritable bowel syndrome; pouchitis; inflammatory bowel disorders

Table 67-3 Glasgow Coma Scale

EYE OPENING (TOTAL POSSIBLE POINTS 4)			
Spontaneous	4		
To voice	3		
To pain	2		
None	1		
VERBAL RESPONSE (TOTAL POSSIBLE POINTS 5)			
OLDER CHILDREN		**INFANTS AND YOUNG CHILDREN**	
Oriented	5	Appropriate words; smiles, fixes, and follows	5
Confused	4	Consolable crying	4
Inappropriate	3	Persistently irritable	3
Incomprehensible	2	Restless, agitated	2
None	1	None	1
MOTOR RESPONSE (TOTAL POSSIBLE POINTS 6)			
Obeys	6		
Localizes pain	5		
Withdraws	4		
Flexion	3		
Extension	2		
None	1		

Table 69-2 Life-Threatening Cardiac Causes of Syncope

Long QT syndromes (congenital and drug induced)
Cardiomyopathies
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Brugada syndrome
Catecholminergic polymorphic ventricular tachycardia
Myocarditis
Wolff-Parkinson-White syndrome
Coronary artery anomalies
Late postoperative arrhythmias
Congenital or acquired complete atrioventricular block
Aortic, mitral, or pulmonic valve stenosis
Primary pulmonary hypertension
Eisenmenger syndrome
Dissecting aortic aneurysm (Marfan syndrome)
Cardiac tumor



Note: The boxes bordered with dashed lines are performed by healthcare providers and not by rescuers

Figure 67-1 Pediatric basic life support algorithm. AED, automated external defibrillator; ALS, advanced life support; CPR, cardiopulmonary resuscitation. *(From Berg MD, Schexnayder SM, Chameides L, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 13,* Circulation *122[Suppl 3]:S862–S875, 2010, Fig. 3, p. S866.)*

Table 69-3 "Red Flags" in the Evaluation of Patients with Syncope

Syncope with activity or exercise or supine
Syncope not associated with prolonged standing
Syncope precipitated by loud noise or extreme emotion
Absence of presyncope or lightheadedness
Family history of syncope, drowning, sudden death, familial ventricular arrhythmia syndromes*, cardiomyopathy
Syncope requiring CPR
Injury with syncope
Anemia
Other cardiac symptoms
Chest pain
Dyspnea
Palpitations
History of cardiac surgery
History of Kawasaki disease
Implanted pacemaker
Abnormal physical examination
Murmur
Gallop rhythm
Loud and single second heart sound
Systolic click
Increased apical impulse (tachycardia)
Irregular rhythm
Hypo- or hypertension
Clubbing
Cyanosis

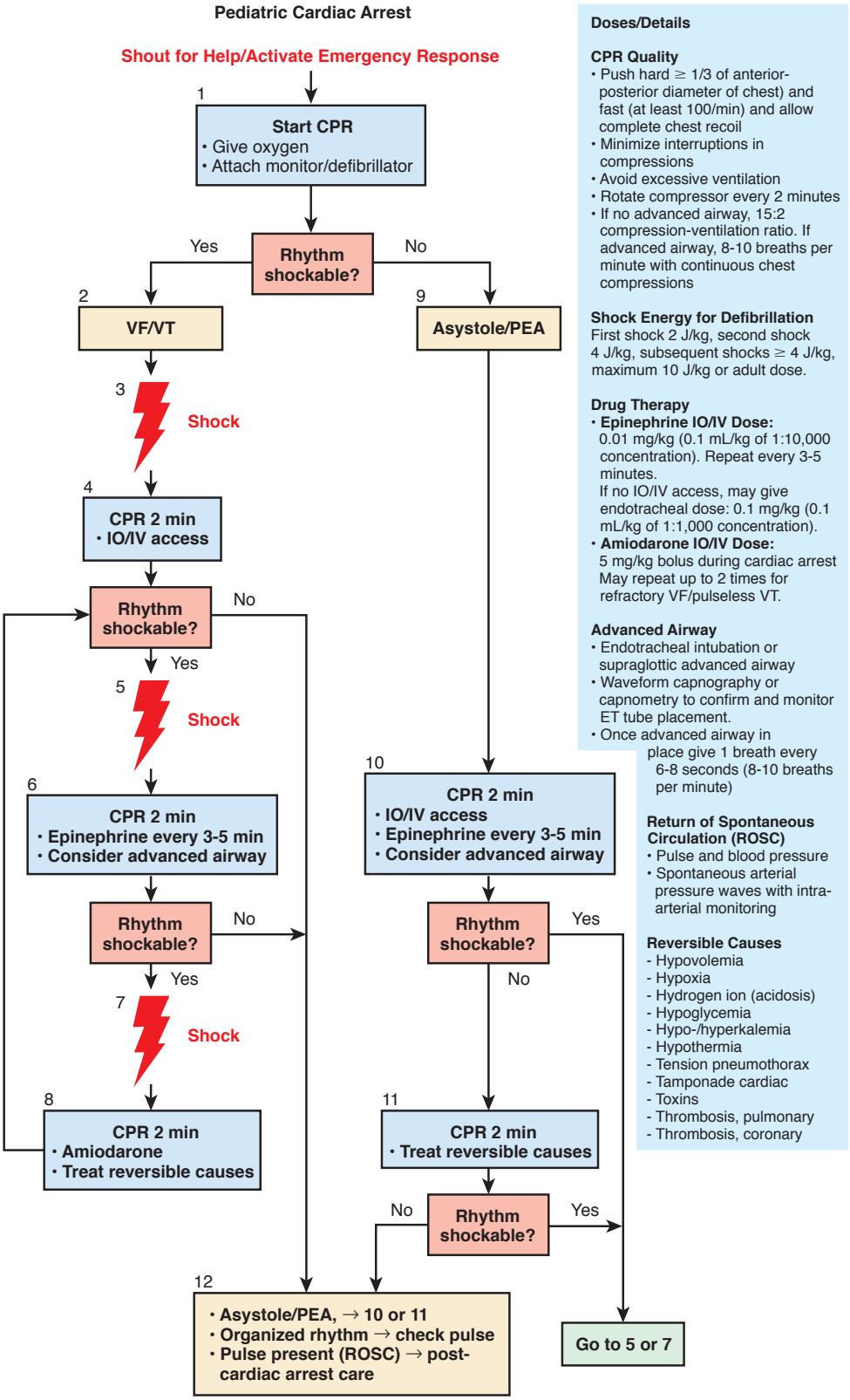


Figure 67-18 Pediatric advanced life support pulseless arrest algorithm. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14,* Circulation *122[Suppl 3]: S876–S908, 2010, Fig. 1, p. S885.)*

Table 67-6 Medications for Pediatric Resuscitation and Arrhythmias

MEDICATION	DOSE	REMARKS
Adenosine	0.1 mg/kg (maximum 6 mg) Repeat: 0.2 mg/kg (maximum 12 mg)	Monitor ECG Rapid IV/IO bolus
Amiodarone	5 mg/kg IV/IO; repeat up to 15 mg/kg Maximum: 300 mg	Monitor ECG and blood pressure Adjust administration rate to urgency (give more slowly when perfusing rhythm is present) Use caution when administering with other drugs that prolong QT interval (consider expert consultation)
Atropine	0.02 mg/kg IV/IO 0.03 mg/kg ET* Repeat once if needed Minimum dose: 0.1 mg Minimum single dose: Child, 0.5 mg Adolescent, 1 mg	Higher doses may be used with organophosphate poisoning
Calcium chloride (10%)	20 mg/kg IV/IO (0.2 mL/kg)	Slowly Adult dose: 5-10 mL
Epinephrine	0.01 mg/kg (0.1 mL/kg 1:10,000) IV/IO 0.1 mg/kg (0.1 mL/kg 1:1,000) ET* Maximum dose: 1 mg IV/IO; 10 mg ET	May repeat q 3-5 min
Glucose	0.5-1 g/kg IV/IO	D10W: 5-10 mL/kg D25W: 2-4 mL/kg D50W: 1-2 mL/kg
Lidocaine	Bolus: 1 mg/kg IV/IO Maximum dose: 100 mg Infusion: 20-50 µg/kg/min ET*: 2-3 mg	
Magnesium sulfate	25-50 mg/kg IV/IO over 10-20 min; faster in torsades de pointes Maximum dose: 2g	
Naloxone	<5 yr or ≤20 kg: 0.1 mg/kg IV/IO/ET* ≥5 yr or >20 kg: 2 mg IV/IO/ET*	Use lower doses to reverse respiratory depression associated with therapeutic opioid use (1-15 µg/kg)
Procainamide	15 mg/kg IV/IO over 30-60 min Adult dose: 20 mg/min IV infusion up to total maximum dose of 17 mg/kg	Monitor EGG and blood pressure Use caution when administering with other drugs that prolong QT interval (consider expert consultation)
Sodium bicarbonate	1 mEq/kg/dose IV/IO slowly	After adequate ventilation

*Flush with 5 mL of normal saline and follow with 5 ventilations.
ECG, electrocardiogram; ET, endotracheal tube; IO, intraosseous; IV, intravenous.
From ECC Committee, Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation *112:IV1–203, 2005.*

Table 67-7 Medications to Maintain Cardiac Output and for Postresuscitation Stabilization*

MEDICATION	DOSE RANGE	COMMENT
Inamrinone	0.75-1 mg/kg IV/IO over 5 min; may repeat 2×; then: 2-20 µg/kg/min	Inodilator
Dobutamine	2-20 µg/kg/min IV/IO	Inotrope; vasodilator
Dopamine	2-20 µg/kg/min IV/IO in low doses; pressor in higher doses	Inotrope; chronotrope; renal and splanchnic vasodilator
Epinephrine	0.1-1 µg/kg/min IV/IO	Inotrope; chronotrope; vasodilator in low doses; vasopressor in higher doses
Milrinone	50-75 µg/kg IV/IO over 10-60 min then 0.5-0.75 µg/kg/min	Inodilator
Norepinephrine	0.1-2 µg/kg/min	Inotrope; vasopressor
Sodium nitroprusside	1-8 µg/kg/min	Vasodilator; prepare only in D5W

*Alternative formula for calculating an infusion: Infusion rate (mL/hr) = [weight (kg) × dose (µg/kg/min) × 60 (min/hr)]/concentration µg/mL).
D5W, 5% dextrose in water; IO, intraosseous; IV, intravenous.
From ECC Committee, Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation *112:IV1–IV203, 2005.*

Table 69-1 Noncardiac Causes of Syncope

- Reflex vasodepressor syncope
  - Neurocardiogenic (vasovagal)
  - Emotion (seeing blood)
  - Pain (needle phobia)
- Miscellaneous situational reflex
  - Tussive
  - Sneeze
  - Exercise/post exercise
  - Swallowing
  - Stretching
  - Defecation
  - Micturition
  - Valsalva (increased intrathoracic pressure)
  - Breath holding spells
- Systemic illness
  - Hypoglycemia
  - Anemia
  - Infection
  - Hypovolemia, dehydration
  - Adrenal insufficiency
  - Narcolepsy/cataplexy
  - Pulmonary embolism
  - Ruptured ectopic pregnancy
- Central nervous system
  - Seizure (atonic, absence, myoclonic-astatic)
  - Stroke/transient ischemic attack
  - Subarachnoid hemorrhage
- Dysautonomia
- Basilar artery migraine
- Drug effects
  - β-Blocking agents
  - Vasodilating agents
  - Opiates
  - Sedatives
  - Drugs prolonging QT interval
  - Diuretics
  - Anticonvulsant agents
  - Antihistamines
  - Antidepressant agents
  - Anxiolytic agents
  - Drugs of abuse
  - Insulin, oral hypoglycemic agents
  - Carbon monoxide
- Other etiologies
  - Carotid sinus sensitivity
  - Subclavian steal
  - Panic attack/anxiety
  - Conversion disorder

Table 68-1 Commonly Used Coma Scores

GLASGOW COMA SCALE	FULL OUTLINE OF UNRESPONSIVENESS (FOUR) SCORE
Eye Opening 1 = does not open eyes 2 = opens eyes in response to noxious stimuli 3 = opens eyes in response to voice 4 = opens eyes spontaneously	*Eye Response* 4 = eyelids open or opened, tracking, or blinking to command 3 = eyelids open but not tracking 2 = eyelids closed but open to loud voice 1 = eyelids closed but open to pain 0 = eyelids remain closed with pain
Verbal Output 1 = makes no sounds 2 = makes incomprehensible sounds 3 = utters inappropriate words 4 = confused and disoriented 5 = speaks normally and oriented	*Motor Response* 4 = thumbs-up, fist, or peace sign 3 = localizing to pain 2 = flexion response to pain 1 = extension response to pain 0 = no response to pain or generalized myoclonus status
Motor Response (Best) 1 = makes no movements 2 = extension to painful stimuli 3 = abnormal flexion to painful stimuli 4 = flexion/withdrawal to painful stimuli 5 = localized to painful stimuli 6 = obeys commands	*Brainstem Reflexes* 4 = pupil and corneal reflexes present 3 = one pupil wide and fixed 2 = pupil or corneal reflexes absent 1 = pupil and corneal reflexes absent 0 = absent pupil, corneal, and cough reflex
	Respiration 4 = not intubated, regular breathing pattern 3 = not intubated, Cheyne-Stokes breathing pattern 2 = not intubated, irregular breathing 1 = breathes above ventilatory rate 0 = breathes at ventilator rate or apnea

Table 68-2 Brainstem Reflex Testing to Determine Brain Death

BRAINSTEM REFLEX	AREA TESTED	HOW TO PERFORM THE EXAM	EXPLANATION OF RESULTS
Pupillary light reflex	CN II and III, midbrain	Shine a light into the eyes while closely observing pupillary size	Midposition (4-6 mm) or fully dilated pupils that are not reactive to light are consistent with brain death. Pinpoint pupils, even if nonreactive, suggest intact function of the Edinger-Westphal nucleus in the midbrain and are therefore not consistent with brain death.
Oculocephalic reflex (doll's-eyes reflex)	CN III, VI, and VIII, midbrain, pons	Manually rotate the patient's head side to side and closely watch the position of the eyes. Should not be performed in a patient with a cervical spine injury.	In an intact patient, the eyes remain fixed on a distant spot, as if maintaining eye contact with that spot. In an exam consistent with brain death, the eyes move in concert with the patient's head movement.
Corneal reflex	CN III, V, and VII, pons	Touch the patient's cornea with a cotton swab.	In the intact patient, the touch results in eyelid closure, and the eye may rotate upward. In an exam consistent with brain death, there is no response.
Oculovestibular reflex	CN III, IV, VI, and VIII, pons, midbrain	Irrigate the tympanic membrane with iced water or saline and look for eye movement.	Absence of eye movement is consistent with brain death.
Gag and cough reflex	CN IX and X, medulla	Touch the posterior pharynx with a tongue depressor or a cotton-tipped swab to stimulate a gag. Advance a suction catheter through the endotracheal tube to the carina to stimulate a cough.	Absence of both a cough and a gag is consistent with brain death.

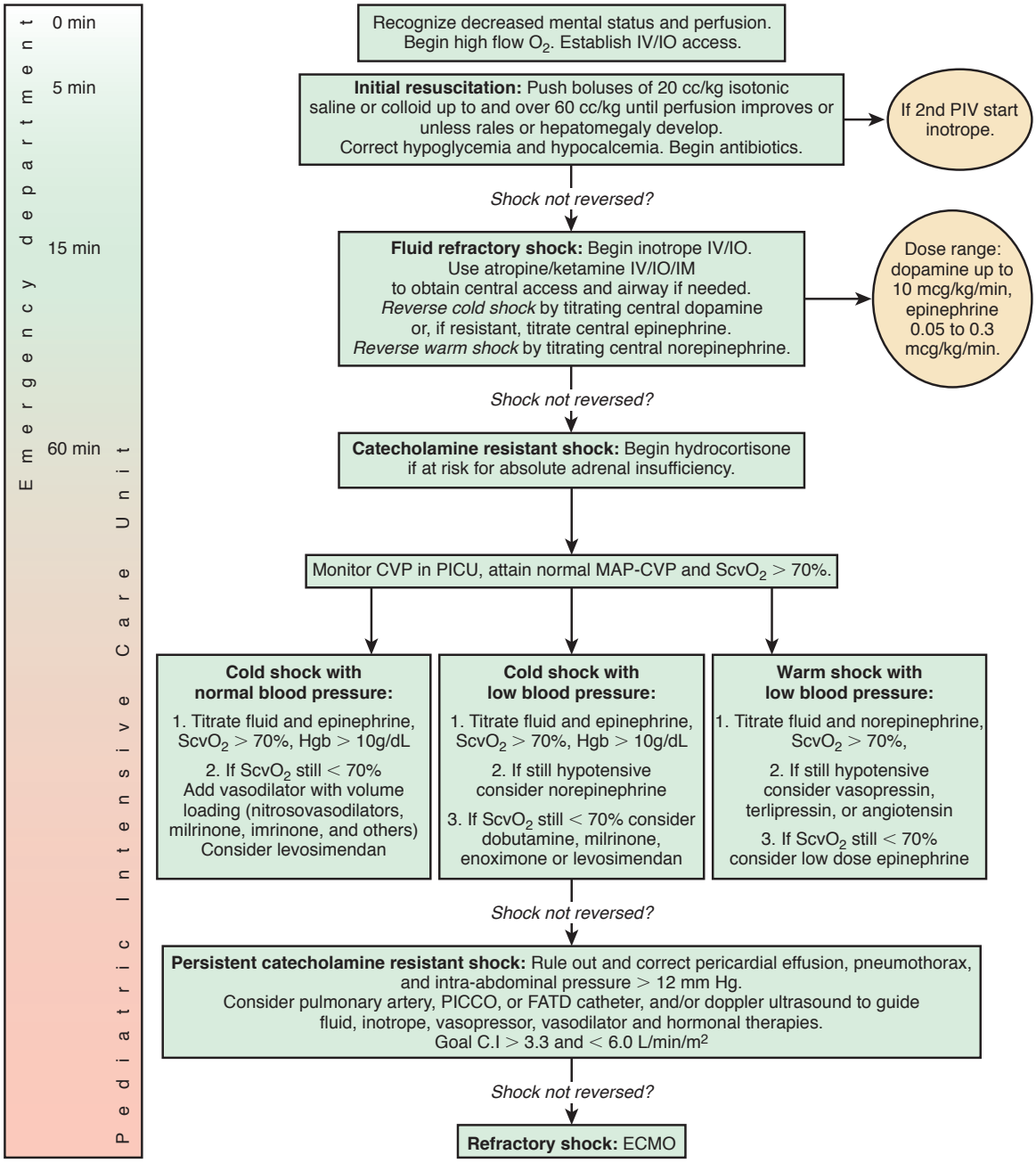
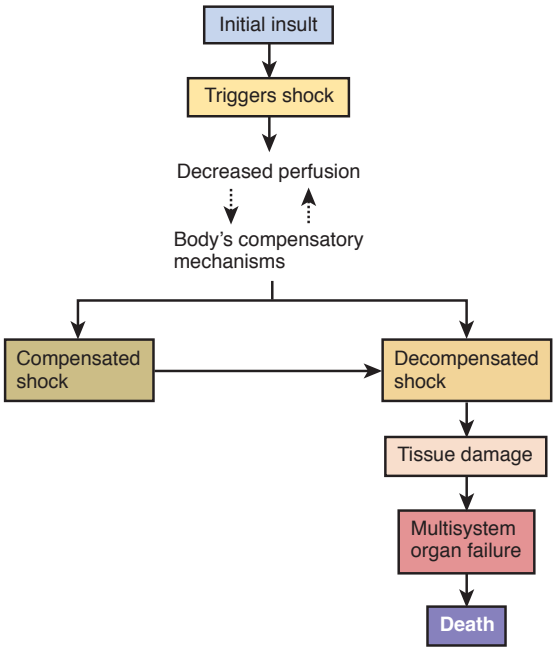


Figure 70-1 Algorithm for time-sensitive, goal-directed, stepwise management of hemodynamic support in infants and children. CI, cardiac index; CRRT, continuous renal replacement therapy; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; FATD, femoral arterial thermodilution; Hgb, hemoglobin; IM, intramuscular; IO, intraosseous; IV, intravenous; MAP, mean arterial pressure; PICCO, pulse contour cardiac output. *(From Brierly J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine,* Crit Care Med *37:666-688, 2009. Copyright 2009, Society of Critical Care Medicine and Lippincott Williams & Wilkins.)*

Table 70-1 Types of Shock

HYPOVOLEMIC	CARDIOGENIC	DISTRIBUTIVE	SEPTIC	OBSTRUCTIVE
Decreased preload secondary to internal or external losses	Cardiac pump failure secondary to poor myocardial function	Abnormalities of vasomotor tone from loss of venous and arterial capacitance	Encompasses multiple forms of shock Hypovolemic: third spacing of fluids into the extracellular, interstitial space Distributive: early shock with decreased afterload Cardiogenic: depression of myocardial function by endotoxins	Decreased cardiac output secondary to direct impediment to right- or left-heart outflow or restriction of all cardiac chambers
POTENTIAL ETIOLOGIES				
Blood loss: hemorrhage; Plasma loss: burns, nephrotic syndrome; Water/electrolyte loss: vomiting, diarrhea	Congenital heart disease Cardiomyopathies: infectious or acquired, dilated or restrictive Ischemia Arrhythmias	Anaphylaxis Neurologic: loss of sympathetic vascular tone secondary to spinal cord or brainstem injury Drugs	Bacterial Viral Fungal (immunocompromised patients are at increased risk)	Tension pneumothorax Pericardial tamponade Pulmonary embolism Anterior mediastinal masses Critical coarctation of the aorta



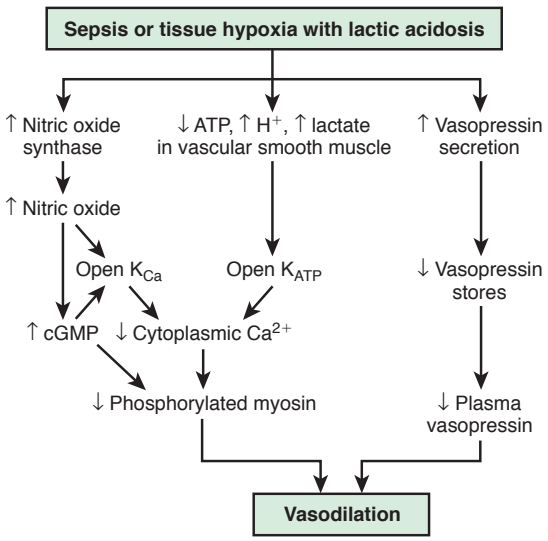


Table 70-2 Criteria for Organ Dysfunction

ORGAN SYSTEM	CRITERIA FOR DYSFUNCTION
Cardiovascular	Despite administration of isotonic intravenous fluid bolus ≥60 mL/kg in 1 hr: decrease in BP (hypotension) systolic BP <90 mm Hg, mean arterial pressure <70 mm Hg, <5th percentile for age, or systolic BP <2 SD below normal for age *or* Need for vasoactive drug to maintain BP in normal range (dopamine >5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) *or* Two of the following: Unexplained metabolic acidosis: base deficit >5.0 mEq/L Increased arterial lactate: >1 mmol/Liter or >2× upper limit of normal Oliguria: urine output <0.5 mL/kg/hr Prolonged capillary refill: >5 sec Core to peripheral temperature gap >3°C (5.4°F)
Respiratory	PaO_2/FIO_2 ratio <300 in absence of cyanotic heart disease or preexisting lung disease *or* $PaCO_2$ >65 torr or 20 mm Hg over baseline $PaCO_2$ *or* Need for >50% FIO_2 to maintain saturation ≥92% *or* Need for nonelective invasive or noninvasive mechanical ventilation
Neurologic	GCS score ≤11 *or* Acute change in mental status with a decrease in GCS score ≥3 points from abnormal baseline
Hematologic	Platelet count <100,000/mm^3 or a decline of 50% in the platelet count from the highest value recorded over the last 3 days (for patients with chronic hematologic or oncologic disorders) *or* INR >1.5 *or* Activated prothrombin time >60 sec
Renal	Serum creatinine >0.5 mg/dL, ≥2× upper limit of normal for age, or 2-fold increase in baseline creatinine value
Hepatic	Total bilirubin ≥4 mg/dL (not applicable for newborn) Alanine transaminase level 2× upper limit of normal for age

BP, blood pressure; FIO_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; INR, international normalized ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, partial pressure arterial oxygen.

Table 70-10 Surviving Sepsis Campaign Care Bundles

To be completed within 3 hr:
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

To completed within 6 hr:
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   Measure central venous pressure (CVP)*
   Measure central venous oxygen saturation ($ScvO_2$)*
7. Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $ScvO_2$ of ≥70%, and normalization of lactate.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Fig. 1, p. 591.*

Table 70-4 Pathophysiology of Shock

EXTRACORPOREAL FLUID LOSS
Hypovolemic shock may be a result of direct blood loss through hemorrhage or abnormal loss of body fluids (diarrhea, vomiting, burns, diabetes mellitus or insipidus, nephrosis)

LOWERING PLASMA ONCOTIC FORCES
Hypovolemic shock may also result from hypoproteinemia (liver injury, or as a progressive complication of increased capillary permeability)

ABNORMAL VASODILATION
Distributive shock (neurogenic, anaphylaxis, or septic shock) occurs when there is loss of vascular tone—venous, arterial, or both (sympathetic blockade, local substances affecting permeability, acidosis, drug effects, spinal cord transection)

INCREASED VASCULAR PERMEABILITY
Sepsis may change the capillary permeability in the absence of any change in capillary hydrostatic pressure (endotoxins from sepsis, excess histamine release in anaphylaxis)

CARDIAC DYSFUNCTION
Peripheral hypoperfusion may result from any condition that affects the heart's ability to pump blood efficiently (ischemia, acidosis, drugs, constrictive pericarditis, pancreatitis, sepsis)

Table 70-3 Signs of Decreased Perfusion

ORGAN SYSTEM	↓ PERFUSION	↓↓ PERFUSION	↓↓↓ PERFUSION
Central nervous system	—	Restless, apathetic, anxious	Agitated/confused, stuporous, coma
Respiration	—	↑ Ventilation	↑↑ Ventilation
Metabolism	—	Compensated metabolic acidemia	Uncompensated metabolic acidemia
Gut	—	↓ Motility	Ileus
Kidney	↓ Urine volume ↑ Urinary specific gravity	Oliguria (<0.5 mL/kg/hr)	Oliguria/anuria
Skin	Delayed capillary refill	Cool extremities	Mottled, cyanotic, cold extremities
Cardiovascular system	↑ Heart rate	↑↑ Heart rate ↓ Peripheral pulses	↑↑ Heart rate ↓ Blood pressure, central pulses only

Table 70-5 Differential Diagnosis of Systemic Inflammatory Response Syndrome

INFECTION
Bacteremia or meningitis (*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis,* group A streptococcus, *Staphylococcus aureus*)
Viral illness (influenza, enteroviruses, hemorrhagic fever group, herpes simplex virus, respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus)
Encephalitis (arboviruses, enteroviruses, herpes simplex virus)
Rickettsiae (Rocky Mountain spotted fever, *Ehrlichia,* Q fever)
Syphilis
Vaccine reaction (pertussis, influenza, measles)
Toxin-mediated reaction (toxic shock, staphylococcal scalded skin syndrome)
CARDIOPULMONARY
Pneumonia (bacteria, virus, mycobacteria, fungi, allergic reaction)
Pulmonary emboli
Heart failure
Arrhythmia
Pericarditis
Myocarditis
METABOLIC-ENDOCRINE
Adrenal insufficiency (adrenogenital syndrome, Addison disease, corticosteroid withdrawal)
Electrolyte disturbances (hyponatremia or hypernatremia; hypocalcemia or hypercalcemia)
Diabetes insipidus
Diabetes mellitus
Inborn errors of metabolism (organic acidosis, urea cycle, carnitine deficiency, mitochondrial disorders)
Hypoglycemia
Reye syndrome
GASTROINTESTINAL
Gastroenteritis with dehydration
Volvulus
Intussusception
Appendicitis
Peritonitis (spontaneous, associated with perforation or peritoneal dialysis)
Necrotizing enterocolitis
Hepatitis
Hemorrhage
Pancreatitis
HEMATOLOGIC
Anemia (sickle cell disease, blood loss, nutritional)
Methemoglobinemia
Splenic sequestration crisis
Leukemia or lymphoma
Hemophagocytic syndromes
NEUROLOGIC
Intoxication (drugs, carbon monoxide, intentional or accidental overdose)
Intracranial hemorrhage
Infant botulism
Trauma (child abuse, accidental)
Guillain-Barré syndrome
Myasthenia gravis
OTHER
Anaphylaxis (food, drug, insect sting)
Hemolytic-uremic syndrome
Kawasaki disease
Erythema multiforme
Hemorrhagic shock–encephalopathy syndrome
Poisoning
Toxic envenomation
Macrophage activation syndrome

Table 70-13 Cardiovascular Drug Treatment of Shock

DRUG	EFFECT(S)	DOSING RANGE	COMMENT(S)
Dopamine	↑ Cardiac contractility Significant peripheral vasoconstriction at >10 μg/kg/min	3-20 μg/kg/min	↑ Risk of arrhythmias at high doses
Epinephrine	↑ Heart rate and ↑ cardiac contractility Potent vasoconstrictor	0.05-3.0 μg/kg/min	May ↓ renal perfusion at high doses ↑ Myocardial O_2 consumption Risk of arrhythmia at high doses
Dobutamine	↑ Cardiac contractility Peripheral vasodilator	1-10 μg/kg/min	—
Norepinephrine	Potent vasoconstriction No significant effect on cardiac contractility	0.05-1.5 μg/kg/min	↑ Blood pressure secondary to ↑ systemic vascular resistance ↑ Left ventricular afterload
Phenylephrine	Potent vasoconstriction	0.5-2.0 μg/kg/min	Can cause sudden hypertension ↑ O_2 consumption

Table 70-11 Recommendations: Hemodynamic Support and Adjunctive Therapy—Adults

FLUID THERAPY OF SEVERE SEPSIS

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock.
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock.
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids.
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients.
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables.

VASOPRESSORS

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg.
2. Norepinephrine as the first choice vasopressor.
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure.
4. Vasopressin 0.03 units/min can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage.
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/min should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) NE is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target.
8. Low-dose dopamine should not be used for renal protection.
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available.

INOTROPIC THERAPY

1. A trial of dobutamine infusion up to 20 μg/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.
2. Not using a strategy to increase cardiac index to predetermined supranormal levels.

CORTICOSTEROIDS

1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day.
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone.
3. In treated patients, hydrocortisone tapered when vasopressors are no longer required.
4. Corticosteroids should not be administered for the treatment of sepsis in the absence of shock.
5. When hydrocortisone is given, use continuous flow.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Table 6, p. 596.*

Table 70-12 Recommendations: Special Considerations in Pediatrics

INITIAL RESUSCITATION 1. For respiratory distress and hypoxemia start with face mask oxygen or if needed and available, high flow nasal cannula oxygen or nasopharyngeal CPAP (NP CPAP). For improved circulation, peripheral intravenous access or intraosseous access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required then cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation. 2. Initial therapeutic end points of resuscitation of septic shock: capillary refill of ≤2 sec, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL kg^{-1} hr^{-1}, and normal mental status. $ScvO_2$ saturation ≥70% and cardiac index between 3.3 and 6.0 L/min/m^2 should be targeted thereafter. 3. Follow American College of Critical Care Medicine-Pediatric Life Support (ACCM-PALS) guidelines for the management of septic shock. 4. Evaluate for and reverse pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock.
ANTIBIOTICS AND SOURCE CONTROL 1. Empiric antibiotics should be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible but this should not delay administration of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (e.g., H1N1, methicillin-resistant *Staphylococcus aureus* [MRSA], chloroquine-resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia). 2. Clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension. 3. Early and aggressive source control. 4. *Clostridium difficile* colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease.
FLUID RESUSCITATION 1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystalloids or albumin with boluses of up to 20 mL/kg crystalloids (or albumin equivalent) over 5-10 minutes, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales exist then inotropic support should be implemented, not fluid resuscitation. In nonhypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises), blood transfusion is considered superior to crystalloid or albumin bolus.
INOTROPES/VASOPRESSORS/VASODILATORS 1. Begin peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation. 2. Patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure should be given vasodilator therapies in addition to inotropes.
EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) 1. Consider ECMO for refractory pediatric septic shock and respiratory failure.
CORTICOSTEROIDS 1. Timely hydrocortisone therapy in children with fluid refractory, catecholamine resistant shock and suspected or proven absolute (classic) adrenal insufficiency.
PROTEIN C AND ACTIVATED PROTEIN CONCENTRATE No recommendation as no longer available.
BLOOD PRODUCTS AND PLASMA THERAPIES 1. Similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (<70 %), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia, a lower target (>7.0 g/dL) can be considered reasonable. 2. Similar platelet transfusion targets in children as in adults. 3. Use plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura.
MECHANICAL VENTILATION 1. Lung-protective strategies during mechanical ventilation.
SEDATION/ANALGESIA/DRUG TOXICITIES 1. We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis. 2. Monitor drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events.
GLYCEMIC CONTROL 1. Control hyperglycemia using a similar target as in adults (≤180 mg/dL). Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant.
DIURETICS AND RENAL REPLACEMENT THERAPY 1. Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent >10% total body weight fluid overload.
DEEP VEIN THROMBOSIS (DVT) PROPHYLAXIS No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.
STRESS ULCER (SU) PROPHYLAXIS No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis
NUTRITION 1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

CPAP, continuous positive airway pressure.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Table 9, p. 614.*

Table 71-1 Typical Localizing Signs for Pulmonary Pathology

SITE OF PATHOLOGY	RESPIRATORY RATE	RETRACTIONS	AUDIBLE SOUNDS
Extrathoracic airway	↑	↑↑↑↑	Stridor
Intrathoracic extrapulmonary	↑	↑↑	Wheezing
Intrathoracic intrapulmonary	↑↑	↑↑	Wheezing
Alveolar interstitial	↑↑↑	↑↑↑	Grunting

Table 71-3 Nonpulmonary Causes of Respiratory Distress

	EXAMPLE(S)	MECHANISM(S)
Cardiovascular	Left-to-right shunt Congestive heart failure Cardiogenic shock	↑ Pulmonary blood/water content Metabolic acidosis Baroreceptor stimulation
Central nervous system	Increased intracranial pressure Encephalitis Neurogenic pulmonary edema Toxic encephalopathy	Stimulation of brainstem respiratory centers
Metabolic	Diabetic ketoacidosis Organic acidemia Hyperammonemia	Stimulation of central and peripheral chemoreceptors
Renal	Renal tubular acidosis Hypertension	Stimulation of central and peripheral chemoreceptors Left ventricular dysfunction → increased pulmonary blood/water content
Sepsis	Toxic shock syndrome Meningococcemia	Cytokine stimulation of respiratory centers Baroreceptor stimulation from shock Metabolic acidosis

Table 71-4 Cardiovascular Pathology Manifesting as Respiratory Distress

I. DECREASED LUNG COMPLIANCE
  A. Left-to-Right Shunts
    1. Ventricular septal defect, atrial septal defect, patent ductus arteriosus, atrioventricular canal, truncus arteriosus
    2. Cerebral or hepatic arteriovenous fistula
  B. Ventricular Failure
    1. Left-heart obstructive lesions
      a) aortic stenosis
      b) coarctation of the aorta
      c) mitral stenosis
      d) interrupted aortic arch
      e) hypoplastic left heart syndrome
    2. Myocardial infarction
      a) anomalous left coronary artery arising from the pulmonary artery
    3. Hypertension
      a) acute glomerulonephritis
    4. Inflammatory/Infectious
      a) myocarditis
      b) pericardial effusion
    5. Idiopathic
      a) dilated cardiomyopathy
      b) hypertrophic obstructive cardiomyopathy
  C. Pulmonary Venous Obstruction
    1. Total anomalous pulmonary venous return with obstruction
    2. Cor triatriatum
II. SHOCK RESULTING IN METABOLIC ACIDOSIS
  A. Left-Heart Obstructive Lesions
  B. Acute Ventricular Failure
    1. Myocarditis, myocardial infarction

Table 71-2 Examples of Anatomic Sites of Lesions Causing Respiratory Failure

LUNG	RESPIRATORY PUMP
CENTRAL AIRWAY OBSTRUCTION Choanal atresia Tonsilloadenoidal hypertrophy Retropharyngeal/peritonsillar abscess Laryngomalacia Epiglottitis Vocal cord paralysis Laryngotracheitis Subglottic stenosis Vascular ring/pulmonary sling Mediastinal mass Foreign-body aspiration Obstructive sleep apnea	THORACIC CAGE Kyphoscoliosis Diaphragmatic hernia Flail chest Eventration of diaphragm Asphyxiating thoracic dystrophy Prune-belly syndrome Dermatomyositis Abdominal distention
PERIPHERAL AIRWAY OBSTRUCTION Asthma Bronchiolitis Foreign-body aspiration Aspiration pneumonia Cystic fibrosis α_1-Antitrypsin deficiency	BRAINSTEM Arnold-Chiari malformation Central hypoventilation syndrome CNS depressants Trauma Increased intracranial pressure CNS infections
ALVEOLAR-INTERSTITIAL DISEASE Lobar pneumonia Acute respiratory distress syndrome/hyaline membrane disease Interstitial pneumonia Hydrocarbon pneumonia Pulmonary hemorrhage/hemosiderosis	SPINAL CORD Trauma Transverse myelitis Spinal muscular atrophy Poliomyelitis Tumor/abscess
	NEUROMUSCULAR Phrenic nerve injury Birth trauma Infant botulism Guillain-Barré syndrome Muscular dystrophy Myasthenia gravis Organophosphate poisoning

Table 71-5 Typical Chronology of Heart Disease Presentation in Children

AGE	MECHANISM	DISEASE
Newborn (1-10 days)	↑ Arteriovenous pressure difference Ductal closure Independent pulmonary and systemic blood flow Pulmonary venous obstruction	Arteriovenous fistula (brain, liver) Single ventricle lesions or severe ventricular outflow obstruction Transposition of the great arteries Total anomalous pulmonary venous return (TAPVR)
Young Infant (1-6 mo)	↓ Pulmonary vascular resistance ↓ Pulmonary artery pressure	Left-to-right shunt Anomalous left coronary artery to the pulmonary artery
Any Age	Rate disturbance Infection Abnormal cardiac myocytes Excess afterload	Tachy- or bradyarrhythmias Myocarditis, pericarditis Cardiomyopathy hypertension

Table 71-7 Simplified Consensus Definition of Acute Lung Injury

- Acute onset (<7 days)
- Severe hypoxemia (PaO_2/FIO_2 <300 for acute lung injury, or <200 for acute respiratory distress syndrome)
- Diffuse bilateral pulmonary infiltrates on frontal radiograph consistent with pulmonary edema (these can be patchy and asymmetric, and pleural effusions can be present)
- Absence of left atrial hypertension (pulmonary artery wedge pressure <18 mm Hg if measured)

From Wheeler AP, Bernard GR: Acute lung injury and the acute respiratory distress syndrome: a clinical review, Lancet *369:1553–1564, 2007.*

Table 71-6 Typical Clinical Manifestations of Respiratory Failure

SITE OF PATHOLOGY	SYMPTOM
Lung and Airways	Nasal flaring, retractions, tachypnea, wheezing stridor, grunting
Chest wall and muscles of respiration	Nasal flaring, tachypnea, paradoxical respirations
Respiratory control	Shallow or slow respirations, abnormal respiratory patterns, apnea

Table 71-8 New Berlin Definition of ARDS in Infancy and Early Childhood

	BERLIN DEFINITION CRITERIA	SUITABILITY IN INFANTS
Timing	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms	Acute time frame is specified
Chest X-rays or tomography scan	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. (Illustrative clinical cases and chest X-rays have been provided)	Including illustrative radiographs is important, because ARDS appearance may be different in children and in adults
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema, if no ARDS risk factors are present	Echocardiography widely used, whereas Swan-Ganz catheters are rarely used in early childhood. Including risk factors in the ARDS definition is important, because they may be different in children and in adults
Oxygenation*		
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O†	Noninvasive CPAP is widely used in early childhood. PEEP threshold (5 cm H_2O) is a value commonly used during early childhood
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O	
Severe	PaO_2/FIO_2 < 100 mm Hg with PEEP ≥ 5 cm H_2O	

*If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 × (barometric pressure/760)].
†This may be delivered noninvasively in the mild acute respiratory distress syndrome group.
CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

Table 71-10 Medications Commonly Used for Intubation

	DRUG	DOSE	ONSET (min)	DURATION (min)	COMMENTS
Sedatives/anesthetics	Midazolam	0.1 mg/kg IV	3-5	60-120	Amnesia Respiratory depression
	Lorazepam	0.1 mg/kg IV	3-5	120-240	Amnesia Respiratory depression
	Ketamine	1-2 mg/kg IV 4-6 mg/kg IM	2-3	10-15	↑ HR, BP, and ICP Bronchodilation
	Propofol	1-3 mg/kg IV	0.5-2	10-15	↓ BP Apnea
	Thiopental	4-7 mg/kg IV	0.5-1	5-10	↓ BP Apnea
Analgesics	Fentanyl	2-5 μg/kg IV	3-5	30-90	Respiratory depression Chest wall rigidity
	Morphine	0.1 mg/kg IV	5-15	120-240	↓ BP Respiratory depression
Neuromuscular blocking agents	Vecuronium	0.1 mg/kg IV	2-3	30-75	↑ HR Renal elimination
	Rocuronium	0.6-1.2 mg/kg IV 1 mg/kg IM	5-15	15-60	↑ HR Renal elimination
	Cisatracurium	0.1 mg/kg IV	2-3	25-30	Histamine release Nonrenal elimination

BP, blood pressure; HR, heart rate; ICP, intracranial pressure; IM, intramuscularly; IV, intravenously.

Table 72-4 Life-Threatening Chest Injuries

TENSION PNEUMOTHORAX
One-way valve leak from the lung parenchyma or tracheobronchial tree
Collapse with mediastinal and tracheal shift to the side opposite the leak
Compromises venous return and decreases ventilation of the other lung
Clinically, manifests as respiratory distress, unilateral absence of breath sounds, tracheal deviation, distended neck veins, tympany to percussion of the involved side, and cyanosis
Relieve first with needle aspiration, then with chest tube drainage
OPEN PNEUMOTHORAX (SUCKING CHEST WOUND)
Effect on ventilation depends on size
MAJOR FLAIL CHEST
Usually caused by blunt injury resulting in multiple rib fractures
Loss of bone stability of the thoracic cage
Major disruption of synchronous chest wall motion
Mechanical ventilation and positive end-expiratory pressure required
MASSIVE HEMOTHORAX
Must be drained with a large-bore tube
Initiate drainage only with concurrent vascular volume replacement
CARDIAC TAMPONADE
Beck Triad:
1. Decreased or muffled heart sounds
2. Distended neck veins from increased venous pressure
3. Hypotension with pulsus paradoxus (decreased pulse pressure during inspiration)
Must be drained

Modified from Krug SE: The acutely ill or injured child. In Behrman RE, Kliegman RM, editors: Nelson essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders, p. 97.*

Table 75-1 Burn Prophylaxis

PREVENT FIRES
Install and use smoke detectors
Control the hot water thermostat—in public buildings, the maximum water temperature should be 48.9°C (120°F)
Keep fire, matches, and lighters out of the reach of children
Avoid cigarette smoking, especially in bed
Do not leave lit candles unattended
Use flame retardant–treated clothing
Use caution when cooking, especially with oil
Keep cloth items off heaters
PREVENT INJURY
Roll, but do not run, if clothing catches fire; wrap in a blanket
Practice escape procedures
Crawl beneath smoke if a fire occurs indoors
Use educational materials*

*National Fire Protection Association pamphlets and videos.

Table 75-2 Indications for Hospitalization for Burns

Burns affecting >10% of BSA
Burns >10-20% of BSA in adolescent/adult
3rd-Degree burns
Electrical burns caused by high-tension wires or lightening
Chemical burns
Inhalation injury, regardless of the amount of BSA burned
Inadequate home or social environment
Suspected child abuse or neglect
Burns to the face, hands, feet, perineum, genitals, or major joints
Burns in patients with preexisting medical conditions that may complicate the acute recovery phase
Associated injuries (fractures)
Pregnancy

Table 75-3 Acute Treatment of Burns

First aid, including washing of wounds and removal of devitalized tissue
Fluid resuscitation
Provision of energy requirements
Control of pain
Prevention of infection—early excision and grafting
Prevention of excessive metabolic expenditures
Control of bacterial wound flora
Use of biologic and synthetic dressings to close the wound

Table 72-5 Differential Diagnosis of Immediately Life-Threatening Cardiopulmonary Injuries

	TENSION PNEUMOTHORAX	MASSIVE HEMOTHORAX	CARDIAC TAMPONADE
Breath sounds	Ipsilaterally decreased more than contralaterally	Ipsilaterally decreased	Normal
Percussion note	Hyperresonant	Dull	Normal
Tracheal location	Contralaterally shifted	Midline or shifted	Midline
Neck veins	Distended	Flat	Distended
Heart tones	Normal	Normal	Muffled

Modified from Cooper A, Foltin GL: Thoracic trauma. In Barkin RM, editor: Pediatric emergency medicine, *ed 2, St. Louis, 1997, Mosby, p. 325.*

Table 72-6 Systemic Responses to Blood Loss in Pediatric Patients

SYSTEM	MILD BLOOD LOSS (<30%)	MODERATE BLOOD LOSS (30-45%)	SEVERE BLOOD LOSS (>45%)
Cardiovascular	Increased heart rate; weak, thready peripheral pulses; normal systolic blood pressure; normal pulse pressure	Markedly increased heart rate; weak, thready central pulses; peripheral pulses absent; low normal systolic blood pressure	Tachycardia followed by bradycardia; central pulses very weak or absent; peripheral pulses absent; hypotension; diastolic blood pressure may be undetectable
Central nervous system	Anxiety; irritability; confusion	Lethargy; dulled response to pain	Coma
Skin	Cool, mottled; capillary refill prolonged	Cyanotic; capillary refill markedly prolonged	Pale and cold
Urine output	Low to very low	Minimal	None

Adapted from American College of Surgeons Committee on Trauma: Advanced trauma life support for doctors: student course manual, *Chicago, 2008, American College of Surgeons, p. 234.*

Table 75-4 Categories of Burn Depth

	1ST-DEGREE BURN	2ND-DEGREE, OR PARTIAL-THICKNESS, BURN	3RD-DEGREE, OR FULL-THICKNESS, BURN
Surface appearance	Dry, no blisters Minimal or no edema Erythematous Blanches, bleeds	Moist blebs, blisters Underlying tissue is mottled pink and white, with fair capillary refill Bleeds	Dry, leathery eschar Mixed white, waxy, khaki, mahogany, soot-stained No blanching or bleeding
Pain	Very painful	Very painful	Insensate
Histologic depth	Epidermal layers only	Epidermis, papillary, and reticular layers of dermis May include domes of subcutaneous layers	Down to and may include fat, subcutaneous tissue, fascia, muscle, and bone
Healing time	2-5 days with no scarring	Superficial: 5-21 days with no grafting Deep partial: 21-35 days with no infection; if infected, converts to full-thickness burn	Large areas require grafting, but small areas may heal from the edges after wks

Table 75-6 Topical Agents Used for Burns

AGENT	EFFECTIVENESS	EASE OF USE
Silvadene cream (silver sulfadiazine)	Good penetration	Changed once daily Residue *must* be washed off with each dressing change
Mafenide acetate cream* (Sulfamylon cream)	Broad spectrum, including *Pseudomonas* Rapid and deep wound penetration	Closed dressings Changed twice daily Residue *must* be washed off with each dressing changed
0.5% Silver nitrate solution	Bacteriostatic Broad spectrum, including some fungi Superficial penetration	Closed bulky dressing soaked every 2 hr and changed once daily
AQUACEL Ag	Dressing impregnated with silver	Applied directly to 2nd-degree burn; occlusive dressing kept for 10 days

Table 75-5 Partial Listing of Some Commonly Used Wound Membranes—Selected Characteristics

MEMBRANE	CHARACTERISTIC(S)
Porcine xenograft	Adheres to coagulum Excellent pain control
Biobrane	Bilaminate Fibrovascular in growth into inner layer
Acticoat	Nonadherent dressing that delivers silver
AQUACEL-Ag	Absorptive hydrofiber that delivers silver
Various semipermeable membranes	Provide vapor and bacterial barrier
Various hydrocolloid dressings	Provide vapor and bacterial barrier Absorb exudates
Various impregnated gauzes	Provide barrier while allowing drainage

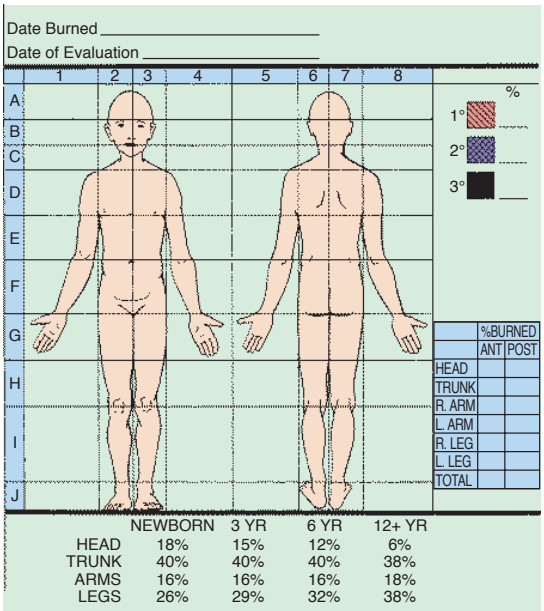


Figure 75-3 Chart to determine the developmentally related percentage of BSA affected by a burn injury. ANT, anterior; POST, posterior; R., right; L., left. *(Courtesy of Shriners Hospital for Crippled Children, Burn Institute, Boston Unit.)*

Table 76-2 Management of Hypothermia

HISTORY AND PHYSICAL
Gentle handling of the patient to prevent arrhythmias
ABCDE: cardiopulmonary resuscitation for ventricular fibrillation and asystole
Underlying disease diagnosis and treatment
Vital signs, pulse oximetry, electrocardiogram
Wet or cold clothing removed and patient placed in warm environment
LABORATORY TESTS
Arterial blood gas analysis corrected for temperature
Electrolytes, BUN creatinine, Ca, Mg, P
CBC with differential, PT/PTT, fibrinogen
Glucose, amylase/lipase
LFT
Additional labs, if appropriate, such as toxicology screen
PASSIVE REWARMING
≥32°C (89.6°F) in patients who are capable of spontaneous thermogenesis
ACTIVE REWARMING
<32°C (89.6°F), cardiovascular instability, patients at risk for developing hypothermia
Close monitoring for core-temperature afterdrop
Acute: external and/or core rewarming
Chronic (<32°C [89.6°F] for longer than 24 hr): core rewarming
Extracorporeal membrane oxygenation
Availability of rapid deployment

ABCDE, *a*irway and possibly *a*ntibiotics, *b*reathing, *c*irculation, *d*isability or neurologic and possible *d*extrose, extracorporeal support if all else fails; BUN, blood urea nitrogen; Ca, calcium; CDC, complete blood count; LFT liver function test; Mg, magnesium; P, phosphorus; PT, prothrombin time; PTT, partial thromboplastin time.

From Burg FD, Ingelfinger JR, Polin RA, Gershon AA (eds): Current pediatric therapy, *ed 18, Philadelphia, 2006, Saunders/Elsevier, Table 4, p. 174.*

Table 77-3 Indications for Genetic Counseling

Advanced parental age
• Maternal age ≥35 yr
• Paternal age ≥50 yr
Previous child with or family history of
• Congenital abnormality
• Dysmorphology
• Intellectual disability
• Isolated birth defect
• Metabolic disorder
• Chromosome abnormality
• Single-gene disorder
Adult-onset genetic disease (presymptomatic testing)
• Cancer
• Huntington disease
Consanguinity
Teratogen exposure (occupational, abuse)
Repeated pregnancy loss or infertility
Pregnancy screening abnormality
• Maternal serum α-fetoprotein
• Maternal triple or quad screen or variant of this test
• Fetal ultrasonography
• Fetal karyotype
Heterozygote screening based on ethnic risk
• Sickle cell anemia
• Tay-Sachs, Canavan, and Gaucher diseases
• Thalassemias
Follow-up to abnormal neonatal genetic testing
Prior to whole genome or exome sequencing
Prior to preimplantation genetic testing

Table 75-7 Common Long-Term Disabilities in Patients with Burn Injuries

DISABILITIES AFFECTING THE SKIN AND SOFT TISSUE
Hypertrophic scars
Susceptibility to minor trauma
Dry skin
Contractures
Itching and neuropathic pain
Alopecia
Chronic open wounds
Skin cancers
ORTHOPEDIC DISABILITIES
Amputations
Contractures
Heterotopic ossification
Temporary reduction in bone density
METABOLIC DISABILITIES
Heat sensitivity
Obesity
PSYCHIATRIC AND NEUROLOGIC DISABILITIES
Sleep disorders
Adjustment disorders
Posttraumatic stress syndrome
Depression
Body image issues
Neuropathy and neuropathic pain
Long-term neurologic effects of carbon monoxide poisoning
Anoxic brain injury
LONG-TERM COMPLICATIONS OF CRITICAL CARE
Deep-vein thrombosis, venous insufficiency, or varicose veins
Tracheal stenosis, vocal cord disorders, or swallowing disorders
Renal or adrenal dysfunction
Hepatobiliary or pancreatic disease
Cardiovascular disease
Reactive airway disease or bronchial polyposis
PREEXISTING DISABILITIES THAT CONTRIBUTED TO THE INJURIES
Risk-taking behavior
Untreated or poorly treated psychiatric disorder

Human Genetics

Instructions:
—Key should contain all information relevant to interpretation of pedigree (e.g., define fill/shading)
—For clinical (non-published) pedigrees include:
a) name of proband/consultand
b) family names/initials of relatives for identification, as appropriate
c) name and title of person recording pedigree
d) historian (person relaying family history information)
e) date of intake/update
f) reason for taking pedigree (e.g., abnormal ultrasound, familial cancer, developmental delay, etc.)
g) ancestry of both sides of family
—Recommended order of information placed below symbol (or to lower right)
a) age; can note year of birth (e.g., b.1978) and/or death (e.g., d. 2007)
b) evaluation (see Figure 75-4)
c) pedigree number (e.g., I-1, I-2, I-3)
—Limit identifying information to maintain confidentiality and privacy

	Male	Female	Gender not specified	Comments
1. Individual	b.1925	30 y	4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.
2. Affected individual				Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.
				With ≥2 conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.
3. Multiple individuals, number known	5	5	5	Number of siblings written inside symbol. (Affected individuals should not be grouped.)
4. Multiple individuals, number unknown or unstated	n	n	n	"n" used in place of "?".
5. Deceased individual	d. 35	d. 4 mo	d. 60's	Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).
6. Consultand				Individual(s) seeking genetic counseling/testing.
7. Proband	P	P		An affected family member coming to medical attention independent of other family members.
8. Stillbirth (SB)	SB 28 wk	SB 30 wk	SB 34 wk	Include gestational age and karyotype, if known.
9. Pregnancy (P)	P LMP: 7/1/2007 47,XY,+21	P 20 wk 46, XX	P	Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.

Pregnancies not carried to term	Affected	Unaffected	
10. Spontaneous abortion (SAB)	17 wks female cyctic hygroma	<10 wks	If gestational age/gender known, write below symbol. Key/legend used to define shading.
11. Termination of pregnancy (TOP)	18 wks 47, XY,+18		Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.
12. Ectopic pregnancy (ECT)	ECT		Write ECT below symbol.

Figure 80-1 Common pedigree symbols, definitions, and abbreviations. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

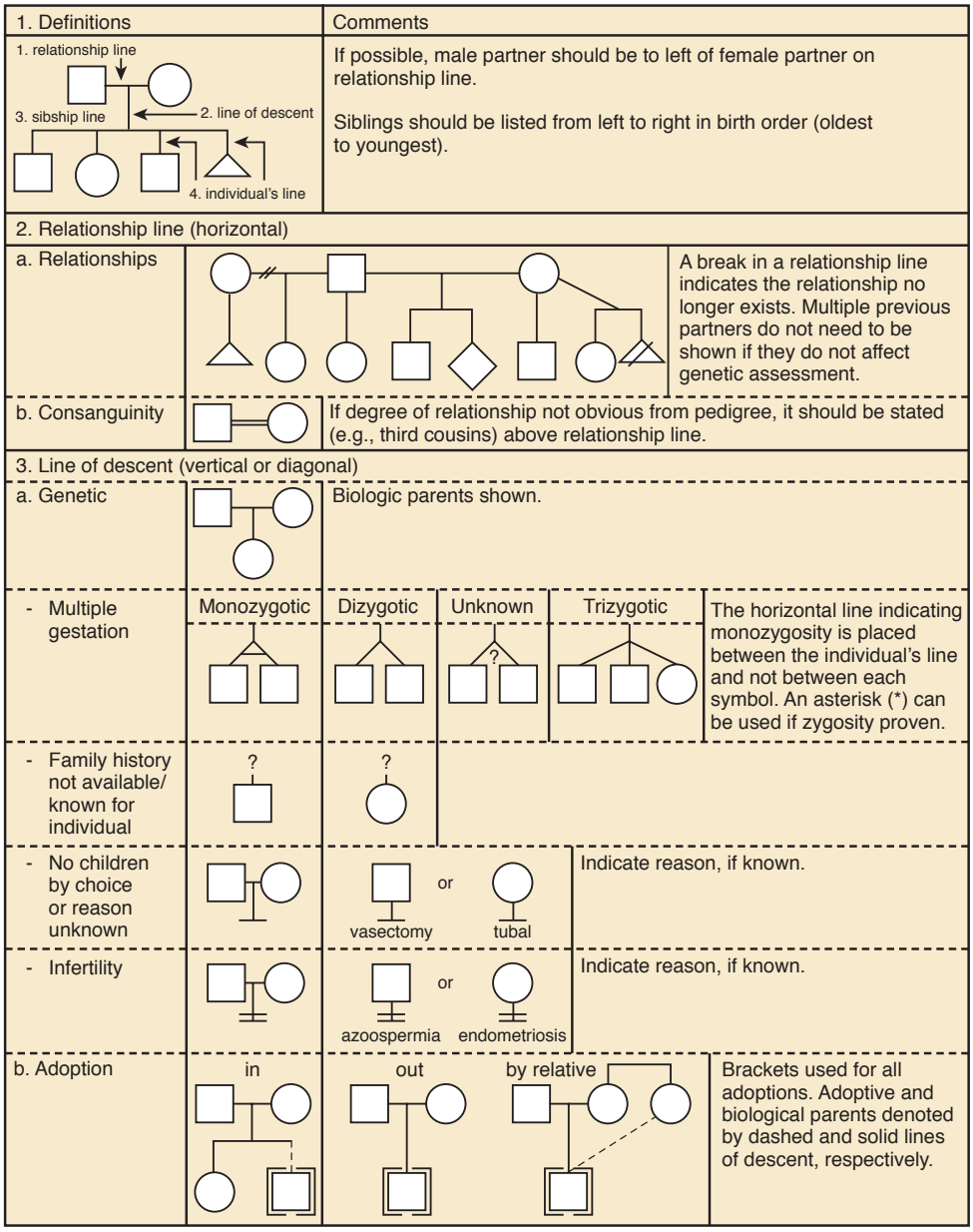


Figure 80-2 Pedigree line definitions. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

Instructions:
— D represents egg or sperm donor
— S represents surrogate (gestational carrier)
— If the woman is both the ovum donor and a surrogate, in the interest of genetic assessment, she will only be referred to as a donor (e.g., 4 and 5); the pregnancy symbol and its line of descent are positioned below the woman who is carrying the pregnancy
— Available family history should be noted on the gamete donor and/or gestational carrier

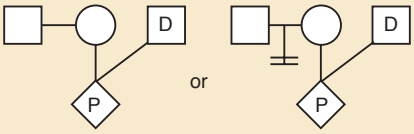
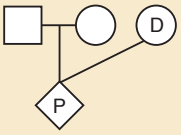
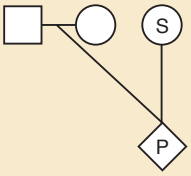
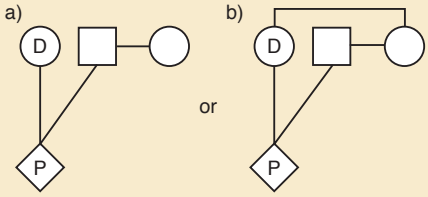
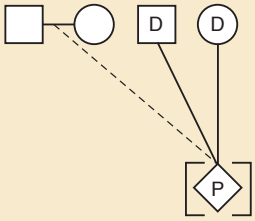
Possible Reproductive Scenarios		Comments
1. Sperm donor		Couple in which woman is carrying pregnancy using donor sperm. No relationship line is shown between the woman carrying the pregnancy and the sperm donor.
2. Ovum donor		Couple in which woman is carrying pregnancy using a donor egg and partner's sperm. The line of descent from the birth mother is solid because there is a biologic relationship that may affect the fetus (e.g., teratogens).
3. Surrogate only		Couple whose gametes are used to impregnate a woman (surrogate) who carries the pregnancy. The line of descent from the surrogate is solid because there is a biological relationship that may affect the fetus (e.g., teratogens).
4. Surrogate ovum donor		Couple in which male partner's sperm is used to inseminate (a) an unrelated woman or (b) a sister who is carrying the pregnancy for the couple.
5. Planned adoption		Couple contracts with a woman to carry a pregnancy using ovum of the woman carrying the pregnancy and donor sperm.

Figure 80-3 Assisted reproductive technology symbols and definitions. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

Instructions:
— E is used for evaluation to represent clinical and/or test information on the pedigree
  a. E is to be defined in key/legend
  b. If more than one evaluation, use subscript (E_1, E_2, E_3) and define in key
  c. Test results should be put in parentheses or defined in key/legend
— A symbol is shaded only when an individual is clinically symptomatic
— For linkage studies, haplotype information is written below the individual. The haplotype of interest should be on left and appropriately highlighted
  Repetitive sequences, trinucleotides, and expansion numbers are written with affected allele first and placed in parentheses
— If mutation known, identify in parentheses

Definition	Symbol	Scenario
1. Documented evaluation (*) Use only if examined/evaluated by you or your research/clinical team or if the outside evaluation has been reviewed and verified.	*	Woman with negative echocardiogram. E− (echo)
2. Carrier—not likely to manifest disease regardless of inheritance pattern		Male carrier of Tay-Sachs disease by patient report (* not used because results not verified).
3. Asymptomatic/presymptomatic carrier—clinically unaffected at this time but could later exhibit symptoms		Woman age 25 with negative mammogram and positive BRCA1 DNA test. 25 y E_1− (mammogram) E_2+ (5385insC BRCA1)
4. Uninformative study (u)	Eu	Man age 25 with normal physical exam and uninformative DNA test for Huntington disease (E_2). 25 y E_1− (physical exam) E_2u (36n/18n)
5. Affected individual with positive evaluation (E+)	E+	Individual with cystic fibrosis and positive mutation study; only one mutation has currently been identified. E+(ΔF508) Eu E+(ΔF508/u)
		10 week male fetus with a trisomy 18 karyotype. P 10 wk E+(CVS) 47,XY,+18

Figure 80-4 Pedigree symbols of genetic evaluation and testing information. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

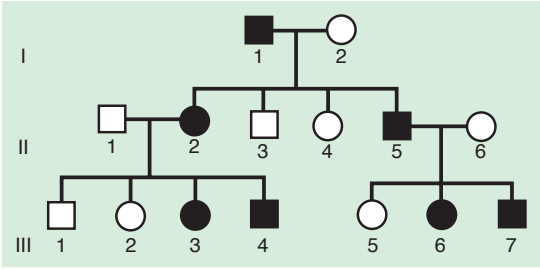


Figure 80-5 Autosomal dominant pedigree. Pedigree showing typical inheritance of a form of achondroplasia *(FGFR3)* inherited as an autosomal dominant trait. *Black,* affected patients.

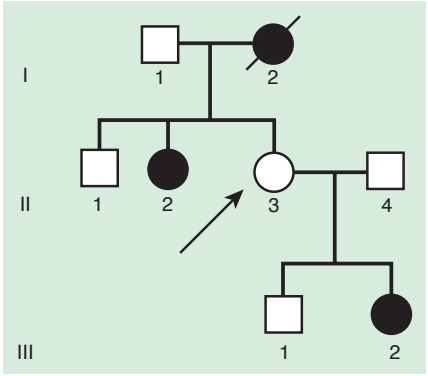


Figure 80-6 Incomplete penetrance. This family segregates a familial cancer syndrome, familial adenomatous polyposis. Individual II.3 is an obligate carrier, but there are no findings to suggest the disorder. This disorder is nonpenetrant in this individual.

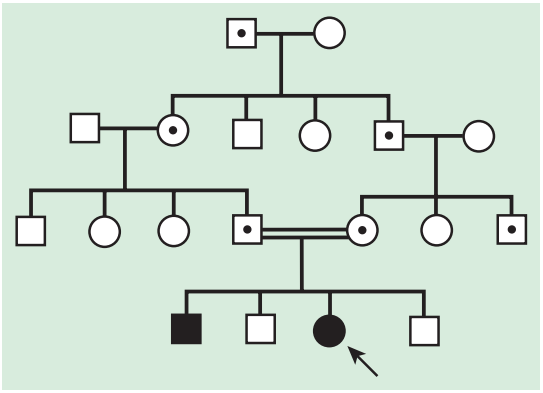


Figure 80-7 Autosomal recessive pedigree with parental consan-guinity. *Central dot,* carriers; *black,* affected patients.

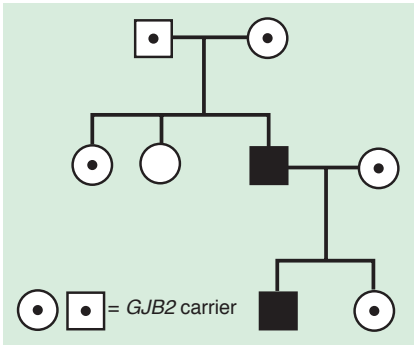


Figure 80-8 Pseudodominant inheritance. *Black,* affected (deaf); *central dot* shows carrier who is asymptomatic (unaffected).

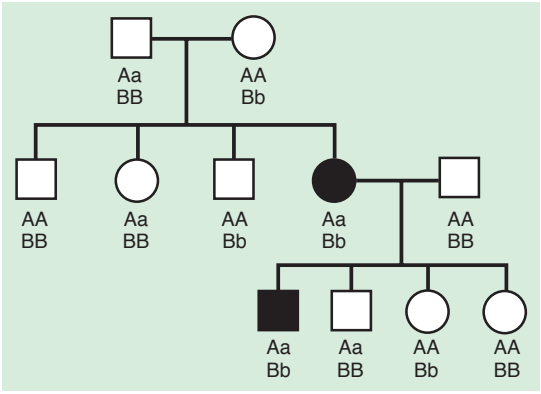


Figure 80-14 Digenic pedigree. Here, the disease alleles are *a* and *b* and they reside on distinct genetic loci or genes. For a person to have the disease, heterozygosity for mutant alleles in both genes (A/a;B/b) is required.

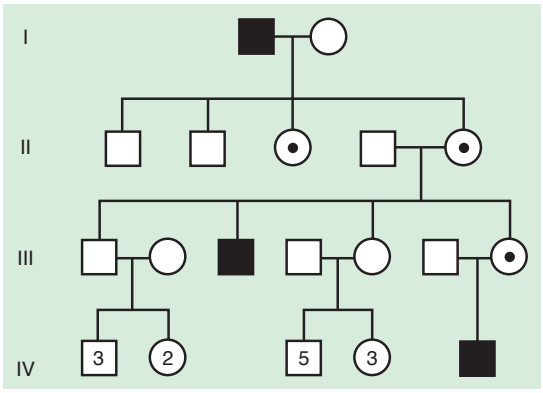


Figure 80-9 Pedigree demonstrating X-linked recessive inheritance.

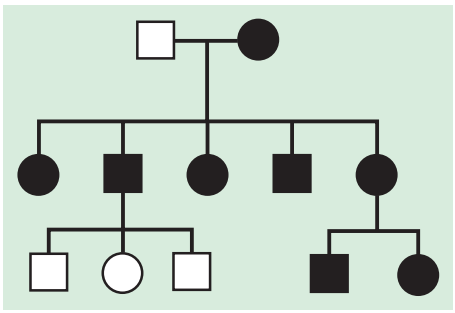


Figure 80-15 Pedigree of a mitochondrial disorder, exhibiting maternal inheritance. *Black,* affected patient.

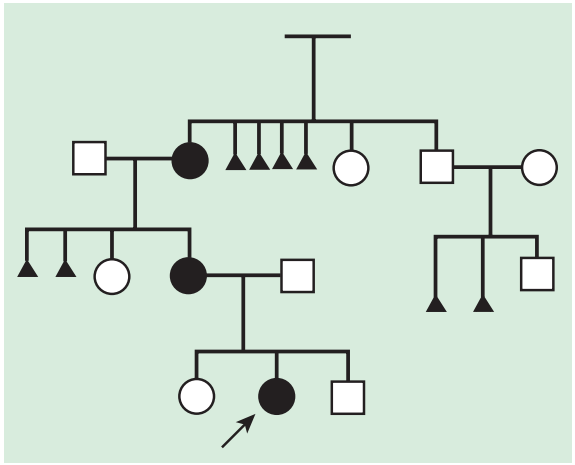


Figure 80-12 Pedigree of an X-linked dominant disorder with male lethality, such as incontinentia pigmenti.

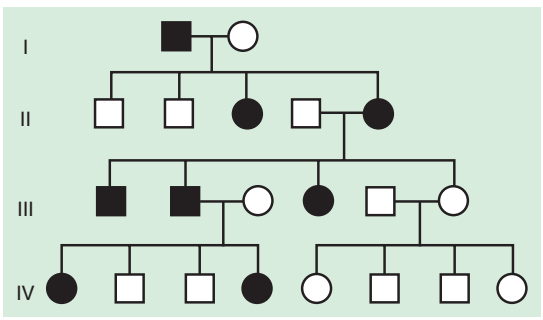


Figure 80-11 Pedigree pattern demonstrating X-linked dominant inheritance. Note there is no father-to-son transmission in this situation, and hemizygosity (i.e., X-linked gene in a male) is not lethal. In some X-linked dominant conditions, X-linked males have a more severe phe-notype and might not survive. In that case, only females manifest the disease (see Fig. 80-12).

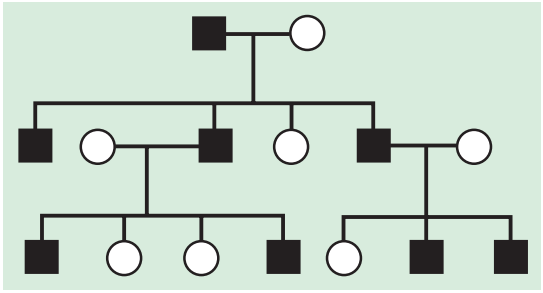


Figure 80-13 Y-linked inheritance. *Black,* affected patient.

Table 81-16 Signs Associated with Turner Syndrome

Short stature
Congenital lymphedema
Horseshoe kidneys
Patella dislocation
Increased carrying angle of elbow (cubitus valgus)
Madelung deformity (chondrodysplasia of distal radial epiphysis)
Congenital hip dislocation
Scoliosis
Widespread nipples
Shield chest
Redundant nuchal skin (in utero cystic hygroma)
Low posterior hairline
Coarctation of aorta
Bicuspid aortic valve
Cardiac conduction abnormalities
Hypoplastic left-heart syndrome and other left-heart abnormalities
Gonadal dysgenesis (infertility, primary amenorrhea)
Gonadoblastoma (increased risk if Y chromosome material is present)
Learning disabilities (nonverbal perceptual motor and visuospatial skills) (in 70%)
Developmental delay (in 10%)
Social awkwardness
Hypothyroidism (acquired in 15-30%)
Type 2 diabetes mellitus (insulin resistance)
Strabismus
Cataracts
Red-green color blindness (as in males)
Recurrent otitis media
Sensorineural hearing loss
Inflammatory bowel disease
Celiac disease (increased incidence)

Table 81-17 Signs Associated with Noonan Syndrome

Short stature
Failure to thrive (use Noonan growth curve)
Tall forehead
Epicanthal folds
Ptosis
Blue-green irises
Hypertelorism
Low nasal bridge, upturned nose
Downward-slanting palpebral fissures
Myopia
Nystagmus
Low-set auricles
Dental malocclusion
Low posterior hairline
Short webbed neck (excessive nuchal skin), cystic hygroma
Shield chest
Pectus carinatum superiorly
Scoliosis
Pigmented villonodular synovitis (polyarticular)
Cubitus valgus
Pulmonary valve stenosis (dysplastic valve)
Hypertrophic cardiomyopathy
Atrial septal defect, ventricular septal defect
Lymphedema
Nevi, lentigines, café-au-lait spots
Cryptorchidism
Small penis
Delayed puberty
Bleeding disorders, including thrombocytopenia and factor deficiencies
Leukemia, myeloproliferative disorders, other malignancies
Cognitive delay (*KRAS* mutation)

Table 81-4 Clinical Features of Down Syndrome in the Neonatal Period

CENTRAL NERVOUS SYSTEM
Hypotonia*
Developmental delay
Poor Moro reflex*

CRANIOFACIAL
Brachycephaly with flat occiput
Flat face*
Upward slanted palpebral fissures*
Epicanthal folds
Speckled irises (Brushfield spots)
Three fontanels
Delayed fontanel closure
Frontal sinus and midfacial hypoplasia
Mild microcephaly
Short hard palate
Small nose, flat nasal bridge
Protruding tongue, open mouth
Small dysplastic ears*

CARDIOVASCULAR
Endocardial Cushing defects
Ventricular septal defect
Atrial septal defect
Patent ductus arteriosus
Aberrant subclavian artery
Pulmonary hypertension

MUSCULOSKELETAL
Joint hyperflexibility*
Short neck, redundant skin*
Short metacarpals and phalanges
Short 5th digit with clinodactyly*
Single transverse palmar creases*
Wide gap between 1st and 2nd toes
Pelvic dysplasia*
Short sternum
Two sternal manubrium ossification centers

GASTROINTESTINAL
Duodenal atresia
Annular pancreas
Tracheoesophageal fistula
Hirschsprung disease
Imperforate anus
Neonatal cholestasis

CUTANEOUS
Cutis marmorata

*Hall's criteria to aid in diagnosis.

Table 81-15 Sex Chromosome Abnormalities

DISORDER	KARYOTYPE	APPROXIMATE INCIDENCE
Klinefelter syndrome	47,XXY 48,XXXY Other (48,XXYY; 49,XXXYY; mosaics)	1/575-1/1,000 males 1/50,000-1/80,000 male births
XYY syndrome	47,XYY	1/800-1,000 males
Other X or Y chromosome abnormalities		1/1,500 males
XX males	46,XX	1/20,000 males
Turner syndrome	45,X Variants and mosaics	1/2,500-1/5,000 females
Trisomy X	47,XXX 48,XXXX and 49,XXXXX	1/1,000 females Rare
Other X chromosome abnormalities		1/3,000 females
XY females	46,XY	1/20,000 females

Table 81-5 Additional Features of Down Syndrome That Can Develop or Become Symptomatic with Time

NEUROPSYCHIATRIC
Developmental delay
Seizures
Autism spectrum disorders
Behavioral disorders (disruptive)
Depression
Alzheimer disease
SENSORY
Congenital or acquired hearing loss
Serous otitis media
Refractive errors (myopia)
Congenital or acquired cataracts
Nystagmus
Strabismus
Glaucoma
Blocked tear ducts
CARDIOPULMONARY
Acquired mitral, tricuspid, or aortic valve regurgitation
Endocarditis
Obstructive sleep apnea
MUSCULOSKELETAL
Atlantoaxial instability
Hip dysplasia
Slipped capital femoral epiphyses
Avascular hip necrosis
Recurrent joint dislocations (shoulder, knee, elbow, thumb)
ENDOCRINE
Congenital or acquired hypothyroidism
Diabetes mellitus
Infertility
Obesity
Hyperthyroidism
HEMATOLOGIC
Transient myeloproliferative syndrome
Acute lymphocytic leukemia
Acute myelogenous leukemia
GASTROINTESTINAL
Celiac disease
Delayed tooth eruption
Respiratory
Obstructed sleep apnea
Frequent infections (sinusitis, nasopharyngitis, pneumonia)
CUTANEOUS
Hyperkeratosis
Seborrhea
Xerosis
Perigenital folliculitis

Table 81-6 Developmental Milestones

	CHILDREN WITH DOWN SYNDROME		UNAFFECTED CHILDREN	
Milestone	**Average (mo)**	**Range (mo)**	**Average (mo)**	**Range (mo)**
Smiling	2	1.5-3	1	1.5-3
Rolling over	6	2-12	5	2-10
Sitting	9	6-18	7	5-9
Crawling	11	7-21	8	6-11
Creeping	13	8-25	10	7-13
Standing	10	10-32	11	8-16
Walking	20	12-45	13	8-18
Talking, words	14	9-30	10	6-14
Talking, sentences	24	18-46	21	14-32

From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, Saunders.*

Table 81-7 Self-Help Skills

	DOWN SYNDROME CHILDREN		UNAFFECTED CHILDREN	
Skill	**Average (mo)**	**Range (mo)**	**Average (mo)**	**Range (mo)**
EATING				
Finger feeding	12	8-28	8	6-16
Using spoon/fork	20	12-40	13	8-20
TOILET TRAINING				
Bladder	48	20-95	32	18-60
Bowel	42	28-90	29	16-48
DRESSING				
Undressing	40	29-72	32	22-42
Putting clothes on	58	38-98	47	34-58

From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, Saunders.*

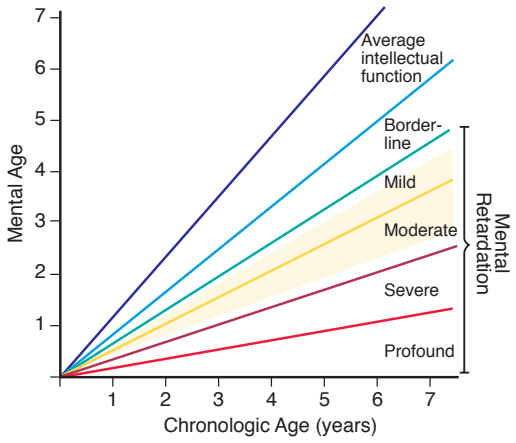


Figure 81-10 The area shaded in yellow denotes the range of intellectual function of the majority of children with Down syndrome. *(From Levine MD, Carey WB, Crocker AC, editors:* Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, WB Saunders, p. 226.)*

Table 81-8 Health Supervision for Children with Down Syndrome

CONDITION	TIME TO SCREEN	COMMENT
Congenital heart disease	Birth; by pediatric cardiologist Young adult for acquired valve disease	50% risk of congenital heart disease; increased risk for pulmonary hypertension
Strabismus, cataracts, nystagmus	Birth or by 6 mo; by pediatric ophthalmologist **Check vision annually**	Cataracts occur in 15%, refractive errors in 50%
Hearing impairment or loss	Birth or by 3 mo with auditory brainstem response or otoacoustic emission testing; check hearing q6mo up to 3 yr if tympanic membrane is not visualized; **annually thereafter**	Risk for congenital hearing loss plus 50-70% risk of serous otitis media
Constipation	Birth	Increased risk for Hirschsprung disease
Celiac disease	At 2 yr or with symptoms	Screen with IgA and tissue transglutaminase antibodies
Hematologic disease	At birth and in adolescence or if symptoms develop	Increased risk for neonatal polycythemia (18%), leukemoid reaction, leukemia (<1%)
Hypothyroidism	Birth; repeat at 6-12 mo and **annually**	Congenital (1%) and acquired (5%)
Growth and development	At each visit Use Down syndrome growth curves	Discuss school placement options Proper diet to avoid obesity
Obstructive sleep apnea	Start at ~1 yr and at each visit	Monitor for snoring, restless sleep
Atlantoaxial subluxation or instability (incidence 10-30%)	At each visit by history and physical exam Radiographs at 3-5 yr or when planning to participate in contact sports Radiographs indicated wherever neurologic symptoms are present even if transient (neck pain, torticollis, gait disturbances, weakness) Many are asymptomatic	Special Olympics recommendations are to screen for high-risk sports, e.g., diving, swimming, contact sports
Gynecologic care	Adolescent girls	Menstruation and contraception issues
Recurrent infections	When present	Check IgG subclass and IgA levels
Psychiatric, behavioral disorders	At each visit	Depression, anxiety, obsessive-compulsive disorder, schizophrenia seem in 10-17% Autism spectrum disorder in 5-10% Early-onset Alzheimer disease

IgA, immunoglobulin A; IgG, immunoglobulin G.

Data from Committee on Genetics: Health supervision for children with Down syndrome, Pediatrics *107:442-449, 2001; and Baum RA, Spader M, Nash PL, et al: Primary care of children and adolescents with Down syndrome: an update,* Curr Probl Pediatr Adolesc Health Care *38:235–268, 2008.*

Table 81-9 Genes Localized to Chromosome 21 That Possibly Affect Brain Development, Neuronal Loss, and Alzheimer Type Neuropathology

SYMBOL	NAME	POSSIBLE EFFECT IN DOWN SYNDROME	FUNCTION
SIM2	Single-minded homolog 2	Brain development	Required for synchronized cell division and establishment of proper cell lineage
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Brain development	Expressed during neuroblast proliferation Believed important homolog in regulating cell-cycle kinetics during cell division
GART	Phosphoribosylglycinamide formyltransferase Phosphoribosylglycinamide synthetase Phosphoribosylaminoimidazole synthetase	Brain development	Expressed during prenatal development of the cerebellum
PCP4	Purkinje cell protein 4	Brain development	Function unknown but found exclusively in the brain and most abundantly in the cerebellum
DSCAM	Down syndrome cell adhesion molecule	Brain development and possible candidate gene for congenital heart disease	Expressed in all molecule regions of the brain and believed to have a role in axonal outgrowth during development of the nervous system
GRIK1	Glutamate receptor, ionotropic kainite1	Neuronal loss	Function unknown, found in the cortex in fetal and early postnatal life and in adult primates, most concentrated in pyramidal cells in the cortex
APP	Amyloid beta (A4) precursor protein (protease nexin-II, Alzheimer disease)	Alzheimer type neuropathy	Seems to be involved in plasticity, neurite outgrowth, and neuroprotection
S100B	S100 calcium binding protein β (neural)	Alzheimer type neuropathy	Stimulates glial formation
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis, adult)	Accelerated aging?	Scavenges free superoxide molecules in the cell and might accelerate aging by producing hydrogen peroxide and oxygen

Table 81-10 Other Rare Aneuploidies and Partial Autosomal Aneuploidies

DISORDER	KARYOTYPE	CLINICAL MANIFESTATIONS
Trisomy 8	47,XX/XY,+8	Growth and mental deficiency are variable The majority of patients are mosaics Deep palmar and plantar furrows are characteristic
Trisomy 9	47,XX/XY,+9	The majority of patients are mosaics Clinical features include craniofacial (high forehead, microphthalmia, low-set malformed ears, bulbous nose) and skeletal (joint contractures) malformations and heart defects (60%)
Trisomy 16	47,XX/XY,+16	The most commonly observed autosomal aneuploidy in spontaneous abortion; the recurrence risk is negligible
Tetrasomy 12p	46,XX[12]/46,XX, +i(12p)[8] (mosaicism for an isochromosome 12p)	Known as Pallister-Killian syndrome. Sparse anterior scalp hair, eyebrows, and eyelashes, prominent forehead, chubby cheeks, long philtrum with thin upper lip and cupid-bow configuration, polydactyly, and streaks of hyper- and hypopigmentation

Table 81-11 Findings That May Be Present in Trisomy 13 and Trisomy 18

TRISOMY 13	TRISOMY 18
HEAD AND FACE	
Scalp defects (e.g., cutis aplasia) Microphthalmia, corneal abnormalities Cleft lip and palate in 60%-80% of cases Microcephaly Microphthalmia Sloping forehead Holoprosencephaly (arhinencephaly) Capillary hemangiomas Deafness	Small and premature appearance Tight palpebral fissures Narrow nose and hypoplastic nasal alae Narrow bifrontal diameter Prominent occiput Micrognathia Cleft lip or palate Microcephaly
CHEST	
Congenital heart disease (e.g., VSD, PDA, and ASD) in 80% of cases Thin posterior ribs (missing ribs)	Congenital heart disease (e.g., VSD, PDA, ASD) Short sternum, small nipples

Continued

Table 81-11 Findings That May Be Present in Trisomy 13 and Trisomy 18—cont'd

TRISOMY 13	TRISOMY 18
EXTREMITIES	
Overlapping of fingers and toes (clinodactyly) Polydactyly Hypoplastic nails, hyperconvex nails	Limited hip abduction Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist Rocker-bottom feet Hypoplastic nails
GENERAL	
Severe developmental delays and prenatal and postnatal growth restriction Renal abnormalities Only 5% live >6 mo	Severe developmental delays and prenatal and postnatal growth restriction Premature birth, polyhydramnios Inguinal or abdominal hernias Only 5% live >1 yr

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
From Behrman RE, Kliegman RM: Nelson essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders, p. 142.*

Table 83-2 Diagnostic Evaluation of the Neurologically Impaired Child

CONSULTATIONS
Genetics/genetic counseling
Neurology
Endocrinology
Immunology
Rheumatology
Dermatology
Cardiology
Neuropsychology
Nutrition
Rehabilitative medicine
  Physical therapy
  Occupational therapy
  Speech therapy

PROCEDURES
Swallow study for aspiration
Abdominal ultrasound (hepatosplenomegaly)
Skeletal survey (dysostosis)
Bone density scan (nonambulatory or growth-failure patients)
Bone age
Electroencephalogram
Muscle biopsy for electron transport chain function and histology
Nerve biopsy

LABORATORY EVALUATIONS
Complete blood count with differential and peripheral smear
Comprehensive metabolic panel
Prothrombin time/partial thromboplastin time (for anesthesia sedation)
Thyroid-stimulating hormone, thyroxine
Vitamins A, E, 1,25-dihydroxyvitamin D
Lactate/pyruvate
Ammonia
Amino acids (plasma and urine)
Organic acids (urine)
Acylcarnitine profile
Total and free carnitine
Lysosomal enzyme analysis in leukocytes and/or fibroblasts
White blood cell coenzyme Q
Purines and pyrimidines (urine)
α-Glucosidase (plasma and urine)
Peroxisomal panel
Oxysterols
Methylmalonic acid and homocystine (plasma)
Copper/ceruloplasmin
Vitamins A and E
Transferrin isoelectric focusing
N- and *O*-glycans (plasma)
Oligosaccharides and free glycans (urine)
Glycosaminoglycans (urine)

ADDITIONAL TESTING IF CLINICALLY INDICATED
Electron microscopy of white blood cell buffy coat for inclusion bodies
Electron microscopy of skin biopsy for evidence of storage
Stool for ova and parasites, occult blood, fecal fat, or fecal calprotectin
Autoimmune antibodies
Vaccine response titers
C3/C4
Quantitative immunoglobulins
T-cell subsets
Conjunctival or salivary gland biopsy

RESEARCH SPECIMENS
Cerebrospinal fluid
Serum
Plasma
Skin biopsy for fibroblasts and/or melanocytes
Isolated DNA/RNA
Urine

STUDIES UNDER SEDATION
3T MRI/magnetic resonance spectroscopy of brain (and spine if indicated)
Skin biopsy
Ophthalmologic exam
Brainstem auditory evoked response
Electroretinogram
Lumbar puncture for biopterin, neopterin, neurotransmitters, folate, and inflammatory markers
Dental exam
Large blood draws
Catheterization for urine
Any part of the physical exam difficult to do in an awake child, including dysmorphology measurements and genital and rectal exam
Electromyography and nerve conduction studies

Table 84-1 Disorders Recommended By the American College of Medical Genetics Task Force for Inclusion in Newborn Screening ("Primary Disorders")*

DISORDERS OF ORGANIC ACID METABOLISM
Isovaleric acidemia
Glutaric aciduria type I
3-Hydroxy-3-methylglutaric aciduria
Multiple carboxylase deficiency
Methylmalonic acidemia, mutase deficiency form
3-Methylcrotonyl-CoA carboxylase deficiency
Methylmalonic acidemia, cblA and cblB forms
Propionic acidemia
β-Ketothiolase deficiency
DISORDERS OF FATTY ACID METABOLISM
Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake defect
DISORDERS OF AMINO ACID METABOLISM
Phenylketonuria
Maple syrup urine disease
Homocystinuria
Citrullinemia
Argininosuccinic acidemia
Tyrosinemia type I
HEMOGLOBINOPATHIES
Sickle cell anemia (hemoglobin S)
Hemoglobin S-β-thalassemia
Hemoglobin SC disease
OTHER DISORDERS
Congenital hypothyroidism
Biotinidase deficiency
Congenital adrenal hyperplasia
Galactosemia
Hearing deficiency
Cystic fibrosis

*At this time, there is state-to-state variation in newborn screening; a list of the disorders that are screened for by each state is available at http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf.

cblA, Cobalamin A defect; cblB, cobalamin B defect; CoA, coenzyme A.

Table 84-2 Secondary Conditions Recommended By American College of Medical Genetics* Task Force for Inclusion in Newborn Screening

ORGANIC ACID METABOLISM DISORDERS
Methylmalonic acidemia, cblC and cblD forms
2-Methyl-3-hydroxybutyric aciduria
Isobutyryl-CoA dehydrogenase deficiency
2-Methylbutyryl-CoA dehydrogenase deficiency
3-Methylglutaconic aciduria
Malonic acidemia
FATTY ACID OXIDATION DISORDERS
Medium-/short-chain 3-OH acyl-CoA dehydrogenase deficiency
Short-chain acyl-CoA dehydrogenase deficiency
Medium-chain ketoacyl-CoA thiolase deficiency
Glutaric acidemia type 2
Carnitine palmitoyltransferase I deficiency
Carnitine palmitoyltransferase II deficiency
Carnitine acylcarnitine translocase deficiency
Dienoyl-CoA reductase deficiency
AMINO ACID METABOLISM DISORDERS
Hyperphenylalaninemia, benign (not phenylketonuria)
Tyrosinemia type II
Tyrosinemia type III
Defects of biopterin cofactor biosynthesis
Defects of biopterin cofactor regeneration
Argininemia
Hypermethioninemia
Citrullinemia type II
HEMOGLOBINOPATHICS
Hemoglobin variants (including hemoglobin E)
OTHERS
Galactose epimerase deficiency
Galactokinase deficiency

*The American College of Medical Genetics task force recommended reporting 25 disorders ("secondary targets") in addition to the primary disorders that can be detected through screening but that do not meet the criteria for primary disorders.

cblC, Cobalamin C defect; cblD, cobalamin D defect; CoA, coenzyme A.

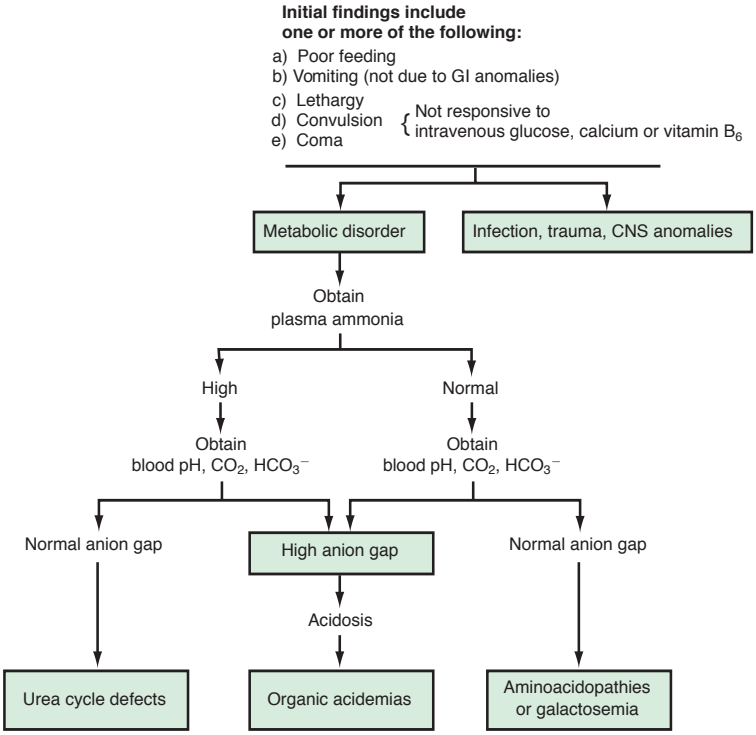


Figure 84-1 Initial clinical approach to a full term newborn infant with a suspected genetic metabolic disorder. This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.

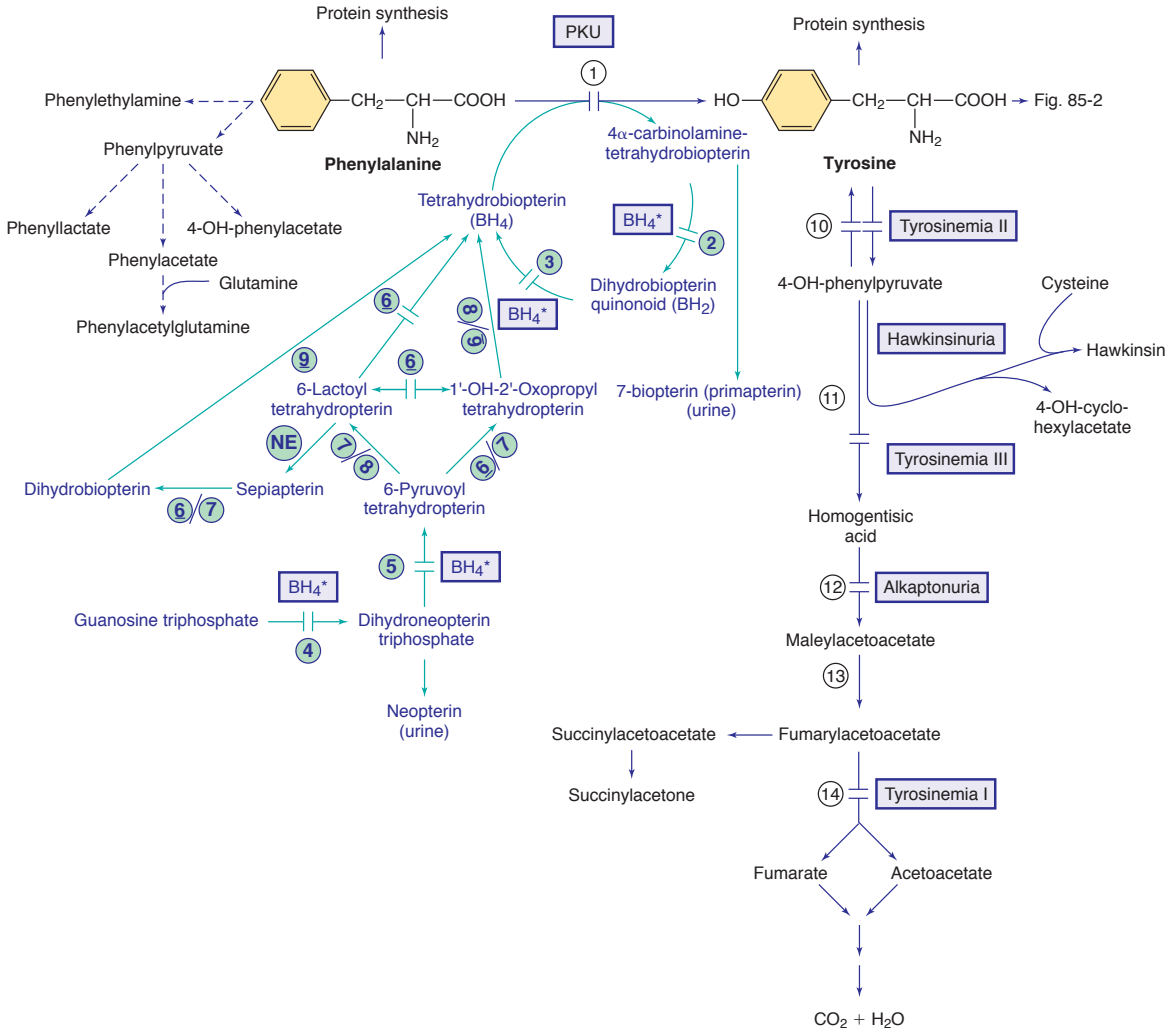


Figure 85-1 Pathways of phenylalanine and tyrosine metabolism. Enzyme defects causing genetic conditions are depicted as horizontal bars crossing the reaction arrow(s). Pathways for synthesis of cofactor BH_4 are shown in purple. PKU* refers to defects of BH_4 metabolism that affect the phenylalanine, tyrosine, and tryptophan hydroxylases (see Figs. 85-2 and 85-5). **Enzymes:** *(1)* Phenylalanine hydroxylase, *(2)* pterin-carbinolamine dehydratase, *(3)* dihydrobiopterin reductase, *(4)* guanosine triphosphate (GTP) cyclohydrolase, *(5)* 6-pyruvoyltetrahydropterin synthase, *(6)* sepiapterin reductase, *(7)* carbonyl reductase, *(8)* aldolase reductase, *(9)* dihydrofolate reductase, *(10)* tyrosine aminotransferase, *(11)* 4-hydroxyphenylpyruvate dioxygenase, *(12)* homogentisic acid dioxygenase, *(13)* maleylacetoacetate isomerase, *(14)* fumarylacetoacetate hydrolase, *(NE)* nonenzymatic.

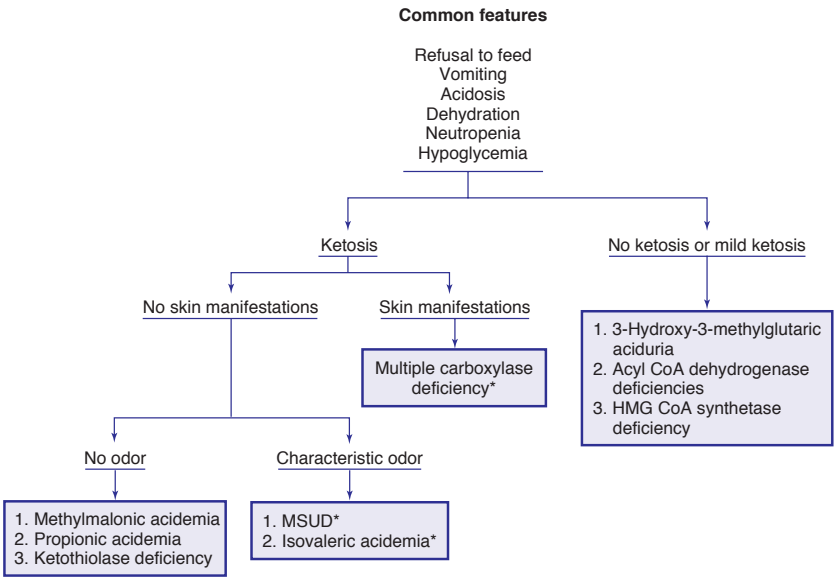


Figure 85-6 Clinical approach to infants with organic acidemia. *Asterisks* indicate disorders in which patients have a characteristic odor (see text and Table 85-2). MSUD, maple syrup urine disease.

Metabolic Disorders

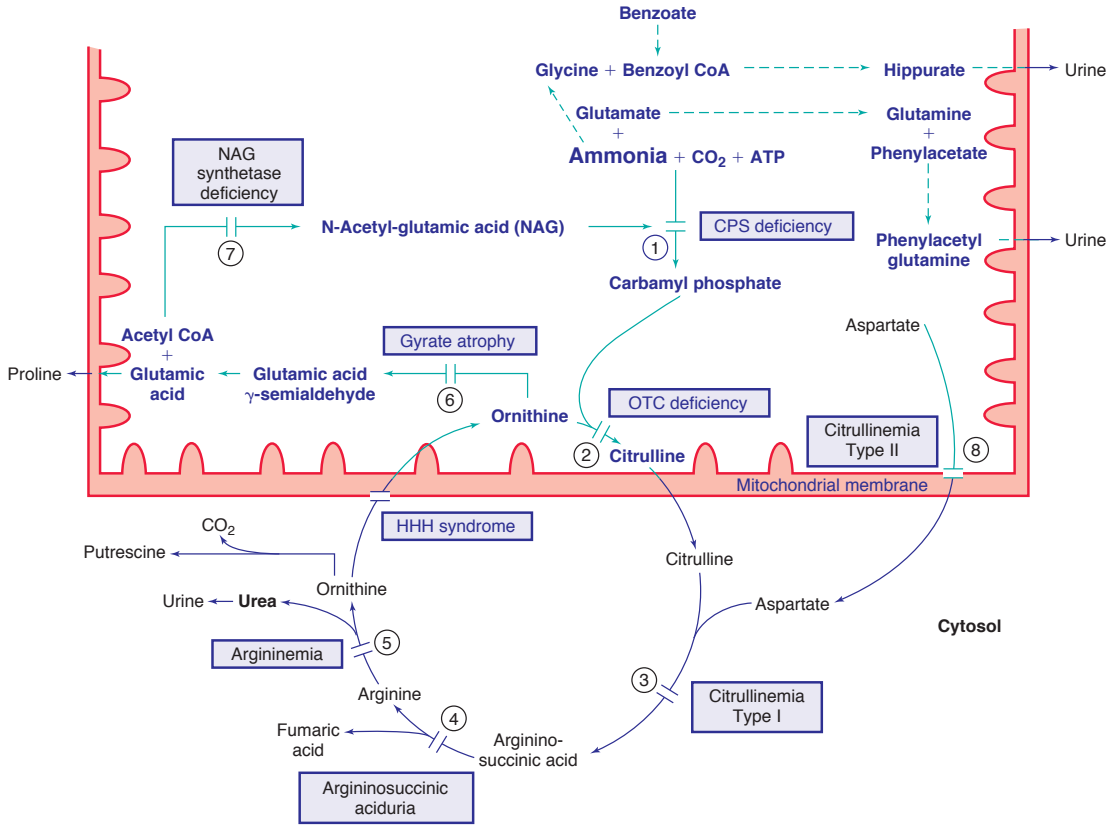


Figure 85-12 Urea cycle: pathways for ammonia disposal and ornithine metabolism. Reactions occurring in the mitochondria are depicted in *purple*. Reactions shown with *interrupted arrows* are the alternate pathways for the disposal of ammonia. **Enzymes:** *(1)* Carbamyl phosphate synthetase (CPS), *(2)* ornithine transcarbamylase (OTC), *(3)* argininosuccinic acid synthetase (AS), *(4)* argininosuccinic acid lyase (AL), *(5)* arginase, *(6)* ornithine 5-aminotransferase, *(7)* *N*-acetylglutamate (NAG) synthetase, *(8)* citrin. HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia.

Table 85-3 Inborn Errors of Metabolism Causing Hyperammonemia

Deficiencies of the urea cycle enzymes
Carbamyl phosphate synthetase
Ornithine transcarbamylase
Argininosuccinate synthetase
Argininosuccinate lyase
Arginase *N*-acetylglutamate synthetase
Organic acidemias
Propionic acidemia
Methylmalonic acidemia
Isovaleric acidemia
β-Ketothiolase deficiency
Multiple carboxylase deficiencies
Medium-chain fatty acid acyl-coenzyme A dehydrogenase deficiency
Glutaric acidemia type I
3-Hydroxy-3-methylglutaric aciduria
Lysinuric protein intolerance
Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome
Transient hyperammonemia of the newborn
Congenital hyperinsulinism with hyperammonemia

Table 84-3 Inborn Errors of Amino Acid Metabolism Associated with Peculiar Odor

INBORN ERROR OF METABOLISM	URINE ODOR
Glutaric acidemia (type II)	Sweaty feet, acrid
Hawkinsinuria	Swimming pool
3-Hydroxy-3-methylglutaric aciduria	Cat urine
Isovaleric acidemia	Sweaty feet, acrid
Maple syrup urine disease	Maple syrup
Hypermethioninemia	Boiled cabbage
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like
Phenylketonuria	Mousey or musty
Trimethylaminuria	Rotting fish
Tyrosinemia	Boiled cabbage, rancid butter

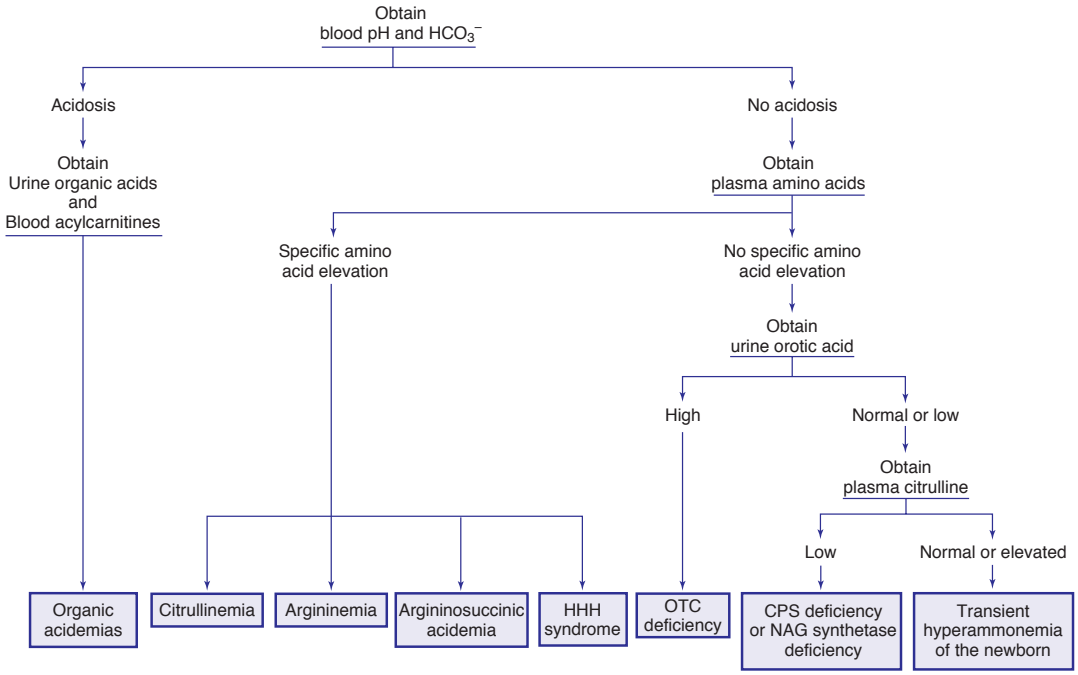


Figure 85-13 **Clinical approach to a newborn infant with symptomatic hyperammonemia.** CPS, carbamyl phosphate synthetase; HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia; NAG, *N*-acetylglutamate; OTC, ornithine transcarbamylase.

Table 85-4 Treatment of Acute Hyperammonemia in an Infant

1. Provide adequate calories, fluid, and electrolytes intravenously (10% glucose, NaCl* and intravenous lipids 1 g/kg/24 hr). Add minimal amounts of protein preferably as a mixture of essential amino acids (0.25 g/kg/24 hr) during the 1st 24 hr of therapy.
2. Give priming doses of the following compounds:
   (To be added to 20 mL/kg of 10% glucose and infused within 1-2 hr)
   - Sodium benzoate 250 mg/kg†
   - Sodium phenylacetate 250 mg/kg†
   - Arginine hydrochloride 200-600 mg/kg as a 10% solution
3. Continue infusion of sodium benzoate† (250-500 mg/kg/24 hr), sodium phenylacetate† (250-500 mg/kg/24 hr), and arginine (200-600 mg/kg/24 hr‡) following the above priming doses. These compounds should be added to the daily intravenous fluid.
4. Initiate peritoneal dialysis or hemodialysis if above treatment fails to produce an appreciable decrease in plasma ammonia.

Table 86-2 Classification of Peroxisomal Disorders

A: DISORDERS OF PEROXISOME IMPORT
A1: Zellweger syndrome
A2: Neonatal adrenoleukodystrophy
A3: Infantile Refsum disease
A4: Rhizomelic chondrodysplasia punctata
B: DEFECTS OF SINGLE PEROXISOMAL ENZYME
B1: X-linked adrenoleukodystrophy
B2: Acyl-CoA oxidase deficiency
B3: Bifunctional enzyme deficiency
B4: Peroxisomal thiolase deficiency
B5: Classic Refsum disease
B6: 2-Methylacyl-CoA racemase deficiency
B7: DHAP acyltransferase deficiency
B8: Alkyl-DHAP synthase deficiency
B9: Mevalonic aciduria
B10: Glutaric aciduria type III
B11: Hyperoxaluria type I
B12: Acatalasemia

CoA, coenzyme A; DHAP, dihydroxyacetone phosphate.

Table 86-10 Major Clinical Characteristics of Smith-Lemli-Opitz Syndrome: Frequent Anomalies (>50% of Patients)

CRANIOFACIAL
Microcephaly
Blepharoptosis
Anteverted nares
Retromicrognathia
Low-set, posteriorly rotated ears
Midline cleft palate
Broad maxillary alveolar ridges
Cataracts (<50%)
SKELETAL ANOMALIES
Syndactyly of toes II/III
Postaxial polydactyly (<50%)
Equinovarus deformity (<50%)
GENITAL ANOMALIES
Hypospadias
Cryptorchidism
Sexual ambiguity (<50%)
DEVELOPMENT
Pre- and postnatal growth retardation
Feeding problems
Mental retardation
Behavioral abnormalities

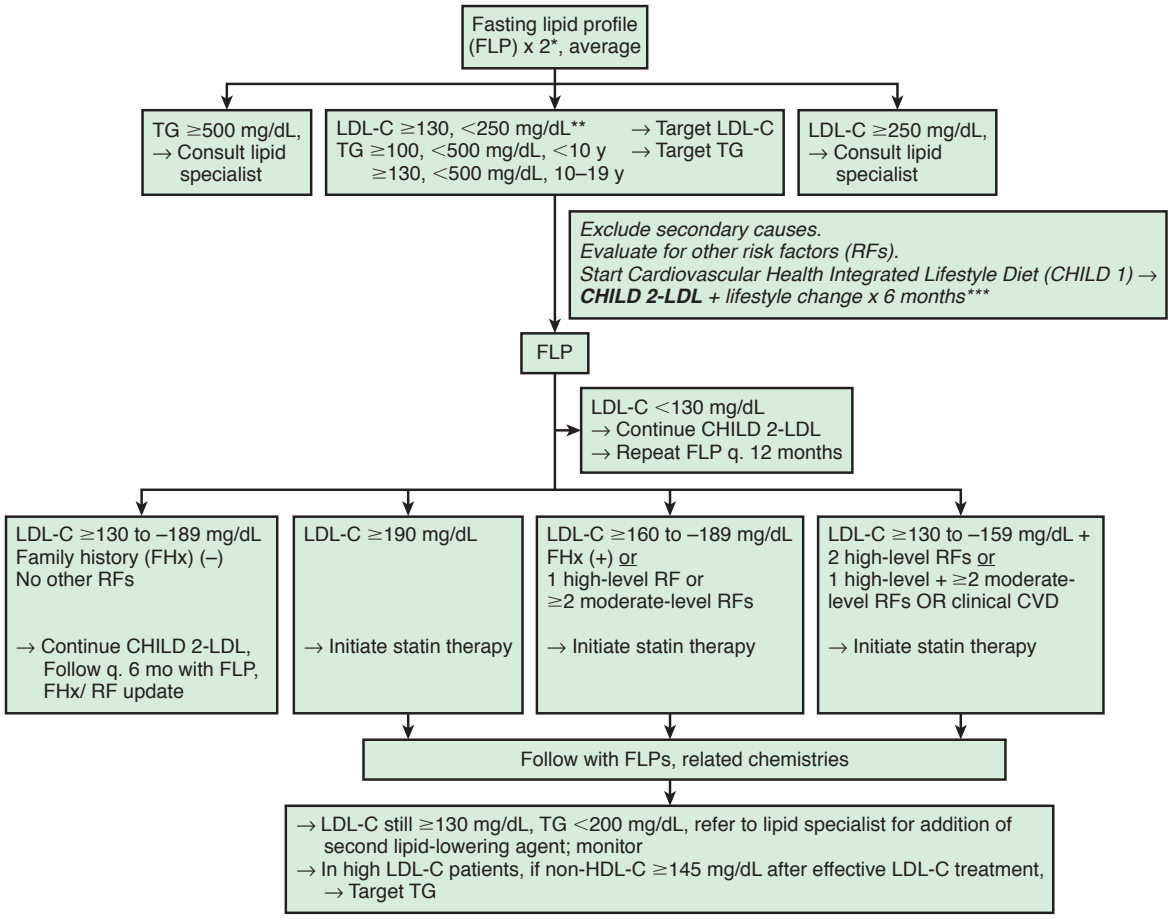
Table 86-11 Characteristic Malformations of Internal Organs in Severely Affected Smith-Lemli-Opitz Patients

CENTRAL NERVOUS SYSTEM
Frontal lobe hypoplasia
Enlarged ventricles
Agenesis of corpus callosum
Cerebellar hypoplasia
Holoprosencephaly
CARDIOVASCULAR
Atrioventricular canal
Secundum atrial septal defect
Patent ductus arteriosus
Membranous ventricular septal defect
URINARY TRACT
Renal hypoplasia or aplasia
Renal cortical cysts
Hydronephrosis
Ureteral duplication
GASTROINTESTINAL
Hirschsprung disease
Pyloric stenosis
Refractory dysmotility
Cholestatic and noncholestatic progressive liver disease
PULMONARY
Pulmonary hypoplasia
Abnormal lobation
ENDOCRINE
Adrenal insufficiency

Table 86-13 Drugs Used for the Treatment of Hyperlipidemia

DRUG	MECHANISM OF ACTION	INDICATION	STARTING DOSE
HMG-CoA reductase inhibitors (statins)	↓ Cholesterol and VLDL synthesis ↑ Hepatic LDL receptors	Elevated LDL	5-80 mg qhs
Bile acid sequestrants: Cholestyramine Colestipol	↑ Bile and excretion	Elevated LDL	 4-32 g daily 5-40 g daily
Nicotinic acid	↓ Hepatic VLDL synthesis	Elevated LDL Elevated TG	100-2,000 mg tid
Fibric acid derivatives: Gemfibrozil	↑ LPL ↓ VLDL	Elevated TG	600 mg bid
Fish oils	↓ VLDL production	Elevated TG	3-10 g daily
Cholesterol absorption inhibitors: Ezetimibe	↓ Intestinal absorption cholesterol	Elevated LDL	 10 mg daily

LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein.



* Obtain FLPs at least 2 weeks but no more than 3 months apart.
** Use of drug therapy is limited to children ≥10 y with defined risk profiles.
*** In a child with LDL-C >190 mg/dL and other RFs, trial of CHILD 2 LDL diet may be abbreviated.

Figure 86-14 Algorithm of the evaluation, risk assessment, follow-up, and treatment of children based on low-density lipoprotein (LDL) cholesterol levels. *FLP,* fasting lipid profile; *TG,* triglycerides. *(From Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary report.* Pediatrics *128(Suppl 5):S213–S256, 2011, Fig. 9-1.)*

Table 86-14 Side Effects of Lipid-Lowering Drugs

DRUG AND SITE OR TYPE OF EFFECT	EFFECT
STATINS	
Skin	Rash
Nervous system	Loss of concentration, sleep disturbance, headache, peripheral neuropathy
Liver	Hepatitis, loss of appetite, weight loss, and increases in serum aminotransferases to 2-3 times the upper limit of the normal range
Gastrointestinal tract	Abdominal pain, nausea, diarrhea
Muscles	Muscle pain or weakness, myositis (usually with serum creatine kinase >1,000U/L), rhabdomyolysis with renal failure
Immune system	Lupus-like syndrome (lovastatin, simvastatin, or fluvastatin)
Protein binding	Diminished binding of warfarin (lovastatin, simvastatin, fluvastatin)
BILE ACID-BINDING RESINS	
Gastrointestinal tract	Abdominal fullness, nausea, gas, constipation, hemorrhoids, anal fissure, activation of diverticulitis, diminished absorption of vitamin D in children
Liver	Mild serum aminotransferase elevations, which can be exacerbated by concomitant treatment with a statin
Metabolic system	Increases in serum triglycerides of ≈10% (greater increases in patients with hypertriglyceridemia)
Electrolytes	Hyperchloremic acidosis in children and patients with renal failure (cholestyramine)
Drug interactions	Binding of warfarin, digoxin, thiazide diuretics, thyroxine, statins
NICOTINIC ACID	
Skin	Flushing, dry skin, pruritus, ichthyosis, acanthosis nigricans
Eyes	Conjunctivitis, cystoid macular edema, retinal detachment
Respiratory tract	Nasal stuffiness
Heart	Supraventricular arrhythmias
Gastrointestinal tract	Heartburn, loose bowel movements or diarrhea
Liver	Mild increase in serum aminotransferases, hepatitis with nausea and fatigue
Muscles	Myositis
Metabolic system	Hyperglycemia (incidence: ≈5% higher in patients with diabetes), increase of 10% in serum uric acid
FIBRATES	
Skin	Rash
Gastrointestinal tract	Stomach upset, abdominal pain (mainly gemfibrozil), cholesterol-saturated bile, increase of 1-2% in gallstone incidence
Genitourinary tract	Erectile dysfunction (mainly clofibrate)
Muscles	Myositis with impaired renal function
Plasma proteins	Interference with binding of warfarin, requiring reduction in the dose of warfarin by ≈30%
Liver	Increased serum aminotransferases

Table 86-15 Clinical Findings in Lysosomal Storage Diseases

NOMENCLATURE	ENZYME DEFECT	HYDROPS FETALIS	COARSE FACIAL FEATURES DYSOSTOSIS MULTIPLEX	HEPATOSPLENOMEGALY
MUCOLIPIDOSES				
Mucolipidoses II, I-cell disease	*N*-Acetylglucosaminylphosphotransferase	(+)	++	+
Mucolipidosis III, Pseudo-Hurler	*N*-Acetylglucosaminylphosphotransferase	–	+	(+)
Mucolipidosis IV	Unknown	–	–	+
SS				
Fabry disease	α-Galactosidase	–	–	–
Farber disease	Ceramidase	–	–	(+)
Galactosialidosis	β-Galactosidase and sialidase	(+)	++	++
GM_1 gangliosidosis	β-Galactosidase	(+)	++	+
GM_2 gangliosidosis (Tay-Sachs disease, Sandhoff disease)	β-Hexosaminidases A and B	–	–	(+)
Gaucher type I	Glucocerebrosidase	–	–	++
Gaucher type II	Glucocerebrosidase	(+)	–	++
Gaucher type III	Glucocerebrosidase	(+)	–	+
Niemann-Pick type A	Sphingomyelinase	(+)	–	++
Niemann-Pick type B	Sphingomyelinase	–	–	++
Metachromatic leukodystrophy	Arylsulfatase A	–	–	–
Krabbe disease	β-Galactocerebrosidase	–	–	–
LIPID STORAGE DISORDERS				
Niemann-Pick type C	Intracellular cholesterol transport	–	–	(+)
Wolman disease	Acid lipase	(+)	–	+
Ceroid lipofuscinosis, infantile (Santavuori-Haltia)	Palmitoyl-protein thioesterase (CLN1)	–	–	–
Ceroid lipofuscinosis, late infantile (Jansky-Bielschowsky)	Pepstatin-insensitive peptidase (CLN2); variants in Finland (CLN5), Turkey (CLN7), and Italy (CLN6)	–	–	–
Ceroid lipofuscinosis, juvenile (Spielmeyer-Vogt)	CLN3, membrane protein	–	–	–
Ceroid lipofuscinosis, adult (Kufs, Parry)	CLN4, probably heterogeneous	(+)	–	–
OLIGOSACCHARIDOSES				
Aspartylglucosaminuria	Aspartylglucosylaminase	–	+	(+)
Fucosidosis	α-Fucosidase	–	++	(+)
α-Mannosidosis	α-Mannosidase	–	++	+
β-Mannosidosis	β-Mannosidase	–	+	(+)
Schindler disease	α-*N*-Acetylgalactosaminidase	–	–	–
Sialidosis I	Sialidase	(+)	–	–
Sialidosis II	Sialidase	(+)	++	+

++, Prominent; +, often present; (+), inconstant or occurring later in the disease course; –, not present; GAG, glycosaminoglycans.
Modified from Hoffmann GF, Nyhan WL, Zschoke J, et al: Storage disorders in inherited metabolic diseases, *Philadelphia, 2002, Lippincott Williams & Wilkins, pp. 346–351.*

	CARDIAC INVOLVEMENT CARDIAC FAILURE	MENTAL DETERIORATION	MYOCLONUS	SPASTICITY	PERIPHERAL NEUROPATHY	CHERRY-RED SPOT	CORNEAL CLOUDING	ANGIOKERATOMATA
	++	++	–	–	–	–	(+)	–
	–	(+)	–	–	–	–	+	–
	–	(+)	–	–	–	–	–	–
	+	–	–	–	–	–	+	++
	++	+	–	–	+	(+)	–	–
	+	++	(+)	+	–	+	+	+
	(+)	++	–	(+)	–	(+)	+	+
	–	++	+	+	–	++	–	–
	–	–	–	–	–	–	–	–
	–	++	+	+	–	–	–	–
	–	+	(+)	(+)	–	–	–	–
	–	+	(+)	–	(+)	(++)	–	–
	–	–	–	–	(+)	(+)	–	–
	–	++	–	+	++	(+)	–	–
	–	++	–	+	++	(+)	–	–
	–	+	–	–	–	(+)	–	–
	(+)	–	–	–	–	(+)	–	–
	–	+	+	+	–	–	–	–
	–	+	+	+	–	–	–	–
	–	+	–	(+)	–	–	–	–
	–	+	–	–	–	–	–	–
	(+)	+	–	–	–	–	(+)	(+)
	+	++	+	+	–	–	–	(+)
	–	++	–	(+)	–	–	++	(+)
	–	+	–	+	+	–	–	(+)
	–	+	+	+	–	–	–	–
	–	–	++	+	+	++	(+)	–
	+	++	(+)	–	–	++	–	+

Table 86-16 Symptoms Encountered in Patients with Lysosomal Storage Disorders

SYSTEM	MANIFESTATIONS
Neurologic	Hypotonia Floppy-infant syndrome Trismus Strabismus Opisthotonus Spasticity Seizures Peripheral neuropathy Developmental delay Irritability Extrapyramidal movement disorder Hydrocephalus
Respiratory	Congenital lobar emphysema Recurrent respiratory infections Hoarseness
Endocrine	Osteopenia Metabolic bone disease Secondary hyperparathyroidism Congenital adrenal hyperplasia
Cardiovascular	Cardiomegaly Congenital heart failure Arrhythmias Wolff-Parkinson-White syndrome Cardiomyopathy
Dysmorphology	
Head and neck	Macrocephaly Enlarged nuchal translucency Microstomia Micrognathia/microretrognathia Long philtrum
Limbs	Bilateral broad thumbs and toes Bilateral club feet
Oral	Macroglossia Molar hypoplasia Hypertrophic gums
Facial	Bilateral epicanthal inferior orbital creases Palpebral edema Hypertelorism Coarse facies Low-set ears
Gastrointestinal	Hepatosplenomegaly Neonatal cholestasis
Bones and joints	Lytic bone lesions Joint contractures Dysostosis multiplex Hyperphosphatasemia Vertebral breaking Broadening of tubular bones Punctuate epiphysis Craniosynostosis Painful joint swelling
Skin	Congenital ichthyosis Collodion infant Hypopigmentation Telangiectasias Extended Mongolian spots
Ocular	Corneal clouding Megalocornea Glaucoma Cherry-red spots Fundi hypopigmentation Bilateral cataracts
Hematologic	Anemia Thrombocytopenia
Hydrops fetalis	Nonimmune hydrops fetalis Congenital ascites

From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal storage disorders in the newborn, Pediatrics *123:1191–1207, 2009.*

Table 87-1 Features of the Disorders of Carbohydrate Metabolism

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
LIVER GLYCOGENOSES			
Type/Common Name			
Ia/Von Gierke	Glucose-6-phosphatase	Growth retardation, hepatomegaly, hypoglycemia; elevated blood lactate, cholesterol, triglyceride, and uric acid levels	Common, severe hypoglycemia
Ib	Glucose-6-phosphate translocase	Same as type Ia, with additional findings of neutropenia and impaired neutrophil function	10% of type Ia
IIIa/Cori or Forbes	Liver and muscle debrancher deficiency (amylo-1,6-glucosidase)	Childhood: hepatomegaly, growth retardation, muscle weakness, hypoglycemia, hyperlipidemia, elevated transaminase levels; liver symptoms can progress to liver failure later in life	Common, intermediate severity of hypoglycemia
IIIb	Liver debrancher deficiency; normal muscle enzyme activity	Liver symptoms same as in type IIIa; no muscle symptoms	15% of type III
IV/Andersen	Branching enzyme	Failure to thrive, hypotonia, hepatomegaly, splenomegaly, progressive cirrhosis (death usually before 5th yr), elevated transaminase levels	Rare neuromuscular variants exist
VI/Hers	Liver phosphorylase	Hepatomegaly, typically mild hypoglycemia, hyperlipidemia, and ketosis	Rare, typically benign glycogenosis; severe presentation also known
Phosphorylase kinase deficiency	Phosphorylase kinase	Hepatomegaly, mild hypoglycemia, hyperlipidemia, and ketosis	Common, typically a benign glycogenosis, severe progressive forms also present
Glycogen synthase deficiency	Glycogen synthase	Early morning drowsiness and fatigue, fasting hypoglycemia, and ketosis, no hepatomegaly	Decreased liver glycogen store
Fanconi-Bickel syndrome	Glucose transporter 2 (GLUT-2)	Failure to thrive, rickets, hepatorenomegaly, proximal renal tubular dysfunction, impaired glucose and galactose utilization	GLUT-2 expressed in liver, kidney, pancreas, and intestine
MUSCLE GLYCOGENOSES			
Type/Common Name			
II/Pompe infantile	Acid α-glucosidase (acid maltase)	Cardiomegaly, hypotonia, hepatomegaly; onset: birth to 6 mo	Common, cardiorespiratory failure leading to death by age 1-2 yr; minimal to no residual enzyme activity
II/Late-onset Pompe (juvenile and adult)	Acid α-glucosidase (acid maltase)	Myopathy, variable cardiomyopathy, respiratory insufficiency; onset: childhood to adulthood	Residual enzyme activity
Danon disease	Lysosome-associated membrane protein 2 (LAMP2)	Hypertrophic cardiomyopathy	Rare, X-linked
PRKAG2 deficiency	Adenosine monophosphate (AMP)-activated protein kinase γ	Hypertrophic cardiomyopathy	Autosomal dominant
V/McArdle	Myophosphorylase	Exercise intolerance, muscle cramps, increased fatigability	Common, male predominance
VII/Tarui	Phosphofructokinase	Exercise intolerance, muscle cramps, hemolytic anemia, myoglobinuria	Prevalent in Japanese and Ashkenazi Jews
Phosphoglycerate kinase deficiency	Phosphoglycerate kinase	As with type V	Rare, X-linked
Phosphoglycerate mutase deficiency	M subunit of phosphoglycerate mutase	As with type V	Rare, majority of patients are African-American
Lactate dehydrogenase deficiency	M subunit of lactate dehydrogenase	As with type V	Rare
GALACTOSE DISORDERS			
Galactosemia with transferase deficiency	Galactose-1-phosphate uridyltransferase	Vomiting, hepatomegaly, cataracts, aminoaciduria, failure to thrive	African-American patients tend to have milder symptoms
Galactokinase deficiency	Galactokinase	Cataracts	Benign
Generalized uridine diphosphate galactose-4-epimerase deficiency	Uridine diphosphate galactose-4-epimerase	Similar to transferase deficiency with additional findings of hypotonia and nerve deafness	A benign variant also exists
FRUCTOSE DISORDERS			
Essential fructosuria	Fructokinase	Urine reducing substance	Benign
Hereditary fructose intolerance	Fructose-1-phosphate aldolase	Acute: vomiting, sweating, lethargy Chronic: failure to thrive, hepatic failure	Prognosis good with fructose restriction

Continued

Table 87-1 Features of the Disorders of Carbohydrate Metabolism—cont'd

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
DISORDERS OF GLUCONEOGENESIS			
Fructose-1,6-diphosphatase deficiency	Fructose-1,6-diphosphatase	Episodic hypoglycemia, apnea, acidosis	Good prognosis, avoid fasting
Phosphoenolpyruvate carboxykinase deficiency	Phosphoenolpyruvate carboxykinase	Hypoglycemia, hepatomegaly, hypotonia, failure to thrive	Rare
DISORDERS OF PYRUVATE METABOLISM			
Pyruvate dehydrogenase complex defect	Pyruvate dehydrogenase	Severe fatal neonatal to mild late onset, lactic acidosis, psychomotor retardation, and failure to thrive	Most commonly caused by $E_{1\alpha}$ subunit, defect X-linked
Pyruvate carboxylase deficiency	Pyruvate carboxylase	Same as above	Rare, autosomal recessive
Respiratory chain defects (oxidative phosphorylation disease)	Complexes I-V, many mitochondrial DNA mutations	Heterogeneous with multisystem involvement	Mitochondrial inheritance
DISORDERS IN PENTOSE METABOLISM			
Pentosuria	L-Xylulose reductase	Urine-reducing substance	Benign
Transaldolase deficiency	Transaldolase	Liver cirrhosis and failure, cardiomyopathy	Autosomal recessive
Ribose-5-phosphate isomerase deficiency	Ribose-5-phosphate isomerase	Progressive leukoencephalopathy and peripheral neuropathy	

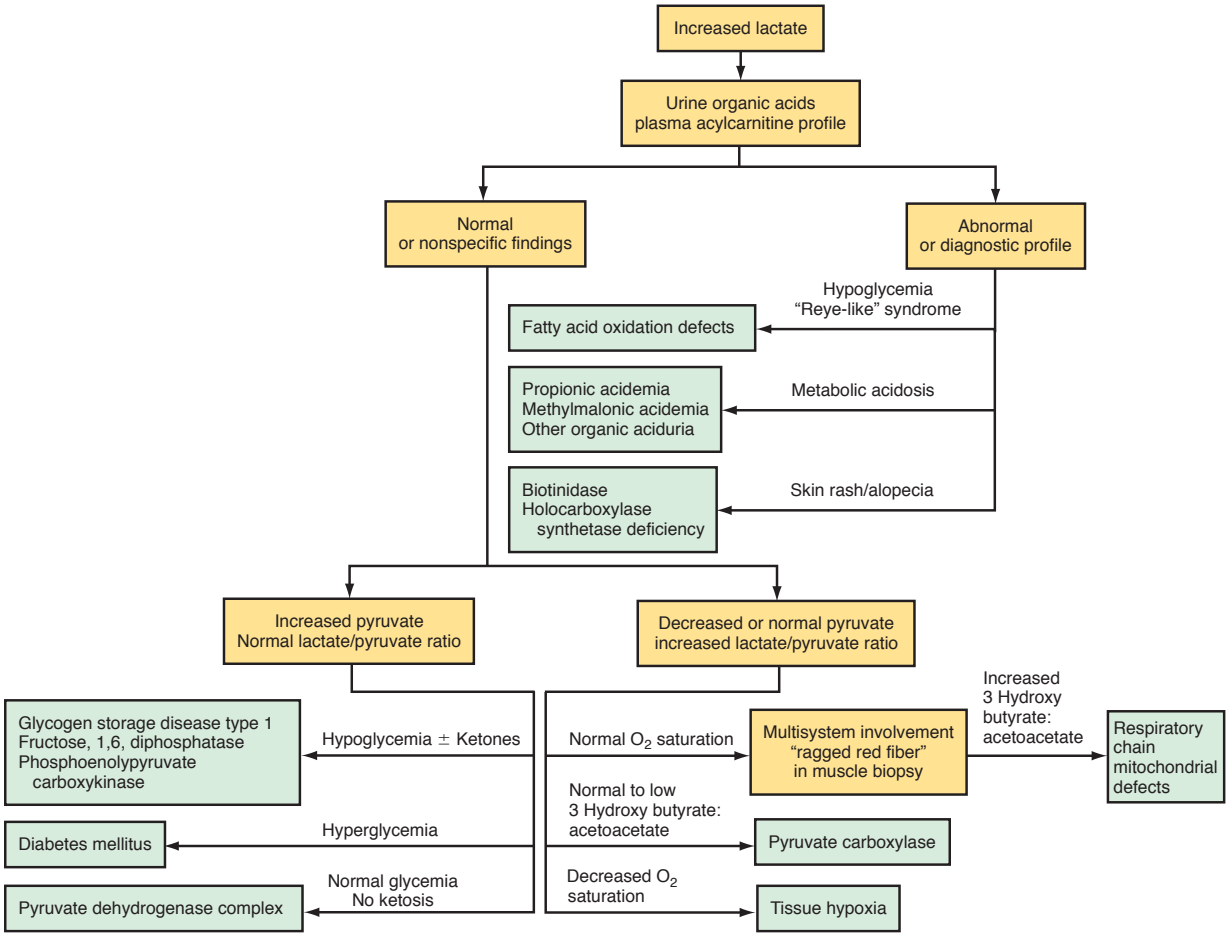


Figure 87-5 Algorithm of the differential diagnosis of lactic acidosis.

Table 87-3 Modified Walker Criteria Applied to Children Referred for Evaluation of Mitochondrial Disease

	MAJOR CRITERIA	MINOR CRITERIA
Clinical	Clinically complete RC encephalomyopathy* or a mitochondrial cytopathy defined as fulfilling 3 criteria†	Symptoms compatible with an RC defect‡
Histology	>2% RRF in skeletal muscle	Smaller numbers of RRF, SSAM, or widespread electron microscopy abnormalities of mitochondria
Enzymology	Cytochrome c oxidase–negative fibers or residual activity of an RC complex <20% in a tissue; <30% in a cell line, or <30% in 2 or more tissues	Antibody-based demonstration of an RC defect or residual activity of an RC complex 20-30% in a tissue, 30-40% in a cell line, or 30-40% in 2 or more tissues
Functional	Fibroblast ATP synthesis rates >3 SD below mean	Fibroblast ATP synthesis rates 2-3 SD below mean, or fibroblasts unable to grow in galactose media
Molecular	Nuclear or mtDNA mutation of undisputed pathogenicity	Nuclear or mtDNA mutation of probable pathogenicity
Metabolic		One or more metabolic indicators of impaired metabolic function

*Leigh disease, Alpers disease, lethal infantile mitochondrial disease, Pearson syndrome, Kearns-Sayre syndrome, MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (myoclonic epilepsy associated with ragged red fibers), NARP (neuropathy, ataxia and retinitis pigmentosa), MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), and LHON (Leber hereditary optic neuropathy).

†(1) Unexplained combination of multisystemic symptoms that is essentially pathognomonic for an RC disorder, (2) a progressive clinical course with episodes of exacerbation or a family history strongly indicative of an mtDNA mutation, and (3) other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing.

‡Added pediatric features: stillbirth associated with a paucity of intrauterine movement, neonatal death or collapse, movement disorder, severe failure to thrive, neonatal hypotonia, and neonatal hypertonia as minor clinical criteria.

ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; RC, respiratory chain; RRF, ragged red fibers; SSAM, subsarcolemmal accumulation of mitochondria.
From Scaglia F, Towbin JA, Craigen WJ, et al: Clinical spectrum, morbidity and mortality in 113 pediatric patients with mitochondrial disease, Pediatrics *114:925–931, 2004.*

Table 87-4 Clues to the Diagnosis of Mitochondrial Disease

NEUROLOGIC
Cerebral stroke-like lesions in a nonvascular pattern
Basal ganglia disease
Encephalopathy: recurrent or with low/moderate dosing of valproate
Neurodegeneration
Epilepsia partialis continua
Myoclonus
Ataxia
MRI findings consistent with Leigh disease
Characteristic MRS peaks
Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
Succinate peak at 2.4 ppm

CARDIOVASCULAR
Hypertrophic cardiomyopathy with rhythm disturbance
Unexplained heart block in a child
Cardiomyopathy with lactic acidosis (>5 mM)
Dilated cardiomyopathy with muscle weakness
Wolff-Parkinson-White arrhythmia

OPHTHALMOLOGIC
Retinal degeneration with signs of night blindness, color vision deficits, decreased visual acuity, or pigmentary retinopathy
Ophthalmoplegia/paresis
Fluctuating, dysconjugate eye movements
Ptosis
Sudden- or insidious-onset optic neuropathy/atrophy

GASTROENTEROLOGIC
Unexplained or valproate-induced liver failure
Severe dysmotility
Pseudoobstructive episodes

OTHER
A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
Exercise intolerance that is not in proportion to weakness
Hypersensitivity to general anesthesia
Episodes of acute rhabdomyolysis

From Haas RH, Parikh S, Falk MJ, et al: Mitochondrial disease: a practical approach for primary care physicians, Pediatrics *120:1326–1333, 2007, Table 1, p. 1327.*

Table 88-1 Recognition Pattern of Mucopolysaccharidoses

	Mucopolysaccharidosis Type						
MANIFESTATIONS	I-H	I-S	II	III	IV	VI	VII
Mental deficiency	+	–	±	+	–	–	±
Coarse facial features	+	(+)	+	+	–	+	±
Corneal clouding	+	+	–	–	(+)	+	±
Visceromegaly	+	(+)	+	(+)	–	+	+
Short stature	+	(+)	+	–	+	+	+
Joint contractures	+	+	+	–	–	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	–	+	+
Mucopolysacchariduria	+	+	+	+	+	+	+

I-H, Hurler disease; I-S, Scheie disease; II Hunter disease; III, Sanfilippo disease; IV, Morquio disease; VI, Maroteaux-Lamy disease; VII Sly disease.

Table 88-2 Mucopolysaccharidoses: Clinical, Molecular, and Biochemical Aspects

MPS TYPE	EPONYM	INHERITANCE	GENE CHROMOSOME	MAIN CLINICAL FEATURES	DEFECTIVE ENZYME	ASSAY	MIM NUMBER
I-H	Pfaundler-Hurler	AR	*IDUA* 4p16.3	Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 yr, Hurler phenotype, mental retardation, corneal clouding, death usually before age 14 yr	α-L-iduronidase	L,F,Ac,CV	252800 607014
I-S	Scheie	AR	*IDUA* 4p16.4	Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood	α-L-iduronidase	L,F,Ac,CV	607016
I-HS	Hurler-Scheie	AR	*IDUA* 4p16.4	Phenotype intermediate between I-H and I-S	α-L-iduronidase	L,F,Ac,Cv	607015
II	Hunter	XLR	*IDS* Xq27.3-28	Severe course similar to I-H but clear corneae. Mild course: less pronounced features, later manifestation, survival to adulthood with mild or without mental deficiency	Iduronate sulfate sulfatase	S,F,Af,Ac,Cv	309900
III-A	Sanfilippo A	AR	*SGSH* 17q25.3	Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas; survival to adulthood possible	Heparan-S-sulfamidase	L,F,Ac,Cv	252900 605270
II-IB	Sanfilippo B	AR	*NAGLU* 17q21		*N*-Acetyl-α-D-glucosaminidase	S,F,Ac,Cv	252920
III-C	Sanfilippo C	AR	*HGSNAT* 8p11.21		Acetyl-CoA:α-glucosaminide *N*-acetyltransferase	F,Ac	252930
III-D	Sanfilippo D	AR	*GNS* 12q14		*N*-Acetylglucosamine-6-sulfatase	F,Ac	252940 607664
IV-A	Morquio A	AR	*GALNS* 16q24.3	Short-trunk dwarfism, fine corneal opacities, characteristic bone dysplasia; final height below 125 cm	*N*-Acetyl-galactosamine-6-sulfatase	L,F,Ac	253000
IV-B	Morquio B	AR	*GLB1* 3p21.33	Same as IV-A, but milder; adult height over 120 cm	β-Galactosidase	L,F,Ac,Cv	253010 230500
VI	Maroteaux-Lamy	AR	*ARSB* 5q11-q13	Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate and severe expression in different families	*N*-Acetyl-galactosamine-4-sulfatase (arylsulfatase B)	L,F,Ac	253200
VII	Sly	AR	*GUSB* 7q21.11	Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes	β-Glucuronidase	S,F,Ac,Cv	253220
IX	Hyaluronidase deficiency	AR	*HYAL1* 3p21.3	Periarticular masses, no Hurler phenotype H	Hyaluronidase 1	S	601492

Ac, cultured amniotic cells; Af, amniotic fluid; Cv, chorionic villi; F, cultured fibroblasts; L, leukocytes; MIM, Mendelian Inheritance in Man Catalogue; S, serum.

Table 88-3 Therapies Aimed at Proximate Causes of Mucopolysaccharidoses

MPS TYPE	STEM CELL TRANSPLANTATION (SCT)	ENZYME REPLACEMENT	REMARKS
I	Yes	Aldurazyme	Transplantation before age 2 yr. Enzyme replacement before and after transplantation
II	Questionable	Elaprase	Lack of neurologic improvement after stem cell transplantation
III	No	No	Experimental: Substrate reduction by flavanoids
IVA	No	Preclinical	Recombinant GALNS trial in course
VI	Yes	Naglazyme	Sustained improvement
VII	Questionable	?	Single SCT attempt without neurologic improvement

GALNS, galactosamine(*N*-acetyl)-6-sulfate sulfatase.

Table 88-4 Symptomatic Management of Mucopolysaccharidoses

PROBLEM	PREDOMINANTLY IN	MANAGEMENT
NEUROLOGIC		
Hydrocephalus	MPS-I, -II, -VI, -VII	Funduscopy, CT scan
Chronic headaches	All	Ventriculoperitoneal shunting
Behavioral disturbance	MPS-III	Behavioral medication, sometimes CT scan, ventriculoperitoneal shunting
Disturbed sleep/wake circle	MPS-III	Melatonin
Seizures	MPS-I, -II, -III	Electroencephalogram, anticonvulsants
Odontoid hypoplasia	MPS-IV	Cervical MRI, upper cervical fusion
Spinal cord compression	All	Laminectomy, dural excision
OPHTHALMOLOGIC		
Corneal opacity	MPS-I, -VI, -VII	Corneal transplant
Glaucoma	MPS-I, -VI, -VII	Medication, surgery
Retinal degeneration	MPS-I, -II	Night light
EARS, AIRWAYS		
Recurrent otitis media	MPS-I, -II, -VI, -VII	Ventilating tubes
Impaired hearing	All except MPS-IV	Audiometry, hearing aids
Obstruction	All except MPS-III	Adenotomy, tonsillectomy, bronchodilator therapy, continuous positive airway pressure at night, laser excision of tracheal lesions, tracheotomy
CARDIAC		
Cardiac valve disease	MPS-I, -II, -VI, -VII	Endocarditis prevention, valve replacement
Coronary insufficiency	MPS-I, -II, -VI, -VII	Medical therapy
Arrhythmias	MPS-I, -II, -VI, -VII	Antiarrhythmic medication, pacemaker
ORAL, GASTROINTESTINAL		
Hypertrophic gums, poor teeth	MPS-I, -II, -VI, -VII	Dental care
Chronic diarrhea	MPS-II	Diet modification, loperamide
MUSCULOSKELETAL		
Joint stiffness	All except MPS-IV	Physical therapy
Weakness	All	Physical therapy, wheelchair
Gross long bone malalignment	All	Corrective osteotomies
Carpal tunnel syndrome	MPS-I, -II, -VI, -VII	Electromyography, surgical decompression
ANESTHESIA	All except MPS-III	Avoid atlantoaxial dislocation, use angulated video intubation laryngoscope and small endotracheal tubes

Table 91-1 The Human Porphyrias: Mutations, Time of Presentation, and Tissue- and Symptom-Based Classifications

DISEASE (ABBREVIATION)	ENZYME (ABBREVIATION)	INHERITANCE	PRESENTATION	Classifications			
				HEPATIC	ERYTHROPOIETIC	ACUTE/ NEUROLOGIC	CUTANEOUS
X-Linked protoporphyria (XLP)	*δ-Aminolevulinate synthase 2 (ALAS2)*	X-linked	Childhood		X		X
δ-Aminolevulinic acid dehydratase porphyria (ADP)	*δ-Aminolevulinic acid dehydratase (ALAD)*	Autosomal recessive	Mostly post puberty	X	X*	X	
Acute intermittent porphyria (AIP)	*Porphobilinogen deaminase (PBGD)*	Autosomal dominant	Post puberty	X		X	
Homozygous AIP		Homozygous dominant	Childhood	X	X	X	
Congenital erythropoietic porphyria (CEP)	*Uroporphyrinogen III synthase (UROS)*	Autosomal recessive	In utero or infancy		X		X
Porphyria cutanea tarda (PCT) type 1	*Uroporphyrinogen decarboxylase (UROD)*	Sporadic	Adults	X			X
PCT type 2†		Autosomal dominant	Adults	X			X
PCT type 3		Unknown	Adults	X			X
Hepatoerythropoietic porphyria (HEP)		Homozygous dominant	Childhood	X	X*		X
Hereditary coproporphyria (HCP)	*Coproporphyrinogen oxidase (CPOX)*	Autosomal dominant	Post puberty	X		X	X
Homozygous HCP		Homozygous dominant	Childhood	X	X	X	X
Variegate porphyria (VP)	*Protoporphyrinogen oxidase (PPOX)*	Autosomal dominant	Post puberty	X		X	X
Homozygous VP		Homozygous dominant	Childhood	X	X	X	X
Erythropoietic protoporphyria (EPP)	*Ferrochelatase (FECH)*	Autosomal recessive(most commonly heteroallelic with hypomorphic allele)	Childhood		X		X

*ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.
†PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT.

Table 91-2 The 3 Most Common Human Porphyrias and Their Major Features

	PRESENTING SYMPTOMS	EXACERBATING FACTORS	MOST IMPORTANT SCREENING TESTS	TREATMENT
Acute intermittent porphyria	Neurologic, adult onset	Drugs (mostly P450-inducers), progesterone, dietary restriction	Urinary porphobilinogen	Hemin, glucose
Porphyria cutanea tarda	Skin blistering and fragility (chronic), adult onset	Iron, alcohol, smoking, estrogens, hepatitis C, HIV, halogenated hydrocarbons	Plasma (or urine) porphyrins	Phlebotomy, low-dose hydroxychloroquine
Erythropoietic protoporphyria	Skin pain and swelling (mostly acute), childhood onset		Erythrocyte (or plasma) porphyrins	Beta-carotene

Table 91-3 Drugs Regarded as Unsafe and Safe in Acute Porphyrias

UNSAFE	SAFE
Barbiturates	Narcotic analgesics
Sulfonamide antibiotics*	Aspirin
Meprobamate* (also mebutamate,* tybutamate*)	Acetaminophen
Carisoprodol*	Phenothiazines
Glutethimide*	Penicillin and derivatives
Methyprylon	Streptomycin
Ethchlorvynol*	Glucocorticoids
Mephenytoin	Bromides
Phenytoin*	Insulin
Succinimides	Atropine
Carbamazepine*	Cimetidine
Clonazepam‡	Ranitidine†
Primidone*	Acetaminophen (paracetamol)
Valproic acid*	Acetazolamide
Pyrazolones (aminopyrine, antipyrine)	Allopurinol
Griseofulvin*	Amiloride
Ergots	Bethanidine
Metoclopramide*‡	Bumetanide
Rifampin*	Cimetidine
Pyrazinamide*‡	Coumarins
Diclofenac*‡	Fluoxetine
Progesterone and synthetic progestins*	Gabapentin
Danazol*	Gentamicin
Alcohol	Guanethidine
Angiotensin-converting enzyme inhibitors (especially enalapril)‡	Ofloxacin
Calcium channel blockers (especially nifedipine)‡	Propranolol
Ketoconazole	Succinylcholine Tetracycline

Table 92-1 Manifestations of Hypoglycemia in Childhood

FEATURES ASSOCIATED WITH ACTIVATION OF AUTONOMIC NERVOUS SYSTEM AND EPINEPHRINE RELEASE*
Anxiety†
Perspiration†
Palpitation (tachycardia)†
Pallor‡
Tremulousness‡
Weakness
Hunger
Nausea
Emesis
FEATURES ASSOCIATED WITH CEREBRAL GLUCOPENIA
Headache†
Mental confusion†
Visual disturbances (↓ acuity, diplopia)†
Organic personality changes†
Inability to concentrate†
Dysarthria
Staring
Paresthesias
Dizziness
Amnesia
Ataxia, incoordination
Refusal to feed‡
Somnolence, lethargy‡
Seizures‡
Coma
Stroke, hemiplegia, aphasia
Decerebrate or decorticate posture

*Some of these features will be attenuated if the patient is receiving β-adrenergic blocking agents.
†Common.
‡Most common manifestations in the newborn.

Table 92-2 Classification of Hypoglycemia in Infants and Children

NEONATAL TRANSITIONAL (ADAPTIVE) HYPOGLYCEMIA
Associated with Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates
Prematurity
Small for gestational age
Normal newborn
Transient Neonatal Hyperinsulinism
Infant of diabetic mother
Small for gestational age
Discordant twin
Birth asphyxia
Infant of toxemic mother

NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIAS
Hyperinsulinism
Recessive K_{ATP} channel HI
Recessive HADH (hydroxyl acyl-CoA dehydrogenase) mutation HI
Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI
Focal K_{ATP} channel HI
Dominant K_{ATP} channel HI
Atypical congenital hyperinsulinemia (no mutations in *ABCC8* or *KCN11* genes)
Dominant glucokinase HI
Dominant glutamate dehydrogenase HI (hyperinsulinism/hyperammonemia syndrome)
Dominant mutations in HNF-4A and HNF-1A (hepatic nuclear factors 4α and 1α) HI with monogenic diabetes of youth later in life
Dominant mutation in SLC16A1(the pyruvate transporter)—exercise-induced hypoglycemia
Acquired islet adenoma
Beckwith-Wiedemann syndrome
Insulin administration (Munchausen syndrome by proxy)
Oral sulfonylurea drugs
Congenital disorders of glycosylation
Counterregulatory Hormone Deficiency
Panhypopituitarism
Isolated growth hormone deficiency
Adrenocorticotropic hormone deficiency
Addison disease
Epinephrine deficiency
Glycogenolysis and Gluconeogenesis Disorders
Glucose-6-phosphatase deficiency (GSD 1a)
Glucose-6-phosphate translocase deficiency (GSD 1b)
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD 3)
Liver phosphorylase deficiency (GSD 6)
Phosphorylase kinase deficiency (GSD 9)
Glycogen synthetase deficiency (GSD 0)
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
Galactosemia
Hereditary fructose intolerance
Lipolysis Disorders
Fatty Acid Oxidation Disorders
Carnitine transporter deficiency (primary carnitine deficiency)
Carnitine palmitoyltransferase-1 deficiency
Carnitine translocase deficiency
Carnitine palmitoyltransferase-2 deficiency
Secondary carnitine deficiencies
Very-long-, long-, medium-, short-chain acyl-CoA dehydrogenase deficiency

OTHER ETIOLOGIES
Substrate-Limited
Ketotic hypoglycemia
Poisoning—drugs
Salicylates
Alcohol
Oral hypoglycemic agents
Insulin
Propranolol
Pentamidine
Quinine
Disopyramide
Ackee fruit (unripe)—hypoglycin
Vacor (rat poison)
Trimethoprim-sulfamethoxazole (with renal failure)
Liver Disease
Reye syndrome
Hepatitis
Cirrhosis
Hepatoma

AMINO ACID AND ORGANIC ACID DISORDERS
Maple syrup urine disease
Propionic acidemia
Methylmalonic acidemia
Tyrosinosis
Glutaric aciduria
3-Hydroxy-3-methylglutaric aciduria

SYSTEMIC DISORDERS
Sepsis
Carcinoma/sarcoma (secreting—insulin-like growth factor II)
Heart failure
Malnutrition
Malabsorption
Antiinsulin receptor antibodies
Antiinsulin antibodies
Neonatal hyperviscosity
Renal failure
Diarrhea
Burns
Shock
Postsurgical
Pseudohypoglycemia (leukocytosis, polycythemia)
Excessive insulin therapy of insulin-dependent diabetes mellitus
Factitious
Nissen fundoplication (dumping syndrome)
Falciparum malaria

GSD, glycogen storage disease; HI, hyperinsulinemia; K_{ATP}, regulated potassium channel.

Table 92-3 Hypoglycemia in Infants and Children: Clinical and Laboratory Features

GROUP	AGE AT DIAGNOSIS (mo)	GLUCOSE* (mg/dL)	INSULIN (μU/mL)	FASTING TIME TO HYPOGLYCEMIA (hr)
HYPERINSULINEMIA (*N* = 12)				
Mean	7.4	23.1	22.4	2.1†
SEM	2.0	2.7	3.2	0.6
NONHYPERINSULINEMIA (*N* = 16)				
Mean	41.8	36.1	5.8	18.2
SEM	7.3	2.4	0.9	2.9

*In hypoglycemia caused by hyperinsulinism β OH butyrate and FFA are low compared with normal at same duration of fasting.
†Milder forms of hyperinsulinism may require up to 18 hr of fasting to provoke hypoglycemia.
SEM, standard error of mean.
Adapted from Antunes JD, Geffner ME, Lippe BM, et al: Childhood hypoglycemia: differentiating hyperinsulinemic from nonhyperinsulinemic causes, J Pediatr *116:105–108, 1990.*

Table 92-4 Correlation of Clinical Features with Molecular Defects in Persistent Hyperinsulinemic Hypoglycemia in Infancy

TYPE	MACROSOMIA	HYPOGLYCEMIA/ HYPERINSULINEMIA	FAMILY HISTORY	MOLECULAR DEFECTS	ASSOCIATED CLINICAL, BIOCHEMICAL, OR MOLECULAR FEATURES	RESPONSE TO MEDICAL MANAGEMENT	RECOMMENDED SURGICAL APPROACH	PROGNOSIS
Sporadic	Present at birth	Moderate/severe in first days to weeks of life	Negative	? *SUR1*/K_{IR} 6.2 Mutations not always identified in diffuse hyperplasia	Loss of heterozygosity in microadenomatous tissue	Generally poor; may respond better to somatostatin than to diazoxide	Partial pancreatectomy if frozen section shows β-cell crowding with small nuclei—suggests microadenoma Subtotal >95% pancreatectomy if frozen section shows giant nuclei in β-cells—suggests diffuse hyperplasia	Excellent if focal adenoma is removed, thereby curing hypoglycemia and retaining sufficient pancreas to avoid diabetes Guarded if subtotal (>95%) pancreatectomy is performed because diabetes develops in, and hypoglycemia persists in
Autosomal recessive	Present at birth	Severe in first days to weeks of life	Positive	*SUR*/K_{IR} 6.2	Consanguinity a feature in some populations	Poor	Subtotal pancreatectomy	Guarded
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glucokinase (activating) Some cases gene unknown	None	Very good to excellent	Surgery usually not required Partial pancreatectomy only if medical management fails	Excellent
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glutamate dehydrogenase (activating)	Modest hyperammonemia	Very good to excellent	Surgery usually not required	Excellent
Beckwith-Wiedemann syndrome	Present at birth	Moderate, spontaneously resolves post 6 mo of age	Negative	Duplicating/ imprinting in chromosome 11p15.1	Macroglossia, omphalocele, hemihypertrophy	Good	Not recommended	Excellent for hypoglycemia; guarded for possible development of embryonal tumors (Wilms hepatoblastoma)
Congenital disorders of glycosylation	Not usual	Moderate/onset post 3 mo of age	Negative	Phosphomannose isomerase deficiency	Hepatomegaly, vomiting, intractable diarrhea	Good with mannose supplement	Not recommended	Fair

Table 92-5 Analysis of Critical Blood Sample During Hypoglycemia and 30 Minutes After Glucagon*

SUBSTRATES
Glucose
Free fatty acids
Ketones
Lactate
Uric acid
Ammonia
HORMONES
Insulin
Cortisol
Growth hormone
Thyroxine, thyroid-stimulating hormone
Insulin-like growth factor binding protein-1†

*Glucagon 50 μg/kg with maximum of 1 mg IV or IM.
†Measure once only before or after glucagon administration. Rise in glucose of ≥40 mg/dL after glucagon given at the time of hypoglycemia strongly suggests a hyperinsulinemic state with adequate hepatic glycogen stores and intact glycogenolytic enzymes. If ammonia is elevated to 100-200 μM, consider activating mutation of glutamate dehydrogenase.

Table 92-6 Criteria for Diagnosing Hyperinsulinism Based on "Critical" Samples (Drawn at a Time of Fasting Hypoglycemia: Plasma Glucose <50 mg/dL)

1. Hyperinsulinemia (plasma insulin >2 μU/mL)*
2. Hypofatty acidemia (plasma free fatty acids <1.5 mmol/L)
3. Hypoketonemia (plasma β-hydroxybutyrate: <2.0 mmol/L)
4. Inappropriate glycemic response to glucagon, 1 mg IV (change in glucose >40 mg/dL)

*Depends on sensitivity of insulin assay.

Table 92-7 Diagnosis of Acute Hypoglycemia in Infants and Children

ACUTE SYMPTOMS PRESENT

1. Obtain blood sample before and 30 min after glucagon administration.
2. Obtain urine as soon as possible. Examine for ketones; if not present and hypoglycemia confirmed, suspect hyperinsulinemia or fatty acid oxidation defect; if present, suspect ketotic, hormone deficiency, inborn error of glycogen metabolism, or defective gluconeogenesis.
3. Measure glucose in the original blood sample. If hypoglycemia is confirmed, proceed with substrate-hormone measurement as in Table 92-5.
4. If glycemic increment after glucagon exceeds 40 mg/dL above basal, suspect hyperinsulinemia.
5. If insulin level at time of confirmed hypoglycemia is >5 μU/mL, suspect endogenous hyperinsulinemia; if >100 μU/mL, suspect factitious hyperinsulinemia (exogenous insulin injection). Admit to hospital for supervised fast.
6. If cortisol is <10 μg/dL or growth hormone is <5 ng/mL, or both, suspect adrenal insufficiency or pituitary disease, or both. Admit to hospital for hormonal testing and neuroimaging.

HISTORY SUGGESTIVE: ACUTE SYMPTOMS NOT PRESENT

1. Careful history for relation of symptoms to time and type of food intake, bearing in mind age of patient. Exclude possibility of alcohol or drug ingestion. Assess possibility of insulin injection, salt craving, growth velocity, intracranial pathology.
2. Careful examination for hepatomegaly (glycogen storage disease; defect in gluconeogenesis); pigmentation (adrenal failure); stature and neurologic status (pituitary disease).
3. Admit to hospital for provocative testing:
   a. 24 hr fast under careful observation; when symptoms provoked, proceed with steps 1-4 as when acute symptoms present.
   b. Pituitary–adrenal function using arginine-insulin stimulation test if indicated.
4. Consider molecular diagnostic test before liver biopsy for histologic and enzyme determinations.
5. Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected (dumping syndrome, etc.).

Table 93-2 Levels of In-Hospital Perinatal Care

MATERNAL	NEONATE
BASIC	
Monitor and care for low-risk patients	Resuscitation
	Stabilization
Triage for high risk for transfer	Well neonatal care
Detection and care of unanticipated labor problems	Nursery care
Emergency cesarean delivery within 30 min	Visitation
	General pediatrician staff (capable of neonatal resuscitation)
Blood bank, anesthesia, radiology, ultrasound, and laboratory support	
Care of postpartum problems	
Obstetrician, nurse, midwife staff	
SPECIAL CARE	
Basic services plus:	*Basic services plus:*
Care of high-risk pregnancies	Care of high-risk neonate with short-term problems
Triage, transfer of high-risk pregnancies (<32 wk, intrauterine growth retardation, preeclampsia, severe maternal medical illness)	Stabilization before transfer (<1,500 g, <32 wk, critically ill)
	Accept convalescing back (reverse) transfers
SUBSPECIALTY CARE	
Basic plus specialty care plus:	*Basic plus specialty care plus:*
Experienced perinatologist (24-hr coverage)	Experienced neonatologist (24-hr coverage)
Evaluation of high-risk therapies	Inborn plus transferred patients
Care for severe maternal medical or obstetric illnesses	Evaluation of high-risk therapies
	All pediatric medical, radiologic, and surgical subspecialties
High-risk fetal care (Rh disease, nonimmune hydrops, life-threatening anomalies)	Neonatal intensive care unit with operating room capabilities
	High-risk follow-up
Outcomes research	Outcomes research
Community education	Community education

From American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, *ed 5, Elk Grove Village, IL, 2002, American Academy of Pediatrics.*

Table 92-8 Clinical Manifestations and Differential Diagnosis in Childhood Hypoglycemia

Condition	Hypoglycemia	Urinary Ketones or Reducing Sugars	Hepatomegaly	Serum		Effect of 24-36 hr Fast on Plasma					Glycemic Response to Glucagon		Glycemic Response to Infusion of	
				LIPIDS	URIC ACID	GLUCOSE	INSULIN	KETONES	ALANINE	LACTATE	FED	FASTED	ALANINE	GLYCEROL
Normal	0	0	0	Normal	Normal	↓	↓	↑	↓	Normal	↑	↓		Not indicated
Hyperinsulinemia	Recurrent severe	0	0	Normal or ↑	Normal	↓↓	↑↑	↓↓	Normal	Normal	↑	↑		Not indicated
Ketotic hypoglycemia	Severe with missed meals	Ketonuria +++	0	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓		Not indicated
Fatty acid oxidation disorder	Severe with missed meals	Absent	0 to + Abnormal liver function test results	Abnormal	↑		Contraindicated				↑	↓		Not indicated
Hypopituitarism	Moderate with missed meals	Ketonuria ++		Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	↑
Adrenal insufficiency	Severe with missed meals	Ketonuria ++	0	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	↑
Enzyme deficiencies	Severe-constant	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	0	0-↓↓	0	0
Glucose-6-phosphatase debrancher	Moderate with fasting	++	++	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	0-↓↓	↑	↑
Phosphorylase	Mild-moderate	Ketonuria ++	+	Normal	Normal	↓	↓	↑↑	↓↓	Normal	0-↑	0-↓↓	↑	↑
Fructose-1, 6-diphosphatase	Severe with fasting	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	↑	0-↓↓	↓	↓
Galactosemia	After milk or milk products	0 Ketones;(s) +	+++	Normal	Normal	↓	↓	↑	↓	Normal	↑	0-↓↓	↑	↑
Fructose intolerance	After fructose	0 Ketones;(s) +	+++	Normal	Normal	↓	↓	↑	↓	Normal	↑	0-↓↓	↑	↑

Details of each condition are discussed in the text.
0, absence; ↑ or ↓ indicates respectively small increase or decrease; ↑↑ or ↓↓ indicates respectively large increase or decrease.

The Newborn Infant

Table 93-3 Morbidities and Sequelae of Perinatal and Neonatal Illness

MORBIDITIES	EXAMPLES
CENTRAL NERVOUS SYSTEM	
Spastic diplegic-quadriplegic cerebral palsy	Hypoxic–ischemic encephalopathy, periventricular leukomalacia, undetermined antenatal factors
Choreoathetotic cerebral palsy	Bilirubin encephalopathy (kernicterus)
Microcephaly	Hypoxic-ischemic encephalopathy, intrauterine infection (rubella, CMV)
Communicating hydrocephalus	Intraventricular hemorrhage, meningitis
Seizures	Hypoxic-ischemic encephalopathy, hypoglycemia
Encephalopathy	Congenital infections (rubella, CMV, HIV, toxoplasmosis)
Educational failure and/or mental retardation	Immaturity, hypoxia, hypoglycemia, cerebral palsy, intraventricular hemorrhage, low socioeconomic status
SENSATION—PERIPHERAL NERVES	
Reduced visual acuity (blindness)	Retinopathy of prematurity
Strabismus	Undetermined, prematurity
Hearing impairment (deafness)	Drug toxicity (furosemide, aminoglycosides), bilirubin encephalopathy, hypoxia ± hyperventilation
Poor speech	Immaturity, chronic illness, hypoxia, prolonged endotracheal intubation, hearing deficit
Paralysis–paresis	Birth trauma—brachial plexus, phrenic nerve, spinal cord
RESPIRATORY	
BPD	Oxygen toxicity, barotrauma
Subglottic stenosis	Endotracheal tube injury
Sudden infant death syndrome	Prematurity, BPD, infant of illicit drug user
Choanal stenosis, nasal septum destruction	Nasotracheal intubation
	Growth failure
CARDIOVASCULAR	
Cyanosis	Precorrective palliative care of congenital cyanotic heart disease, cor pulmonale from BPD, reactive airway
Heart failure	Precorrective palliative care of complex congenital heart disease, BPD, ventricular septal defect
GASTROINTESTINAL	
Short-gut syndrome	Necrotizing enterocolitis, gastroschisis, malrotation-volvulus, cystic fibrosis, intestinal atresia
Cholestatic liver disease (cirrhosis, hepatic failure)	Hyperalimentation toxicity, sepsis, short-gut syndrome
Failure to thrive	Short-gut syndrome, cholestasis, BPD, cerebral palsy, severe congenital heart disease
Inguinal hernia	Unknown
MISCELLANEOUS	
Cutaneous scars	Chest tube or intravenous catheter placement, hyperalimentation, subcutaneous infiltration, fetal puncture, intrauterine varicella, cutis aplasia
Absence of radial artery pulse	Frequent arterial puncture
Hypertension	Renal thrombi, repair of coarctation of aorta

BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus.

Table 93-4 Incidence of Adverse Outcome According to Completed Week of Gestation at Delivery for Infants Born by Caesarean Section

OUTCOME	WK 37 (N = 934)	WK 38 (N = 3909)	WK 39 (N = 6512)	WK 40 (N = 1385)	WK 41 (N = 1385)	WK 42 (N = 113)
Respiratory distress syndrome	3.7	1.9	0.9	0.9	0.8	1.8
Transient tachypnea of the newborn	4.8	3.9	2.7	2.5	4.8	6.2
Admission to the neonatal intensive care unit	12.8	8.1	5.9	4.8	7.9	14.2
Suspected sepsis	6.6	3.9	2.4	2.6	3.6	10.6
Treated hypoglycemia	2.4	0.9	0.7	0.8	1.6	1.8
Ventilation	1.9	0.9	0.4	0.4	0.4	

From Tita AT, Landon MB, Spong CY, et al: Timing of elective repeat cesarean delivery at term and neonatal outcomes, N Engl J Med *360:111–120, 2009.*

Table 93-1 Major Causes of Perinatal and Neonatal Mortality

FETAL
Placental insufficiency
Intrauterine infection
Severe congenital malformations (anomalies)
Umbilical cord accident
Abruptio placentae
Hydrops fetalis
PRETERM
Severe immaturity
Respiratory distress syndrome
Intraventricular hemorrhage
Congenital anomalies
Infection
Necrotizing enterocolitis
Bronchopulmonary dysplasia (BPD)
FULL TERM
Congenital anomalies
Birth asphyxia
Trauma
Infection
Meconium aspiration pneumonia
Persistent pulmonary hypertension (PPHN)

Table 94-3 Factors Affecting the Apgar Score*

FALSE-POSITIVE (NO FETAL ACIDOSIS OR HYPOXIA; LOW APGAR SCORE)
Prematurity
Analgesics, narcotics, sedatives
Magnesium sulfate
Acute cerebral trauma
Precipitous delivery
Congenital myopathy
Congenital neuropathy
Spinal cord trauma
Central nervous system anomaly
Lung anomaly (diaphragmatic hernia)
Airway obstruction (choanal atresia)
Congenital pneumonia and sepsis
Previous episodes of fetal asphyxia (recovered)
Hemorrhage-hypovolemia
FALSE-NEGATIVE (ACIDOSIS; NORMAL APGAR SCORE)
Maternal acidosis
High fetal catecholamine levels
Some full-term infants

*Regardless of the etiology, a low Apgar score because of fetal asphyxia, immaturity, central nervous system depression, or airway obstruction identifies an infant needing immediate resuscitation.

Table 93-2 Levels of In-Hospital Perinatal Care

MATERNAL	NEONATE
BASIC	
Monitor and care for low-risk patients	Resuscitation Stabilization
Triage for high risk for transfer	Well neonatal care
Detection and care of unanticipated labor problems	Nursery care
Emergency cesarean delivery within 30 min	Visitation
	General pediatrician staff (capable of neonatal resuscitation)
Blood bank, anesthesia, radiology, ultrasound, and laboratory support	
Care of postpartum problems	
Obstetrician, nurse, midwife staff	
SPECIAL CARE	
Basic services plus:	*Basic services plus:*
Care of high-risk pregnancies	Care of high-risk neonate with short-term problems
Triage, transfer of high-risk pregnancies (<32 wk, intrauterine growth retardation, preeclampsia, severe maternal medical illness)	Stabilization before transfer (<1,500 g, <32 wk, critically ill) Accept convalescing back (reverse) transfers
SUBSPECIALTY CARE	
Basic plus specialty care plus:	*Basic plus specialty care plus:*
Experienced perinatologist (24-hr coverage)	Experienced neonatologist (24-hr coverage)
Evaluation of high-risk therapies	Inborn plus transferred patients
Care for severe maternal medical or obstetric illnesses	Evaluation of high-risk therapies All pediatric medical, radiologic, and surgical subspecialties
High-risk fetal care (Rh disease, nonimmune hydrops, life-threatening anomalies)	Neonatal intensive care unit with operating room capabilities High-risk follow-up
Outcomes research	Outcomes research
Community education	Community education

From American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, *ed 5, Elk Grove Village, IL, 2002, American Academy of Pediatrics.*

Table 94-5 Criteria for Discharge from the Normal Newborn Nursery*

Uncomplicated antepartum, intrapartum, postpartum courses
Vaginal delivery
Singleton at 38-42 wk: appropriate for gestational age
Normal vital signs including respiratory rate <60 breaths/min; axillary temperature 36.1-37°C (97.0-98.6°F) in open crib
Physical examination reveals no abnormalities requiring continued hospitalization
Urination; stool × 1
At least 2 uneventful, successful feedings
No excessive bleeding 2 hr after circumcision
No jaundice within 24 hr of birth; if jaundice, appropriate management and follow-up are in place
Evidence of parental knowledge, ability, and confidence to care for the baby at home:
- Feeding
- Cord, skin, genital care
- Recognition of illness (jaundice, poor feeding, lethargy, fever, etc.)
- Infant safety (car seat, supine sleep position, etc.)

Availability of family and physician support (physician follow-up)
Laboratory evaluation:
- Syphilis
- Hepatitis B surface antigen and vaccination or appointment for vaccination
- Coombs test and blood type if clinically indicated
- Expanded metabolic screening: phenylketonuria, thyroid, galactosemia, sickle cell
- Hearing screening

No social risks:
- Substance abuse
- History of child abuse
- Domestic violence
- Mental illness
- Teen mother
- Homelessness
- Barriers to follow-up

Source of continuing medical care is identified

*It is not likely that all these criteria will be met before 48 hr of age.
Adapted from American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, *ed 7, Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Table 94-6 Ten Steps to Successful Breastfeeding

Every facility providing maternity services and care for newborn infants should accomplish the following:

1. Have a written breastfeeding policy that is routinely communicated to all healthcare staff.
2. Train all healthcare staff in the skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within a half hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk unless *medically* indicated.
7. Practice rooming-in (allow mothers and infants to remain together) 24 hr a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called *dummies* or *soothers*) to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

From Protecting, promoting and supporting breastfeeding: the special role of maternity services. A joint WHO/UNICEF statement. *Geneva, 1989, World Health Organization.*

Table 94-7 Drugs and Breastfeeding

CONTRAINDICATED
Amphetamines
Antineoplastic agents
Bromocriptine
Chloramphenicol
Clozapine
Cocaine
Cyclophosphamide
Diethylstilbestrol
Doxorubicin
Ecstasy
Ergots
Gold salts
Heroin
Immunosuppressants
Iodides
Kava
Lithium
Methimazole
Methamphetamine
Phencyclidine (PCP)
Radiopharmaceuticals
Thiouracil
Yohimbe

AVOID OR GIVE WITH CAUTION
Alcohol
Amiodarone
Anthraquinones (laxatives)
Aspirin (salicylates)
Atropine
β-Adrenergic blocking agents
Benzodiazepines
Birth control pills
Bromides
Buprenorphine/naltrexone
Bupropion
Calciferol
Cascara
Ciprofloxacin
Codeine
Dicumarol
Dihydrotachysterol
Domperidone
Estrogens
Hydrocodone
Marijuana
Metoclopramide
Metronidazole
Meperidine
Oxycodone
Phenobarbital*
Primidone
Psychotropic drugs
Reserpine
Salicylazosulfapyridine (sulfasalazine)

PROBABLY SAFE
Acetaminophen
Acyclovir
Aldomet
Anesthetics
Antibiotics (not chloramphenicol)
Antiepileptics
Antihistamines*
Antithyroid (not methimazole)
Bishydroxycoumarin (dicumarol)
Chlorpromazine*
Cyclosporine
Depo-Provera
Digoxin
Dilantin (phenytoin)
Diuretics
Fluoxetine
Furosemide
Haloperidol*
Hydralazine
Indomethacin, other nonsteroidal antiinflammatory drugs
Low-molecular-weight heparins
Metformin
Methadone*
Morphine
Muscle relaxants
Paroxetine
Prednisone
Propranolol
Propylthiouracil
Sedatives*
Sertraline
Theophylline
Vitamins
Warfarin

*Watch for sedation.

Table 94-8 Summary of Infectious Agents Detected in Milk and Newborn Disease

INFECTIOUS AGENT	DETECTED IN BREAST MILK?	BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?
BACTERIA			
Mastitis/*Staphylococcus aureus*	Yes	No	No, unless breast abscess present
Mycobacterium tuberculosis:			
Active disease	Yes	No	Yes, because of aerosol spread, or tuberculosis mastitis
Purified protein derivative skin test result positive, chest radiograph findings negative	No	No	No
Escherichia coli, other Gram-negative rods	Yes, stored	Yes, stored	—
Group B streptococci	Yes	Yes	No*
Listeria monocytogenes	Yes	Yes	No*
Coxiella burnetii	Yes	Yes	No*
Syphilis	No	No	No†

Continued

Table 94-8 Summary of Infectious Agents Detected in Milk and Newborn Disease—cont'd

INFECTIOUS AGENT	DETECTED IN BREAST MILK?	BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?
VIRUSES			
HIV	Yes	Yes	Yes, developed countries
Cytomegalovirus:			
Term infant	Yes	Yes	No
Preterm infant	Yes	Yes	Evaluate on an individual basis
Hepatitis B virus	Yes, surface antigen	No	No, developed countries‡
Hepatitis C virus	Yes	No	No§
Hepatitis E virus	Yes	No	No
Human T-cell leukemia virus (HTLV)-1	Yes	Yes	Yes, developed countries
HTLV-2	Yes	?	Yes, developed countries
Herpes simplex virus	Yes	No/?yes	No, unless breast vesicles present
Rubella			
Wild type	Yes	Yes, rare	No
Vaccine	Yes	No	No
Varicella-zoster virus	Yes	No	No, cover active lesions¶
Epstein-Barr virus	Yes	No	No
Human herpesvirus (HHV)-6	No	No	No
HHV-7	Yes	No	No
West Nile virus	Possible	Possible	Unknown
PARASITES			
Toxoplasma gondii	Yes	Yes, 1 case	No

*Provided that the mother and child are taking appropriate antibiotics.
†Treat mother and child if active disease.
‡Immunize and immune globulin at birth.
§Provided that the mother is HIV-seronegative. Mothers should be counseled that breast milk transmission of hepatitis C virus has not been documented, but is theoretically possible.
¶Provide appropriate antivaricella therapy or prophylaxis to newborn.
Modified from Jones CA: Maternal transmission of infectious pathogens in breast milk, J Paediatr Child Health *37:576–582, 2001.*

Table 94-2 Apgar Evaluation of Newborn Infants*

SIGN	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

*Sixty sec after complete birth of the infant (disregarding the cord and placenta), the 5 objective signs listed here are evaluated, and each is given a score of 0, 1, or 2. A total score of 10 indicates an infant in the best possible condition. An infant with a score of 0-3 requires immediate resuscitation.
Modified from Apgar V: A proposal for a new method of evaluation of the newborn infant, Curr Res Anesth Analg *32:260–267, 1953.*

Table 95-1 Factors Associated with High-Risk Pregnancy

ECONOMIC
Poverty
Unemployment
Uninsured, underinsured health insurance
Poor access to prenatal care
CULTURAL–BEHAVIORAL
Low educational status
Poor healthcare attitudes
No care or inadequate prenatal care
Cigarette, alcohol, illicit drug use
Age <20 or >40 yr
Unmarried
Short interpregnancy interval
Lack of support group (husband, family, religion)
Stress (physical, psychologic)
Black race
BIOLOGIC–GENETIC
Previous low birthweight or preterm infant
Low weight for height
Poor weight gain during pregnancy
Short stature
Poor nutrition
Consanguinity
Intergenerational effects
Low maternal birthweight
Hereditary diseases (inborn error of metabolism)
REPRODUCTIVE
Previous cesarean section
Previous infertility
Conception by reproductive technology
Prolonged gestation
Prolonged labor
Previous infant with cerebral palsy, mental retardation, birth trauma, congenital anomalies
Abnormal lie (breech)
Multiple gestations
Premature rupture of membranes
Infection (systemic, amniotic, extra-amniotic, cervical)
Preeclampsia or eclampsia
Uterine bleeding (abruptio placentae, placenta previa)
Parity (0 or >5 previous deliveries)
Uterine or cervical anomalies
Fetal disease
Abnormal fetal growth
Idiopathic premature labor
Iatrogenic prematurity
High or low levels of maternal serum α-fetoprotein
MEDICAL
Diabetes mellitus
Hypertension
Congenital heart disease
Autoimmune disease
Sickle cell anemia
Intercurrent surgery or trauma
Sexually transmitted infection
Maternal hypercoagulable states
Exposure to prescription medications
TORCH (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex) infection

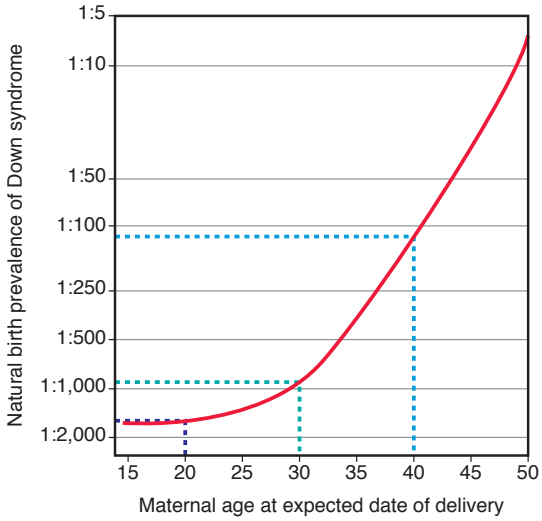


Figure 95-1 Natural birth prevalence of Down syndrome according to maternal age.

Table 95-4 Conditions Associated with Disorders of Amniotic Fluid Volume

OLIGOHYDRAMNIOS
Amniotic fluid leak/rupture of membranes
Intrauterine growth restriction
Fetal anomalies
Twin–twin transfusion (donor)
Renal agenesis (Potter syndrome)
Urethral atresia
Prune-belly syndrome
Pulmonary hypoplasia
Amnion nodosum
Indomethacin
Angiotensin-converting enzyme inhibitors or receptor antagonists
Intestinal pseudoobstruction
POLYHYDRAMNIOS
Congenital anomalies:
Anencephaly
Hydrocephaly
Tracheoesophageal fistula
Duodenal atresia
Spina bifida
Cleft lip or palate
Cystic adenomatoid lung malformation
Diaphragmatic hernia
Syndromes:
Achondroplasia
Klippel-Feil
Trisomy 18
Trisomy 21
TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex)
Hydrops fetalis
Multiple congenital anomalies
Other:
Diabetes mellitus
Twin–twin transfusion (recipient)
Fetal anemia
Fetal heart failure
Polyuric renal disease
Neuromuscular diseases
Nonimmune hydrops
Chylothorax
Teratoma
Idiopathic

Table 95-2 Maternal Conditions Affecting the Fetus or Neonate

DISORDER	EFFECT(S)	MECHANISM(S)
Autoantibody against folate receptors	Neural tube defects	Blockage of cellular uptake of folate
Cervical neoplasia	Preterm premature rupture of membranes	Associated with loop electrosurgical excision procedure or cone therapy
Cholestasis	Preterm delivery, intrauterine fetal demise	Unknown, possibly hepatitis E
Cyanotic heart disease	Intrauterine growth restriction	Low fetal oxygen delivery
Diabetes mellitus:		
Mild	Large for gestational age, hypoglycemia	Fetal hyperglycemia—produces hyperinsulinemia; insulin promotes growth
Severe	Growth restriction	Vascular disease, placental insufficiency
Drug addiction	Intrauterine growth restriction, neonatal withdrawal	Direct drug effect plus poor diet
Endemic goiter	Hypothyroidism	Iodine deficiency
Graves disease	Transient neonatal thyrotoxicosis	Placental immunoglobulin passage of thyroid-stimulating antibody
Herpes gestationis (noninfectious)	Bullous rash, intrauterine fetal demise	Autoantibody similar to that in bullous pemphigoid
Hyperparathyroidism	Neonatal hypocalcemia	Maternal calcium crosses to fetus and suppresses fetal parathyroid gland
Hypertension	Intrauterine growth restriction, intrauterine fetal demise	Placental insufficiency, fetal hypoxia
Idiopathic thrombocytopenic purpura	Thrombocytopenia	Nonspecific maternal platelet antibodies cross placenta
Isoimmune neutropenia or thrombocytopenia	Neutropenia or thrombocytopenia	Specific antifetus neutrophil or platelet antibody crosses placenta after sensitization of mother
Malignant melanoma	Placental or fetal tumor	Metastasis
Myasthenia gravis	Transient neonatal myasthenia	Immunoglobulin to acetylcholine receptor crosses placenta
Myotonic dystrophy	Neonatal myotonic dystrophy, congenital contractures, respiratory insufficiency	Genetic anticipation
Obesity	Macrosomia, hypoglycemia	Unknown
Phenylketonuria	Microcephaly, retardation	Elevated fetal phenylalanine values
Poor nutrition	Intrauterine growth restriction, adult insulin resistance	Reduced fetal nutrients, nutritional programming
Preeclampsia, eclampsia	Intrauterine growth restriction, thrombocytopenia, neutropenia, fetal demise	Uteroplacental insufficiency, fetal hypoxia, vasoconstriction
Renal transplantation	Intrauterine growth restriction	Uteroplacental insufficiency
Rhesus or other blood group sensitization	Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice	Antibody crosses placenta and is directed to fetal cells with antigen
Sickle cell anemia	Preterm birth, intrauterine growth restriction, stillbirth	Maternal sickling producing fetal hypoxia
Systemic lupus erythematosus	Congenital heart block, rash, anemia, thrombocytopenia, neutropenia	Antibody directed to fetal heart, red and white blood cells, and platelets

Table 95-3 Maternal Infections Affecting the Fetus or Newborn

INFECTION	MODE(S) OF TRANSMISSION	OUTCOME
BACTERIA		
Group B streptococcus	Ascending cervical	Sepsis, pneumonia
Escherichia coli	Ascending cervical	Sepsis, pneumonia
Listeria monocytogenes	Transplacental	Sepsis, pneumonia
Ureaplasma urealyticum	Ascending cervical	Pneumonia, meningitis
Mycoplasma hominis	Ascending cervical	Pneumonia
Chlamydia trachomatis	Vaginal passage	Conjunctivitis, pneumonia
Syphilis	Transplacental, vaginal passage	Congenital syphilis
Borrelia burgdorferi	Transplacental	Prematurity, fetal demise
Neisseria gonorrhoeae	Vaginal passage	Ophthalmia (conjunctivitis), sepsis, meningitis
Mycobacterium tuberculosis	Transplacental	Prematurity, fetal demise, congenital tuberculosis
Granulocytic ehrlichiosis	Transplacental	Sepsis
VIRUS		
Rubella	Transplacental	Congenital rubella
Cytomegalovirus	Transplacental, breast milk (rare)	Congenital cytomegalovirus or asymptomatic
HIV	Transplacental, vaginal passage, breast milk	Congenital acquired immunodeficiency syndrome
Hepatitis B	Vaginal passage, transplacental, breast milk	Neonatal hepatitis, chronic hepatitis B surface antigen carrier state
Hepatitis C	Transplacental	Uncommon, but neonatal hepatitis, chronic carrier state possible
Lymphocytic choriomeningitis	Transplacental	Fetal, neonatal death; hydrocephalus, chorioretinitis
Herpes simplex type 2 or 1	Transplacental	Congenital herpes simplex virus
	Vaginal passage, ascending	Neonatal encephalitis, disseminated viremia
Varicella-zoster	Transplacental:	
	Early	Congenital anomalies
	Late	Neonatal varicella
Parvovirus	Transplacental	Fetal anemia, hydrops
Coxsackie B	Fecal-oral	Myocarditis, meningitis, hepatitis
Poliomyelitis	Transplacental	Congenital poliomyelitis
Epstein-Barr	Transplacental	Anomalies(?)
Rubeola	Transplacental	Abortion, fetal measles
West Nile	Transplacental	Chorioretinitis, focal cerebral necrosis
Dengue virus	Transplacental	Thrombocytopenia, lymphocytosis
PARASITES		
Toxoplasmosis	Transplacental	Congenital toxoplasmosis or asymptomatic
Malaria	Transplacental	Abortion, prematurity, intrauterine growth restriction
Trypanosomiasis	Transplacental	Congenital Chagas disease
Hookworm	None	Maternal anemia, low birthweight
FUNGI		
Candida	Ascending, cervical	Sepsis, pneumonia, rash
PRION		
Creutzfeldt-Jakob disease	Transplacental, colostrum	Hypothetical route, no long-term data

Table 97-1 Factors That Define an Infant as Being High Risk

DEMOGRAPHIC SOCIAL FACTORS
Maternal age <16 or >40 yr
Illicit drug, alcohol, cigarette use
Poverty
Unmarried
Emotional or physical stress

PAST MEDICAL HISTORY
Genetic disorders
Diabetes mellitus
Hypertension
Asymptomatic bacteriuria
Rheumatologic illness (systemic lupus erythematosus)
Immune-mediated diseases (immunoglobulin G crossing placenta)
Long-term medication (see Tables 96-5 and 96-6 in Chapter 96)

PREVIOUS PREGNANCY
Intrauterine fetal demise
Neonatal death
Prematurity
Intrauterine growth restriction
Congenital malformation
Incompetent cervix
Blood group sensitization, neonatal jaundice
Neonatal thrombocytopenia
Hydrops
Inborn errors of metabolism

PRESENT PREGNANCY
Vaginal bleeding (abruptio placentae, placenta previa)
Sexually transmitted infections (colonization: herpes simplex, group B streptococcus, chlamydia, syphilis, hepatitis B, HIV)
Multiple gestation
Preeclampsia
Premature rupture of membranes
Short interpregnancy time
Poly-/oligohydramnios
Acute medical or surgical illness
Inadequate prenatal care
Familial or acquired hypercoagulable states
Abnormal fetal ultrasonographic findings
Treatment of infertility

LABOR AND DELIVERY
Premature labor (<37 wk)
Postdates pregnancy (≥42 wk)
Fetal distress
Immature lethicin:sphingomyelin ratio; absence of phosphatidylglycerol
Breech presentation
Meconium-stained fluid
Nuchal cord
Cesarean section
Forceps delivery
Apgar score <4 at 1 min

NEONATE
Birthweight <2,500 or >4,000 g
Birth <37 or ≥42 wk of gestation
Small or large for gestational age
Respiratory distress, cyanosis
Congenital malformation
Pallor, plethora, petechiae

Table 96-1 Fetal Diagnosis and Assessment

METHOD	COMMENT(S) AND INDICATION(S)
IMAGING	
Ultrasound (real-time)	Biometry (growth), anomaly (morphology) detection Biophysical profile Amniotic fluid volume, hydrops
Ultrasound (Doppler)	Velocimetry (blood flow velocity) Detection of increased vascular resistance secondary to fetal hypoxia
Embryoscopy	Early diagnosis of limb anomaly
Fetoscopy	Detection of facial, limb, cutaneous anomalies
MRI	Defining of lesions before fetal surgery
FLUID ANALYSIS	
Amniocentesis	Fetal maturity (L:S ratio), karyotype (cytogenetics), biochemical enzyme analysis, molecular genetic DNA diagnosis, bilirubin, or α-fetoprotein determination Bacterial culture, pathogen antigen, or genome detection
Cordocentesis (percutaneous umbilical blood sampling)	Detection of blood type, anemia, hemoglobinopathies, thrombocytopenia, acidosis, hypoxia, polycythemia, immunoglobulin M antibody response to infection Rapid karyotyping and molecular DNA genetic diagnosis Fetal therapy (see Table 96-5)
FETAL TISSUE ANALYSIS	
Chorionic villus biopsy	Karyotype, molecular DNA genetic analysis, enzyme assays
Skin biopsy	Hereditary skin disease*
Liver biopsy	Enzyme assay*
Circulating fetal DNA or cells in maternal blood or plasma	Molecular DNA genetic analysis including microarray analysis, chromosome number, specific gene testing, or genetic sequencing
MATERNAL SERUM α-FETOPROTEIN CONCENTRATION	
Elevated	Twins, neural tube defects (anencephaly, spina bifida), intestinal atresia, hepatitis, nephrosis, fetal demise, incorrect gestational age
Reduced	Trisomies, aneuploidy
MATERNAL CERVIX	
Fetal fibronectin	Indicates risk of preterm birth
Bacterial culture	Identifies risk of fetal infection (group B streptococcus, *Neisseria gonorrhoeae*)
Fluid	Determination of premature rupture of membranes
ANTEPARTUM BIOPHYSICAL MONITORING	
Nonstress test	Fetal distress; hypoxia
Contraction stress test	Fetal distress; hypoxia
Biophysical profile and modified biophysical profile	Fetal distress; hypoxia
Intrapartum fetal heart rate monitoring	See Fig. 96-4

*DNA genetic analysis on chorionic villus samples, amniocytes from amniocentesis, or fetal cells recovered from the maternal circulation may obviate the need for direct fetal tissue biopsy if the gene or genetic marker is available (e.g., the gene for Duchenne muscular dystrophy).
L:S, lecithin:sphingomyelin ratio.

Table 96-2 Biophysical Profile Scoring: Technique and Interpretation

BIOPHYSICAL VARIABLE	NORMAL SCORE (2)	ABNORMAL SCORE (0)
Fetal breathing movements (FBMs)	At least 1 episode of FBM of at least 30 sec duration in 30 min observation	Absence of FBM or no episode ≥30 sec in 30 min
Gross body movement	At least 3 discrete body/limb movements in 30 min (episodes of active continuous movement considered a single movement)	2 or fewer episodes of body/limb movements in 30 min
Fetal tone	At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk Opening and closing of hand considered evidence of normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absence of fetal movement with the hand held in complete or partial deflection
Reactive fetal heart rate (FHR)	At least 2 episodes of FHR acceleration of ≥15 beats/min and at least 15 sec in duration associated with fetal movement in 30 min	Less than 2 episodes of acceleration of FHR or acceleration of <15 beats/min in 30 min
Qualitative amniotic fluid (AF) volume*	At least 1 pocket of AF that measures at least 2 cm in 2 perpendicular planes	Either no AF pockets or a pocket <2 cm in 2 perpendicular planes

*Modification of the criteria for reduced amniotic fluid from less than 1 cm to less than 2 cm would seem reasonable. Ultrasound is used for biophysical assessment of the fetus.
From Creasy RK, Resnik R, Iams JD, editors: Maternal-fetal medicine: principles and practice, *ed 5, Philadelphia, 2004, Saunders.*

Table 96-3 Characteristics of Decelerations of the Fetal Heart Rate

LATE DECELERATION
- Visually apparent, usually symmetric *gradual* decrease and return of the fetal heart rate (FHR) associated with a uterine contraction.
- A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the nadir of the FHR.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively.

EARLY DECELERATION
- Visually apparent, usually symmetric *gradual* decrease and return of the FHR associated with a uterine contraction.
- A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the FHR nadir.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The nadir of the deceleration occurs at the same time as the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively.

VARIABLE DECELERATION
- Visually apparent, *abrupt* decrease in FHR.
- An *abrupt* FHR decrease is defined as duration <30 sec from the onset of the deceleration to the beginning of the FHR nadir of the deceleration.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The decrease in FHR is ≥15 beats/min, lasting ≥15 sec, and <2 min in duration.
- When variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions.

From Macones GA, Hankins GDV, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, Obstet Gynecol *112:661–666, 2008.*

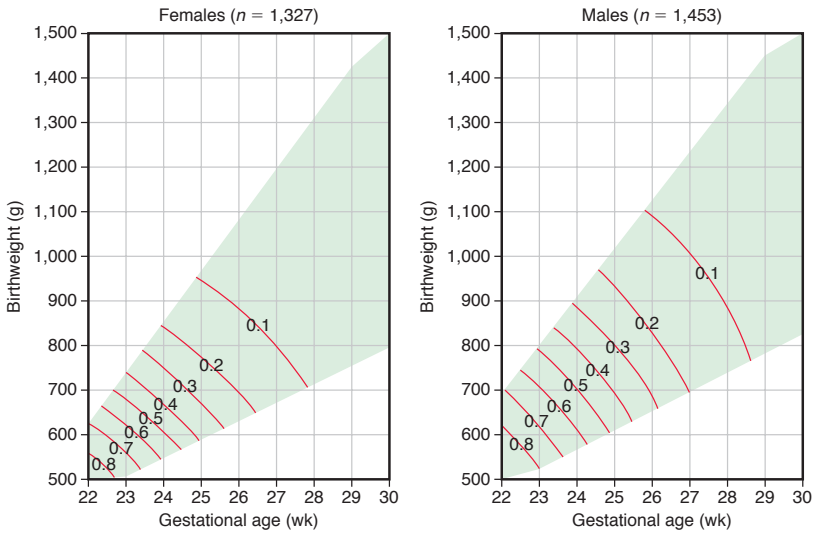


Figure 97-1 Estimated mortality risk by birthweight and gestational age based on singleton infants in National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers between January 1, 1995, and December 31, 1996. *(From Lemons JA, Bauer CR, Oh W, et al: Very low birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996,* Pediatrics *107:E1, 2001; available at* www.pediatrics.org.cgi/content/full/107/1/el.*)*

Table 96-4 Three-Tier Fetal Heart Rate Interpretation System

CATEGORY I
Category I fetal heart rate (FHR) tracings include all of the following:
- Baseline rate: 110-160 beats per minute (beats/min)
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

CATEGORY II
Category II FHR tracings include all FHR tracings not categorized as category I or category III. Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples of category II FHR tracings include any of the following:

Baseline rate
- Bradycardia not accompanied by absence of baseline variability
- Tachycardia

Baseline FHR variability
- Minimal baseline variability
- Absence of baseline variability not accompanied by recurrent decelerations
- Marked baseline variability

Accelerations
- Absence of induced accelerations after fetal stimulation

Periodic or episodic decelerations
- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration, ≥2 min but <10 min
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics, such as slow return to baseline, "overshoots," and "shoulders"

CATEGORY III
Category III FHR tracings include either:
- Absence of baseline FHR variability and any of the following:
- Recurrent late decelerations
- Recurrent variable decelerations
- Bradycardia
- Sinusoidal pattern

Table 96-5 Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn

DRUG	EFFECT ON FETUS
Accutane (isotretinoin)	Facial-ear anomalies, heart disease, CNS anomalies
Alcohol	Congenital cardiac, CNS, limb anomalies; IUGR; developmental delay; attention deficits; autism
Aminopterin	Abortion, malformations
Amphetamines	Congenital heart disease, IUGR, withdrawal
Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists	Oligohydramnios, IUGR, renal failure, Potter-like syndrome
Azathioprine	Abortion
Busulfan (Myleran)	Stunted growth; corneal opacities; cleft palate; hypoplasia of ovaries, thyroid, and parathyroids
Carbamazepine	Spina bifida, possible neurodevelopmental delay
Carbimazole	Scalp defects, choanal atresia, esophageal atresia, developmental delay
Carbon monoxide	Cerebral atrophy, microcephaly, seizures
Chloroquine	Deafness
Chorionic villus sampling	Probably no effect, possibly limb reduction
Cigarette smoking	LBW for gestational age
Cocaine/crack	Microcephaly, LBW, IUGR, behavioral disturbances
Cyclophosphamide	Multiple malformations
Danazol	Virilization
17α-Ethinyl testosterone (Progestoral)	Masculinization of female fetus
Hyperthermia	Spina bifida
Infliximab	Possible increased risk of live vaccine associated disease in infant; neutropenia
Lithium	Ebstein anomaly, macrosomia
Lopinavir-ritonavir	Transient adrenal dysfunction
6-Mercaptopurine	Abortion
Methyl mercury	Minamata disease, microcephaly, deafness, blindness, mental retardation
Methyltestosterone	Masculinization of female fetus
Misoprostol	Arthrogryposis, cranial neuropathies (Möbius syndrome), equinovarus
Mycophenolate mofetil	Craniofacial, limb, cardiovascular, CNS anomalies
Norethindrone	Masculinization of female fetus
Penicillamine	Cutis laxa syndrome
Phenytoin	Congenital anomalies, IUGR, neuroblastoma, bleeding (vitamin K deficiency)
Polychlorinated biphenyls	Skin discoloration—thickening, desquamation, LBW, acne, developmental delay
Prednisone	Oral clefts

Table 96-5 Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn—cont'd

DRUG	EFFECT ON FETUS
Progesterone	Masculinization of female fetus
Quinine	Abortion, thrombocytopenia, deafness
Selective serotonin reuptake inhibitors	Small increased risk of congenital anomalies, persistent pulmonary hypertension of newborn
Statins	IUGR, limb deficiencies, VACTERAL
Stilbestrol (diethylstilbestrol [DES])	Vaginal adenocarcinoma in adolescence
Streptomycin	Deafness
Tetracycline	Retarded skeletal growth, pigmentation of teeth, hypoplasia of enamel, cataract, limb malformations
Thalidomide	Phocomelia, deafness, other malformations
Toluene (solvent abuse)	Craniofacial abnormalities, prematurity, withdrawal symptoms, hypertonia
Topiramate	Cleft lip
Trimethadione and paramethadione	Abortion, multiple malformations, mental retardation
Valproate	CNS (spina bifida), facial and cardiac anomalies, limb defects, impaired neurologic function, autism spectrum disorder
Vitamin D	Supravalvular aortic stenosis, hypercalcemia
Warfarin (Coumadin)	Fetal bleeding and death, hypoplastic nasal structures

Table 96-6 Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant*

Acebutolol—IUGR, hypotension, bradycardia
Acetazolamide—metabolic acidosis
Amiodarone—bradycardia, hypothyroidism
Anesthetic agents (volatile)—CNS depression
Adrenal corticosteroids—adrenocortical failure (rare)
Ammonium chloride—acidosis (clinically inapparent)
Aspirin—neonatal bleeding, prolonged gestation
Atenolol—IUGR, hypoglycemia
Baclofen—withdrawal
Blue cohosh herbal tea—neonatal heart failure
Bromides—rash, CNS depression, IUGR
Captopril, enalapril—transient anuric renal failure, oligohydramnios
Caudal-paracervical anesthesia with mepivacaine (accidental introduction of anesthetic into scalp of baby)—bradypnea, apnea, bradycardia, convulsions
Cholinergic agents (edrophonium, pyridostigmine)—transient muscle weakness
CNS depressants (narcotics, barbiturates, benzodiazepines) during labor—CNS depression, hypotonia
Cephalothin—positive direct Coombs test reaction
Dexamethasone—periventricular leukomalacia
Fluoxetine and other SSRIs—transient neonatal withdrawal, hypertonicity, minor anomalies, preterm birth, prolonged QT interval
Haloperidol—withdrawal
Hexamethonium bromide—paralytic ileus
Ibuprofen—oligohydramnios, pulmonary hypertension
Imipramine—withdrawal
Indomethacin—oliguria, oligohydramnios, intestinal perforation, pulmonary hypertension
Intravenous fluids during labor (e.g., salt-free solutions)—electrolyte disturbances, hyponatremia, hypoglycemia
Iodide (radioactive)—goiter
Iodides—goiter
Lead—reduced intellectual function
Magnesium sulfate—respiratory depression, meconium plug, hypotonia
Methimazole—goiter, hypothyroidism
Morphine and its derivatives (addiction)—withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)
Naphthalene—hemolytic anemia (in G6PD-deficient infants)
Nitrofurantoin—hemolytic anemia (in G6PD-deficient infants)
Oxytocin—hyperbilirubinemia, hyponatremia
Phenobarbital—bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation
Primaquine—hemolytic anemia (in G6PD-deficient infants)
Propranolol—hypoglycemia, bradycardia, apnea

Continued

Table 96-6 Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant—cont'd

Propylthiouracil—goiter, hypothyroidism
Pyridoxine—seizures
Reserpine—drowsiness, nasal congestion, poor temperature stability
Sulfonamides—interfere with protein binding of bilirubin; kernicterus at low levels of serum bilirubin, hemolysis with G6PD deficiency
Sulfonylurea agents—refractory hypoglycemia
Sympathomimetic (tocolytic β-agonist) agents—tachycardia
Thiazides—neonatal thrombocytopenia (rare)
Tumor necrosis factor blocking agents—neutropenia
Valproate—developmental delay
Zolpidem (Ambien)—low birthweight

*See also Table 96-5.
CNS, central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; SSRI, selective serotonin reuptake inhibitor.

Table 99-5 HIE in Term Infants

SIGNS	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalographic findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr-14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

Table 96-7 Significance of Fetal Ultrasonographic Anatomic Findings

PRENATAL OBSERVATION	DEFINITION	DIFFERENTIAL DIAGNOSIS	SIGNIFICANCE	POSTNATAL EVALUATION
Dilated cerebral ventricles	Ventriculomegaly ≥10 mm	Hydrocephalus Hydranencephalous Dandy-Walker cyst Agenesis of corpus callosum	Transient isolated ventriculomegaly is common and usually benign Persistent or progressive ventriculomegaly more worrisome Identify associated cranial and extracranial anomalies Bilateral ventriculomegaly increases risk of developmental delay Unilateral ventriculomegaly may be normal variant	Serial head US or CT Evaluate for extracranial anomalies
Choroid plexus cysts	Size ~10 mm: unilateral or bilateral 1-3% incidence	Abnormal karyotype (trisomy 18, 21) Aneuploidy risk 1:100 if isolated. ↑ Risk (1:3) with other anomalies. Risk ↑ if large, complex, or bilateral cysts or advanced maternal age	Often isolated, benign; resolves by 24-28 wk Fetus should be examined for other organ anomalies; then amniocentesis should be performed for karyotype	Head US or CT Examine for extracranial anomalies; karyotype if indicated
Nuchal pad thickening	≥6 mm at 15-20 wk	Cystic hygroma trisomy 21, 18 Turner syndrome (XO) Nonchromosomal syndromes Normal (~25%)	≈50% of affected fetuses have chromosome abnormalities Amniocentesis for karyotype needed	Evaluate for multiple organ malformations; karyotype if indicated
Dilated renal pelvis	Pyelectasis ≥5 to 10 mm 0.6-1% incidence	Uteropelvic junction obstruction Vesicoureteral reflux Posterior ureteral valves Entopic ureterocele Large-volume nonobstruction	Often "physiologic" and transient Reflux is common If dilation is >10 mm or associated with caliectasis, pathologic cause should be considered If large bladder present, posterior urethral valves and megacystics-megaduodenum syndrome should be considered	Repeat ultrasonography on day 5 and at 1 mo; voiding cystourethrogram, prophylactic antibiotics
Echogenic bowel	0.6% incidence	CF, meconium peritonitis, trisomy 21 or 18, other chromosomal abnormalities cytomegalovirus, toxoplasmosis, GI obstruction	Often normal (65%) 10% of affected fetuses have CF; 1.5% have aneuploidy	Sweat chloride and DNA testing Karyotype Surgery for obstruction Evaluation for TORCH (toxoplasmosis, other agents, rubella, CMV, herpes simplex) syndrome
Stomach appearance	Small or absent or with double bubble	Upper GI obstruction (esophageal atresia) Double bubble signifies duodenal atresia Abnormal karyotype Polyhydramnios Stomach in chest signifies diaphragmatic hernia	Must also consider neurologic disorders that reduce swallowing Over 30% with double bubble have trisomy 21	Chromosomes, kidney, ureter, and bladder radiograph if indicated, upper GI series, neurologic evaluation

Table 99-2 Multiorgan Systemic Effects of Asphyxia

SYSTEM	EFFECT(S)
CNS	HIE, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stunning, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, RDS
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integument	Subcutaneous fat necrosis
Hematology	Disseminated intravascular coagulation

Table 96-8 Fetal Therapy

DISORDER	POSSIBLE TREATMENT
HEMATOLOGIC	
Anemia with hydrops (erythroblastosis fetalis)	Umbilical vein packed red blood cell transfusion
Thalassemia	Fetal stem cell transplantation
Isoimmune thrombocytopenia	Umbilical vein platelet transfusion, maternal IVIG
Autoimmune thrombocytopenia (ITP)	Maternal steroids and IVIG
Chronic granulomatous disease	Fetal stem cell transplantation
METABOLIC-ENDOCRINE	
Maternal phenylketonuria (PKU)	Phenylalanine restriction
Fetal galactosemia	Galactose-free diet (?)
Multiple carboxylase deficiency	Biotin if responsive
Methylmalonic acidemia	Vitamin B_{12} if responsive
21-Hydroxylase deficiency	Dexamethasone
Maternal diabetes mellitus	Tight insulin control during pregnancy, labor, and delivery
Fetal goiter	Maternal hyperthyroidism—maternal propylthiouracil Fetal hypothyroidism—intra-amniotic thyroxine
Bartter syndrome	Maternal indomethacin may prevent nephrocalcinosis and postnatal sodium losses
Neonatal iron storage disease (alloimmune)	Maternal IVIG
FETAL DISTRESS	
Hypoxia	Maternal oxygen, position
Intrauterine growth restriction	Maternal oxygen, position, improve macronutrients and micronutrients if deficient
Oligohydramnios, premature rupture of membranes with variable deceleration	Amnioinfusion (antepartum and intrapartum)
Polyhydramnios	Amnioreduction (serial), indomethacin (if from increased urine output) if indicated
Supraventricular tachycardia	Maternal digoxin,* flecainide, procainamide, amiodarone, quinidine
Lupus anticoagulant	Maternal aspirin, prednisone
Meconium-stained fluid	Amnioinfusion
Congenital heart block	Dexamethasone, pacemaker (with hydrops)
Premature labor	Magnesium sulfate, antibiotics sympathomimetics, indomethacin
RESPIRATORY	
Pulmonary immaturity	Betamethasone
Bilateral chylothorax—pleural effusions	Thoracentesis, pleuroamniotic shunt
CONGENITAL ABNORMALITIES†	
Neural tube defects	Folate, vitamins (prevention); fetal surgery‡
Posterior urethral valves, urethral atresia (lower urinary tract obstruction)	Percutaneous vesicoamniotic shunt
Cystic adenomatoid malformation (with hydrops)	Pleuroamniotic shunt or resection‡
Fetal neck masses	Secure an airway with EXIT procedure‡
INFECTIOUS DISEASE	
Group B streptococcus colonization	Ampicillin, penicillin
Chorioamnionitis	Antibiotics
Toxoplasmosis	Spiramycin, pyrimethamine, sulfadiazine, and folic acid
Syphilis	Penicillin
Tuberculosis	Antituberculosis drugs
Lyme disease	Penicillin, ceftriaxone
Parvovirus	Intrauterine red blood cell transfusion for hydrops, severe anemia
Chlamydia trachomatis	Erythromycin
HIV-AIDS	Maternal and neonatal antiretroviral therapy (see Chapter 276)
Cytomegalovirus	Ganciclovir by umbilical vein

Continued

Table 96-8 Fetal Therapy

DISORDER	POSSIBLE TREATMENT
OTHER	
Nonimmune hydrops (anemia)	Umbilical vein packed red blood cell transfusion
Narcotic abstinence (withdrawal)	Maternal low-dose methadone
Severe combined immunodeficiency disease	Fetal stem cell transplantation
Sacrococcygeal teratoma (with hydrops)	In utero resection or catheter directed vessel obliteration
Twin-twin transfusion syndrome	Repeated amniocentesis, yttrium-aluminum-garnet (YAG) laser photocoagulation of shared vessels
Twin reversed arterial perfusion (TRAP) syndrome	Digoxin, indomethacin, cord occlusion
Multifetal gestation	Selective reduction
Neonatal hemochromatosis	Maternal IVIG

*Drug of choice (may require percutaneous umbilical cord sampling and umbilical vein administration if hydrops is present). Most drug therapy is given to the mother, with subsequent placental passage to the fetus.
†Detailed fetal ultrasonography is needed to detect other anomalies; karyotype is also indicated.
‡EXIT permits surgery and other procedures.
EXIT, ex utero intrapartum treatment; IVIG, intravenous immunoglobulin; (?), possible but not proved efficacy.

Table 97-3 Identifiable Causes of Preterm Birth

FETAL
Fetal distress
Multiple gestation
Erythroblastosis
Nonimmune hydrops
PLACENTAL
Placental dysfunction
Placenta previa
Abruptio placentae
UTERINE
Bicornuate uterus
Incompetent cervix (premature dilation)
MATERNAL
Preeclampsia
Chronic medical illness (cyanotic heart disease, renal disease)
Infection (*Listeria monocytogenes*, group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis)
Drug abuse (cocaine)
OTHER
Premature rupture of membranes
Polyhydramnios
Iatrogenic
Trauma

Table 97-4 Factors Often Associated with Intrauterine Growth Restriction

FETAL
Chromosomal disorders
Chronic fetal infections (cytomegalic inclusion disease, congenital rubella, syphilis)
Congenital anomalies—syndrome complexes
Irradiation
Multiple gestation
Pancreatic hypoplasia
Insulin deficiency (production or action of insulin)
Insulin-like growth factor type I deficiency
PLACENTAL
Decreased placental weight, cellularity, or both
Decrease in surface area
Villous placentitis (bacterial, viral, parasitic)
Infarction
Tumor (chorioangioma, hydatidiform mole)
Placental separation
Twin transfusion syndrome
MATERNAL
Toxemia
Hypertension or renal disease, or both
Hypoxemia (high altitude, cyanotic cardiac or pulmonary disease)
Malnutrition (micronutrient or macronutrient deficiencies)
Chronic illness
Sickle cell anemia
Drugs (narcotics, alcohol, cigarettes, cocaine, antimetabolites)

Table 98-3 Common Life-Threatening Congenital Anomalies

NAME	MANIFESTATIONS
Choanal atresia	Respiratory distress in delivery room, nasogastric tube cannot be passed through nares Suspect CHARGE (coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies) syndrome
Pierre Robin syndrome Stickler syndrome	Micrognathia, cleft palate, airway obstruction
Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in chest, respiratory distress
Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation, nasogastric tube cannot be placed in stomach Suspect VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia) syndrome
Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention Suspect trisomy 21, cystic fibrosis, cocaine
Gastroschisis, omphalocele	Polyhydramnios, intestinal obstruction
Renal agenesis, Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
Neural tube defects: anencephalus, meningomyelocele	Polyhydramnios, elevated α-fetoprotein, decreased fetal activity
Ductus-dependent congenital heart disease	Cyanosis, hypotension, murmur

Table 98-2 Pain in the Neonate: General Considerations

- Pain in newborns is often unrecognized and/or undertreated.
- If a procedure is painful in adults, it should be considered painful in newborns.
- Healthcare institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.
- Pharmacologic agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Educational programs to increase the skills of healthcare professionals in the assessment and management of stress and pain in neonates should be provided.
- Further research is needed to develop and validate neonatal pain assessment tools that are useful in the clinical setting; to determine optimal behavioral and pharmacologic interventions; and to study long-term effects of pain and pain management.

Adapted from Prevention and management of pain and stress in the neonate: American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee, Pediatrics *105:454–461, 2000; and Anand KJS; International Evidence-Based Group for Neonatal Pain: Consensus statement for the prevention and management of pain in the newborn,* Arch Pediatr Adolesc Med *155:173–180, 2001.*

Table 97-5 Problems of Infants Small for Gestational Age or with Intrauterine Growth Retardation*

PROBLEM	PATHOGENESIS
Intrauterine fetal demise	Hypoxia, acidosis, infection, lethal anomaly
Perinatal asphyxia	↓ Uteroplacental perfusion during labor ± chronic fetal hypoxia–acidosis; meconium aspiration syndrome
Hypoglycemia	↓ Tissue glycogen stores, ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, large brain
Polycythemia–hyperviscosity	Fetal hypoxia with ↑ erythropoietin production
Reduced oxygen consumption/hypothermia	Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores
Dysmorphology	Syndrome anomalads, chromosomal-genetic disorders, oligohydramnios-induced deformation, TORCH (*toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex*) infection

*Other problems include pulmonary hemorrhage and those common to the gestational age-related risks of prematurity if born at less than 37 wk.
↓, Decreased; ↑, increased.

Table 97-6 Neonatal Problems Associated with Premature Infants

RESPIRATORY
Respiratory distress syndrome (hyaline membrane disease)*
Bronchopulmonary dysplasia
Pneumothorax, pneumomediastinum; interstitial emphysema
Congenital pneumonia
Apnea*

CARDIOVASCULAR
Patent ductus arteriosus*
Hypotension
Bradycardia (with apnea)*

HEMATOLOGIC
Anemia (early or late onset)

GASTROINTESTINAL
Poor gastrointestinal function—poor motility*
Necrotizing enterocolitis
Hyperbilirubinemia—direct and indirect*
Spontaneous gastrointestinal isolated perforation

METABOLIC-ENDOCRINE
Hypocalcemia*
Hypoglycemia*
Hyperglycemia*
Late metabolic acidosis
Hypothermia*
Euthyroid but low thyroxine status
Osteopenia

CENTRAL NERVOUS SYSTEM
Intraventricular hemorrhage*
Periventricular leukomalacia
Seizures
Retinopathy of prematurity
Deafness
Hypotonia*

RENAL
Hyponatremia*
Hypernatremia*
Hyperkalemia*
Renal tubular acidosis
Renal glycosuria
Edema

OTHER
Infections* (congenital, perinatal, nosocomial: bacterial, viral, fungal, protozoal)

*Common.

Neuromuscular maturity

	−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							

Figure 97-6 Neuromuscular criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants,* J Pediatr *119:417–423, 1991.)*

Physical maturity

	−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 on ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola–no bud	Stripped 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	Slightly 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, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Figure 97-5 Physical criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants.

Score	Weeks
– 10	20
– 5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Maturity Rating

Figure 97-7 Maturity rating. The physical and neurologic scores are added to calculate gestational age.

Table 97-7 Potential Adverse Reactions to Drugs Administered to Premature Infants

DRUG	REACTION(S)
Oxygen	Retinopathy of prematurity, bronchopulmonary dysplasia
Sulfisoxazole	Kernicterus
Chloramphenicol	Gray baby syndrome—shock, bone marrow suppression
Vitamin K analogs	Jaundice
Novobiocin	Jaundice
Hexachlorophene	Encephalopathy
Benzyl alcohol	Acidosis, collapse, intraventricular bleeding
Intravenous vitamin E	Ascites, shock
Phenolic detergents	Jaundice
$NaHCO_3$	Intraventricular hemorrhage
Amphotericin	Anuric renal failure, hypokalemia, hypomagnesemia
Reserpine	Nasal stuffiness
Indomethacin	Oliguria, hyponatremia, intestinal perforation
Cisapride	Prolonged QTc interval
Tetracycline	Enamel hypoplasia
Tolazoline	Hypotension, gastrointestinal bleeding
Calcium salts	Subcutaneous necrosis
Aminoglycosides	Deafness, renal toxicity
Enteric gentamicin	Resistant bacteria
Prostaglandins	Seizures, diarrhea, apnea, hyperostosis, pyloric stenosis
Phenobarbital	Altered state, drowsiness
Morphine	Hypotension, urine retention, withdrawal
Pancuronium	Edema, hypovolemia, hypotension, tachycardia, vecuronium contractions, prolonged hypotonia
Iodine antiseptics	Hypothyroidism, goiter
Fentanyl	Seizures, chest wall rigidity, withdrawal
Dexamethasone	Gastrointestinal bleeding, hypertension, infection, hyperglycemia, cardiomyopathy, reduced growth
Furosemide	Deafness, hyponatremia, hypokalemia, hypochloremia, nephrocalcinosis, biliary stones
Heparin (not low-dose prophylactic use)	Bleeding, intraventricular hemorrhage, thrombocytopenia
Erythromycin	Pyloric stenosis

Table 97-8 Sequelae of Low Birthweight

IMMEDIATE	LATE
Hypoxia, ischemia	Mental retardation, spastic diplegia, microcephaly, seizures, poor school performance
Intraventricular hemorrhage	Mental retardation, spasticity, seizures, hydrocephalus
Sensorineural injury	Hearing, visual impairment, retinopathy of prematurity, strabismus, myopia
Respiratory failure	Bronchopulmonary dysplasia, cor pulmonale, bronchospasm, malnutrition, subglottic stenosis
Necrotizing enterocolitis	Short-bowel syndrome, malabsorption, malnutrition, infectious diarrhea
Cholestatic liver disease	Cirrhosis, hepatic failure, malnutrition
Nutrient deficiency	Osteopenia, fractures, anemia, growth failure
Social stress	Child abuse or neglect, failure to thrive, divorce
Other	Sudden infant death syndrome, infections, inguinal hernia, cutaneous scars (chest tube, patent ductus arteriosus ligation, intravenous infiltration), gastroesophageal reflux, hypertension, craniosynostosis, cholelithiasis, nephrocalcinosis, cutaneous hemangiomas

Table 101-1 Potential Causes of Neonatal Apnea and Bradycardia

Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), spinal cord injury after general anesthesia
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center, sleep state

Table 98-1	Differential Diagnosis of Cyanosis in the Newborn
CENTRAL OR PERIPHERAL NERVOUS SYSTEM HYPOVENTILATION	
Birth asphyxia	
Intracranial hypertension, hemorrhage	
Oversedation (direct or through maternal route)	
Diaphragm palsy	
Neuromuscular diseases	
Seizures	
RESPIRATORY DISEASE	
Airway	
Choanal atresia/stenosis	
Pierre Robin syndrome	
Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)	
Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)	
Lung	
Respiratory distress syndrome	
Transient tachypnea	
Meconium aspiration	
Pneumonia (sepsis)	
Pneumothorax	
Congenital diaphragmatic hernia	
Pulmonary hypoplasia	
CARDIAC RIGHT-TO-LEFT SHUNT	
Abnormal connections (pulmonary blood flow normal or increased)	
Transposition of great vessels	
Total anomalous pulmonary venous return	
Truncus arteriosus	
Hypoplastic left heart syndrome	
Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis	
Obstructed pulmonary blood flow (pulmonary blood flow decreased)	
Pulmonic atresia with intact ventricular septum	
Tetralogy of Fallot	
Critical pulmonic stenosis with patent foramen ovale or atrial septal defect	
Tricuspid atresia	
Single ventricle with pulmonic stenosis	
Ebstein malformation of the tricuspid valve	
Persistent fetal circulation (persistent pulmonary hypertension of newborn)	
METHEMOGLOBINEMIA	
Congenital (hemoglobin M, methemoglobin reductase deficiency)	
Acquired (nitrates, nitrites)	
Inadequate ambient O_2 or less O_2 delivered than expected (rare)	
Disconnection of O_2 supply to nasal cannula, head hood	
Connection of air, rather than O_2, to a mechanical ventilator	
SPURIOUS/ARTIFACTUAL	
Oximeter artifact (poor contact between probe and skin, poor pulse searching)	
Arterial blood gas artifact (contamination with venous blood)	
OTHER	
Hypoglycemia	
Adrenogenital syndrome	
Polycythemia	
BLOOD LOSS	

Table 97-9	Readiness for Discharge of High-Risk Infants Criteria
Resolution of acute life-threatening illnesses	
Ongoing follow-up for chronic but stable problems:	
Bronchopulmonary dysplasia	
Intraventricular hemorrhage	
Necrotizing enterocolitis after surgery or recovery	
Ventricular septal defect, other cardiac lesions	
Anemia	
Retinopathy of prematurity	
Hearing problems	
Apnea	
Cholestasis	
Stable temperature regulation	
Gain of weight with oral feedings:	
Breastfeeding	
Bottle-feeding	
Gastric tube	
Free of significant apnea; home monitoring for apnea if needed	
Appropriate immunizations and planning for respiratory syncytial virus prophylaxis if indicated	
Hearing screenings	
Ophthalmologic examination if <27 wk of gestation or <1,250 g at birth	
Mother's knowledge, skill, confidence documented in:	
Administration of medications (diuretics, methylxanthines, aerosols, etc.)	
Use of oxygen, apnea monitors, oximeters	
Nutritional support:	
Timing	
Volume	
Mixing concentrated formulas	
Recognition of illness and deterioration	
Basic cardiopulmonary resuscitation	
Infant safety (see Table 97-1)	
Scheduling of referrals:	
Primary care provider	
Neonatal follow-up clinic	
Occupational therapy/physical therapy	
Imaging (head ultrasound)	
Assessment of and solution to social risks (see Table 97-1)	

Adapted from American Academy of Pediatrics, American College of Obstetricians: Guidelines for perinatal care, *ed 7, Elk Grove Village, IL, 2013, American Academy of Pediatrics.*

Table 101-1	Potential Causes of Neonatal Apnea and Bradycardia
Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), spinal cord injury after general anesthesia
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center, sleep state

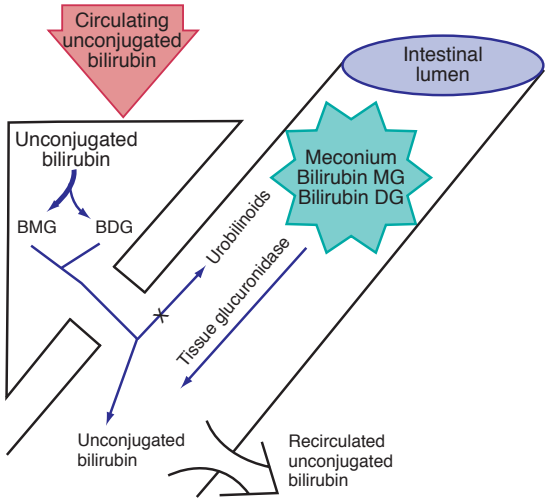


Figure 102-6 The neonatal production rate of bilirubin is 6-8 mg/kg/24 hr (in contrast to 3-4 mg/kg/24 hr in adults). Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (bilitranslocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione S-transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults do. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucuronide (BDG) must be deconjugated by tissue β-glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

Table 102-2 Risk Factors for Development of Severe Hyperbilirubinemia in Infants ≥35 Wk of Gestation (in Approximate Order of Importance)

MAJOR RISK FACTORS
Predischarge TSB or TcB level in the high-risk zone (see Fig. 102-8)
Jaundice observed in the 1st 24 hr
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (glucose-6-phosphate dehydrogenase deficiency), elevated end-title CO concentration
Gestational age 35-36 wk
Previous sibling received phototherapy
Cephalohematoma or significant bruising
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
East Asian race*
MINOR RISK FACTORS
Predischarge TSB or TcB level in the high intermediate-risk zone
Gestational age 37-38 wk
Jaundice observed before discharge
Previous sibling with jaundice
Macrosomic infant of a diabetic mother
Maternal age ≥25 yr
Male gender
DECREASED RISK (THESE FACTORS ARE ASSOCIATED WITH DECREASED RISK OF SIGNIFICANT JAUNDICE, LISTED IN ORDER OF DECREASING IMPORTANCE)
TSB or TcB level in the low-risk zone (see Fig. 102-8)
Gestational age ≥41 wk
Exclusive bottle-feeding
Black race
Discharge from hospital after 72 hr

*Race as defined by mother's description.
TcB, transcutaneous bilirubin; TSB, total serum bilirubin.
From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics *114:297–316, 2004.*

Table 102-3 Laboratory Evaluation of the Jaundiced Infant ≥35 Wk of Gestation

INDICATIONS	ASSESSMENTS
Jaundice in 1st 24 hr	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (i.e., crossing percentiles [see Fig. 102-8]) and unexplained by history and physical examination	Blood type and Coombs test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin It is an option to perform reticulocyte count, G6PD, and $ETCO_c$, if available Repeat TSB in 4-24 hr depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, ETCO if available
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism

$ETCO_c$, end tidal carbon monoxide concentration; G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.
From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics *114:297–316, 2004.*

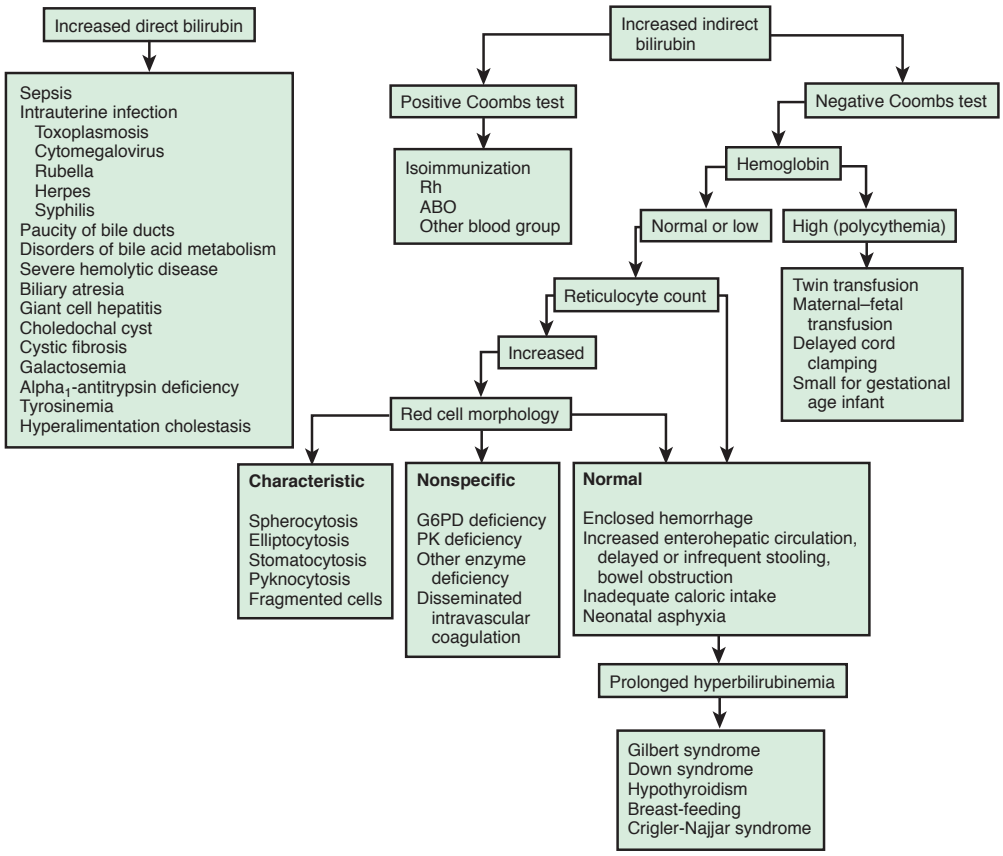


Figure 102-7 Schematic approach to the diagnosis of neonatal jaundice. G6PD, glucose-6-phosphate dehydrogenase; PK, pyruvate kinase. *(From Oski FA: Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, editors:* Schaffer and Avery's diseases of the newborn, *ed 6, Philadelphia, 1991, WB Saunders.)*

Table 101-2 Definition of BPD: Diagnostic Criteria*

	GESTATIONAL AGE	
	<32 Wk	**≥32 Wk**
Time point of assessment	36 wk postmenstrual age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**	>28 days but <56 days postnatal age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**
Mild BPD	Breathing room air at 36 wk postmenstrual age or discharge home, whichever comes first	Breathing room air by 56 days postnatal age or discharge home, whichever comes first
Moderate BPD	Need† for <30% oxygen at 36 wk postmenstrual age or discharge home, whichever comes first	Need† for <30% oxygen at 56 days postnatal age or discharge home, whichever comes first
Severe BPD	Need† for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk postmenstrual age or discharge home, whichever comes first	Need† for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge home, whichever comes first

*BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most commonly respiratory distress syndrome. Persistence of the clinical features of respiratory disease (tachypnea, retractions, crackles) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with >21% oxygen and/or PPV for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless parenchymal lung disease also develops and they have clinical features of respiratory distress. A day of treatment with >21% oxygen means that the infant received >21% oxygen for more than 12 hr on that day. Treatment with >21% oxygen and/or PPV at 36 wk postmenstrual age or at 56 days postnatal age or discharge should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and after 36 wk postmenstrual age, 56 days postnatal age, or discharge.

†A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

BPD, bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; PPV, positive-pressure ventilation.

From Jobe AH, Bancalari E: Bronchopulmonary dysplasia, Am J Respir Crit Care Med *163:1723–1729, 2001.*

Table 102-4 Diagnostic Features of the Various Types of Neonatal Jaundice

DIAGNOSIS	NATURE OF VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	REMARKS
		Appears	Disappears	mg/dL	Age in Days		
"Physiologic jaundice":							Usually relates to degree of maturity
Full-term	Indirect	2-3 days	4-5 days	10-12	2-3	<5	
Premature	Indirect	3-4 days	7-9 days	15	6-8	<5	
Hyperbilirubinemia caused by metabolic factors:							Metabolic factors: hypoxia, respiratory distress, lack of carbohydrate
Full-term	Indirect	2-3 days	Variable	>12	1st wk	<5	Hormonal influences: cretinism, hormones, Gilbert syndrome
Premature	Indirect	3-4 days	Variable	>15	1st wk	<5	Genetic factors: Crigler-Najjar syndrome, Gilbert syndrome Drugs: vitamin K, novobiocin
Hemolytic states and hematoma	Indirect	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Erythroblastosis: Rh, ABO, Kell congenital hemolytic states: spherocytic, nonspherocytic Infantile pyknocytosis Drug: vitamin K Enclosed hemorrhage—hematoma
Mixed hemolytic and hepatotoxic factors	Indirect and direct	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Infection: bacterial sepsis, pyelonephritis, hepatitis, toxoplasmosis, cytomegalic inclusion disease, rubella, syphilis Drug: vitamin K
Hepatocellular damage	Indirect and direct	Usually 2-3 days; may appear by 2nd wk	Variable	Unlimited	Variable	Variable, can be >5	Biliary atresia; paucity of bile ducts, familial cholestasis, galactosemia; hepatitis and infection

Table 103-2 Transfusion Protocol

HEMATOCRIT (%)	HEMOGLOBIN (g/dL)	RESPIRATORY SUPPORT AND/OR SYMPTOMS	TRANSFUSION VOLUME
≤35	≤11	Infants requiring moderate or significant mechanical ventilation (mean arterial pressure >8 cm H_2O and FIO_2 >0.4)	15 mL/kg PRBCs* over 2-4 hr
≤30	≤10	Infants requiring minimal respiratory support (any mechanical ventilation or endotracheal/nasal continuous positive airway pressure >6 cm H_2O and FIO_2 ≤0.4)	15 mL/kg PRBCs over 2-4 hr
≤25	≤8	Infants not requiring mechanical ventilation but who are receiving supplemental O_2 or CPAP with an FIO_2 ≤0.4 and in whom 1 or more of the following is present: • ≤24 hr of tachycardia (heart rate >180 beats/min) or tachypnea (respiratory rate >80 breaths/min) • An increased oxygen requirement from the previous 48 hr, defined as a ≥4-fold increase in nasal canula flow (i.e., from 0.25 to 1 L/min) or an increase in nasal CPAP ≥20% from the previous 48 hr (i.e., 5-6 cm H_2O) • Weight gain <10 g/kg/day over the previous 4 days while infant is receiving ≥100 kcal/kg/day • An increase in episodes of apnea and bradycardia (>9 episodes in a 24-hr period or ≥2 episodes in 24 hr requiring bag and mask ventilation) while infant is receiving therapeutic doses of methylxanthines • Undergoing surgery	20 mL/kg PRBCs over 2-4 hr (divide into 2 10-mL/kg volumes if infant is fluid sensitive)
≤20	≤7	Asymptomatic and an absolute reticulocyte count <100,000 cells/μL	20 mL/kg PRBCs over 2-4 hr (2 10-mL/kg volumes)

*RBCs should be irradiated prior to transfusion.
CPAP, continuous positive airway pressure; FIO_2, fractional inspired oxygen; PRBCs, packed red blood cells.
From Ohls RK, Ehrenkranz RA, Wright LL, et al: Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial, Pediatrics *108:934–942, 2001.*

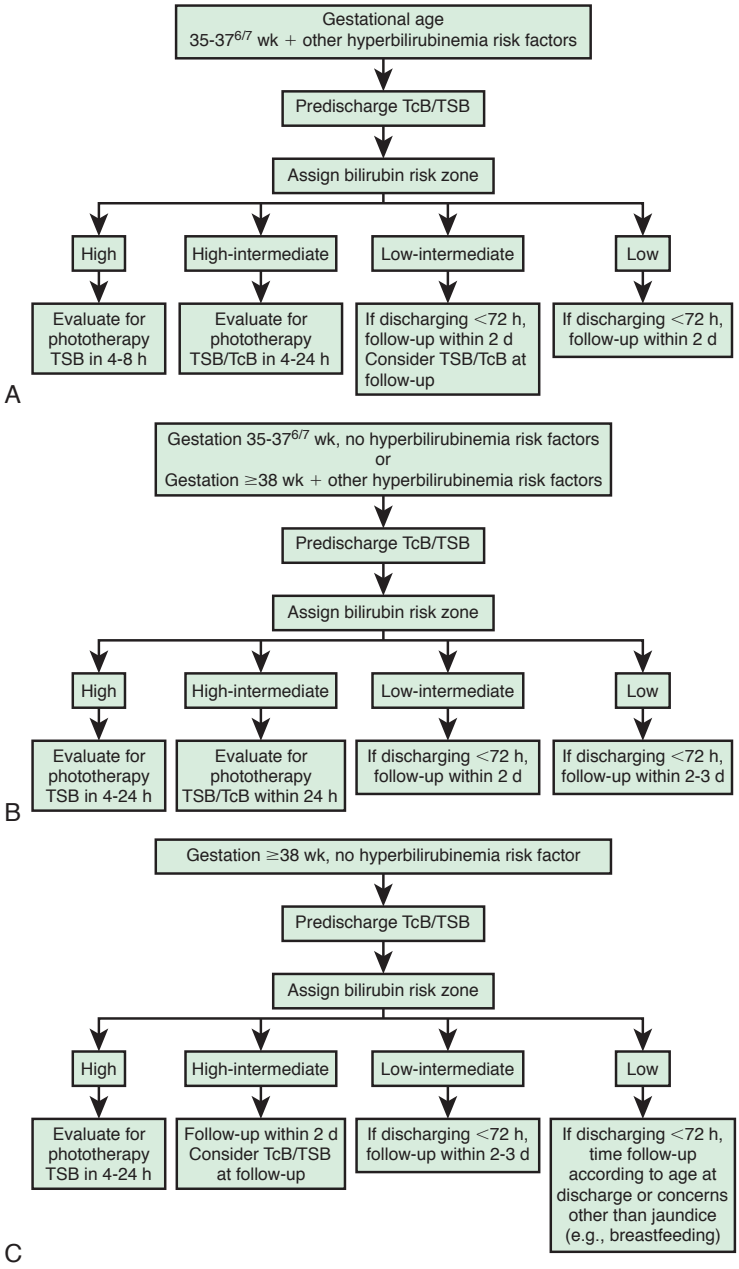


Figure 102-10 Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia. TcB, transcutaneous bilirubin; TSB, total serum bilirubin. *(From Maisels MJ, Bhutani VK, Bogen D, et al: Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: an update with clarifications,* Pediatrics *124:1193–1198, 2009.)*

Table 102-7 Example of a Clinical Pathway for Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion

TREATMENT
Use intensive phototherapy and/or exchange transfusion as indicated in Figs. 102-11 and 102-12
LABORATORY TESTS
TSB and direct bilirubin levels
Blood type (ABO, Rh)
Direct antibody test (Coombs)
Serum albumin
Complete blood cell count with differential and smear for red cell morphology
Reticulocyte count
End-tidal CO concentration (if available)
Glucose-6-phosphate dehydrogenase if suggested by ethnic or geographic origin or if poor response to phototherapy
Urine for reducing substances
If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture
INTERVENTIONS
If TSB ≥25 mg/dL (428 μmol/L) or ≥20 mg/dL (342 μmol/L) in a sick infant or infant <38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary
In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2-3 mg/dL (34-51 μmol/L) of exchange level (see Fig. 102-12), administer intravenous immunoglobulin 0.5-1 g/kg over 2 hr and repeat in 12 hr if necessary
If infant's weight loss from birth is >12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids
FOR INFANTS RECEIVING INTENSIVE PHOTOTHERAPY:
Breastfeed or bottle-feed (formula or expressed breast milk) every 2-3 hr
If TSB ≥25 mg/dL (428 μmol/L), repeat TSB within 2-3 hr
If TSB 20-25 mg/dL (342-428 μmol/L), repeat within 3-4 hr. If TSB <20 mg/dL (342 μmol/L), repeat in 4-6 hr. If TSB continues to fall, repeat in 8-12 hr
If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Fig. 102-12, consider exchange transfusion (see Fig. 102-12 for exchange transfusion recommendations)
When TSB is <13-14 mg/dL (239 μmol/L), discontinue phototherapy
Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 hr after discharge to check for rebound

Table 103-1 Normal Red Blood Cell Values from 18 Wk of Gestation to 14 Wk of Life

AGE	HEMOGLOBIN (g/dL)	HEMATOCRIT (%)	MCV (μ^3)	RETICULOCYTES (%)
GESTATIONAL (WK)				
18-20*	11.5 ± 0.8	36 ± 3	134 ± 8.8	N/A
21-22*	12.3 ± 0.9	39 ± 3	130 ± 6.2	N/A
23-25*	12.4 ± 0.8	39 ± 2	126 ± 6.2	N/A
26-27	19.0 ± 2.5	62 ± 8	132 ± 14.4	9.6 ± 3.2
28-29	19.3 ± 1.8	60 ± 7	131 ± 13.5	7.5 ± 2.5
30-31	19.1 ± 2.2	60 ± 8	127 ± 12.7	5.8 ± 2.0
32-33	18.5 ± 2.0	60 ± 8	123 ± 15.7	5.0 ± 1.9
34-35	19.6 ± 2.1	61 ± 7	122 ± 10.0	3.9 ± 1.6
36-37	19.2 ± 1.7	64 ± 7	121 ± 12.5	4.2 ± 1.8
38-40	19.3 ± 2.2	61 ± 7	119 ± 9.4	3.2 ± 1.4
POSTNATAL (DAYS)				
1	19.0 ± 2.2	61 ± 7	119 ± 9.4	3.2 ± 1.4
2	19.0 ± 1.9	60 ± 6	115 ± 7.0	3.2 ± 1.3
3	18.7 ± 3.4	62 ± 9	116 ± 5.3	2.8 ± 1.7
4	18.6 ± 2.1	57 ± 8	114 ± 7.5	1.8 ± 1.1
5	17.6 ± 1.1	57 ± 7	114 ± 8.9	1.2 ± 0.2
6	17.4 ± 2.2	54 ± 7	113 ± 10.0	0.6 ± 0.2
7	17.9 ± 2.5	56 ± 9	118 ± 11.2	0.5 ± 0.4
POSTNATAL (WK)				
1-2	17.3 ± 2.3	54 ± 8	112 ± 19.0	0.5 ± 0.3
2-3	15.6 ± 2.6	46 ± 7	111 ± 8.2	0.8 ± 0.6
3-4	14.2 ± 2.1	43 ± 6	105 ± 7.5	0.6 ± 0.3
4-5	12.7 ± 1.6	36 ± 5	101 ± 8.1	0.9 ± 0.8
5-6	11.9 ± 1.5	36 ± 6	102 ± 10.2	1.0 ± 0.7
6-7	12.0 ± 1.5	36 ± 5	105 ± 12.0	1.2 ± 0.7
7-8	11.1 ± 1.1	33 ± 4	100 ± 13.0	1.5 ± 0.7
8-9	10.7 ± 0.9	31 ± 3	93 ± 12.0	1.8 ± 1.0
9-10	11.2 ± 0.9	32 ± 3	91 ± 9.3	1.2 ± 0.6
10-11	11.4 ± 0.9	34 ± 2	91 ± 7.7	1.2 ± 0.7
11-12	11.3 ± 0.9	33 ± 3	88 ± 7.9	0.7 ± 0.3
12-14	11.9	37	86.8	0.9

*Based on samples collected in utero. Results expressed as mean value ±1 standard deviation from the mean except for postnatal weeks 12-14 in which only the mean value is given.

From Bizzarro MJ, Colson E, Ehrenkranz RA: Differential diagnosis and management of anemia in the newborn, Pediatr Clin North Am *51:1087–1107, 2004.*

Table 103-3 Etiology of Hydrops Fetalis*

CATEGORY	DISORDER(S)
Anemia	Immune (Rh, Kell) hemolysis α-Thalassemia Red blood cell enzyme deficiencies (glucose-6-phosphate dehydrogenase) Fetomaternal hemorrhage Donor in twin-to-twin transfusion Diamond-Blackfan syndrome
Cardiac dysrhythmias	Supraventricular tachycardia Atrial flutter Congenital heart block
Structural heart lesions	Premature closure of foramen ovale Tricuspid insufficiency Hypoplastic left heart Endocardial cushion defect Cardiomyopathy Endocardial fibroelastosis Tuberous sclerosis with cardiac rhabdomyoma Pericardial teratoma
Vascular	Chorioangioma of placenta, chorionic vessels, or umbilical vessels Umbilical artery aneurysm Angiomyxoma of umbilical cord True knot of umbilical cord Hepatic hemangioma Cerebral arteriovenous malformation (aneurysm of vein of Galen) Angioosteohypertrophy (Klippel-Trénaunay syndrome) Thrombosis of renal or umbilical vein or inferior vena cava Recipient in twin-to-twin transfusion
Lymphatic	Lymphangiectasia Cystic hygroma Chylothorax, chylous ascites Noonan syndrome Multiple pterygium syndrome
Central nervous system	Absent corpus callosum Encephalocele Intracranial hemorrhage Holoprosencephaly
Thoracic lesions	Cystic adenomatoid malformation of lung Mediastinal teratoma Diaphragmatic hernia Sequestered lung
Teratomas	Choriocarcinoma Sacrococcygeal teratoma
Tumors and storage diseases	Neuroblastoma Hepatoblastoma Gaucher disease Niemann-Pick disease Mucolipidosis GM_1 gangliosidosis Mucopolysaccharidosis
Chromosome abnormalities	Trisomy 13, 15, 16, 18, 21 XX/XY, 45XO Partial duplication of chromosomes 11, 15, 17, 18 Partial deletion of chromosomes 13, 18 Triploidy Tetraploidy
Bone diseases	Osteogenesis imperfecta Asphyxiating thoracic dystrophy Skeletal dysplasias
Congenital infections	Cytomegalovirus Parvovirus Rubella Toxoplasmosis Syphilis Leptospirosis Chagas disease
Others	Bowel obstruction with perforation and meconium peritonitis, volvulus Hepatic fibrosis Beckwith-Wiedemann syndrome Prune-belly syndrome Congenital nephrosis Infant of a diabetic mother Myotonic dystrophy Neu-Laxova syndrome Maternal therapy with indomethacin Fetal akinesia
Idiopathic	Multiple congenital anomaly syndromes

*The incidence of nonimmune (nonhemolytic) hydrops fetalis is 1/2,000-1/3,500 live births.
Modified from Phibbs R. In Polin N, Fox W, editors: Fetal and neonatal physiology, *ed 2, Philadelphia, 1998, WB Saunders.*

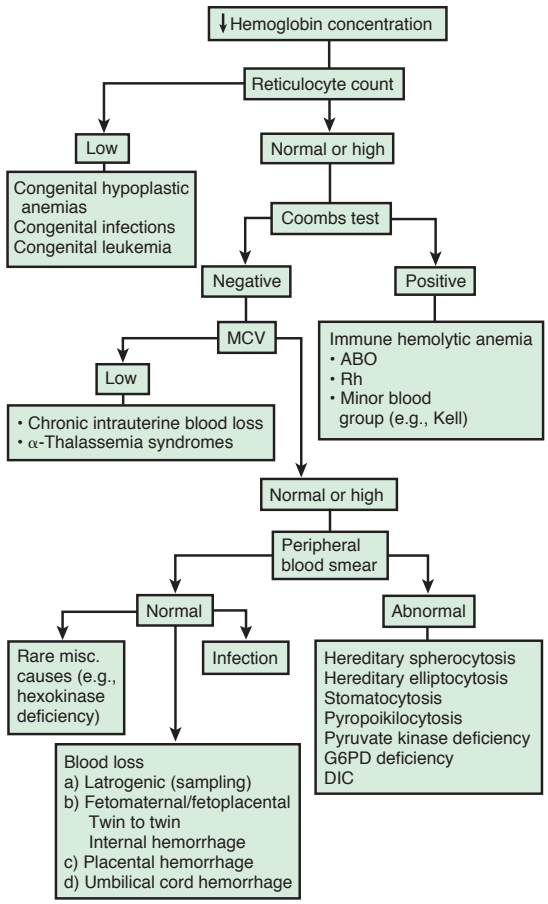


Figure 103-2 Diagnostic approach to anemia in newborn infants. DIC, disseminated intravascular coagulation; G6PD, glucose-6- phosphate dehydrogenase; MCV, mean corpuscular volume.

Table 106-1 Neurobehavioral Scale

DOMAIN	ITEMS
Physiologic	Labored breathing Nasal flaring
Autonomic	Sweating Spit-up Hiccoughing Sneezing Nasal stuffiness Yawning
Central nervous system	Abnormal sucking Choreiform movements Athetoid postures and movements Tremors Cogwheel movements Startles Hypertonia Back arching Fisting Cortical thumb Myoclonic jerks Generalized seizures Abnormal posture
Skin	Pallor Mottling Lividity Overall cyanosis Circumoral cyanosis Periocular cyanosis
Visual	Gaze aversion during orientation Pull-down during orientation Fuss/cry during orientation Obligatory following during orientation End-point nystagmus during orientation Sustained spontaneous nystagmus Visual locking Hyperalertness Setting sun sign Roving eye movements Strabismus Tight blinking Other abnormal eye signs
Gastrointestinal	Gagging/choking Loose stools, watery stools Excessive gas, bowel sounds
State	High-pitched cry Monotone-pitch cry Weak cry No cry Extreme irritability Abrupt state changes Inability to achieve quiet awake state (state 4)

Table 106-2 Pharmacologic Therapy for Neonatal Abstinence Syndrome

DRUG	INITIAL DOSING	DOSING INCREASES	RESCUE DOSING	ADD ADJUVANT THERAPY	WEANING SCHEDULE
Morphine	0.1 mg kg^{-1} $dose^{-1}$ orally every 4 hr	Increase by 20–30% every 12 hr until scores <8 × 24 hr	Repeat previous dose between scheduled dose intervals	At morphine dose of 1.25 mg kg^{-1} $dose^{-1}$, add phenobarbital or clonidine	Decrease by 10% every 24 hr, while scores <8. Discontinue when 0.15 kg^{-1} $dose^{-1}$
Methadone	0.1 mg kg^{-1} $dose^{-1}$ orally every 12 hr	Calculate entire methadone dose for previous 24 hr and divide by two for BID dosing	Additional dosing of 0.025 mg kg^{-1} $dose^{-1}$ every 4 hr while scoring >8. Max dose 0.5 mg kg^{-1} $dose^{-1}$	When max dosing has been reached	Decrease by 10% every 1-2 wk. Discontinue when 0.05 mg kg^{-1} $dose^{-1}$
Buprenorphine	15.9 µg kg^{-1} $dose^{-1}$ divided in 3 doses, orally	Increase by 25%	Max dose 60 µg kg^{-1} $dose^{-1}$		After 3 days of stabilization, decrease by 10% while scores <8. Discontinue when dose is 10% of initial dose
Phenobarbital	20 mg/kg loading	Maintenance dose 5 mg/kg		Adjuvant	
Clonidine	0.5 to 1.5 µg/kg orally	Increase by over 1 to 2 days to target dose 3 to 5 µg kg^{-1} day^{-1}, divided every 4–6 hr		Adjuvant	No taper required

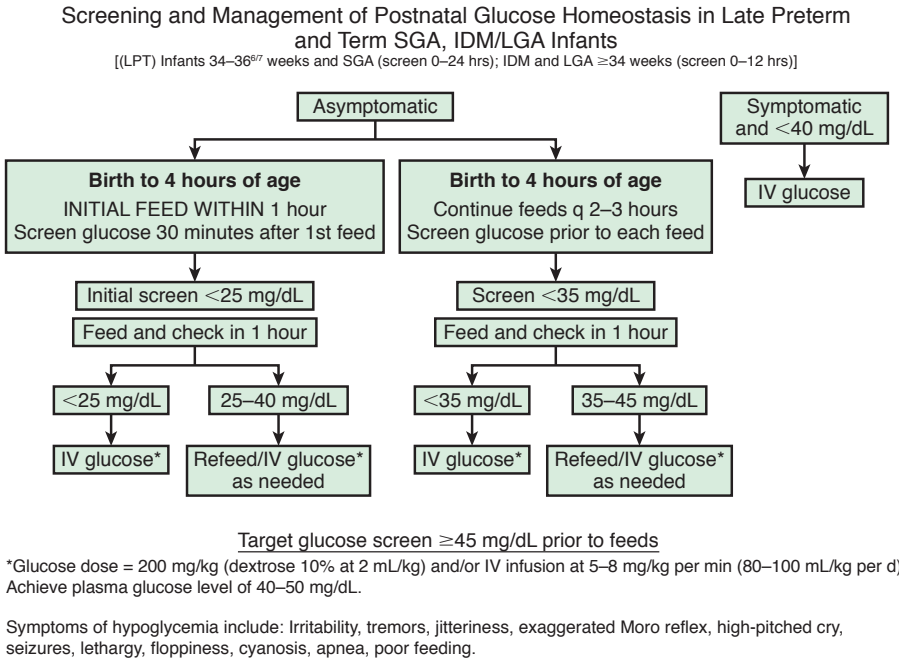


Figure 107-3 Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34-36 wk) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. LPT and SGA, screen 0-24 hr; IDM and LGA ≥34 wk, screen 0-12 hr. IV indicates intravenous.

Table 108-1 Mechanisms, Terminology, and Definitions of Dysmorphology

TERMINOLOGY	DEFINITION	EXAMPLE
Malformation sequence	Single, local tissue morphogenesis abnormality that produces a chain of subsequent defects	DiGeorge sequence of primary fourth branchial arch and 3rd and 4th pharyngeal pouch defects that lead to aplasia or hypoplasia of the thymus and parathyroid glands, aortic arch anomalies, and micrognathia
Deformation sequence	Mechanical (uterine) forces that alter structure of intrinsically normal tissue	Oligohydramnios produces deformations by in utero compression of limbs (dislocated hips, equinovarus foot deformity), crumpled ears, dislocated nose, or small thorax
Disruption sequence	In utero tissue destruction after a period of normal morphogenesis	Amnionic membrane rupture sequence, leading to amputation of fingers/toes, tissue fibrosis, and destructive tissue bands
Dysplasia sequence	Poor organization of cells into tissues or organs	Neurocutaneous melanosis sequence with poor migration of melanocyte precursor cells from the neural crest to the periphery, manifesting as melanocytic hamartosis of skin, meninges, and so forth
Malformation syndrome	Appearance of multiple malformations in unrelated tissues without an understandable unifying cause; with enhanced genetic investigation, a single etiology may become identified	Trisomy 21 Teratogens

Table 109-8 Definitions of Systemic Inflammatory Respiratory Response Syndrome and Sepsis in Pediatric Patients

SIRS: The systemic inflammatory response to a variety of clinical insults, manifested by 2 or more of the following conditions:
- Temperature instability <35°C (95°F) or >38.5°C (101.3°F)
- Respiratory dysfunction:
  - Tachypnea >2 SD above the mean for age
  - Hypoxemia (PaO_2 <70 mm Hg on room air)
- Cardiac dysfunction:
  - Tachycardia >2 SD above the mean for age
  - Delayed capillary refill >3 sec
  - Hypotension >2 SD below the mean for age
- Perfusion abnormalities:
  - Oliguria (urine output <0.5 mL/kg/hr)
  - Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25)
  - Altered mental status

Sepsis: The systemic inflammatory response to an infectious process

Table 108-2 Examples of Malformations with Distinct Causes, Clinical Features, and Pathogenesis

DISORDER	CAUSE/INHERITANCE	CLINICAL FEATURES	PATHOGENESIS
Spondylocostal dysostosis syndromes	Mendelian autosomal recessive	Abnormal vertebral segmentation Neural tube defects	*DLL3* mutations; mutations can also be present in other genes
Rubinstein-Taybi syndrome	Mendelian autosomal recessive	Mental retardation Broad thumbs, toes Hypoplastic maxillae Prominent nose Congenital heart disease	*CBP* mutations or haploinsufficiency
X-linked lissencephaly	Mendelian X-linked	Male: Severe mental retardation Seizures Female: Variable	*DCX* mutation
Aniridia	Autosomal semidominant	Reduced or absent iris	*PAX6* mutations
Waardenburg syndrome	Autosomal semidominant	Deafness White forelock Wide-spaced eyes Pale eye pigment	*PAX3* mutations *MITF* mutations
Holoprosencephaly	Loss of function or heterozygosity	Microcephaly Cyclopia Single central incisor	*SHH* mutations
Velocardiofacial syndrome	Microdeletion 22q11.2	Conotruncal congenital heart disease Cleft palate T-cell defects Facial anomalies	*TBX1* haploinsufficiency/mutations; haploinsufficiency for other genes in the deleted interval
Down syndrome	Chromosomal	Mental retardation Characteristic dysmorphic features Congenital heart disease Increased risk of leukemia Alzheimer disease	50% increase of estimated 250 genes on chromosome 21 Trisomy 21
Neural tube defects	Multifactorial	Meningomyelocele	Defects in folate sensitive enzymes or folic acid uptake
Fetal alcohol syndrome	Teratogenic	Microcephaly Developmental delay Facial abnormalities Behavioral abnormalities	Ethanol toxicity to developing brain
Retinoic acid embryopathy	Teratogenic	Microtia Congenital heart disease	Isotretinoin effects on neural crest and branchial arch development

Table 108-4 Childhood Diseases and Syndromes Associated with Motile and Sensory Ciliopathies

PEDIATRIC CILIOPATHY	CLINICAL MANIFESTATIONS	GENE(S)
MOTOR		
Primary ciliary dyskinesia	Chronic bronchitis, rhinosinusitis, otitis media, laterality defects, infertility, CHD	*DNAI1, DNAH5, DNAH11, DNAI2, KTU, TXNDC3, LRRC50, RSPH9, RSPH4A, CCDC40, CCDC39*
SENSORY		
Autosomal recessive polycystic kidney disease	RFD, CHF	*PKHD1*
Nephronophthisis	RFD, interstitial nephritis, CHF, RP	*NPHP1-8, ALMS1, CEP290*
Bardet-Biedl syndrome	Obesity, polydactyly, ID, RP, renal anomalies, anosmia, CHD	*BBS1-12, MKS1, MKS3, CEP290*
Meckel-Gruber syndrome	RFD, polydactyly, ID, CNS anomalies, CHD, cleft lip, cleft palate	*MKS1-6, CC2D2A, CEP290, TMEM216*
Joubert syndrome	CNS anomalies, ID, ataxia, RP, polydactyly, cleft lip, cleft palate	*NPHP1, JBTS1, JBTS3, JBTS4, CORS2, AHI1, CEP290, TMEM216*
Alstrom syndrome	Obesity, RP, DM, hypothyroidism, hypogonadism, skeletal dysplasia, cardiomyopathy, pulmonary fibrosis	*ALMS1*
Orofaciodigital syndrome type 1	Polydactyly, syndactyly, cleft lip, cleft palate, CNS anomalies, ID, RFD	*OFD1*
Ellis van Creveld syndrome	Chondrodystrophy, polydactyly, ectodermal dysplasia, CHD	*EVC, EVC2*
Jeune asphyxiating thoracic dystrophy	Narrow thorax, RFD, RP, dwarfism, polydactyly	*IFT80*
Sensenbrenner syndrome	Dolichocephaly, ectodermal dysplasia, dental dysplasia, narrow thorax, RFD, CHD	*IFT122, IFT43, WDR35*
Short rib-polydactyly syndromes	Narrow thorax, short limb dwarfism, polydactyly, renal dysplasia	*WDR35, DYNC2H1, NEK1*

CHD, congenital heart disease; CHF, congenital hepatic fibrosis; CNS, central nervous system; DM, diabetes mellitus; ID, intellectual disabilities; RFD, renal fibrocystic disease; RP, retinitis pigmentosa.

From Ferkol TW, Leigh MW: Ciliopathies: the central role of cilia in a spectrum of pediatric disorders. J Pediatr *160:366-371, 2012.*

Table 108-3 Causes of Congenital Malformations

MONOGENIC (7.5% of major anomalies)
X-linked hydrocephalus
Achondroplasia
Ectodermal dysplasia
Apert syndrome
Treacher Collins syndrome
CHROMOSOMAL (6% of major anomalies)
Trisomy 21, 18, 13
XO, XXY
Deletions 4p–, 5p–, 7q–, 13q–, 18p–, 18q–, 22q–
Prader-Willi syndrome (50% of affected patients have deletion of chromosome 15)
MATERNAL INFECTION (2% of major anomalies)
Intrauterine infections (e.g., herpes simplex virus, cytomegalovirus, varicella-zoster virus, rubella virus, and toxoplasmosis)
MATERNAL ILLNESS (3.5% of major anomalies)
Diabetes mellitus
Phenylketonuria
Hyperthermia
UTERINE ENVIRONMENT (% unknown)
Deformation
Uterine pressure, oligohydramnios: clubfoot, torticollis, congenital hip dislocation, pulmonary hypoplasia, 7th nerve palsy
Disruption
Amniotic bands, congenital amputations, gastroschisis, porencephaly, intestinal atresia
Twinning
ENVIRONMENTAL AGENTS (% unknown)
Polychlorinated biphenyls
Herbicides
Mercury
Alcohol
MEDICATIONS (% unknown)
Thalidomide
Diethylstilbestrol
Phenytoin
Warfarin
Cytotoxic drugs
Paroxetine
Angiotensin-converting enzyme inhibitors
Isotretinoin (vitamin A)
D-Penicillamine
Valproic acid
UNKNOWN ETIOLOGIES
Polygenetic
Associated with infertility (spontaneous or with treatment)
Anencephaly/spina bifida
Cleft lip/palate
Pyloric stenosis
Congenital heart disease
SPORADIC SYNDROME COMPLEXES
VATER (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial and renal anomalies) syndrome
Pierre Robin syndrome
Prune-belly syndrome
NUTRITIONAL
Low folic acid–neural tube defects

Table 109-4 Clinical Manifestations of Transplacental Infections

MANIFESTATION	PATHOGEN
Intrauterine growth restriction	CMV, *Plasmodium*, rubella, toxoplasmosis, *Treponema pallidum, Trypanosoma cruzi,* VZV
Congenital anatomic defects:	
Cataracts	Rubella
Cardiac defects	Rubella
Hydrocephalus	HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis
Intracranial calcification	CMV, HIV, toxoplasmosis, *T. cruzi*
Limb hypoplasia	VZV
Microcephaly	CMV, HSV, rubella, toxoplasmosis
Microphthalmos	CMV, rubella, toxoplasmosis
Neonatal organ involvement:	
Anemia	CMV, parvovirus, *Plasmodium,* rubella, toxoplasmosis, *T. cruzi, T. pallidum*
Carditis	Coxsackieviruses, rubella, *T. cruzi*
Encephalitis	CMV, enteroviruses, HSV, rubella, toxoplasmosis, *T. cruzi, T. pallidum*
Hepatitis	CMV, enteroviruses, HSV
Hepatosplenomegaly	CMV, enteroviruses, HIV, HSV, *Plasmodium,* rubella, *T. cruzi, T. pallidum*
Hydrops	Parvovirus, *T. pallidum,* toxoplasmosis
Lymphadenopathy	CMV, HIV, rubella, toxoplasmosis, *T. pallidum*
Osteitis	Rubella, *T. pallidum*
Petechiae, purpura	CMV, enteroviruses, rubella, *T. cruzi*
Pneumonitis	CMV, enteroviruses, HSV, measles, rubella, toxoplasmosis, *T. pallidum,* VZV
Retinitis	CMV, HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis, *T. pallidum,* West Nile virus
Rhinitis	Enteroviruses, *T. pallidum*
Skin lesions	Enteroviruses, HSV, measles, rubella, *T. pallidum,* VZV
Thrombocytopenia	CMV, enteroviruses, HIV, HSV, rubella, toxoplasmosis, *T. pallidum*
Late sequelae:	
Convulsions	CMV, enteroviruses, rubella, toxoplasmosis
Deafness	CMV, rubella, toxoplasmosis
Dental/skeletal problems	Rubella, *T. pallidum*
Endocrinopathies	Rubella, toxoplasmosis
Eye pathology	HSV, rubella, toxoplasmosis, *T. cruzi, T. pallidum,* VZV
Hepatitis	Hepatitis B
Mental retardation	CMV, HIV, HSV, rubella, toxoplasmosis, *T. cruzi,* VZV
Nephrotic syndrome	*Plasmodium, T. pallidum*

Table 109-5 Initial Signs and Symptoms of Infection in Newborn Infants

GENERAL	**CARDIOVASCULAR SYSTEM**
Fever, temperature instability	Pallor; mottling; cold, clammy skin
"Not doing well"	Tachycardia
Poor feeding	Hypotension
Edema	Bradycardia
GASTROINTESTINAL SYSTEM	**CENTRAL NERVOUS SYSTEM**
Abdominal distention	Irritability, lethargy
Vomiting	Tremors, seizures
Diarrhea	Hyporeflexia, hypotonia
Hepatomegaly	Abnormal Moro reflex
RESPIRATORY SYSTEM	Irregular respirations
Apnea, dyspnea	Full fontanel
Tachypnea, retractions	High-pitched cry
Flaring, grunting	**HEMATOLOGIC SYSTEM**
Cyanosis	Jaundice
RENAL SYSTEM	Splenomegaly
Oliguria	Pallor
	Petechiae, purpura
	Bleeding

Table 108-6 Minor Anomalies and Phenotype Variants*

CRANIOFACIAL
Large fontanel
Flat or low nasal bridge
Saddle nose, upturned nose
Mild micrognathia
Cutis aplasia of scalp
EYE
Inner epicanthal folds
Telecanthus
Slanting of palpebral fissures
Hypertelorism
Brushfield spots
EAR
Lack of helical fold
Posteriorly rotated pinna
Preauricular with or without auricular skin tags
Small pinna
Auricular (preauricular) pit or sinus
Folding of helix
Darwinian tubercle
Crushed (crumpled) ear
Asymmetric ear sizes
Low-set ears
SKIN
Dimpling over bones
Capillary hemangioma (face, posterior neck)
Dermal melanosis (African Americans, Asians)
Sacral dimple
Pigmented nevi
Redundant skin
Cutis marmorata
HAND
Simian creases
Bridged upper palmar creases
Clinodactyly of 5th digit
Hyperextensibility of thumbs
Single flexion crease of 5th digit (hypoplasia of middle phalanx)
Partial cutaneous syndactyly
Polydactyly
Short, broad thumb
Narrow, hyperconvex nails
Hypoplastic nails
Camptodactyly
Shortened 4th digit
FOOT
Partial syndactyly of 2nd and 3rd toes
Asymmetric toe length
Clinodactyly of 2nd toe
Overlapping toes
Nail hypoplasia
Wide gap between hallux and 2nd toe (wide sandal gap)
Deep plantar crease between hallux and 2nd toe
OTHERS
Mild calcaneovalgus
Hydrocele
Shawl scrotum
Hypospadias
Hypoplasia of labia majora

*Approximately 15% of newborns have 1 minor anomaly, 0.8% have 2 minor anomalies, and 0.5% have 3 minor anomalies. If 2 minor anomalies are present, the probability of an underlying syndrome or a major anomaly (congenital heart disease, renal, central nervous system, limbic) is 5-fold that in the general population. If 3 minor anomalies are present, the probability that there is a major anomaly is 20-30%.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, Elsevier Saunders, 2004.*

Table 108-7 Clinical Indications for Chromosome Analysis, or Array CGH*

At least 1 major and 2 minor malformations
At least 2 major malformations
Developmental *or* growth retardation with 2 or more major or minor anomalies

Table 109-2 Etiologic Agents of Neonatal Pneumonia According to Timing of Acquisition

TRANSPLACENTAL	POSTNATAL
CMV	Adenovirus
HSV	*Candida* species*
Mycobacterium Tuberculosis	Coagulase-negative staphylococci
Rubella virus	CMV
Treponema pallidum	Enteric bacteria*
VZV	Enteroviruses
PERINATAL	Influenza viruses A, B
Anaerobic bacteria	Parainfluenza
Chlamydia	*Pseudomonas**
CMV	RSV
Enteric bacteria	*Staphylococcus aureus*
Group B streptococci	*Mycobacterium tuberculosis*
Haemophilus influenzae	
HSV	
Listeria monocytogenes	
Mycoplasma	

*More likely with mechanical ventilation or indwelling catheters, or after abdominal surgery.

Table 109-1 Nonbacterial Causes of Systemic Neonatal Infections

VIRUSES	MYCOPLASMA
Adenovirus	*Mycoplasma hominis*
CMV	*Ureaplasma urealyticum*
Enteroviruses	**FUNGI**
Parechoviruses	*Candida* species
Hepatitis B virus	*Malassezia* species
HSV	**PROTOZOA**
HIV	Plasmodia
Parvovirus	*Toxoplasma gondii*
Rubella virus	*Trypanosoma cruzi*
VZV	

Table 109-6 Clinical Criteria for the Diagnosis of Sepsis in the International Setting

Integrated Management of Childhood Illness (IMCI) and WHO Criteria for Severe Infections in Children
NEUROLOGIC: convulsions, drowsy or unconscious, decreased activity, bulging fontanel
RESPIRATORY: respiratory rate >60 breaths/min, grunting, severe chest indrawing, central cyanosis
CARDIAC: poor perfusion, rapid and weak pulse
GASTROINTESTINAL: jaundice, poor feeding, abdominal distention
DERMATOLOGIC: skin pustules, periumbilical erythema or purulence
MUSCULOSKELETAL: edema or erythema overlying bones or joints
OTHER: Temperature >37.7°C (99.9°F; or feels hot) or <35.5°C (95.9°F; or feels cold)

Table 108-5 Definitions of Common Clinical Signs of Dysmorphic Syndromes

SIGN	DEFINITION
Brachycephaly	A condition in which head shape is shortened from front to back along the sagittal plane; the back of the skull and face are flatter than normal
Brachydactyly	A condition of having short digits
Brushfield spots	Speckled white rings about ⅔ of the distance to the periphery of the iris of the eye
Camptodactyly	Permanent flexion of one or more fingers associated with missing inner phalangeal creases indicating lack of finger movement from before 8 wk of gestation
Clinodactyly	A medial or lateral curving of the fingers; usually refers to incurving of the 5th finger
Hypoplastic nail	An unusually small nail on a digit
Low-set ears	This designation is made when the helix meets the cranium at a level below a horizontal plane that is an extension of a line through both inner canthi
Melia	A suffix meaning "limb" (e.g., amelia—missing limb; brachymelia—short limb)
Ocular hypertelorism	Increased distance between the pupils of the 2 eyes, also known as increased interpupillary distance)
Plagiocephaly	A condition in which head shape is asymmetric in the sagittal or coronal plane that can result from asymmetry in suture closure or from asymmetry of brain growth
Posterior parietal hair whorl	A single whorl occurs to the right or left of midline and within 2 cm anterior to the posterior fontanel in 95% of cases. The whorl represents the focal point from which the posterior scalp skin was under growth tension during brain growth between the 10th and 16th wk of fetal development. Aberrant position of the whorl reflects an early defect in brain development
Postaxial polydactyly	Extra finger or toe present on the lateral side of the hand or foot
Preaxial polydactyly	Extra finger or toe present on the medial side of the hand or foot
Prominent lateral palatine ridges	Relative overgrowth of the lateral palatine ridges secondary to a deficit of tongue thrust into the hard palate
Scaphocephaly	A condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic, Also termed dolichocephaly.
Shawl scrotum	The scrotal skin joins around the superior aspect of the penis and represents a mild deficit in full migration of the labial-scrotal folds
Short palpebral fissures	Decreased horizontal distance of the eyelid folds based on measurement from the inner to the outer canthus
Syndactyly	Incomplete separation of the fingers. It most commonly occurs between the 3rd and 4th fingers and between the 2nd and 3rd toes
Synophrys	Eyebrows that meet in the midline
Telecanthus	Lateral displacement of the inner canthi. The inner canthal distance (ICD) is increased, but the interpupillary distance (IPD) is normal.
Widow's peak	**V**-shaped midline, downward projection of the scalp hair in the frontal region. It represents an upper forehead intersection of the bilateral fields of periocular hair growth suppression. It usually occurs because the fields are widely spaced, as in ocular hypertelorism

Table 109-7	Serious Systemic Illness in Newborns: Differential Diagnosis of Neonatal Sepsis

CARDIAC
Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN)
Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN

GASTROINTESTINAL
Necrotizing enterocolitis
Spontaneous gastrointestinal perforation
Structural abnormalities
Hepatic failure (inborn errors of metabolism, neonatal iron storage disease)

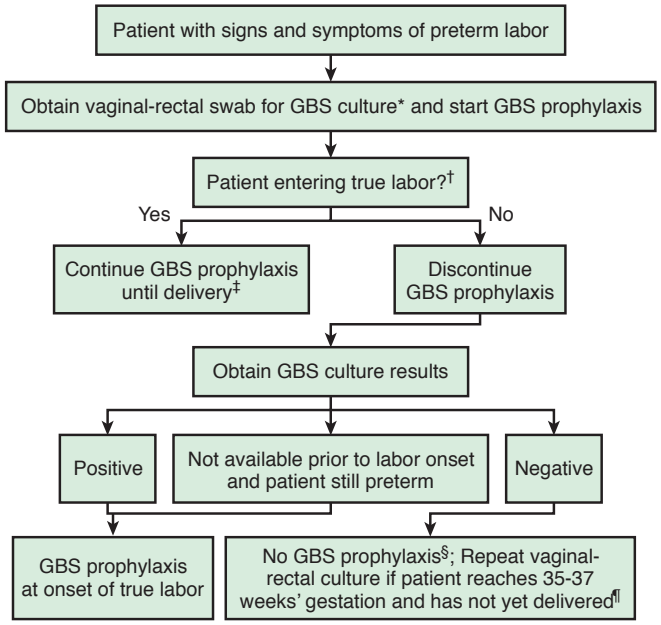
HEMATOLOGIC
Neonatal purpura fulminans
Immune-mediated thrombocytopenia
Immune-mediated neutropenia
Severe anemia
Malignancies (congenital leukemia)
Langerhans cell histiocytosis
Hereditary clotting disorders
Familial hemophagocytosis syndrome

METABOLIC
Hypoglycemia
Adrenal disorders: Adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia
Inborn errors of metabolism: Organic acidurias, lactic acidoses, urea cycle disorders, galactosemia

NEUROLOGIC
Intracranial hemorrhage: spontaneous, caused by child abuse
Hypoxic-ischemic encephalopathy
Neonatal seizures
Infant botulism

RESPIRATORY
Respiratory distress syndrome
Aspiration pneumonia: amniotic fluid, meconium, or gastric contents
Lung hypoplasia
Tracheoesophageal fistula
Transient tachypnea of the newborn

Algorithm for GBS intrapartum prophylaxis for women with preterm labor (PTL)



* If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

† Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis.

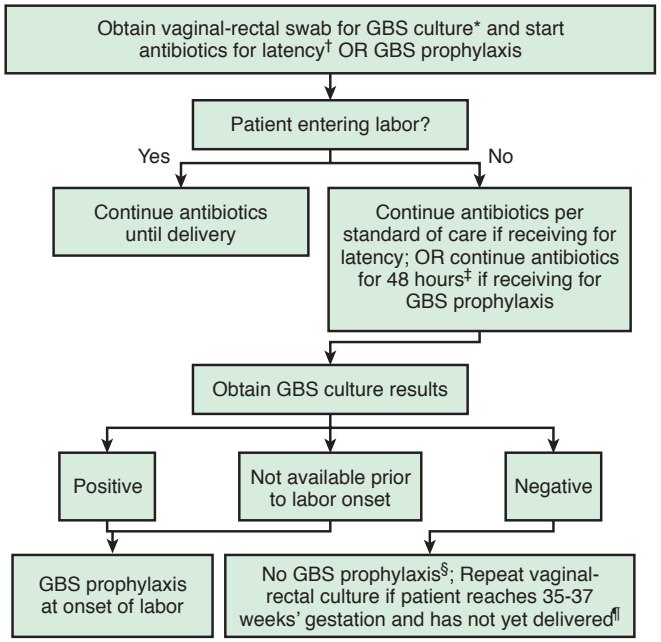
‡ If GBS culture results become available before delivery and are negative, then discontinue GBS prophylaxis.

§ Unless subsequent GBS culture before delivery is positive.

¶ A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is re-admitted with signs and symptoms of PTL and had a negative GBS screen >5 weeks prior, she should be re-screened and managed according to this algorithm at that time.

Figure 109-6 Algorithm for GBS intrapartum prophylaxis for women with preterm labor. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010,* MMWR Recomm Rep *59[RR-10]:1–36, 2010.)*

Algorithm for GBS intrapartum prophylaxis for women with preterm premature rupture of membranes (pPROM)



* If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

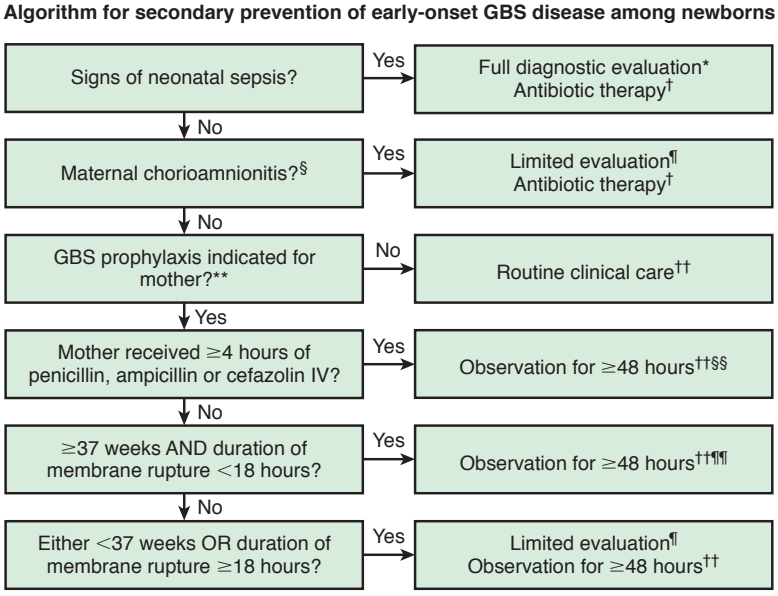
† Antibiotics given for latency in the setting of pPROM that include Ampicillin 2g IVx1, followed by 1g IV Q6 hrs for at least 48 hours are adequate for GBS prophylaxis. If other regimens are used, GBS prophylaxis should be initiated in addition.

‡ GBS prophylaxis should be discontinued at 48 hours for women with pPROM who are not in labor. If results from a GBS screen performed on admission become available during the 48 hour period and are negative, GBS prophylaxis should be discontinued at that time.

§ Unless subsequent GBS culture prior to delivery is positive.

¶ A negative GBS screen is considered valid for 5 weeks. If a patient with pPROM is entering labor and had a negative GBS screen >5 weeks prior, she should be re-screened and managed according to this algorithm at that time.

Figure 109-7 Algorithm for GBS intrapartum prophylaxis for women with preterm premature rupture of membranes. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010,* MMWR Recomm Rep *59[RR-10]:1–36, 2010.)*



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and LP (if patient stable anough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens), and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth), and CBC with differential and platelets (at birth and/or at 6-12 hours of life).

** GBS prophylaxis indicated in one or more of the following: (1) mother GBS positive within preceding 5 weeks, (2) GBS status unknown with one or more intrapartum risk factors including <37 weeks' gestation, ROM ≥18 hours or T ≥100.4°F (38.0°C), (3) GBS bacteriuria during current pregnancy, (4) history of a previous infant with GBS disease.

†† If signs of sepsis develop, a full diagnostic evaluation should be done and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at 6-12 hours of age.

Figure 109-8 Algorithm for secondary prevention of early-onset GBS disease among newborns. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010,* MMWR Recomm Rep *59[RR-10]:1–36, 2010.)*

Table 109-9 Indications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset GBS Disease

INTRAPARTUM GBS PROPHYLAXIS INDICATED	INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy	GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)	Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: Delivery at <37 weeks' gestation* Amniotic membrane rupture ≥18 hr Intrapartum temperature ≥38.0°C (100.4°F)† Intrapartum NAAT‡ positive for GBS	Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

*Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 109-7 and 109-8.

†If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

‡If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic membrane rupture ≥18 hr, or temperature ≥38.0°C[100.4°F]) is present, then intrapartum antibiotic prophylaxis is indicated.

GBS, group B streptococcus; NAAT, nucleic acid amplification test.

From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep *59(RR-10):1–36, 2010.*

Table 109-12 Management and Prevention of Neonatal Sepsis

CONDITION	THERAPY	ADDITIONAL CONSIDERATIONS
Empiric management		
Early-onset sepsis	Ampicillin + aminoglycoside. 10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections.	Consider a third-generation cephalosporin (cefotaxime preferred) or carbapenem for meningitis. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Late-onset sepsis	Vancomycin + aminoglycoside. Duration dependent on pathogen and site.	Alternatives to vancomycin may be considered based on local epidemiology and clinical presentation. Aminoglycoside based regimen preferred to cephalosporin given reduced risk of resistance. Consider cephalosporin if meningitis suspected. Consider a carbapenem if third-generation cephalosporin recently received. Consider amphotericin for fungal etiologies. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Nonantimicrobial treatment strategies		
Recombinant G-CSF Recombinant G-MSF	Enhance neutrophil number and function, but no reduction in infection when administered as prophylaxis or improvement in survival when administered as therapy.	Insufficient evidence to support the clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections.
IVIG[§]	Augments antibody-dependent cytotoxicity and improves neutrophilic function, *but* no evidence that IVIG in suspected or proven sepsis reduces death.	Insufficient evidence from 10 RCTs or quasi-RCTs to support use in neonates with confirmed or suspected sepsis.
Prevention strategies		
IAP	Administration of penicillin or ampicillin 4 hr prior to parturition.	Successfully reduces rates of EOS caused by GBS. No effect on LOS GBS.
Fluconazole prophylaxis	Administration of weight-based dosing to neonates weighing less than 1,500 g.	Most beneficial in NICUs with high baseline rates of invasive candidiasis.
BLF supplementation with a probiotic, *Lactobacillus rhamnosus* (GG)	BLF is a human milk glycoprotein with a role in innate immune response. LGG enhances the activity of lactoferrin.	BLF supplementation with and without LGG reduced the incidence of 1st LOS in 472 VLBW neonates in large randomized, double-blind RCT. Additional confirmatory studies warranted.

BLF, bovine lactoferrin supplementation; EOS, early-onset sepsis; GBS, group B streptococcus; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IAP, intrapartum antimicrobial prophylaxis; IVIG, intravenous immunoglobulin, LGG, *Lactobacillus rhamnosus* GG; LOS, late-onset sepsis; NICUs, neonatal intensive care unit; RCTs, randomized, controlled trials; VLBW, very low birthweight.

Created with data from Carr R, Modi N, Doré C: G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev *(3):CD003066, 2003; Brocklehurst P, Farrell B, King A, et al; INIS Collaborative Group: Treatment of neonatal sepsis with intravenous immune globulin.* N Engl J Med *365:1201–1211, 2011; Manzoni P, Decembrino L, Stolfi I, et al; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology. Lactoferrin and prevention of late-onset sepsis in the pre-term neonates.* Early Hum Dev *86(Suppl 1):59–61, 2010.*

Used with permission from Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. Am J Perinatol *30(2):131–141, 2013.*

Adolescent Development

Table 110-1 Milestones in Early, Middle, and Late Adolescent Development

VARIABLE	EARLY ADOLESCENCE	MIDDLE ADOLESCENCE	LATE ADOLESCENCE
Approximate age range	10-13 yr	14-17 yr	18-21 yr
Sexual maturity rating*	1-2	3-5	5
Physical	• Females: Secondary sex characteristics (breast, pubic, axillary hair), start of growth spurt • Males: testicular enlargement, start of genital growth	• Females: peak growth velocity, menarche (if not already attained) • Males: growth spurt, secondary sex characteristics, nocturnal emissions, facial and body hair, voice changes • Change in body composition • Acne	• Physical maturation slows • Increased lean muscle mass in males
Cognitive and moral	• Concrete operations • Egocentricity • Unable to perceive long-term outcome of current decisions • Follow rules to avoid punishment	• Emergence of abstract thought (formal operations) • May perceive future implications, but may not apply in decision making • Strong emotions may drive decision making • Sense of invulnerability • Growing ability to see others' perspectives	• Future-oriented with sense of perspective • Idealism • Able to think things through independently • Improved impulse control • Improved assessment of risk vs. reward • Able to distinguish law from morality
Self-concept/identity formation	• Preoccupied with changing body • Self-consciousness about appearance and attractiveness	• Concern with attractiveness • Increasing introspection	• More stable body image • Attractiveness may still be of concern • Consolidation of identity
Family	• Increased need for privacy • Exploration of dependence/independence boundaries	• Conflicts over control and independence • Struggle for greater autonomy • Increased separation from the parents	• Emotional and physical separation from family • Increased autonomy • Reestablishment of "adult" relationship with parents
Peers	• Same-sex peer affiliations	• Intense peer group involvement • Preoccupation with peer culture • Conformity	• Peer group and values recede in importance
Sexual	• Increased interest in sexual anatomy • Anxieties and questions about pubertal changes • Limited capacity for intimacy	• Testing ability to attract partner • Initiation of relationships and sexual activity • Questions of sexual orientation	• Consolidation of sexual identity • Focus on intimacy and formation of stable relationships • Planning for future and commitment

Table 110-2 Sexual Maturity Rating Stages in Females

SMR STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

SMR, sexual maturity rating.
From Tanner JM: Growth at adolescence, *ed 2, Oxford, England, 1962, Blackwell Scientific.*

Table 110-3 Sexual Maturity Rating Stages in Males

SMR STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

SMR, sexual maturity rating.
From Tanner JM: Growth at adolescence, *ed 2, Oxford, England, 1962, Blackwell Scientific.*

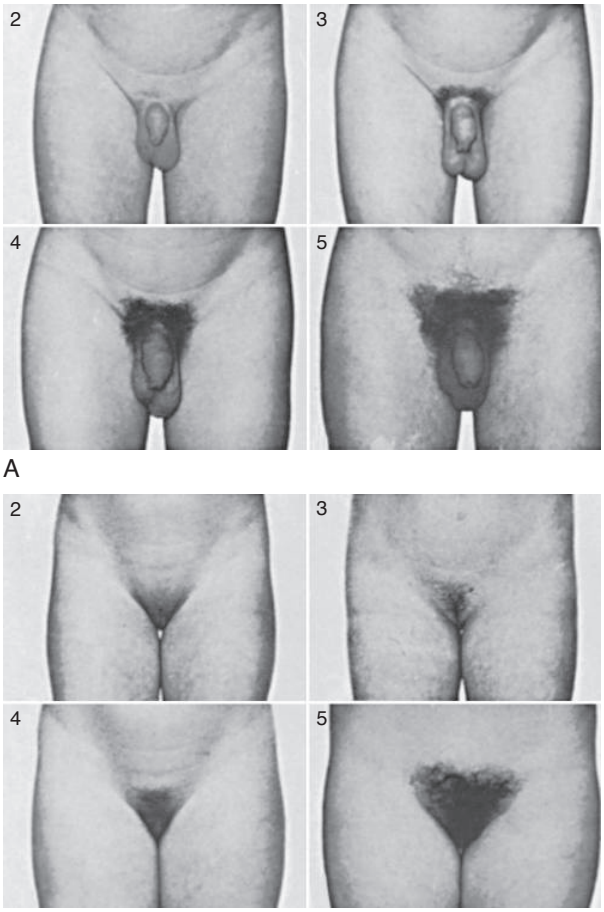


Figure 110-1 Sexual maturity ratings (2-5) of pubic hair changes in adolescent males *(A)* and females *(B)* (see Tables 110-2 and 110-3).

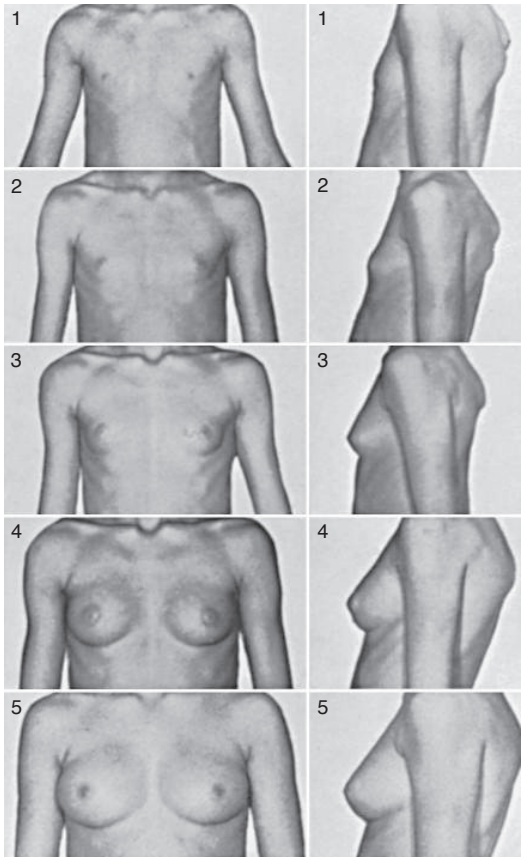


Figure 110-2 Sexual maturity ratings (1-5) of breast changes in adolescent females. *(Courtesy of J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London, London, England.)*

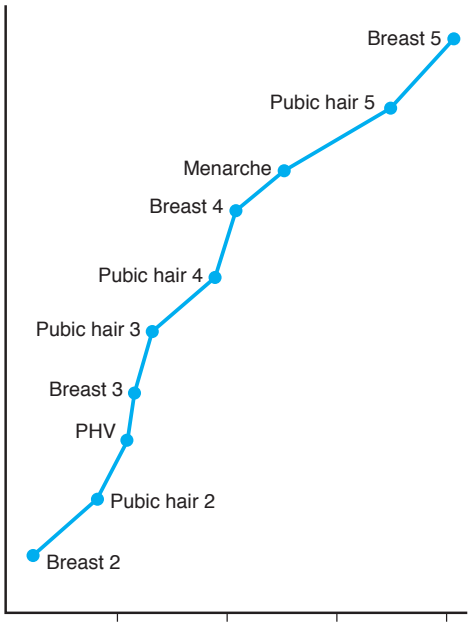


Figure 110-4 Sequence of pubertal events in females. PHV, peak height velocity.

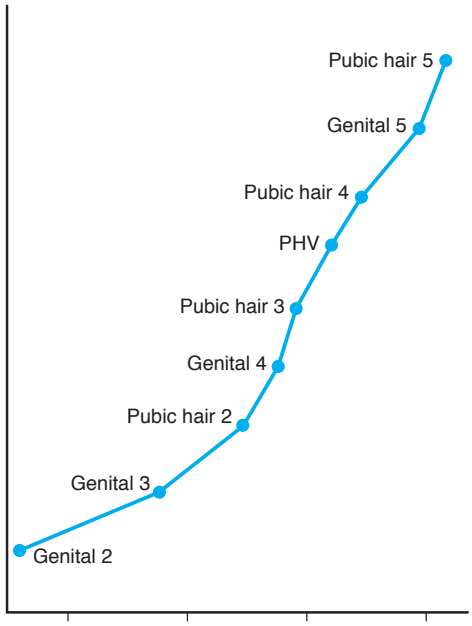


Figure 110-3 Sequence of pubertal events in males. PHV, peak height velocity. *(From Root AW: Endocrinology of puberty, J Pediatr 83:1, 1973.)*

Table 110-4 Summary of DSM 5 Diagnostic Criteria for Gender Dysphoria

GENDER DYSPHORIA IN CHILDREN (302.6) (F64.2)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 6 of the following (1 of which must be criterion A1):
   1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
   2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
   3. A strong preferences for cross-gender roles in make-believe play or fantasy play.
   4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
   5. A strong preference for playmates of the other gender.
   6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
   7. A strong dislike of one's sexual anatomy.
   8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.
B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

GENDER DYSPHORIA IN ADOLESCENTS OR ADULTS

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 2 of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
   4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).
B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

SPECIFY IF POSTTRANSITION: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen, namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Adapted from the American Psychiatric Association, Diagnostic and statistical manual of mental disorders, *ed 5, Washington, DC, 2013, American Psychiatric Publishing.*

Table 111-2 Leading Causes of Death Among 15-19 Yr Olds by Gender, United States, 2010*

LEADING CAUSES OF DEATH	MALE	FEMALE
#1	Accidents (unintentional injuries)	Accidents (unintentional injuries)
#2	Assault (homicide)	Intentional self-harm (suicide)
#3	Intentional self-harm (suicide)	Assault (homicide)

*Based on data from Heron M: Deaths: Leading causes for 2009. National vital statistics reports; vol 62. No. 6. Hyattsville, MD, 2013, National Center for Health Statistics.

Table 112-3 Adolescent Screening Recommendations

		11-14 YR OLD VISIT	15-17 YR OLD VISIT	18-21 YR OLD VISIT
Universal Screening		**Action**	**Action**	**Action**
Vision (once during each of 3 adolescent age groups)		Snellen test	Snellen test	Snellen test
Dyslipidemia		Lipid screen (once between 9-11 yr)	NA	Lipid screen (once between 18-21 yr)
Selective Screening	**Risk Assessment**	**Action If RA+**	**Action If RA+**	**Action If RA+**
Vision at other ages	+ on risk screening questions	Snellen test	Snellen test	Snellen test
Hearing	+ on risk screening questions	Audiometry	Audiometry	Audiometry
Anemia	+ on risk screening questions	Hemoglobin or hematocrit	Hemoglobin or hematocrit	Hemoglobin or hematocrit
Tuberculosis	+ on risk screening questions	Tuberculin skin test	Tuberculin skin test	Tuberculin skin test
Dyslipidemia	+ on risk screening questions and not previously screened with normal results	Lipid screen	Lipid screen	Lipid screen
STIs	Sexually active	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)
	Sexually active and + on risk screening questions	Syphilis test	Syphilis test	Syphilis test
HIV	Discuss and offer	HIV test*	HIV test*	HIV test*
Pregnancy	Sexually active, without contraception, late menses or amenorrhea	Urine hCG	Urine hCG	Urine hCG (without late or absent menses or heavy or irregular bleeding)
Cervical dysplasia†	NA	NA	NA	Pap smear at age 21 yr
Alcohol or drug use	+ on risk screening questions	Administer alcohol and drug screening tool	Administer alcohol and drug screening tool	Administer alcohol and drug screening tool

*CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. American Academy of Pediatrics recommends routine HIV screening offered to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends routine HIV screening offered to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

†Screening for Cervical Cancer. April 2012. U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm.

hCG, human chorionic gonadotropin; NA, not applicable; RA, risk assessment.

Adapted from Hagan JF, Shaw JS, Duncan PM, eds. Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, *3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008; and American Academy of Pediatrics, Committee on Practice and Ambulatory Medicine, Bright Futures Periodicity Schedule Workgroup: 2014 recommendations for pediatric preventive health care,* Pediatrics *133(3):568–570, 2014.*

Table 114-6 The Most Common Toxic Syndromes

ANTICHOLINERGIC SYNDROMES	
Common signs	Delirium with mumbling speech, tachycardia, dry, flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, and decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.
Common causes	Antihistamines, antiparkinsonian medication, atropine, scopolamine, amantadine, antipsychotic agents, antidepressant agents, antispasmodic agents, mydriatic agents, skeletal muscle relaxants, and many plants (notably jimson weed and Amanita muscaria).
SYMPATHOMIMETIC SYNDROMES	
Common signs	Delusions, paranoia, tachycardia (or bradycardia if the drug is a pure α-adrenergic agonist), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, and hyperreflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.
Common causes	Cocaine, amphetamine, methamphetamine (and its derivatives 3,4-methylenedioxyamphetamine, 3,4-met hylenedioxymethamphetamine, 3,4-methylenedioxyethamphetamine, and 2,5-dimethoxy-4-bromoamphetamine), and OTC decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.
OPIATE, SEDATIVE, OR ETHANOL INTOXICATION	
Common signs	Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia, pulmonary edema, decreased bowel sounds, hyporeflexia, and needle marks. Seizures may occur after overdoses of some narcotics, notably propoxyphene.
Common causes	Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, and guanabenz.
CHOLINERGIC SYNDROMES	
Common signs	Confusion, central nervous system depression, weakness, salivation, lacrimation, urinary and fecal incontinence, gastrointestinal cramping, emesis, diaphoresis, muscle fasciculations, pulmonary edema, miosis, bradycardia or tachycardia, and seizures.
Common causes	Organophosphate and carbamate insecticides, physostigmine, edrophonium, and some mushrooms.

From Kulig K: Initial management of ingestions of toxic substances, N Engl J Med *326:1678, 1992. ©1992 Massachusetts Medical Society. All rights reserved.*

Table 114-7 CRAFFT Mnemonic Tool

- Have you ever ridden in a **C**ar driven by someone (including yourself) who was high or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to **R**elax, feel better about yourself or fit in?
- Do you ever use alcohol or drugs while you are by yourself (**A**lone)?
- Do you ever **F**orget things you did while using alcohol or drugs?
- Do your Family or **F**riends ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into **T**rouble while you were using alcohol or drugs?

From the Center for Adolescent Substance Abuse Research (CeASAR). The CRAFFT Screening Interview. © John R. Knight, MD, Boston Children's Hospital, 2015.

Table 114-8 Urine Screening for Drugs Commonly Abused by Adolescents

DRUG	MAJOR METABOLITE	INITIAL	FIRST CONFIRMATION	SECOND CONFIRMATION	APPROXIMATE RETENTION TIME
Alcohol (blood)	Acetaldehyde	GC	IA		7-10 hr
Alcohol (urine)	Acetaldehyde	GC	IA		10-13 hr
Amphetamines		TLC	IA	GC, GC/MS	48 hr
Barbiturates		IA	TLC	GC, GC/MS	Short-acting (24 hr); long-acting (2-3 wk)
Benzodiazepines		IA	TLC	GC, GC/MS	3 days
Cannabinoids	Carboxy- and hydroxymetabolites	IA	TLC	GC/MS	3-10 days (occasional user); 1-2 mo (chronic user)
Cocaine	Benzoylecgonine	IA	TLC	GC/MS	2-4 days
Methaqualone	Hydroxylated metabolites	TLC	IA	GC/MS	2 wk
Opiates					
Heroin	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Morphine	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Codeine	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Phencyclidine		TLC	IA	GC, GC/MS	8 days

GC, gas chromatography; IA, immunoassay; MS, mass spectrometry; TLC, thin-layer chromatography.

Modified from Drugs of abuse—urine screening [physician information sheet]. Los Angeles, Pacific Toxicology. From MacKenzie RG, Kipke MD: Substance use and abuse. In Friedman SB, Fisher M, Schonberg SK, editors: Comprehensive adolescent health care, *St. Louis, 1998, Mosby.*

Table 114-17 Signs and Symptoms of Intoxication and Withdrawal

	OPIATES	AMPHETAMINES/COCAINE	BENZODIAZEPINES
INTOXICATION			
Behavior	Apathy and sedation; disinhibition; psychomotor retardation; impaired attention and judgment	Euphoria and sensation of increased energy; hypervigilance; grandiosity, aggression, argumentative; labile mood; repetitive stereotyped behaviors; hallucinations, usually with intact orientation; paranoid ideation; interference with personal functioning	Euphoria; apathy and sedation; abusiveness or aggression; labile mood; impaired attention; anterograde amnesia; impaired psychomotor performance; interference with personal functioning
Signs	Drowsiness; slurred speech; pupillary constriction (except anoxia from severe overdose—dilation); decreased level of consciousness	Dilated pupils; tachycardia (occasionally bradycardia, cardiac arrhythmias); hypertension; nausea/vomiting; sweating and chills; evidence of weight loss; dilated pupils; chest pain; convulsions	Unsteady gait; difficulty in standing; slurred speech; nystagmus; decreased level consciousness; erythematous skin lesions or blisters
Overdose	Respiratory depression; hypothermia	Sympathomimetic symptoms	Hypotension; hyperthermia; depression of gag reflex; coma
Withdrawal	Craving to use; lacrimation; yawning; rhinorrhea/sneezing; muscle aches or cramps; abdominal cramps; nausea/vomiting/diarrhoea; sweating; dilated pupils; anorexia; irritability; tremor; piloerection/chills; restlessness; disturbed sleep	Dysphoric mood (sadness/anhedonia); lethargy and fatigue; psychomotor retardation or agitation; craving; increased appetite; insomnia or hypersomnia; bizarre or unpleasant dreams	Tremor of tongue, eyelids, or outstretched hands; nausea or vomiting; tachycardia; postural hypotension; psychomotor agitation; headache; insomnia; malaise or weakness; transient visual, tactile, or auditory hallucinations or illusions; paranoid ideation; grand mal convulsions

Table 122-1 Predisposition to Specific Infections in Humans

PATHOGEN	PRESENTATION	AFFECTED GENE/ CHROMOSOMAL REGION	FUNCTIONAL DEFECT	NOTES
BACTERIA				
Streptococcus pneumoniae	Invasive disease	*IRAK-4, MyD88*	Impaired production of inflammatory cytokines following TLR stimulation	Also susceptible to other pyogenic bacteria such as *Staphylococcus aureus*
Neisseria	Invasive disease	MAC components (C5, C6, C7, C8A, C8B, C8G, C9)	MAC deficiency	
	Invasive disease, poor prognosis	*PFC*	Properdin deficiency	
Mycobacteria	MSMD	*IL12B, IL12RB1, IKBKG*	Impaired IFN-γ response to IL-12, IL-23	Also susceptible to *Salmonella typhi* infections
		IFNGR1, IFNGR2, STAT1	Impaired cellular response to IFN-γ	
Mycobacterium leprae	Leprosy	*PARK2*	Unknown	Possible E3-ubiquitin ligase dysfunction
		LTA	Unknown	
VIRUSES				
Herpes simplex (type 1)	Herpes simplex encephalitis	*UNC93B1, TLR3, STAT1*	Impaired production of type 1 IFNs	STAT1 and NEMO deficiency also predispose to HSV infections, amongst other infections
Epstein-Barr virus	XLP	*SH2DIA*	SAP deficiency	Fulminant infectious mononucleosis, malignant and nonmalignant lymphoproliferative disorders, dysgammaglobulinemia, autoimmunity
		XIAP/BIRC4	XIAP deficiency	
Human papillomaviruses	Epidermodysplasia verruciformis	*EVER1/TMC6*	EVER1 deficiency	Altered neutrophil mobilization, T-cell lymphopenia, recurrent bacterial respiratory infections chronic cutaneous/genital papillomavirus disease
		EVER2/TMC8	EVER2 deficiency	
	WHIM	*CXCR4*	Truncated CXCR4	
PARASITES				
Plasmodium falciparum	Malaria fever episodes	10p15	Unknown	Linkage studies
	Severe malaria	*GNAS*	Unknown	SNP association studies
	Severe malaria	*IFNR1*	Unknown	SNP association studies
Schistosoma mansoni	Intensity of infection	5q311-q33	Unknown	
	Hepatic fibrosis	6q22-q23, *IFNR1*	Unknown	
Leishmania donovani	Visceral leishmaniasis (kala-azar)	22q12, 2q35 *(NRAMP1)*	Unknown	
YEAST				
Candida	APECED, chronic candidiasis	*Aire, STAT1, CARD9*	Unknown	APS-1 chronic candidiasis, chronic hyperthyroidism, Addison disease
Deep dermatophytosis	Tissue invasion	*CARD9*	Unknown	Autosomal recessive

APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MAC, membrane attack complex; MSMD, mendelian susceptibility to mycobacterial disease; NEMO, nuclear factor kappa B essential modulator; SAP, SLAM-associated protein; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; XIAP, X-linked inhibitor of apoptosis; XLP, X-linked lymphoproliferative disease.

Modified from Pessach I, Walter J, Notarangelo LD: Recent advances in primary immunodeficiencies: identification of novel genetic defects and unanticipated phenotypes, Pediatr Res *65:3R–12R, 2009.*

Immunology

Table 122-2 Characteristic Clinical Patterns in Some Primary Immunodeficiencies

FEATURES	DIAGNOSIS
IN NEWBORNS AND YOUNG INFANTS (0-6 MO)	
Hypocalcemia, unusual facies and ears, heart disease	DiGeorge anomaly
Delayed umbilical cord detachment, leukocytosis, recurrent infections	Leukocyte adhesion defect
Persistent thrush, failure to thrive, pneumonia, diarrhea	Severe combined immunodeficiency
Bloody stools, draining ears, atopic eczema	Wiskott-Aldrich syndrome
Pneumocystis jiroveci pneumonia, neutropenia, recurrent infections	X-linked hyper-IgM syndrome
IN INFANTS AND YOUNG CHILDREN (6 MO-5 YR)	
Severe progressive infectious mononucleosis	X-linked lymphoproliferative syndrome
Recurrent staphylococcal abscesses, staphylococcal pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis	Hyper-IgE syndrome
Persistent thrush, nail dystrophy, endocrinopathies	Chronic mucocutaneous candidiasis
Short stature, fine hair, severe varicella	Cartilage hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infection	Chédiak-Higashi syndrome
Abscesses, suppurative lymphadenopathy, antral outlet obstruction, pneumonia, osteomyelitis	Chronic granulomatous disease
IN OLDER CHILDREN (OLDER THAN 5 YR) AND ADULTS	
Progressive dermatomyositis with chronic enterovirus encephalitis	X-linked agammaglobulinemia
Sinopulmonary infections, neurologic deterioration, telangiectasia	Ataxia-telangiectasia
Recurrent neisserial meningitis	C6, C7, or C8 deficiency
Sinopulmonary infections, splenomegaly, autoimmunity, malabsorption	Common variable immunodeficiency

Table 122-3 Common Clinical Features of Immunodeficiency

Usually present	Recurrent upper respiratory infections Severe bacterial infections Persistent infections with incomplete or no response to therapy Paucity of lymph nodes and tonsils
Often present	Persistent sinusitis or mastoiditis (*Streptococcus pneumoniae, Haemophilus, Pneumocystis jiroveci, Staphylococcus aureus, Pseudomonas* spp.) Recurrent bronchitis or pneumonia Failure to thrive or growth retardation for infants or children; weight loss for adults Intermittent fever Infection with unusual organisms Skin lesions: rash, seborrhea, pyoderma, necrotic abscesses, alopecia, eczema, telangiectasia Recalcitrant thrush Diarrhea and malabsorption Hearing loss caused by chronic otitis Chronic conjunctivitis Arthralgia or arthritis Bronchiectasis Evidence of autoimmunity, especially autoimmune thrombocytopenia or hemolytic anemia Hematologic abnormalities: aplastic anemia, hemolytic anemia, neutropenia, thrombocytopenia History of prior surgery, biopsy
Occasionally present	Lymphadenopathy Hepatosplenomegaly Severe viral disease (e.g., EBV, CMV, adenovirus, varicella, herpes simplex) Chronic encephalitis Recurrent meningitis Deep infections: cellulitis, osteomyelitis, organ abscesses Chronic gastrointestinal disease, infections, lymphoid hyperplasia, sprue-like syndrome, atypical inflammatory bowel disease Autoimmune disease such as autoimmune thrombocytopenia, hemolytic anemia, rheumatologic disease, alopecia, thyroiditis, pernicious anemia Pyoderma gangrenosum Adverse reaction to vaccines Delayed umbilical cord detachment Chronic stomatitis or peritonitis

Table 122-4 Characteristic Features of Primary Immunodeficiency

CHARACTERISTIC	PREDOMINANT T-CELL DEFECT	PREDOMINANT B-CELL DEFECT	GRANULOCYTE DEFECT	COMPLEMENT DEFECT
Age at the onset of infection	Early onset, usually 2-6 mo of age	Onset after maternal antibodies diminish, usually after 5-7 mo of age, later childhood to adulthood	Early onset	Onset at any age
Specific pathogens involved	Bacteria: common Gram-positive and Gram-negative bacteria and mycobacteria Viruses: CMV, EBV, adenovirus, parainfluenza 3, varicella, enterovirus Fungi: *Candida* and *Pneumocystis jiroveci*	Bacteria: pneumococci, streptococci, staphylococci, *Haemophilus, Campylobacter, Mycoplasma* Viruses: enterovirus* Fungi and parasites: giardia, cryptosporidia	Bacteria: staphylococci, *Pseudomonas, Serratia, Klebsiella, Salmonella* Fungi and parasites: *Candida, Nocardia, Aspergillus*	Bacteria: pneumococci, *Neisseria*
Affected organs	Extensive mucocutaneous candidiasis, lungs, failure to thrive, protracted diarrhea	Recurrent sinopulmonary infections, chronic gastrointestinal symptoms, malabsorption, arthritis, enteroviral meningoencephalitis*	Skin: abscesses, impetigo, cellulitis Lymph nodes: suppurative adenitis Oral cavity: gingivitis, mouth ulcers Internal organs: abscesses, osteomyelitis	Infections: meningitis, arthritis, septicemia, recurrent sinopulmonary infections
Special features	Graft-vs-host disease caused by maternal engraftment or nonirradiated blood transfusion Postvaccination disseminated BCG or varicella Hypocalcemic tetany in infancy†	Autoimmunity Lymphoreticular malignancy: lymphoma, thymoma Postvaccination paralytic polio	Prolonged attachment of umbilical cord, poor wound healing	Autoimmune disorders: SLE, vasculitis, dermatomyositis, scleroderma, glomerulonephritis, angioedema

*X-linked (Bruton) agammaglobulinemia.
†DiGeorge anomaly.
BCG, Bacille Calmette-Guérin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus.
Modified from Woroniecka M, Ballow M: Office evaluation of children with recurrent infection, Pediatr Clin North Am *47:1211–1224, 2000.*

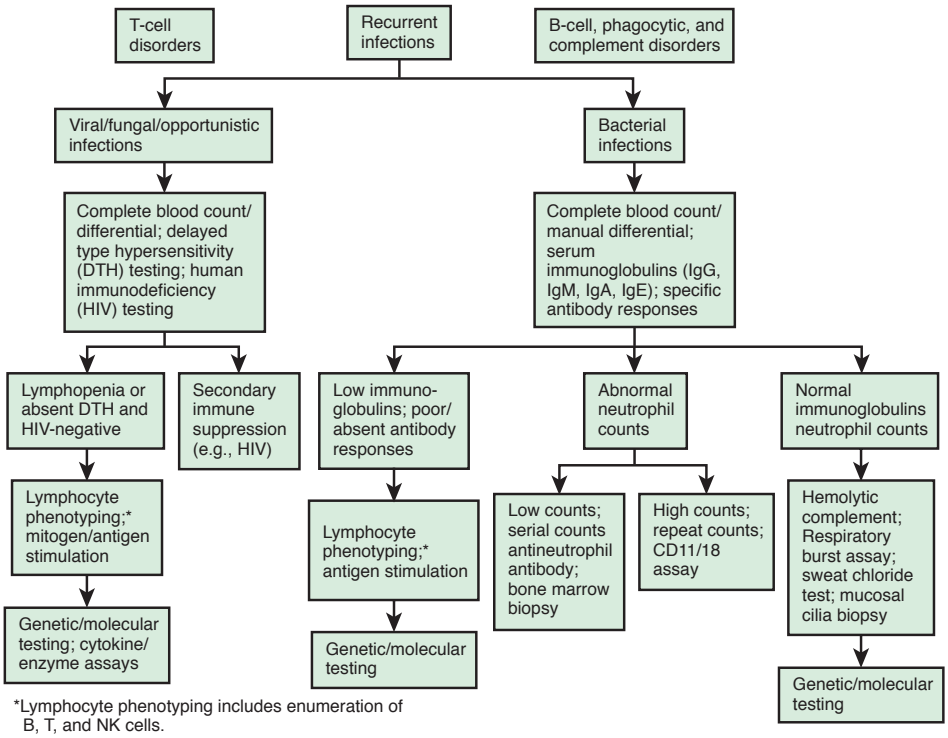


Figure 122-1 **A diagnostic testing algorithm for primary immunodeficiency diseases.** DTH, delayed-type hypersensitivity. *(From Lindegren ML, Kobrynski L, Rasmussen SA: Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders,* MMWR Recomm Rep *53[RR-1]:1–29, 2004.)*

Table 122-5 Special Physical Features Associated with Immunodeficiency Disorders

CLINICAL FEATURES	DISORDERS
DERMATOLOGIC	
Eczema	Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency
Sparse and/or hypopigmented hair	Cartilage hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome
Ocular telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Severe dermatitis	Omenn syndrome
Erythroderma	Omenn syndrome, SCID, graft-vs-host disease, Comel-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver and rectum especially	Chronic granulomatous disease
Recurrent abscesses or cellulitis	Chronic granulomatous disease, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	Chronic granulomatous disease, severe combined immunodeficiency, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, -17, -23 deficiencies; *CARD9* deficiency; *STAT1* deficiency
Vitiligo	B-cell defects, mucocutaneous candidiasis
Alopecia	B-cell defects, mucocutaneous candidiasis
Chronic conjunctivitis	B-cell defects
EXTREMITIES	
Clubbing of the nails	Chronic lung disease due to antibody defects
Arthritis	Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome
ENDOCRINOLOGIC	
Hypoparathyroidism	DiGeorge syndrome, mucocutaneous candidiasis
Endocrinopathies (autoimmune)	Mucocutaneous candidiasis
Diabetes, hypothyroid	IPEX and IPEX-like syndromes
Growth hormone deficiency	X-linked agammaglobulinemia
Gonadal dysgenesis	Mucocutaneous candidiasis
HEMATOLOGIC	
Hemolytic anemia	B- and T-cell immune defects, ALPS
Thrombocytopenia, small platelets	Wiskott-Aldrich syndrome
Neutropenia	Hyper-IgM syndrome, Wiskott-Aldrich variant, chronic granulomatous disease
Immune thrombocytopenia	B-cell immune defects, ALPS
SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T- and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage hair hypoplasia

ADA, Adenosine deaminase deficiency; AID, activation-induced cytidine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CVID, common variable immunodeficiency; GVHD, graft-vs-host disease; Ig, immunoglobulin; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.

From Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, Saunders, p 1599.*

Table 122-6 Initial Screening Immunologic Testing of the Child with Recurrent Infections

COMPLETE BLOOD COUNT, MANUAL DIFFERENTIAL, AND ERYTHROCYTE SEDIMENTATION RATE
Absolute lymphocyte count (normal result [Chapter 727] rules against T-cell defect)
Absolute neutrophil count (normal result [Chapter 727] rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections)
Platelet count (normal result excludes Wiskott-Aldrich syndrome)
Howell-Jolly bodies (absence rules against asplenia)
Erythrocyte sedimentation rate (normal result indicates chronic bacterial or fungal infection unlikely)
SCREENING TESTS FOR B-CELL DEFECTS
Immunoglobulin (Ig) A measurement; if abnormal, IgG and IgM measurement
Isohemagglutinins
Antibody titers to blood group substances, tetanus, diphtheria, *Haemophilus influenzae*, and pneumococcus
SCREENING TESTS FOR T-CELL DEFECTS
Absolute lymphocyte count (normal result indicates T-cell defect unlikely)
Flow cytometry to examine for the presence of naïve T cells (CD3+CD45RA+ cells)
SCREENING TESTS FOR PHAGOCYTIC CELL DEFECTS
Absolute neutrophil count
Respiratory burst assay
SCREENING TEST FOR COMPLEMENT DEFICIENCY
CH_{50}

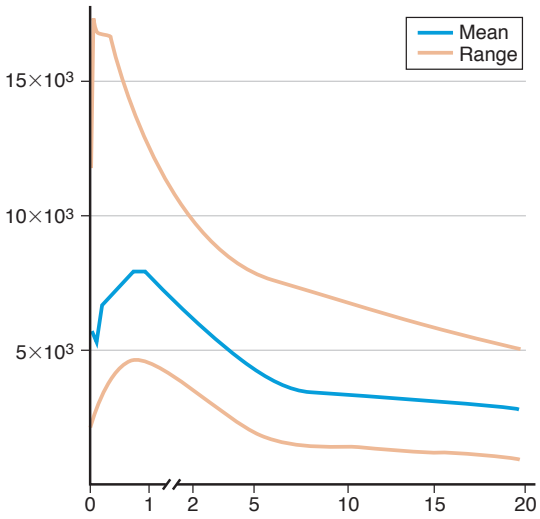


Figure 122-2 Absolute lymphocyte counts in normal individual during maturation. *(Data graphed from Altman PL:* Blood and other body fluids. *Prepared under the auspices of the Committee on Biological Handbooks. Washington, DC, 1961, Federation of American Societies for Experimental Biology.)*

Table 126-5 Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome

REQUIRED
1. Chronic nonmalignant lymphoproliferation (>6 mo lymphadenopathy and/or splenomegaly)
2. Elevated peripheral blood double-negative T cells
ACCESSORY
Primary
Defective in vitro Fas-mediated apoptosis (in 2 separate assays)
Somatic or germline mutation in ALPS causative gene (FAS, FASL, CASP10)
Secondary
1. Elevated biomarkers (Any of following)
a. Plasma soluble FASL >200 pg/mL
b. Plasma IL-10 >20 pg/mL
c. Plasma or serum vitamin B_{12} >1500 ng/L
d. Plasma IL-18 >500 pg/mL
2. Immunohistochemical findings consistent with ALPS as determined by experienced histopathologist
3. Autoimmune cytopenias and polyclonal hypergammaglobulinemia
4. Family history of ALPS or nonmalignant lymphoproliferation
DIAGNOSIS
Definitive: Required plus 1 primary accessory criterion
Probable: Required plus 1 secondary accessory criterion
Of note, probable and definitive ALPS should be treated the same in the clinic

Modified from Teachey DT: New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome. Curr Opin Pediatr *24:1–8, 2013, Table 2, p. 4.*

Table 122-7 Laboratory Tests in Immunodeficiency

SCREENING TESTS	ADVANCED TESTS	RESEARCH/SPECIAL TESTS
B-CELL DEFICIENCY		
IgG, IgM, IgA, and IgE levels	B-cell enumeration (CD19 or CD20)	Advanced B-cell phenotyping
Isohemagglutinin titers		Biopsies (e.g., lymph nodes)
Ab response to vaccine antigens (e.g., tetanus, diphtheria, pneumococci, *Haemophilus influenzae*)	Ab responses to boosters or to new vaccines	Ab responses to special antigens (e.g., bacteriophage φX174), mutation analysis
T-CELL DEFICIENCY		
Lymphocyte count	T-cell subset enumeration (CD3, CD4, CD8)	Advanced flow cytometry
Chest x-ray examination for thymic size*	Proliferative responses to mitogens, antigens, allogeneic cells	Enzyme assays (e.g., ADA, PNP)
		Thymic imaging
Delayed skin tests (e.g., *Candida*, tetanus toxoid)	HLA typing	Mutation analysis
	Chromosome analysis	T-cell activation studies
		Apoptosis studies
		Biopsies
PHAGOCYTIC DEFICIENCY		
WBC count, morphology	Adhesion molecule assays (e.g., CD11b/CD18, selectin ligand)	Mutation analysis
Respiratory burst assay	Mutation analysis	Enzyme assays (e.g., MPO, G6PD, NADPH oxidase)
COMPLEMENT DEFICIENCY		
CH_{50} activity	AH50, activity	
C3 level	Component assays	
C4 level	Activation assays (e.g., C3a, C4a, C4d, C5a)	

*In infants only.

Ab, antibody; ADA, adenosine deaminase; C, complement; CH, hemolytic complement; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leukocyte antigen; Ig, immunoglobulin; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; PNP, purine nucleoside phosphorylase; WBC, white blood cell; φX, phage antigen.

Modified from Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, Saunders.*

Table 122-8 2003 Modified IUIS Classification of Primary and Secondary Immunodeficiencies

GROUPS AND DISEASES	INHERITANCE
A. PREDOMINANTLY ANTIBODY DEFICIENCIES	
XL agammaglobulinemia	XL
AR agammaglobulinemia	AR
Hyper-IgM syndromes	XL and AR
a. CD40L defect	XL
b. AID defect	AR
c. CD40 defect	AR
d. UNG defect	AR
e. Other hyper-IgM defects	AR
Ig heavy-chain gene deletions	AR
κ Chain deficiency mutations	AR
Selective IgA deficiency	AD
Common variable immunodeficiency	AD
B. SEVERE COMBINED IMMUNODEFICIENCIES	
$T^-B^+NK^-$ SCID	
a. X-linked (γc deficiency)	XL
b. Autosomal recessive (Jak3 deficiency)	AR
$T^-B^+NK^+$ SCID	
a. IL-7 Rα deficiency	AR
b. CD3δ, CD3ε, or CD3ζ deficiencies	AR
c. CD45 deficiency	AR
$T^-B^-NK^+$ SCID	
a. RAG-1/2 deficiency	AR
b. Artemis defect	AR
Omenn Syndrome	
a. RAG-1/2 deficiency	AR
b. IL-7Rα deficiency	AR
c. γc deficiency	XL
Combined Immunodeficiencies	
a. Purine nucleoside phosphorylase deficiency	AR
b CD8 deficiency (ZAP-70 defect)	AR
c. MHC class II deficiency	AR
d. MHC class I deficiency caused by TAP-1/2 mutations	AR
Reticular dysgenesis	AR
C. OTHER CELLULAR IMMUNODEFICIENCIES	
Wiskott-Aldrich syndrome	XL
Ataxia-telangiectasia	AR
DiGeorge anomaly	?
D. DEFECTS OF PHAGOCYTIC FUNCTION	
Chronic Granulomatous Disease	
a. XL	XL
b. AR	AR
1. p22 phox deficiency	
2. p47 phox deficiency	
3. p67 phox deficiency	
Leukocyte adhesion defect 1	AR
Leukocyte adhesion defect 2	AR
Neutrophil G6PD deficiency	XL
Myeloperoxidase deficiency	AR
Secondary granule deficiency	AR
Shwachman syndrome	AR
Severe congenital neutropenia (Kostmann)	AR
Cyclic neutropenia (elastase defect)	AR
Leukocyte mycobacterial defects	AR
IFN-γR1 or R2 deficiency	AR
IFN-γR1 deficiency	AD
IL-12Rβ1 deficiency	AR
IL-12p40 deficiency	AR
STAT1 deficiency	AD
E. IMMUNODEFICIENCIES ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS	
Fas deficiency	AD
Fas ligand deficiency	
FLICE or caspase 8 deficiency	
Unknown (caspase 3 deficiency)	
F. COMPLEMENT DEFICIENCIES	
C1q deficiency	AR
C1r deficiency	AR
C4 deficiency	AR
C2 deficiency	AR
C3 deficiency	AR
C5 deficiency	AR
C6 deficiency	AR
C7 deficiency	AR
C8α deficiency	AR
C8β deficiency	AR
C9 deficiency	AR
C1 inhibitor	AD
Factor I deficiency	AR
Factor H deficiency	AR
Factor D deficiency	AR
Properdin deficiency	XL
G. IMMUNODEFICIENCY ASSOCIATED WITH OR SECONDARY TO OTHER DISEASES	
Chromosomal Instability or Defective Repair	
Bloom syndrome	
Fanconi anemia	
ICF syndrome	
Nijmegen breakage syndrome	
Seckel syndrome	
Xeroderma pigmentosum	
Chromosomal Defects	
Down syndrome	
Turner syndrome	
Chromosome 18 rings and deletions	
Skeletal Abnormalities	
Short-limbed skeletal dysplasia	
Cartilage-hair hypoplasia	
Immunodeficiency with Generalized Growth Retardation	
Schimke immuno-osseous dysplasia	
Immunodeficiency with absent thumbs	
Dubowitz syndrome	
Growth retardation, facial anomalies, and immunodeficiency	
Progeria (Hutchinson-Gilford syndrome)	
Immunodeficiency with Dermatologic Defects	
Partial albinism	
Dyskeratosis congenita	
Netherton syndrome	
Acrodermatitis enteropathica	
Anhidrotic ectodermal dysplasia	
Papillon-Lefèvre syndrome	
Hereditary Metabolic Defects	
Transcobalamin 2 deficiency	
Methylmalonic acidemia	
Type 1 hereditary orotic aciduria	
Biotin-dependent carboxylase deficiency	
Mannosidosis	
Glycogen storage disease, type 1b	
Chédiak-Higashi syndrome	
Hypercatabolism of Immunoglobulin	
Familial hypercatabolism	
Intestinal lymphangiectasia	
H. OTHER IMMUNODEFICIENCIES	
Hyper-IgE syndromes	AD and AR
Chronic mucocutaneous candidiasis	
Chronic mucocutaneous candidiasis with polyendocrinopathy (APECED)	AR
Hereditary or congenital hyposplenia or asplenia	
Ivemark syndrome	
IPEX syndromes	XL
Ectodermal dysplasia (NEMO defect)	XL

AD, autosomal dominant; ADA, adenosine deaminase; AID, activation-induced cytidine deaminase; APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; AR, autosomal recessive; caspase, cysteinyl aspartate specific proteinase; FLICE, Fas-associating protein with death domain–like IL-1–converting enzyme; G6PD, glucose 6-phosphate dehydrogenase; ICF, immunodeficiency, centromeric instability, facial anomalies; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy; IUIS, International Union of Immunological Societies; MHC, major histocompatibility complex; NEMO, nuclear factor B essential modulator; SCID, severe combined immunodeficiency; TAP-2, transporter associated with antigen presentation; UNG, uracil-N-glycosylase; XL, X-linked.

Modified from (no authors listed) Primary immunodeficiency diseases. Report of an International Union of Immunological Studies Scientific Committee, Clin Exp Immunol *118:1–28, 1999; Chapel H, Geha R, Rosen F: IUIS PID (Primary Immunodeficiencies) Classification committee: Primary immunodeficiency diseases: an update,* Clin Exp Immunol *132:9–15, 2003; Stiehm ER, Ochs HD, Winkelstein JA:* Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

Table 126-3 Hyperimmunoglobulin E Syndromes

	AUTOSOMAL DOMINANT OR SPORADIC (JOB SYNDROME)	AUTOSOMAL RECESSIVE
Gene	*STAT3*	*DOCK8:* less often *TYK2*
INFECTIONS		
Sinopulmonary		
Recurrent bacterial	*S. aureus*, pneumococcus, *H. influenzae*	*S. aureus*, pneumococcus, *H. influenzae*
Pneumatoceles/bronchiectasis	Common	No
Fungal	Aspergillus species	No
Cutaneous		
Abscesses	*S. aureus*	*S. aureus*
Viral	No	HPV, HSV, VZV, MCV
Mucocutaneous candidiasis	Common	Common
ATOPIC DISORDERS		
Newborn eosinophilic pustules	Common	No
Eczema	Common	Common
Asthma	No	Common
Allergies/Anaphylaxis	No	Common
MUSCULOSKELETAL		
Osteopenia, pathologic fractures	Common	No
Scoliosis	Common	No
Retained primary teeth	Common	No
Hyperextensible	Common	No
OTHER FEATURES		
Coarse facies*	Common in adolescent	No
Coronary artery tortuosity/aneurysm	Common	No
UBO on brain MRI	Common	No
Lymphomas	Yes	Higher incidence
Cutaneous malignancy	No	Yes
Mortality	Adulthood	Childhood

*Coarse facies includes broad nose, prominent forehead and chin, deep set eyes

HPV, human papillomavirus; HSV, herpes simplex virus; MCV, molluscum virus; UBO, unidentified bright objects of cerebral cortex on T_2 MRI; VZV, varicella-zoster virus.

Table 126-4 Infection in the Host Compromised by B- and T-Cell Immunodeficiency Syndromes

IMMUNODEFICIENCY SYNDROME	OPPORTUNISTIC ORGANISMS ISOLATED MOST FREQUENTLY	APPROACH TO TREATMENT OF INFECTIONS	PREVENTION OF INFECTIONS
B-cell immunodeficiencies	Encapsulated bacteria (*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae*, and *Neisseria meningitidis*), *Pseudomonas aeruginosa, Campylobacter* sp., enteroviruses, rotaviruses, *Giardia lamblia, Cryptosporidium* sp., *Pneumocystis jiroveci, Ureaplasma urealyticum*, and *Mycoplasma pneumoniae*	1. IVIG 200-800 mg/kg 2. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 3. Incision and drainage if abscess present 4. Antibiotic selection on the basis of sensitivity data	1. Maintenance IVIG for patients with quantitative and qualitative defects in IgG metabolism (400-800 mg/kg q 3-5 wk) 2. In chronic recurrent respiratory disease, vigorous attention to postural drainage 3. In selected cases (recurrent or chronic pulmonary or middle ear), prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole
T-cell immunodeficiencies	Encapsulated bacteria (*S. pneumoniae, H. influenzae, S. aureus*), facultative intracellular bacteria (*Mycobacterium tuberculosis*, other *Mycobacterium* sp., and *Listeria monocytogenes*); *Escherichia coli; P. aeruginosa; Enterobacter* sp.; *Klebsiella* sp.; *Serratia marcescens; Salmonella* sp.; *Nocardia* sp.; viruses (cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, rotaviruses, adenoviruses, enteroviruses, respiratory syncytial virus, measles virus, vaccinia virus, and parainfluenza viruses); protozoa (*Toxoplasma gondii* and *Cryptosporidium* sp.); and fungi (*Candida* sp., *Cryptococcus neoformans, Histoplasma capsulatum*, and *P. jiroveci*)	1. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 2. Incision and drainage if abscess present 3. Antibiotic selection on the basis of sensitivity data 4. Early antiviral treatment for herpes simplex, cytomegalovirus, and varicella-zoster viral infections 5. Topical and nonadsorbable antimicrobial agents frequently are useful	1. Prophylactic administration of trimethoprim-sulfamethoxazole for prevention of *P. jiroveci* pneumonia 2. Oral nonadsorbable antimicrobial agents to lower concentration of gut flora 3. No live virus vaccines or bacillus Calmette-Guérin vaccine 4. Careful tuberculosis screening

IVIG, intravenous immunoglobulin.

From Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

Table 126-6 Clinical and Laboratory Features of IPEX and IPEX-Like Disorders

	IPEX	CD25	STAT5B	STAT1	ITCH
AUTOIMMUNITY					
Eczema	+++	+++	++	++	++
Enteropathy	+++	+++	++	++	++
Endocrinopathy	+++	++	+	++	++
Allergic disease	+++	+	+	++	++
Cytopenias	++	++	++	–	
Lung disease	+	++	+++	+	+++
INFECTIONS					
Yeast	–	++	–	+++	–
Herpes virus	–	+++ (EBV/CMV)	++ (VZV)	++	–
Bacterial	+/–	++	++	++	+
Associated features	None	None	Growth failure	Vascular anomalies	Dysmorphic growth failure
Serum immunoglobulins	Elevated	Elevated or normal	Elevated or normal	Low, normal, or high	Elevated
Serum IgE	Elevated	Normal or elevated	Normal or elevated	Normal or mildly elevated	Elevated
CD25 expression	Normal	Absent	Normal or low	Normal	Not tested
CD4+CD45RO	Elevated	Elevated	Elevated	Normal or high	Not tested
FOXP3 expression	Absent or normal	Normal or low	Normal or low	Normal	Not tested
IGF-1, IGFBP-3	Normal	Normal	Low	Normal	Not tested
Prolactin	Normal	Normal	Elevated	Normal	Not tested

CMV, cytomegalovirus; EBV, Epstein Barr Virus; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor–binding protein 3; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; VZV, varicella zoster virus; ITCH, ubiquitin ligase deficiency.

From: Verbsky JW, Chatila TA: Immune dysregulation, polyendocrinopathy, enteropathy, X–linked (IPEX) and IPEX–related disorders: an evolving web of heritable autoimmune diseases. Curr Opin Pediatr *25:708–715, 2013, Table 1, p. 709.*

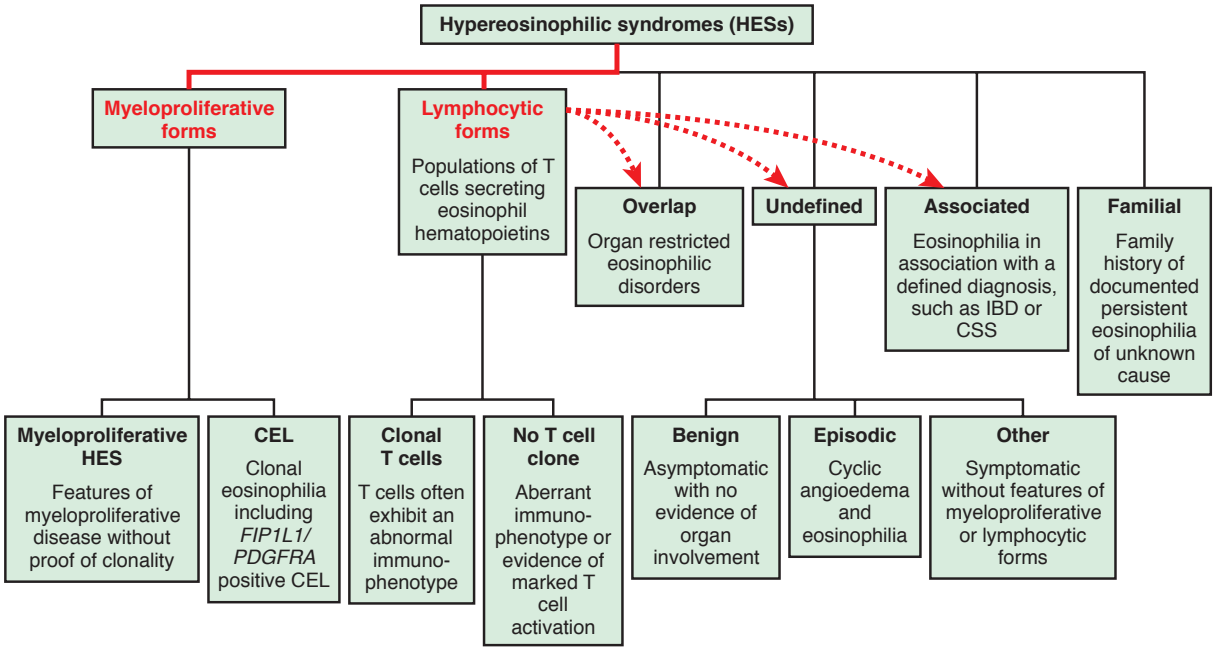


Figure 129-1 Revised classification of hypereosinophilic syndromes. Changes from the previous classification are indicated in *red. Dashed arrows* identify hypereosinophilic syndrome (HES) forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin–producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. *IBD,* Inflammatory bowel disease. *(From Simon HU, Rothenberg ME, Bocher BS, et al: Refining the definition of hypereosinophilic syndrome.* J Allergy Clin Immunol *126:45–49, 2010, Fig. 1, p. 47.)*

Table 130-3 Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	TYPE 1 (LAD1)	TYPE 2 (LAD2 OR CDG-IIC)	TYPE 3 (LAD3)	E-SELECTIN DEFICIENCY	RAC2 DEFICIENCY
OMIM	116920	266265	612840	131210	602049
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive	Unknown	Autosomal dominant
Affected protein(s)	Integrin β_2 common chain (CD18)	Fucosylated proteins (e.g., sialyl-Lewis^x, CD15s)	Kindlin 3	Endothelial E-selectin expression	Rac2
Neutrophil function affected	Chemotaxis, tight adherence	Rolling, tethering	Chemotaxis, adhesion, superoxide production	Rolling, tethering	Chemotaxis, superoxide production
Delayed umbilical cord separation	Yes (severe phenotype only)	Yes	Yes	Yes	Yes
Leukocytosis/ neutrophilia	Yes	Yes	Yes	No (mild neutropenia)	Yes

OMIM, Online Mendelian Inheritance in Man.

From Leung DYM: Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Table 12-4, p. 139.*

Table 129-1 Causes of Eosinophilia

ALLERGIC DISORDERS
Allergic rhinitis
Asthma
Acute and chronic urticaria
Pemphigoid
Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
Eosinophilic gastrointestinal disorders
Interstitial nephritis
INFECTIOUS DISEASES
Tissue-Invasive Helminth Infections
Trichinosis
Toxocariasis
Strongyloidosis
Ascariasis
Filariasis
Schistosomiasis
Echinococcosis
Pneumocystis carinii
Toxoplasmosis
Scarlet fever
Amebiasis
Malaria
Bronchopulmonary aspergillosis
Coccidioidomycosis
Scabies
MALIGNANT DISORDERS
Brain tumors
Hodgkin disease and T-cell lymphoma
Acute myelogenous leukemia
Myeloproliferative disorders
Eosinophilic leukemia
GASTROINTESTINAL DISORDERS
Inflammatory bowel disease
Peritoneal dialysis
Chronic active hepatitis
Eosinophilic gastrointestinal disorders:
• Eosinophilic esophagitis
• Eosinophilic gastroenteritis
• Eosinophilic colitis
RHEUMATOLOGIC DISEASE
Rheumatoid arthritis
Eosinophilic fasciitis
Scleroderma
IMMUNODEFICIENCY DISEASE
Hyperimmunoglobulin E syndromes
Wiskott-Aldrich syndrome
Graft-versus-host disease
Omenn syndrome
Severe congenital neutropenia
Hypersensitivity pneumonia
MISCELLANEOUS
Thrombocytopenia with absent radii
Churg-Strauss syndrome (eosinophilic granulomatosis with vasculitis)
Vasculitis
Adrenal insufficiency
Postirradiation of abdomen
Histiocytosis with cutaneous involvement
Hypereosinophilic syndromes
Autoimmune lymphoproliferative syndromes (ALPS)
Immune dysregulation, polyendocrinopathy, X-linked (IPEX)

Table 130-1 Infections and WBC Defects: Features That Can Be Seen in Phagocyte Disorders

SEVERE INFECTIONS		RECURRENT INFECTIONS		SPECIFIC INFECTIONS		UNUSUALLY LOCATED INFECTIONS	
TYPE OF INFECTION	**DIAGNOSIS TO CONSIDER**	**SITE OF INFECTION**	**DIAGNOSIS TO CONSIDER**	**MICROORGANISM**	**DIAGNOSIS TO CONSIDER**	**SITE OF INFECTION**	**DIAGNOSIS TO CONSIDER**
Cellulitis	Neutropenia, LAD CGD, HIES	Cutaneous	Neutropenia, CGD, LAD, HIES	*Staphylococcus epidermidis*	Neutropenia, LAD	Umbilical cord	LAD
Colitis	Neutropenia, CGD	Gums	LAD, neutrophil motility disorders	*Serratia marcescens, Nocardia, Burkholderia cepacia*	CGD	Liver abscess	CGD
Osteomyelitis	CGD, MSMD pathway defects	Upper and lower respiratory tract	Neutropenia, HIES, functional neutrophil disorders	*Aspergillus*	Neutropenia, CGD, HIES	Gums	LAD, neutrophil motility disorders
		Gastrointestinal tract	CGD, MSMD pathway defects (salmonella)	Nontuberculous mycobacteria, BCG	MSMD pathway defects, SCID, CGD		
		Lymph nodes	CGD, MSMD pathway defects (mycobacteria)	*Candida*	Neutropenia, CGD, MPO		
		Osteomyelitis	CGD, MSMD				

BCG, bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyperimmunoglobulin E syndrome; LAD, leukocyte adhesion deficiency; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.
From Leung DYM: Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Table 12-1, p. 134.*

Table 130-2 Clinical Disorders of Neutrophil Function

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DEGRANULATION ABNORMALITIES			
Chédiak-Higashi syndrome	Autosomal recessive; disordered coalescence of lysosomal granules; responsible gene is *CHSI/LYST*, which encodes a protein hypothesized to regulate granule fusion	Decreased neutrophil chemotaxis, degranulation, and bactericidal activity; platelet storage pool defect; impaired NK function, failure to disperse melanosomes	Neutropenia; recurrent pyogenic infections, propensity to develop marked hepatosplenomegaly as a manifestation of the hemophagocytic syndrome
Specific granule deficiency	Autosomal recessive; functional loss of myeloid transcription factor arising from a mutation or arising from reduced expression of *Gfi-1* or *C/EBPε*, which regulates specific granule formation	Impaired chemotaxis and bactericidal activity; bilobed nuclei in neutrophils; defensins, gelatinase, collagenase, vitamin B_{12}–binding protein, and lactoferrin	Recurrent deep-seated abscesses
ADHESION ABNORMALITIES			
Leukocyte adhesion deficiency 1	Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins (β_2 integrins) on leukocyte membranes most commonly arising from failure to express CD18 messenger RNA	Decreased binding of C3bi to neutrophils and impaired adhesion to ICAM1 and ICAM2	Neutrophilia; recurrent bacterial infection associated with a lack of pus formation
Leukocyte adhesion deficiency 2	Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol-conjugates arising from mutations of the GDP-fucose transporter	Decreased adhesion to activated endothelium expressing ELAM	Neutrophilia; recurrent bacterial infection without pus
Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome)	Autosomal recessive; impaired integrin function arising from mutations of *FERMT3* which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to β-integrin and thereby transmits integrin activation	Impaired neutrophil adhesion and platelet activation	Neutrophilia; recurrent infections, bleeding tendency

Continued

Table 130-2 Clinical Disorders of Neutrophil Function—cont'd

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DISORDERS OF CELL MOTILITY			
Enhanced motile responses; FMF	Autosomal recessive gene responsible for FMF on chromosome 16 which encodes for a protein called pyrin; pyrin regulates caspase-1 and thereby IL-1β secretion; mutated pyrin may lead to heightened sensitivity to endotoxin, excessive IL-1β production, and impaired monocyte apoptosis	Excessive accumulation of neutrophils at inflamed sites, which may be the result of excessive IL-1β production	Recurrent fever, peritonitis, pleuritis, arthritis, and amyloidosis
DEPRESSED MOTILE RESPONSES			
Defects in the generation of chemotactic signals	IgG deficiencies; C3 and properdin deficiency can arise from genetic or acquired abnormalities; mannose-binding protein deficiency predominantly in neonates	Deficiency of serum chemotaxis and opsonic activities	Recurrent pyogenic infections
Intrinsic defects of the neutrophil, e.g., LAD, Chédiak-Higashi syndrome, specific granule deficiency, neutrophil actin dysfunction, neonatal neutrophils	In the neonatal neutrophil there is diminished ability to express β_2 integrins, and there is a qualitative impairment in β_2-integrin function	Diminished chemotaxis	Propensity to develop pyogenic infections
Direct inhibition of neutrophil mobility, e.g., drugs	Ethanol, glucocorticoids, cyclic AMP	Impaired locomotion and ingestion; impaired adherence	Possible cause for frequent infections; neutrophilia seen with epinephrine arises from cyclic AMP release from endothelium
Immune complexes	Bind to Fc receptors on neutrophils in patients with rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory states	Impaired chemotaxis	Recurrent pyogenic infections
Hyper-IgE syndrome	Autosomal dominant; responsible gene is *Stat3*	Impaired chemotaxis at times; impaired regulation of cytokine production	Recurrent skin and sinopulmonary infections, eczema, mucocutaneous candidiasis, eosinophilia, retained primary teeth, minimal trauma fractures, scoliosis, and characteristic facies
Hyper-IgE syndrome–AR	Autosomal recessive; more than 1 gene likely contributes to its etiology	High IgE levels, impaired lymphocyte activation to staphylococcal antigens	Recurrent pneumonia without pneumatoceles sepsis, enzyme, boils, mucocutaneous candidiasis, neurologic symptoms, eosinophilia
MICROBICIDAL ACTIVITY			
Chronic granulomatous disease	X-linked and autosomal recessive; failure to express functional $gp91^{phox}$ in the phagocyte membrane in $p22^{phox}$ (AR). Other AR forms of CGD arise from failure to express protein $p47^{phox}$ or $p67^{phox}$	Failure to activate neutrophil respiratory burst leading to failure to kill catalase-positive microbes	Recurrent pyogenic infections with catalase-positive microorganisms
G6PD deficiency	Less than 5% of normal activity of G6PD	Failure to activate NADPH-dependent oxidase, and hemolytic anemia	Infections with catalase-positive microorganisms
Myeloperoxidase deficiency	Autosomal recessive; failure to process modified precursor protein arising from missense mutation	H_2O_2-dependent antimicrobial activity not potentiated by myeloperoxidase	None
Rac2 deficiency	Autosomal dominant; dominant negative inhibition by mutant protein of Rac2-mediated functions	Failure of membrane receptor–mediated O_2^- generation and chemotaxis	Neutrophilia, recurrent bacterial infections
Deficiencies of glutathione reductase and glutathione synthetase	AR; failure to detoxify H_2O_2	Excessive formation of H_2O_2	Minimal problems with recurrent pyogenic infections

AMP, adenosine monophosphate; AR, autosomal recessive; C, complement; CD, cluster of differentiation; CGD, chronic granulomatous disease; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; Ig, immunoglobulin; IL-1, interleukin-1; LAD, leukocyte adhesion deficiency; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

Modified from Curnutte JT, Boxer LA: Clinically significant phagocytic cell defects. In Remington JS, Swartz MN, editors: Current clinical topics in infectious disease, *ed 6, New York, 1985, McGraw-Hill, p 144.*

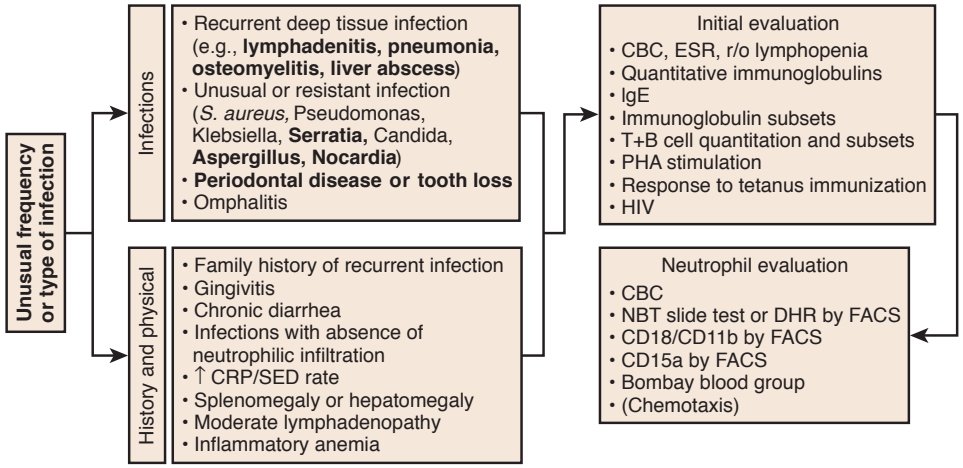


Figure 130-1 Algorithm for clinical evaluation of patients with recurrent infections. Shown are the evaluations that can be done in a routine clinical laboratory. The CBC can detect marked leukocytosis in LAD and giant granules of Chédiak-Higashi may be seen on the smear. Chemotaxis and all other neutrophil functions assays require highly specialized research laboratories. *CBC,* complete blood count; *CD,* cluster of differentiation; *CRP,* C-reactive protein; *DHR,* dihydrorhodamine; *ESR,* erythrocyte sedimentation rate; *HIV,* human immunodeficiency virus; *Ig,* immunoglobulin; *NBT,* nitro blue tetrazolium. *(Modified from Dinauer, MC, Coates TD, Disorders of neutrophil function. In Hoffman R, Benz EJ, Silberstein LE, Helsop H, Weitz J, Anastasi J, editors:* Hematology: basic principles and practice, *ed 6, Philadelphia, 2012, WB Saunders, pp. 655–674.)*

Table 131-1 Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION	
• History of acute or chronic leukopenia	
• General medical history	Congenital syndromes (Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport)
• Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies	
• Spleen size	Hypersplenism
• History of drug exposure	Drug-associated neutropenia
• Complete blood count with differential and reticulocyte counts	Neutropenia, aplastic anemia, autoimmune cytopenias
IF ANC <1,000/μL *Evaluation of Acute Onset Neutropenia*	
• Repeat blood counts in 3-4 weeks	Transient myelosuppression (e.g., viral)
• Serology and cultures for infectious agents	Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia
• Discontinue drug(s) associated with neutropenia	Drug-associated neutropenia
• Test for antineutrophil antibodies	Autoimmune neutropenia
• Measure quantitative immunoglobulins (G, A, and M), lymphocyte subsets	Neutropenia associated with disorders of immune function
IF ANC <500/μL ON 3 SEPARATE TESTS	
• Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia
• Glucocorticoid stimulation test	Chronic benign or idiopathic neutropenia, some autoimmune neutropenias
• Serial CBCs (3/wk for 6 wk)	Cyclic neutropenia
• Exocrine pancreatic function	Shwachman-Diamond syndrome
• Skeletal radiographs	Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
IF ALC <1000/μL	
• Repeat blood counts in 3-4 weeks	Transient leukopenia (e.g., viral)
IF ALC <1000/μL ON 3 SEPARATE TESTS	
• HIV-1 antibody or RNA test	HIV-1 infection, AIDS
• Quantitative immunoglobulins (G, A, and M), lymphocyte subsets	Congenital or acquired disorders of immune function
IF THERE IS PANCYTOPENIA	
• Bone marrow aspiration and biopsy	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia
• Bone marrow cytogenetics	Myelodysplasia, leukemia
• Vitamin B_{12} and folate levels	Vitamin deficiencies

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

Table 131-2 Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Clinical features and laboratory findings of the infectious agent
Drug-induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody
Immune neutropenia	Alloimmune, autoimmune	Myeloid hyperplasia with left shift in bone marrow (may appear to be "arrest" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, malignant cells in bone marrow
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

Table 131-3 Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12} or folate deficiency	Malnutrition; congenital deficiency of B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hypersegmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birth weight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect secondary to mutation of *PIG-A* gene	Pancytopenia, thrombosis

Table 131-4 Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella
Bacterial	*Anaplasma* (formerly *Ehrlichia*) *phagocytophilum*, brucella, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	Psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

Table 131-5 Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses required
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasia

Table 131-6 Intrinsic Disorders of Myeloid Precursor Cells

SYNDROME	INHERITANCE *(GENE)*	CLINICAL FEATURES (INCLUDING STATIC NEUTROPENIA UNLESS OTHERWISE NOTED)
PRIMARY DISORDERS OF MYELOPOIESIS		
Cyclic neutropenia	AD *(ELANE)*	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD (primarily *ELANE*, also *GFI* and others)	Risk of MDS/AML
	AR *(G6PC3, HAX1)* (*HAX1* = Kostmann syndrome)	*G6PC3:* cardiac and urogenital anomalies, venous angiectasias; *HAX1:* neurologic abnormalities, risk of MDS/AML
	XL *(WAS)*	Neutropenic variant of Wiskott-Aldrich syndrome
DISORDERS OF MOLECULAR PROCESSING		
Shwachman-Diamond syndrome	Ribosomal defect: AR *(SBDS)*	Pancreatic insufficiency, metaphysical dysostosis, bone marrow failure, MDS/AML
Dyskeratosis congenita	Telomerase defects: XL *(DKC1)*, AD *(TERC)*, AR *(TERT)*	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure
DISORDERS OF VESICULAR TRAFFICKING		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired natural killer cell function, HLH
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired natural killer cell function, neurological impairment, HLH
Cohen syndrome	AR *(COH1)*	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism
Hermansky-Pudlak syndrome, type II	AR *(AP3P1)*	Cyclic neutropenia, partial albinism, HLH
p14 deficiency	Probable AR *(MAPBPIP)*	Partial albinism, decreased B and T cells
VPS45 defects	AR *(VPS45)*	neutrophil dysfunction, bone marrow fibrosis, nephromegaly
DISORDERS OF METABOLISM		
Glycogen storage disease, type 1b	AR *(G6PT1)*	Hepatic enlargement, growth retardation, impaired neutrophil motility
Barth syndrome	XL *(TAZ1)*	Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria
Pearson syndrome	Mitochondrial (DNA deletions)	Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys
NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION		
Common variable immunodeficiency	Familial, sporadic *(TNFRSF13B)*	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or *TNFRSF13B*)	Decreased IgA
Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL *(HIGM1)*	Absent IgG, elevated IgM, autoimmune cytopenias
WHIM syndrome	AD *(CXCR4)*	Warts, hypogammaglobulinemia, infections, myelokathexis
Cartilage-hair hypoplasia	AR *(RMKP)*	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	Probable AR *(SMARCAL1)*	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure
X-linked agammaglobulinemia	BTK	Agammaglobulinemia, neutropenia in ~25%

AD, autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; Ig, immunoglobulin; MDS, myelodysplasia; XL, X-linked, BTK, Briton tyrosine kinase.

Table 131-7 Causes of Lymphocytopenia

ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury
INHERITED	
Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxia-telangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome

PUVA, psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

Table 132-1 Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

Table 132-2 Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial infections	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis typhoid
Nonbacterial infections	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

Table 132-2 Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial infections	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis typhoid
Nonbacterial infections	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

Table 136-1 Indications to Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia after an isolated extramedullary relapse
- Relapsed Hodgkin or non-Hodgkin lymphoma
- Stage IV or relapsed neuroblastoma
- High-risk, relapsed, or resistant brain tumors
- Stage IV Ewing sarcoma
- Life-threatening autoimmune diseases resistant to conventional treatments

Table 132-1 Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

Table 135-1 Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia

First complete remission for patients at very high risk of relapse

- Translocation t(9;22) or t(4;11)
- Early thymocyte precursor phenotype
- Nonresponder after 1 wk of corticosteroid therapy and
  - T-immunophenotype or
  - >100,000 cells/μL at diagnosis
- Not in remission at the end of the induction phase
- Marked hypodiploidy (<43 chromosomes)
- High levels of minimal residual disease at the end of induction therapy

Second complete remission

Third or later complete remission

- Acute myeloid leukemia in 1st complete remission or in advanced disease phase
- Philadelphia chromosome–positive chronic myeloid leukemia
- Myelodysplastic syndromes
- Hodgkin and non-Hodgkin lymphomas
- Selected solid tumors
  - Metastatic neuroblastoma
  - Rhabdomyosarcoma refractory to conventional treatment
  - Very-high-risk Ewing sarcoma
- Severe acquired aplastic anemia
- Fanconi anemia
- Congenital dyskeratosis
- Diamond-Blackfan anemia
- Thalassemia major
- Sickle cell disease
- Variants of severe combined immunodeficiency
- Hyperimmunoglobulin M syndrome
- Leukocyte adhesion deficiency
- Omenn syndrome
- Wiskott-Aldrich syndrome
- Chédiak-Higashi syndrome
- Kostmann syndrome (infantile malignant agranulocytosis), chronic granulomatous disease and other severe neutrophil defects
- X-linked lymphoproliferative disease (Duncan syndrome)
- Hemophagocytic lymphohistiocytosis
- Selected severe variants of platelet function disorders (e.g., Glanzmann thromboasthenia, or congenital amegakaryocytic thrombocytopenia)
- Selected types of mucopolysaccharidosis (Hurler disease) or other liposomal/peroxisomal disorders (Krabbe disease, adrenoleukodystrophy)
- Infantile malignant osteopetrosis
- Life-threatening cytopenia unresponsive to conventional treatments

Allergic Disorders

Table 141-2 Nonallergic Diseases Associated with Increased Serum IgE Concentrations

PARASITIC INFESTATIONS
Ascariasis
Capillariasis
Echinococcosis
Fascioliasis
Filariasis
Hookworm
Onchocerciasis
Malaria
Paragonimiasis
Schistosomiasis
Strongyloidiasis
Trichinosis
Visceral larva migrans
INFECTIONS
Allergic bronchopulmonary aspergillosis
Candidiasis, systemic
Coccidioidomycosis
Cytomegalovirus mononucleosis
Human immunodeficiency virus type 1 infections
Infectious mononucleosis (Epstein-Barr virus)
Leprosy
Pertussis
Viral respiratory infections
IMMUNODEFICIENCY
Autosomal dominant hyperimmunoglobulin E syndrome (*STAT3* mutations)
Autosomal recessive hyperimmunoglobulin E syndrome (*DOCK8, TYK2* mutations)
IgA deficiency, selective
Nezelof syndrome (cellular immunodeficiency with immunoglobulins)
Thymic hypoplasia (DiGeorge anomaly)
Wiskott-Aldrich syndrome
NEOPLASTIC DISEASES
Hodgkin disease
IgE myeloma
Bronchial carcinoma
OTHER DISEASES AND DISORDERS
Alopecia areata
Bone marrow transplantation
Burns
Cystic fibrosis
Dermatitis, chronic acral
Erythema nodosum, streptococcal infection
Guillain-Barré syndrome
Kawasaki disease
Liver disease
Medications
Nephritis, drug-induced interstitial
Nephrotic syndrome
Pemphigus, bullous
Polyarteritis nodosa, infantile
Primary pulmonary hemosiderosis
Rheumatoid arthritis

Table 141-3 Determination of Specific IgE by Skin Testing Versus In Vitro Testing

VARIABLE	SKIN TEST*	sIgE ASSAY
Risk of allergic reaction	Yes (especially ID)	No
Relative sensitivity	High	High
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermographism	Yes	No
Broad selection of antigens	Fewer	Yes
Immediate results	Yes	No
Expensive	No	Yes
Lability of allergens	Yes	No
Results evident to patient	Yes	No

*Skin testing may be the prick test or intradermal (ID) injection.

Table 141-1 Differential Diagnosis of Childhood Eosinophilia

PHYSIOLOGIC
Prematurity
Infants receiving hyperalimentation
Hereditary
INFECTIOUS
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)
Mycobacterial (tuberculosis, leprosy)
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)
PULMONARY
Allergic (rhinitis, asthma)
Churg-Strauss syndrome
Loeffler syndrome
Hypersensitivity pneumonitis
Eosinophilic pneumonia (chronic, acute)
Pulmonary interstitial eosinophilia
DERMATOLOGIC
Atopic dermatitis
Pemphigus
Dermatitis herpetiformis
Infantile eosinophilic pustular folliculitis
Eosinophilic fasciitis (Schulman syndrome)
Eosinophilic cellulitis (Wells syndrome)
Kimura disease (angiolymphoid hyperplasia with eosinophilia)
HEMATOLOGIC/ONCOLOGIC
Neoplasm (lung, gastrointestinal, uterine)
Leukemia/lymphoma
Myelofibrosis
Myeloproliferative (FIP1L1-PDGFRA–positive) hypereosinophilic syndrome
Lymphatic hypereosinophilic syndrome
Systemic mastocytosis
IMMUNOLOGIC
T-cell immunodeficiencies
Hyperimmunoglobulin E (Job) syndrome
Wiskott-Aldrich syndrome
Graft-versus-host disease
Drug hypersensitivity
Postirradiation
Postsplenectomy
ENDOCRINE
Addison disease
Hypopituitarism
CARDIOVASCULAR
Loeffler disease (fibroplastic endocarditis)
Congenital heart disease
Hypersensitivity vasculitis
Eosinophilic myocarditis
GASTROINTESTINAL
Benign proctocolitis
Inflammatory bowel disease
Eosinophilic gastrointestinal diseases (EGID)

FIP1L1-PDGFRA, FIP1-like 1–platelet-derived growth factor receptorα.

Table 143-1 Causes of Nonallergic Rhinitis

Structural/mechanical factors:
- Deviated septum/septal wall anomalies
- Hypertrophic turbinates
- Adenoidal hypertrophy
- Foreign bodies

Nasal tumors:
- Benign
- Malignant
- Choanal atresia

Infectious:
- Acute
- Chronic

Inflammatory/immunologic:
- Granulomatosis with polyangiitis
- Sarcoidosis
- Midline granuloma
- Systemic lupus erythematosus
- Sjögren syndrome
- Nasal polyposis

Physiologic:
- Ciliary dyskinesia syndrome
- Atrophic rhinitis

Hormonally induced:
- Hypothyroidism
- Pregnancy
- Oral contraceptives
- Menstrual cycle
- Exercise
- Atrophic

Drug induced:
- Rhinitis medicamentosa
- Oral contraceptives
- Antihypertensive therapy
- Aspirin
- Nonsteroidal antiinflammatory drugs

Reflex induced:
- Gustatory rhinitis
- Chemical or irritant induced
- Posture reflexes
- Nasal cycle
- Environmental factors:
- Odors
- Temperature
- Weather/barometric pressure
- Occupational
- Nonallergic rhinitis with eosinophilia syndrome
- Perennial nonallergic rhinitis (vasomotor rhinitis)
- Emotional factors

Table 142-2 Classification of Antihistamines (H_1-Antagonists)

CLASS	EXAMPLES
ETHYLENEDIAMINES	
First-generation	Antazoline, pyrilamine, tripelennamine
TYPE II ETHANOLAMINES	
First-generation	Carbinoxamine, clemastine, diphenhydramine
TYPE III ALKYLAMINES	
First-generation	Brompheniramine, chlorpheniramine, triprolidine
Second-generation	Acrivastine
TYPE IV PIPERAZINES	
First-generation	Cyclizine, hydroxyzine, meclizine
Second-generation	Cetirizine, levocetirizine
TYPE V PIPERIDINES	
First-generation	Azatadine, cyproheptadine, ketotifen
Second-generation	Fexofenadine, loratadine, desloratadine
TYPE VI PHENOTHIAZINES	
First-generation	Methdilazine, promethazine

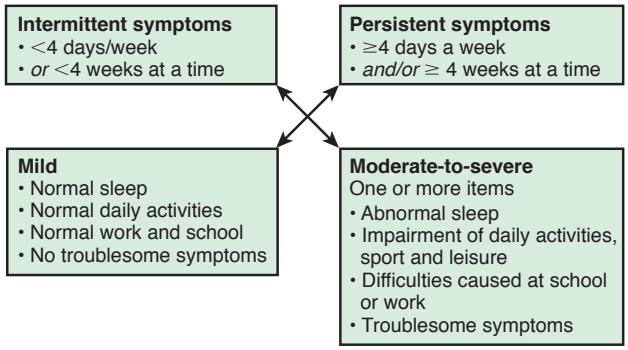


Figure 143-1 ARIA classification of allergic rhinitis. Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-to-severe persistent seasonal rhinitis in June and July and be suitable for specific allergen immunotherapy.

Table 142-1 Environmental Control of Allergen Exposure

ALLERGEN	CONTROL MEASURES
Dust mites	Encase bedding in airtight, allergen-impermeable covers Wash bedding weekly in water at temperatures >54.4°C (130°F) Remove wall-to-wall carpeting Replace curtains with blinds Remove upholstered furniture Reduce indoor humidity Minimize bedroom and living room clutter
Animal dander	Avoid furred pets Keep animals out of patient's bedroom
Cockroaches	Control available food and water sources Keep kitchen/bathroom surfaces dry and free of standing water Seal cracks in walls Use professional extermination services; safe pesticide should be used in baits
Mold	Repair moisture-prone areas Avoid high humidity in patient's bedroom Use high-efficiency particulate air (HEPA) filters in living areas Repair water leaks Replace carpets with hardwood floors Regularly check basements, attics, and crawl spaces for standing water and mold
Pollen	Keep automobile and house windows closed Control timing of outdoor exposure Restrict camping, hiking, and leaf raking Drive in an air-conditioned automobile Air-condition the home Install portable HEPA filters

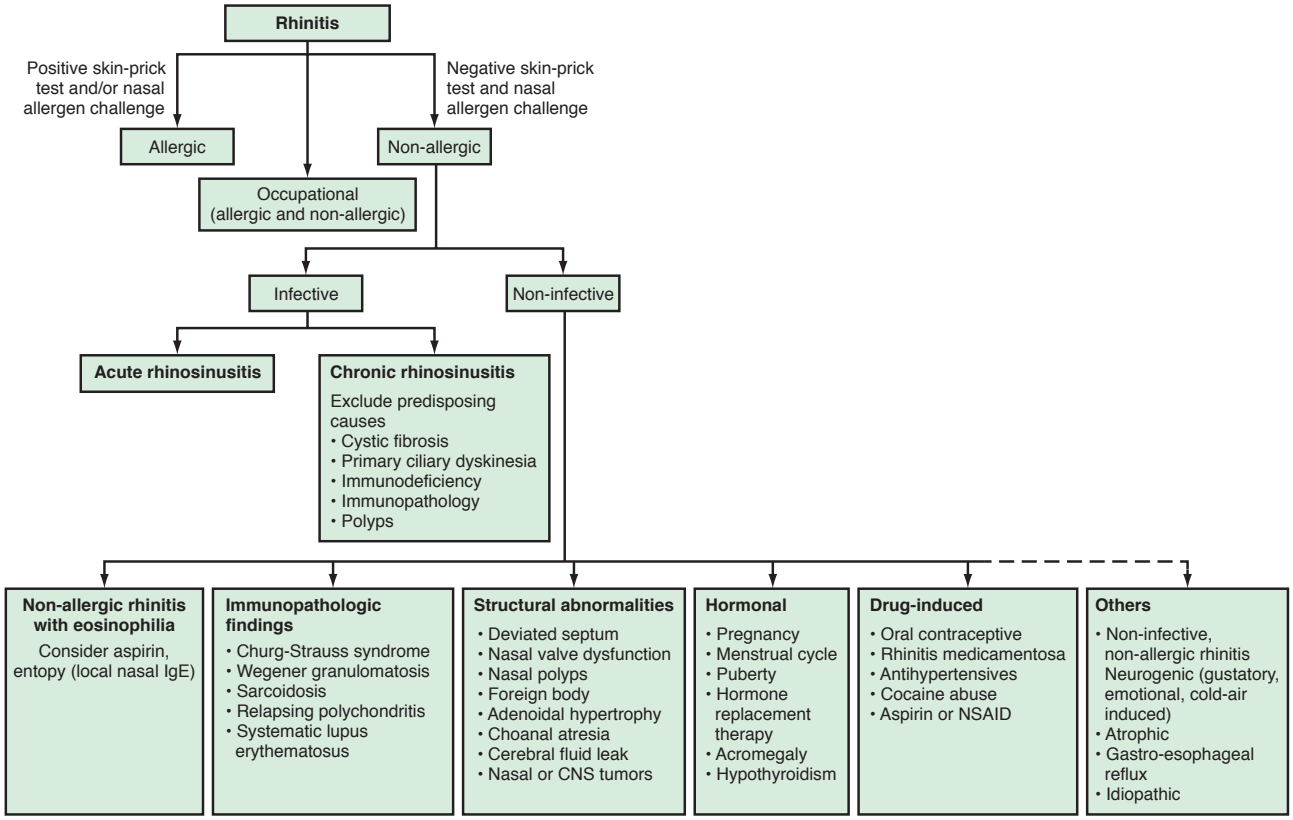


Figure 143-2 Diagnostic algorithm for rhinitis. Nasal allergen challenge is a research procedure and is not undertaken routinely. Causes likely to be seen in children are highlighted in italics. NSAID, nonsteroidal antiinflammatory drug. *(From Greiner AN, Hellings PW, Rotiroti G, Scadding GK: Allergic rhinitis. Lancet 378:2112-2120, 2011 [Fig. 3, p. 2116].)*

Table 143-2 Oral Allergic Rhinitis Treatments (Prescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
SECOND-GENERATION ANTIHISTAMINES			
Desloratadine			
Clarinex Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Clarinex Tablets	5 mg	Tabs	Children 12 mo-5 yr of age: 1.25 mg once daily
Clarinex Syrup	0.5 mg/mL	Syrup	Children 6-11 yr of age: 2.5 mg once daily Adults and adolescents ≥12 yr of age: 5 mg once daily
Levocetirizine dihydrochloride			
Xyzal Oral Solution	0.5 mg/mL	Solution	6 mo-5 yr: max 1.25 mg once daily in the P.M. 6-11 yr: max 2.5 mg once daily in the P.M.
LEUKOTRIENE ANTAGONIST			
Montelukast			
Singulair	10 mg	Tablets	6 mo-5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

*Contains phenylalanine.

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19. Philadelphia, 2012 Mosby.*

Table 143-3 Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
FIRST-GENERATION H_1 ANTAGONISTS			
Chlorpheniramine maleate			
Chlor-Trimeton	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (maximum 6 mg/day)
Chlor-Trimeton Syrup	2 mg/5 mL	Syrup	6-11 yr: 2 mg every 4-6 hr (maximum 12 mg/day) >12 yr 4 mg every 4-6 hr (maximum 24 mg/day)
SECOND-GENERATION H_1 ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup	1 mg/mL	Syrup	6-12 mo: 2.5 mg once daily
Children's Zyrtec Chewable	5 mg, 10 mg	Chewable tablets	12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Zyrtec tablets	5 mg, 10 mg	Tablets	2-5 yr: 2.5 mg/day; may be increased to a maximum of 5 mg/day given either as a single dose or divided into 2 doses
Zyrtec Liquid Gels	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into 2 doses
Fexofenadine HCl			
Children's Allegra	30 mg	Tablet	
Children's Allegra ODT*	30 mg	Orally disintegrating tablets	6 mo-<2 yr: 15 mg (2.5 mL) every 12 hr
Children's Allegra Oral Suspension	30 mg/5 mL	Suspension	>2-11 yr: 30 mg every 12 hr
Allegra	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg once daily
Loratadine			
Alavert ODT*	10 mg	Orally disintegrating tablets	2-5 yr: 5 mg once daily.
	10 mg	Tablets	>6 yr: 10 mg once daily or 5 mg twice daily
	10 mg	Liquid-filled caps	
	5 mg	Chewable tablets	
	1 mg/mL	Syrup	

*Contains phenylalanine.

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19, Philadelphia, 2012, Mosby.*

Table 143-4 Combined Antihistamine + Sympathomimetic (Examples)

GENERIC	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate Phenylephrine HCl Sudafed Sinus & Allergy	4 mg 10 mg	Tablets	>12 yr: 1 tablet every 4 hr not to exceed 6 tablets per day
Cetirizine + pseudoephedrine Zyrtec-D 12 hour	5 mg cetirizine + 120 mg pseudoephedrine	Extended release tablet	>12 yr: 1 tablet every 12 hr

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19, Philadelphia, 2012, Mosby.*

Table 143-5 Miscellaneous Intranasal Sprays

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Ipratropium bromide: Atrovent nasal spray (0.06%)	*I:* Symptomatic relief of rhinorrhea *M:* Anticholinergic Colds (symptomatic relief of rhinorrhea): 5-12 yr: 2 sprays in each nostril 3 times/day ≥12 yr and adults: 2 sprays in each nostril 3-4 times/day	Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin Safety and efficacy of use beyond 4 days in patients with the common cold have not been established *Adverse effects:* Epistaxis, nasal dryness, nausea
Azelastine: Astelin	*I:* Treatment of rhinorrhea, sneezing, and nasal pruritus *M:* Antagonism of histamine H_1-receptor 6-12 yr: 1 spray bid >12 yr: 1-2 sprays bid	May cause drowsiness *Adverse effects:* Headache, somnolence, bitter taste
Cromolyn sodium: NasalCrom	*I:* AR. *M:* Inhibition of mast cell degranulation >2 yr: 1 spray tid-qid; max ×6 /day	Not effective immediately; requires frequent administration
Oxymetazoline: Afrin, Nostrilla	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic agonist, vasoconstricting agent 0.05% solution: instill 2-3 sprays into each nostril twice daily; therapy should not exceed 3 days	Excessive dosage may cause profound central nervous system (CNS) depression Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month Use with caution in patients with hyperthyroidism, heart disease, hypertension, and diabetes *Adverse effects:* Hypertension, palpitations, reflex bradycardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision
Phenylephrine: Neo-Synephrine	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic, vasoconstricting agent 2-6 yr: 1 drop every 2-4 hr of 0.125% solution as needed. *Note:* Therapy should not exceed 3 continuous days 6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed. *Note:* Therapy should not exceed 3 continuous days >12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion. *Note:* Therapy should not exceed 3 continuous days	Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month 0.16% and 0.125% solutions are not commercially available *Adverse effects:* Reflex bradycardia, excitability, headache, anxiety, and dizziness

Table 143-6 Intranasal Inhaled Corticosteroids

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Beclomethasone: Beconase AQ (42 µg/spray) Qnasl (80 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid >12 yr: 1 or 2 sprays in each nostril bid	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Flunisolide	6-14 yr: 1 spray each nostril 3 times daily *or* 2 sprays in each nostril twice daily; not to exceed 4 sprays/day in each nostril ≥15 yr: 2 sprays each nostril twice daily (morning and evening); may increase to 2 sprays 3 times daily; maximum dose: 8 sprays/day in each nostril (400 µg/day)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth

Continued

Table 143-6 Intranasal Inhaled Corticosteroids—cont'd

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Triamcinolone Nasacort AQ (55 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-6 yr; 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone propionate (available as a generic preparation): Flonase (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator ≥4 yr: 1-2 sprays in each nostril qd	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Ritonavir significantly increases fluticasone serum concentrations and may result in systemic corticosteroid effects Use fluticasone with caution in patients receiving ketoconazole or other potent cytochrome P450 3A4 isoenzyme inhibitor *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone furoate: Veramyst (27.5 µg/spray)	2-12 yr: Initial dose: 1 spray (27.5 µg/spray) per nostril once daily (55 µg/day) Patients who do not show adequate response may use 2 sprays per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 55 µg once daily Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 µg/spray) per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril once daily (55 µg/day) Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day	
Mometasone: Nasonex (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-12 yr: 1 spray in each nostril qd >12 yr: 2 sprays in each nostril qd	Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses Preventive treatment of seasonal AR should begin 2-4 wk prior to pollen season Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Budesonide: Rhinocort Aqua (32 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 6-12 yr: 2 sprays in each nostril qd >12 yr: up to 4 sprays in each nostril qd (maximum dose)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Ciclesonide: Omnaris Zetonna (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-12 yr: 1-2 sprays in each nostril qd >12 yr: 2 sprays in each nostril qd	Prior to initial use, gently shake, then prime the pump by actuating 8 times If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears
Azelastine/fluticasone (137 µg azelastine/50 µg fluticasone) Dymista	>12 yr: 1 spray in each nostril bid	Shake bottle gently before using. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator tip ¼ to ½ inch into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray

Table 144-2 Asthma Patterns in Childhood, Based on Natural History and Asthma Management

TRANSIENT NONATOPIC WHEEZING
Common in early preschool years
Recurrent cough/wheeze, primarily triggered by common respiratory viral infections
Usually resolves during the preschool and lower school years, without increased risk for asthma in later life
Reduced airflow at birth, suggestive of relatively narrow airways. AHR near birth. Improves by school age

PERSISTENT ATOPY-ASSOCIATED ASTHMA
Begins in early preschool years
Associated with atopy in early preschool years:
- Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
- Biologic (e.g., early inhalant allergen sensitization, increased serum immunoglobulin E, increased blood eosinophils)
- Highest risk for persistence into later childhood and adulthood

Lung function abnormalities:
- Those with onset before 3 yr of age acquire reduced airflow by school age
- Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood

ASTHMA WITH DECLINING LUNG FUNCTION
Children with asthma with progressive increase in airflow limitation
Associated with hyperinflation in childhood, male gender

ASTHMA MANAGEMENT TYPES
(From national and international asthma management guidelines)
SEVERITY CLASSIFICATION*
- Intrinsic disease severity while not on asthma medications

Intermittent
Persistent:
- Mild
- Moderate
- Severe

CONTROL CLASSIFICATION*
- Clinical assessment while asthma being managed and treated

Well controlled
Not well controlled
Very poorly controlled
MANAGEMENT PATTERNS
- **Easy-to-treat:** well controlled with low levels of daily controller therapy
- **Difficult-to-treat:** well controlled with multiple and/or high levels of controller therapies
- **Exacerbators:** despite being well controlled, continue to have severe exacerbations
- **Refractory:** continue to have poorly controlled asthma despite multiple and high levels of controller therapies

*From National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3): *Guideline for the diagnosis and management of asthma.* NIH Publication No. 07-4051. Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
AHR, airways hyperresponsiveness.

Table 144-1 Early Childhood Risk Factors for Persistent Asthma

Parental asthma
Allergy:
- Atopic dermatitis (eczema)
- Allergic rhinitis
- Food allergy
- Inhalant allergen sensitization
- Food allergen sensitization

Severe lower respiratory tract infection:
- Pneumonia
- Bronchiolitis requiring hospitalization

Wheezing apart from colds
Male gender
Low birthweight
Environmental tobacco smoke exposure
Reduced lung function at birth

Table 144-4 Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting*

	MILD	MODERATE	SEVERE	SUBSET: RESPIRATORY ARREST IMMINENT
SYMPTOMS				
Breathlessness	While walking	While at rest (infant—softer, shorter cry, difficulty feeding)	While at rest (infant—stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
SIGNS				
Respiratory rate†	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min)‡	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent	May be present	Often present	Absence suggests respiratory muscle fatigue
	<10 mm Hg	10-25 mm Hg	>25 mm Hg (adult) 20-40 mm Hg (child)	
FUNCTIONAL ASSESSMENT				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40-69% or response lasts <2 hr	<40%	<25%§
Pao_2 (breathing air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or				
PCO_2	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
SaO_2 (breathing air) at sea level	>95% (test not usually necessary)	90-95% (test not usually necessary)	<90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents			

*Notes:
- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

†Normal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.
‡Normal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.
§Peak expiratory flow testing may not be needed in very severe attacks.

Modified from EPR–3. Expert panel report 3: guidelines for the diagnosis and management of asthma, *NIH Publication No. 07-4051, Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program.* http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

Table 144-5 Differential Diagnosis of Childhood Asthma

UPPER RESPIRATORY TRACT CONDITIONS
Allergic rhinitis*
Chronic rhinitis*
Sinusitis*
Adenoidal or tonsillar hypertrophy
Nasal foreign body
MIDDLE RESPIRATORY TRACT CONDITIONS
Laryngotracheobronchomalacia*
Laryngotracheobronchitis (e.g., pertussis)*
Laryngeal web, cyst, or stenosis
Exercise-induced laryngeal obstruction
Vocal cord dysfunction*
Vocal cord paralysis
Tracheoesophageal fistula
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
Foreign body aspiration*
Chronic bronchitis from environmental tobacco smoke exposure*
Toxic inhalations
LOWER RESPIRATORY TRACT CONDITIONS
Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
Viral bronchiolitis*
Gastroesophageal reflux*
Causes of bronchiectasis:
Cystic fibrosis
Immune deficiency
Allergic bronchopulmonary mycoses (e.g., aspergillosis)
Chronic aspiration
Immotile cilia syndrome, primary ciliary dyskinesia
Bronchiolitis obliterans
Interstitial lung diseases
Hypersensitivity pneumonitis
Pulmonary eosinophilia, Churg-Strauss vasculitis
Pulmonary hemosiderosis
Tuberculosis
Pneumonia
Pulmonary edema (e.g., congestive heart failure)
Medications associated with chronic cough:
Acetylcholinesterase inhibitors
β-Adrenergic antagonists
Angiotensin-converting enzyme inhibitors

*More common asthma masqueraders.

Table 144-6 Similarities and Differences Between Vocal Cord Dysfunction and Asthma

VOCAL CORD DYSFUNCTION	ASTHMA
Extrathoracic	Intrathoracic
Rare (?never) hypoxemia	+ Hypoxemia
No hypercapnia/acidosis	+ Hypercapnia/acidosis
Normal expiratory spirometry	Reduced expiratory flow
Abnormal inspiratory loop (in some)	Normal inspiratory loop
Start/stop abruptly; few symptoms between episodes	Persistent symptoms
Frequent emergency department/office visits	Frequent emergency department/office visits
Multiple medications	Multiple medications

From Noyes BE, Kemp JS: Vocal cord dysfunction in children. Paediat Respir Rev *8:155–163, 2007 (Table 2, p. 159).*

Table 144-7 Lung Function Abnormalities in Asthma

Spirometry (in clinic):
- Airflow limitation:
- Low FEV_1 (relative to percentage of predicted norms)
- FEV_1:FVC ratio <0.80

Bronchodilator response (to inhaled β-agonist):
- Improvement in FEV_1 ≥12% and ≥200 mL*

Exercise challenge:
- Worsening in FEV_1 ≥15%*

Daily peak flow or FEV_1 monitoring: day to day and/or A.M.-to-P.M. variation ≥20%*

*Main criteria consistent with asthma.
FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Table 144-3 Asthma Triggers

Common viral infections of the respiratory tract
Aeroallergens in sensitized asthmatic patients

INDOOR ALLERGENS
- Animal dander
- Dust mites
- Cockroaches
- Molds

SEASONAL AEROALLERGENS
- Pollens (trees, grasses, weeds)
- Seasonal molds

AIR POLLUTANTS
- Environmental tobacco smoke
- Ozone
- Nitrogen dioxide
- Sulfur dioxide
- Particulate matter
- Wood- or coal-burning smoke
- Mycotoxins
- Endotoxin
- Dust

STRONG OR NOXIOUS ODORS OR FUMES
- Perfumes, hairsprays
- Cleaning agents

OCCUPATIONAL EXPOSURES
- Farm and barn exposures
- Formaldehydes, cedar, paint fumes

Cold dry air
Exercise
Crying, laughter, hyperventilation

COMORBID CONDITIONS
- Rhinitis
- Sinusitis
- Gastroesophageal reflux

DRUGS
- Aspirin and other nonsteroidal antiinflammatory drugs
- β-Blocking agents
- Sulfiting agents
- Tartrazine

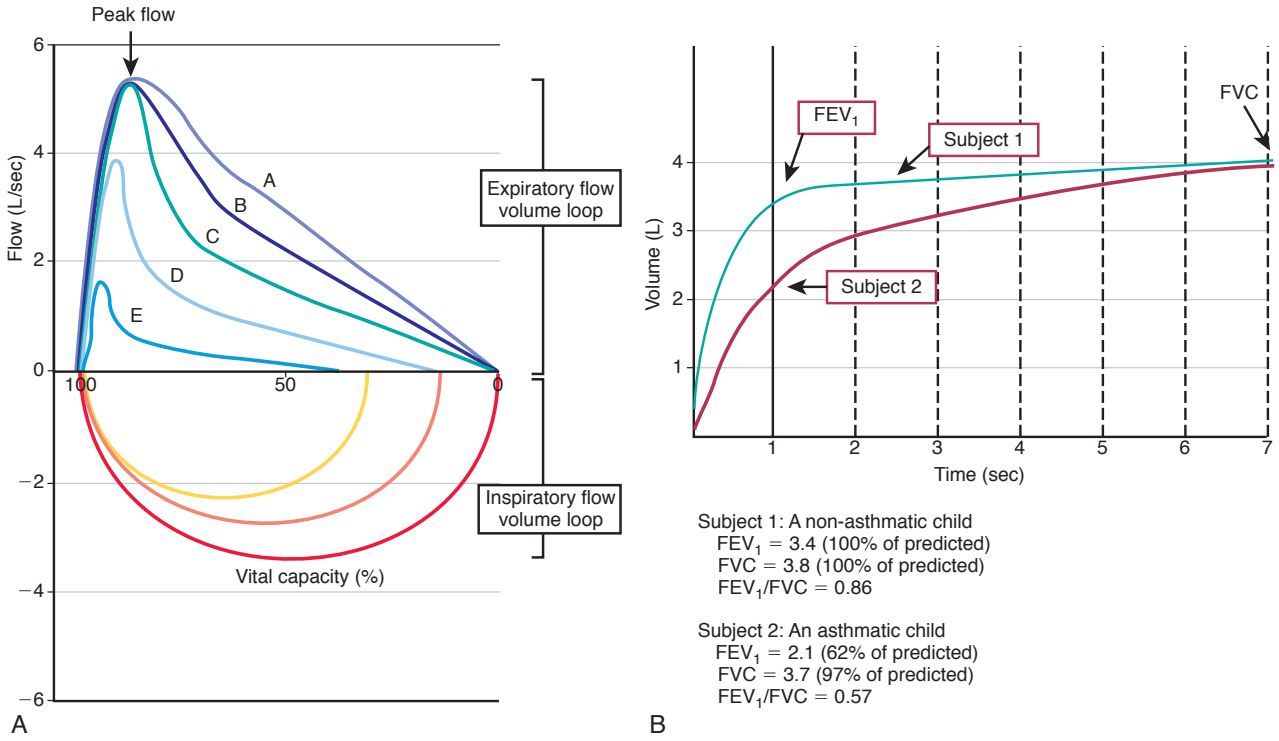


Figure 144-2 Spirometry. *A,* Spirometric flow-volume loops. A is an expiratory flow-volume loop of a nonasthmatic person without airflow limitation. B through E are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping." *B,* Spirometric volume-time curves. Subject 1 is a nonasthmatic person; subject 2 is an asthmatic patient. Note how the FEV_1 and FVC lung volumes are obtained. The FEV_1 is the volume of air exhaled in the 1st sec of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort, or forced vital capacity. Note that subject 2's FEV_1 and FEV_1:FVC ratio are smaller than subject 1's, demonstrating airflow limitation. Also, subject 2's FVC is very close to what is expected.

Table 144-10 Key Elements of Productive Clinic Visits for Asthma

Specify goals of asthma management
Explain basic facts about asthma:
- Contrast normal vs asthmatic airways
- Link airways inflammation, "twitchiness," and bronchoconstriction
- Long-term-control and quick-relief medications
- Address concerns about potential adverse effects of asthma pharmacotherapy

Teach, demonstrate, and have patient show proper technique for:
- Inhaled medication use (spacer use with metered-dose inhaler)
- Peak flow measures

Investigate and manage factors that contribute to asthma severity:
- Environmental exposures
- Comorbid conditions

Create written 2-part asthma management plan:
- Daily management
- Action plan for asthma exacerbations

Regular follow-up visits:
- Twice yearly (more often if asthma not well-controlled)
- Monitor lung function annually

Table 144-11 Control of Factors Contributing to Asthma Severity

ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES:

Environmental tobacco smoke elimination or reduction in home and automobiles

Allergen exposure elimination or reduction in sensitized asthmatic patients:
- Animal danders: pets (cats, dogs, rodents, birds)
- Pests (mice, rats)
- Dust mites
- Cockroaches
- Molds

Other airway irritants:
- Wood- or coal-burning smoke
- Strong chemical odors and perfumes (e.g., household cleaners)
- Dusts

TREAT COMORBID CONDITIONS:
- Rhinitis
- Sinusitis
- Gastroesophageal reflux

Table 144-8 Assessing Asthma Severity and Initiating Treatment for Patients Who Are Not Currently Taking Long-Term Control Medications*

	CLASSIFICATION OF ASTHMA SEVERITY			
		PERSISTENT		
	Intermittent	**Mild**	**Moderate**	**Severe**
COMPONENTS OF SEVERITY				
Impairment				
Daytime symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings:				
Age 0-4 yr	0	1-2×/mo	3-4×/mo	>1×/wk
Age ≥5 yr	≤2×/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
Short-acting β_2-agonist use for symptoms (not for prevention of exercise-induced bronchospasm)	≤2 days/wk	>2 days/wk but not daily, and not more than 1× on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function:				
FEV_1 % predicted, age ≥5 yr	Normal FEV_1 between exacerbations >80% predicted	≥80% predicted	60-80% predicted	<60% predicted
FEV_1:FVC ratio†:				
Age 5-11 yr	>85%	>80%	75-80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
Risk				
Exacerbations requiring systemic corticosteroids:				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic corticosteroids **or** ≥4 wheezing episodes/yr lasting >1 day *and* risk factors for persistent asthma		
Age ≥ 5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
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				
All ages	Step 1	Step 2		
Age 0-4 yr			Step 3	Step 3
Age 5-11 yr			Step 3, medium-dose ICS option	Step 3, medium-dose ICS option **or** Step 4
Age ≥12 yr			Consider a short course of systemic corticosteroids	Consider a short course of systemic corticosteroids
In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly. If no clear benefit is observed within 4-6 wk, consider adjusting therapy or alternative diagnoses.				

*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 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a 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 mo, 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.

†Normal FEV_1:FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroids.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—

Table 144-9 Assessing Asthma Control and Adjusting Therapy in Children*

	CLASSIFICATION OF ASTHMA CONTROL		
	Well-Controlled	**Not Well-Controlled**	**Very Poorly Controlled**
COMPONENTS OF CONTROL			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1×/mo	>1×/mo	>1×/wk
Age 5-11 yr	≤1×/mo	≥2×/mo	≥2×/wk
Age ≥12 yr	≤2×/mo	1-3×/wk	≥4×/wk
Short-acting β_2-agonist use for symptoms (not for exercise-induced bronchospasm pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
FEV_1/FVC:	>80%	75-80%	<75%
Age ≥ 12 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
Validated questionnaires†:			
Age ≥ 12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15
Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Reduction in lung growth *or* progressive loss of lung function	Evaluation requires long-term follow-up care.		
RECOMMENDED ACTION FOR TREATMENT	Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well-controlled for at least 3 mo.	Step up‡ (1 step) and reevaluate in 2-6 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.	Consider short course of oral corticosteroids. Step up§ (1-2 steps) and reevaluate in 2 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. 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.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. 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 not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

†Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:
- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0
- ACQ, Asthma Control Questionnaire; MID = 0.5
- ACT, Asthma Control Test; MID not determined

‡ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

§Before step-up therapy: (a) review adherence to medications, inhaler technique, and environmental control; (b) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

Table 144-12 Stepwise Approach for Managing Asthma in Children*

AGE	THERAPY†	INTERMITTENT ASTHMA	PERSISTENT ASTHMA: DAILY MEDICATION				
		STEP DOWN if possible (and asthma is well controlled at least 3 months)		ASSESS CONTROL	STEP UP if needed (first check inhaler technique, adherence, environmental control, and comorbid condition)		
		Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
0-4 yr	Preferred	SABA prn	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + *either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA *and* Oral corticosteroid
	Alternative		Cromolyn or montelukast				
5-11 yr	Preferred	SABA prn	Low-dose ICS	*Either* low-dose ICS ± LABA, LTRA, or theophylline *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA *and* Oral corticosteroid
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline		Medium-dose ICS + *either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline *and* Oral corticosteroid
≥12 yr	Preferred	SABA prn	Low-dose ICS	Low-dose ICS + LABA *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA *and* Consider omalizumab for patients with allergies	High-dose ICS + LABA + oral corticosteroid *and* Consider omalizumab for patients with allergies
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS + LTRA, theophylline, or zileuton	Medium-dose ICS + LTRA, theophylline, or zileuton		
Each step: Patient education, environmental control, and management of comorbidities.							
Age ≥5 yr: Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.							
QUICK-RELIEF MEDICATION FOR ALL PATIENTS							
SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.							
Caution: Use of SABA >2 days/wk for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment.							
For ages 0-4 yr: With viral respiratory infection: SABA q4-6h up to 24 hr (longer with physician consult). Consider short course of systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.							

*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 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited. The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.
- Zileuton is less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function.

†Alphabetical order is used when more than 1 treatment option is listed within *either* preferred or alternative therapy.

ICS, inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; prn, as needed; SABA, inhaled short-acting β_2-agonist.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

Table 144-13 Usual Dosages for Long-Term Control Medications

Medication	AGE		
	0-4 yr	5-11 yr	≥12 yr
INHALED CORTICOSTEROIDS (see Table 144-13)			
Methylprednisolone: 2, 4, 8, 16, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL, 15 mg/5 mL Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/mL, 5 mg/5 mL	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control • Short-course "burst": 1-2 mg/kg/day; maximum 30 mg/day for 3-10 days	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control • Short-course "burst": 1-2 mg/kg/day; maximum 60 mg/day for 3-10 days	• 7.5-60 mg daily in a single dose in A.M. or qod as needed for control • Short-course "burst" to achieve control: 40-60 mg/day as single or 2 divided doses for 3-10 days
Fluticasone/salmeterol: DPI: 100, 250, or 500 mg/50 mg HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg	NA	1 inhalation bid; dose depends on level of severity or control	1 inhalation bid; dose depends on level of severity or control 2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol: HFA: 80 µg/4.5 µg, 160 µg/4.5 µg	NA		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol HFA: 100 µg/5 µg, 200 µg/5 µg			2 inhalations bid; dose depends on level of severity or control
Cromolyn: Nebulizer 20 mg/ampule	1 ampule qid; NA <2 yr of age	1 ampule qid	1 ampule qid
Leukotriene receptor antagonists: Montelukast: 4 or 5 mg chewable tablet 4 mg granule packets 10 mg tablet	4 mg qhs (1-5 yr of age)	5 mg qhs (6-14 yr)	10 mg qhs
Zafirlukast: 10- or 20-mg tablet	NA	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)
5-Lipoxygenase inhibitor: Zileuton CR: 600-mg tablet	NA	NA	1,200 mg twice daily (give 2 tablets bid)
Theophylline: Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual max: • <1 yr of age: 0.2 (age in wk) + 5 = mg/kg/day • >1 yr of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day
Immunomodulators: Omalizumab (anti-IgE): Subcutaneous injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection	NA	NA	150-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level

bid, Twice a day; DPI, dry powder inhaler; HFA, hydrofluoroalkane Ig, immunoglobulin; MDI, metered-dose inhaler; q, every; qhs, every night; qid, 4 times a day; qod, every other day; SC, subcutaneous.

Table 144-14 Estimated Comparative Inhaled Corticosteroid Doses

Drug	LOW DAILY DOSE BY AGE			MEDIUM DAILY DOSE BY AGE			HIGH DAILY DOSE BY AGE		
	0-4 yr	5-11 yr	≥12 yr	0-4 yr	5-11 yr	≥12 yr	0-4 yr	5-11 yr	≥12 yr
Beclomethasone HFA, 40 or 80 µg/puff	NA	80-160 µg	80-240 µg	NA	>160-320 µg	>240-480 µg	NA	>320 µg	>480 µg
Budesonide DPI 90, 180, or 200 µg/inhalation	NA	180-400 µg	180-600 µg	NA	>400-800 µg	>600-1200 µg	NA	>800 µg	>1200 µg
Budesonide inhaled suspension for nebulization, 0.25, 0.5, and 1.0 mg dose	0.25-0.5 mg	0.5 mg	NA	>0.5-1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
Flunisolide, 250 µg/puff	NA	500-750 µg	500-1000 µg	NA	1000-1250 µg	>1000-2000 µg	NA	>1250 µg	>2000 µg
Flunisolide HFA, 80 µg/puff	NA	160 µg	320 µg	NA	320 µg	>320-640 µg	NA	≥640 µg	>640 µg
Fluticasone HFA/MDI: 44, 110, or 220 µg/puff	176 µg	88-176 µg	88-264 µg	>176-352 µg	>176-352 µg	>264-440 µg	>352 µg	>352 µg	>440 µg
Fluticasone DPI, 50, 100, or 250 µg/inhalation	NA	100-200 µg	100-300 µg	NA	>200-400 µg	>300-500 µg	NA	>400 µg	>500 µg
Mometasone DPI, 110 µg and 220 µg/inhalation	NA	NA	220 µg	NA	NA	440 µg	NA	NA	>440 µg
Triamcinolone acetonide, 75 µg/puff	NA	300-600 µg	300-750 µg	NA	>600-900 µg	>750-1500 µg	NA	>900 µg	>1500 µg

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not approved and no data available for this age group.

Adapted, from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

Table 144-15 Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 144-11)	• Monitor blood pressure and weight with each physician visit • Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay • Encourage regular physical exercise • Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed • Avoid smoking and alcohol • Ensure TSH status if patient has history of thyroid abnormality
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 144-11) At least 4 courses oral corticosteroid/yr	As above, plus: • Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma • Baseline bone densitometry (DEXA scan) • Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥ 7 oral corticosteroid burst treatments/year Very-high-dose ICS (e.g., fluticasone propionate ≥800 µg/day)	As above, plus: • DEXA scan: if DEXA Z score ≤1.0, recommend close monitoring (every 12 mo) • Consider referral to a bone or endocrine specialist • Bone age assessment • Complete blood count • Serum calcium, phosphorus, alkaline phosphatase determinations • Urine calcium and creatinine measurements • Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin • Urine telopeptides for those receiving long-term systemic or frequent oral corticosteroid treatment • Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)

*Risk factors for osteoporosis: Presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, and alcohol intake).

DEXA, dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; TSH, thyroid-stimulating hormone.

Table 144-16 Management of Asthma Exacerbation (Status Asthmaticus)

RISK ASSESSMENT ON ADMISSION		
Focused history	• Onset of current exacerbation • Frequency and severity of daytime and nighttime symptoms and activity limitation • Frequency of rescue bronchodilator use • Current medications and allergies • Potential triggers • History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes	
Clinical assessment	• Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status • Pulse oximetry • Lung function (defer in patients with moderate to severe distress or history of labile disease)	
Risk factors for asthma morbidity and death	See Table 144-17	
TREATMENT		
Drug and Trade Name	**Mechanisms of Action and Dosing**	**Cautions and Adverse Effects**
Oxygen (mask or nasal cannula)	Treats hypoxia	• Monitor pulse oximetry to maintain O_2 saturation >92% • Cardiorespiratory monitoring
Inhaled short-acting β-agonists:	Bronchodilator	• During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, $\dot{V}/\dot{Q}$ mismatch, and hypoxemia • Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum: 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	• Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume
Albuterol MDI (90 μg/puff)	2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed	• For MDI: use spacer/holding chamber
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum: 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	• Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects
Systemic corticosteroids:	Antiinflammatory	• If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis • For daily dosing, 8 A.M. administration minimizes adrenal suppression • Children may benefit from dosage tapering if course exceeds 7 days • Adverse effects monitoring: Frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 578); see Table 144-15 for adverse effects screening recommendations

Continued

Table 144-16 Management of Asthma Exacerbation (Status Asthmaticus)—cont'd

Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution	0.5-1 mg/kg every 6-12 hr for 48 hr, then 1-2 mg/kg/day bid (maximum: 60 mg/day)	
Depo-Medrol (IM); Solu-Medrol (IV)	Short-course "burst" for exacerbation: 1-2 mg/kg/day qd or bid for 3-7 days	
Anticholinergics:	Mucolytic/bronchodilator	• Should not be used as first-line therapy; added to β_2-agonist therapy
Ipratropium: Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 µg/inhalation)	Nebulizer: 0.5 mg q6-8h (tid-qid) as needed MDI: 2 puffs qid	
Ipratropium with albuterol: DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	1 vial by nebulizer qid	• Nebulizer: may mix ipratropium with albuterol
Injectable sympathomimetic epinephrine: Adrenalin 1 mg/mL (1:1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	Bronchodilator SC or IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min	• For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)
Terbutaline: Brethine 1 mg/mL	Continuous IV infusion (terbutaline only): 2-10 µg/kg loading dose, followed by 0.1-0.4 µg/kg/min Titrate in 0.1-0.2 µg/kg/min increments every 30 min, depending on clinical response	• Terbutaline is β-agonist–selective relative to epinephrine • Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium • Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia
RISK ASSESSMENT FOR DISCHARGE		
Medical stability	Discharge to home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air	
Home supervision	Capability to administer intervention and to observe and respond appropriately to clinical deterioration	
Asthma education	See Table 144-9	

IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist; SC, subcutaneous; $\dot{V}/\dot{Q}$, ventilation–perfusion.

Table 148-4 Treatment of Urticaria and Angioedema

CLASS/DRUG	DOSE	FREQUENCY
ANTIHISTAMINES, TYPE H_1 (SECOND GENERATION)		
Fexofenadine	6-11 yr: 30 mg	bid
	>12 yr: 60 mg	
	Adult: 180 mg	Once daily
Loratadine	2-5 yr: 5 mg	Once daily
	>6 yr: 10 mg	
Desloratadine	6-11 mo: 1 mg	Once daily
	12 mo-5 yr: 1.25 mg	
	6-11 yr: 2.5 mg	
	>12 yr: 5 mg	
Cetirizine	6-23 mo: 2.5 mg	Once daily
	2-6 yr: 2.5-5mg	
	>6 yr: 5-10 mg	
Levocetirizine	6 mo-5 yr: 1.25 mg	Once daily
	6-11 yr: 2.5 mg	Once daily
	>12 yr: 5 mg	Once daily
ANTIHISTAMINES, TYPE H_2		
Cimetidine	Infants: 10-20 mg/kg/day	Divided q6-12h
	Children: 20-40 mg/kg/day	
Ranitidine	1 mo-16 yr: 5-10 mg/kg/day	Divided q12h
Famotidine	3-12 mo: 1 mg/kg/day	Divided q12h
	1-16 yr: 1-2 mg/kg/day	
LEUKOTRIENE PATHWAY MODIFIERS		
Montelukast	12 mo-5 yr: 4 mg	Once daily
	6-14 yr: 5 mg	
	>14 yr: 10 mg	
Zafirlukast	5-11 yr: 10 mg	bid
IMMUNOMODULATORY DRUGS		
Cyclosporine	4-6 mg/kg/day	Once daily*
Sulfasalazine	>6 yr: 30 mg/kg/day	Divided q6h†
Intravenous immunoglobulin (IVIG)	400 mg/kg/day	5 consecutive days

*Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

†Monitor complete blood count and liver function tests at baseline, every 2 wk for 3 mo, and then every 1-3 mo.

Table 144-17 Risk Factors for Asthma Morbidity and Mortality

BIOLOGIC
- Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)
- Sudden asphyxia episodes (respiratory failure, arrest)
- Two or more hospitalizations for asthma in past year
- Three or more emergency department visits for asthma in past year
- Increasing and large diurnal variation in peak flows
- Use of >2 canisters of short-acting β-agonists per month
- Poor response to systemic corticosteroid therapy
- Male gender
- Low birthweight
- Nonwhite (especially black) ethnicity
- Sensitivity to *Alternaria*

ENVIRONMENTAL
- Allergen exposure
- Environmental tobacco smoke exposure
- Air pollution exposure
- Urban environment

ECONOMIC AND PSYCHOSOCIAL
- Poverty
- Crowding
- Mother <20 yr old
- Mother with less than high school education
- Inadequate medical care:
  - Inaccessible
  - Unaffordable
  - No regular medical care (only emergency)
  - Lack of written asthma action plan
  - No care sought for chronic asthma symptoms
  - Delay in care of asthma exacerbations
  - Inadequate hospital care for asthma exacerbation
- Psychopathology in the parent or child
- Poor perception of asthma symptoms or severity
- Alcohol or substance abuse

Table 145-1 Clinical Features of Atopic Dermatitis

MAJOR FEATURES
- Pruritus
- Facial and extensor eczema in infants and children
- Flexural eczema in adolescents
- Chronic or relapsing dermatitis
- Personal or family history of atopic disease

ASSOCIATED FEATURES
- Xerosis
- Cutaneous infections (*Staphylococcus aureus,* group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)
- Nonspecific dermatitis of the hands or feet
- Ichthyosis, palmar hyperlinearity, keratosis pilaris
- Nipple eczema
- White dermatographism and delayed blanch response
- Anterior subcapsular cataracts, keratoconus
- Elevated serum immunoglobulin E levels
- Positive results of immediate-type allergy skin tests
- Early age at onset
- Dennie lines (Dennie-Morgan infraorbital folds)
- Facial erythema or pallor
- Course influenced by environmental and/or emotional factors

Table 145-2 Differential Diagnosis of Atopic Dermatitis

CONGENITAL DISORDERS
Netherton syndrome
Familial keratosis pilaris
CHRONIC DERMATOSES
Seborrheic dermatitis
Contact dermatitis (allergic or irritant)
Nummular eczema
Psoriasis
Ichthyoses
INFECTIONS AND INFESTATIONS
Scabies
HIV-associated dermatitis
Dermatophytosis
Insect bites
Onchocerciasis
MALIGNANCIES
Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome)
Letterer-Siwe disease (Langerhans cell histiocytosis)
AUTOIMMUNE DISORDERS
Dermatitis herpetiformis
Pemphigus foliaceus
Graft-versus-host disease
Dermatomyositis
IMMUNODEFICIENCIES
Wiskott-Aldrich syndrome
Severe combined immunodeficiency syndrome
Hyperimmunoglobulin E syndromes (autosomal dominant and recessive types)
Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome
METABOLIC DISORDERS
Zinc deficiency
Pyridoxine (vitamin B_6) and niacin
Multiple carboxylase deficiency
Phenylketonuria

Modified from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2003, Mosby, p. 562.*

Table 145-5 Selected Topical Corticosteroid Preparations*

GROUP 1
Clobetasol propionate (Temovate) 0.05% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel
Fluocinonide (Vanos) 0.1% cream
GROUP 2
Mometasone furoate (Elocon) 0.1% ointment
Halcinonide (Halog) 0.1% cream
Fluocinonide (Lidex) 0.05% ointment/cream
Desoximetasone (Topicort) 0.25% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% cream
GROUP 3
Fluticasone propionate (Cutivate) 0.005% ointment
Halcinonide (Halog) 0.1% ointment
Betamethasone valerate (Valisone) 0.1% ointment
GROUP 4
Mometasone furoate (Elocon) 0.1% cream
Triamcinolone acetonide (Kenalog) 0.1% ointment/cream
Fluocinolone acetonide (Synalar) 0.025% ointment
GROUP 5
Fluocinolone acetonide (Synalar) 0.025% cream
Hydrocortisone valerate (Westcort) 0.2% ointment
GROUP 6
Desonide (DesOwen) 05% ointment/cream/lotion
Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
GROUP 7
Hydrocortisone (Hytone) 2.5% , 1%, 0.5% ointment/cream/lotion

*Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).

Table 145-3 List of Aggravating Factors and Counselling for AD Patients

Clothing: avoid skin contact with irritating fibers (wool, large-fiber textiles); do not use tight and too warm clothing to avoid excessive sweating. New nonirritating clothing designed for AD children is being evaluated
Tobacco: avoid exposure
Cool temperature in bedroom and avoid too many bed covers
Increase emollient use with cold weather
Avoid exposure to herpes sores; urgent visit if flare of unusual aspect
Vaccines: normal schedule in noninvolved skin, including egg-allergic patients (see text)
Sun exposure: no specific restriction. Usually helpful because of improvement of epidermal barrier. Encourage summer holidays in altitude or at beach resorts
Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool
Food allergens
Maintain breast feeding until 4 mo if possible
Otherwise normal diet, unless an allergy work-up has proven the need to exclude a specific food
Indoor aeroallergens
House dust mites
Use adequate ventilation of housing; keep the rooms well aerated even in winter
Avoid wall-to-wall carpeting
Remove dust with a wet sponge
Vacuum floors and upholstery with an adequately filtered cleaner once a week
Avoid soft toys in bed (cradle), except washable ones
Wash bed sheets at a temperature higher than 55° every 10 days
Use bed and pillow encasings made of Gore-Tex or similar material
Furred pets: advise to avoid. If allergy is demonstrated, be firm on avoidance measures, such as pet removal
Pollen: close windows during peak pollen season on warm and dry weather and restrict, if possible, stays outdoors. Windows may be open at night and early in the morning or during rainy weather. Avoid exposure to risk situations (lawn mowing). Use pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen

From Darsow U, Wollenberg A, Simon D, et al: ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol *24:317–328, 2010 (Table 2, p. 321).*

Table 145-4 Categorization of Physical Severity of Atopic Eczema

Clear—Normal skin, with no evidence of atopic eczema
Mild—Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate—Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe—Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

From Lewis-Jones S, Mugglestone MA; Guideline Development Group: Management of atopic eczema in children aged up to 12 years: summary of NICE guidance, BMJ *335:1263–1264, 2007.*

Table 147-1 Topical Ophthalmic Medications for Allergic Conjunctivitis

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Azelastine hydrochloride 0.05% Optivar	Antihistamine Children ≥3 yr: 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Emedastine difumarate 0.05% Emadine	Antihistamine Children ≥3 yr: 1 gtt qid	Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.
Levocabastine hydrochloride 0.05% Livostin	Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment.
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms. Not for use with contact lenses.
0.3%/Naphazoline hydrochloride 0.025% Naphcon-A, Opcon-A	Children >6 yr: 1-2 gtt qid	
Cromolyn sodium 4% Crolom, Opticrom	Mast cell stabilizer Children >4 yr 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.
Lodoxamide tromethamine 0.1% Alomide	Mast cell stabilizer Children ≥2 yr: 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.
Nedocromil sodium 2% Alocril	Mast cell stabilizer Children ≥3 yr 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.
Pemirolast potassium 0.1% Alamast	Mast cell stabilizer Children >3 yr: 1-2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Epinastine hydrochloride 0.05% Elestat	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid	Contact lenses should be removed prior to use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.

Continued

Table 147-1 Topical Ophthalmic Medications for Allergic Conjunctivitis—cont'd

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Ketotifen fumarate 0.025% Zaditor	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Olopatadine hydrochloride 0.1%, 0.2% Patanol Pataday	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart) 1 gtt q day	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer Children > 2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Bepotastine besilate 1.5% Bepreve	Antihistamine/mast cell stabilizer Children >2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Ketorolac tromethamine 0.5% Acular	NSAID Children ≥3 yr: 1 gtt qid	Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period of time, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight-threatening. Do not use while wearing contact lenses.
Fluorometholone 0.1%, 0.25% suspension (0.1%, 0.25%) and ointment (0.1%) FML, FML Forte, Flarex	Fluorinated corticosteroid Children ≥2 yr, 1 gtt into conjunctival sac of affected eye(s) bid-qid. During initial 24–48 hr, dosage may be increased to 1 gtt q 4 hr. Ointment (approximately 1.3 cm in length) into the conjunctival sac of affected eye(s) 1–3 times daily. May be applied q 4 hr during initial 24–48 hr of therapy	If improvement does not occur after 2 days, patient should be reevaluated. Patient should remove soft contact lenses prior to administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 minutes after administration. Close monitoring for development of glaucoma and cataracts.

Table 148-3 Diagnostic Testing for Urticaria and Angioedema

DIAGNOSIS	DIAGNOSTIC TESTING
Food and drug reactions	Elimination of offending agent, skin testing, and challenge with suspected foods
Autoimmune urticaria	Autologous serum skin test; antithyroid antibodies; antibodies against the high-affinity IgE receptor
Thyroiditis	Thyroid-stimulating hormone; antithyroid antibodies
Infections	Appropriate cultures or serology
Collagen vascular diseases and cutaneous vasculitis	Skin biopsy, CH_{50}, C1q, C4, C3, factor B, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins
Malignancy with angioedema	CH_{50}, C1q, C4, C1-INH determinations
Cold urticaria	Ice cube test
Solar urticaria	Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin
Dermatographism	Stroking with narrow object (e.g., tongue blade, fingernail)
Pressure urticaria	Application of pressure for defined time and intensity
Vibratory urticaria	Vibration for 4 min
Aquagenic urticaria	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermographism
Hereditary angioedema	C4, C2, CH_{50}, C1-INH testing by protein and function
Familial cold urticaria	Challenge by cold exposure, measurement of temperature, white blood cell count, erythrocyte sedimentation rate, and skin biopsy
C3b inactivator deficiency	C3, factor B, C3b inactivator determinations
Chronic idiopathic urticaria	Skin biopsy, immunofluorescence (negative result), autologous skin test

Table 148-2 Etiology of Chronic Urticaria

Idiopathic/autoimmune	Approximately 30% of chronic urticaria cases are physical urticaria and 60-70% are idiopathic. Of the idiopathic cases approximately 35-40% have anti-IgE or anti-FcεRI (high-affinity IgE receptor α chain) autoantibodies (autoimmune chronic urticaria)
Physical	Dermatographism Cholinergic urticaria Cold urticaria Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Leukocytoclastic vasculitis
Autoinflammatory/ periodic fever syndromes	NOMID (neonatal onset multisystem inflammatory disease) Muckle-Wells syndrome Familial cold autoinflammatory syndrome Cold urticarial, immunodeficiency, autoimmunity as a result of *PLCG2* deficiency
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor) Acquired angioedema Angiotensin-converting enzyme inhibitors

Table 148-1 Etiology of Acute Urticaria

Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, strawberries (direct mast cell degranulation)
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	Bacterial (streptococcal pharyngitis, *Mycoplasma*, sinusitis); viral (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); parasitic *(Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella);* fungal (dermatophytes, *Candida*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or IV immunoglobulin administration

Table 149-1 Symptoms and Signs of Anaphylaxis in Infants

ANAPHYLAXIS SYMPTOMS THAT INFANTS CANNOT DESCRIBE	ANAPHYLAXIS SIGNS THAT MAY BE DIFFICULT TO INTERPRET/UNHELPFUL IN INFANTS, AND WHY	ANAPHYLAXIS SIGNS IN INFANTS
GENERAL Feeling of warmth, weakness, anxiety, apprehension, impending doom	Nonspecific behavioral changes such as persistent crying, fussing, irritability, fright, suddenly becoming quiet	
SKIN/MUCUS MEMBRANES Itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, etc.; mouth-tingling or metallic taste	Flushing (may also occur with fever, hyperthermia, or crying spells)	Rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations will be absent in young infants); angioedema (face, tongue, oropharynx)
RESPIRATORY Nasal congestion, throat tightness; chest tightness; shortness of breath	Hoarseness, dysphonia (common after a crying spell); drooling or increased secretions (common in infants)	Rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis
GASTROINTESTINAL Dysphagia, nausea, abdominal pain/cramping	Spitting up/regurgitation (common after feeds), loose stools (normal in infants, especially if breastfed); colicky abdominal pain	Sudden, profuse vomiting
CARDIOVASCULAR Feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing	Hypotension (need appropriate-size blood pressure cuff; low systolic blood pressure for children is defined as <70 mm Hg from 1 mo to 1 yr, and less than (70 mm Hg + [2 × age in yr]) from 1-10 yr; tachycardia, defined as >140 beats/min from 3 mo to 2 yr, inclusive; loss of bowel and bladder control (ubiquitous in infants)	Weak pulse, arrhythmia, diaphoresis/sweating, collapse/unconsciousness
CENTRAL NERVOUS SYSTEM Headache	Drowsiness, somnolence (common in infants after feeds)	Rapid onset of unresponsiveness, lethargy, or hypotonia; seizures

Adapted from Simons FER. Anaphylaxis in infants: can recognition and management be improved? J Allergy Clin Immunol *120:537–540, 2007.*

Table 149-2 Anaphylaxis Triggers in the Community*

ALLERGEN TRIGGERS (IgE-DEPENDENT IMMUNOLOGIC MECHANISM)*
Foods (e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose])
Food additives (e.g., spices, colorants, vegetable gums, and contaminants)
Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, and fire ants)
Medications (e.g., β-lactam antibiotics, ibuprofen)
Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy])
Natural rubber latex
Vaccines
Inhalants (rare) (e.g., horse or hamster dander, grass pollen)
Previously unrecognized allergens (foods, venoms, biting insect saliva, medications, biologic agents)
OTHER IMMUNE MECHANISMS (IGE INDEPENDENT)
IgG mediated (infliximab, high-molecular-weight dextrans)
Immune aggregates (IVIG)
Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing)
Complement activation
Physical factors (e.g., exercise†, cold, heat, sunlight/ultraviolet radiation)
Ethanol
Idiopathic*

*In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.

†Exercise with or without a cotrigger, such as a food or medication, cold air, or cold water.

IVIG, intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug.

Adapted from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *New York, 2010, Elsevier, p. 652.*

Table 149-3 Patient Risk Factors for Anaphylaxis

AGE-RELATED FACTORS
Infants: anaphylaxis can be hard to recognize, especially if the first episode; patients cannot describe symptoms
Adolescents and young adults: increased risk taking behaviors such as failure to avoid known triggers and to carry an epinephrine autoinjector consistently
Pregnancy: risk of iatrogenic anaphylaxis—for example, from β lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex
Older people: increased risk of death because of concomitant disease and drugs
CONCOMITANT DISEASES
Asthma and other chronic respiratory diseases
Cardiovascular diseases
Mastocytosis
Allergic rhinitis and eczema*
Depression, cognitive dysfunction, substance misuse
DRUGS
β-Adrenergic blockers†
Angiotensin-converting enzyme (ACE) inhibitors†
Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient's ability to recognize triggers and symptoms
COFACTORS THAT AMPLIFY ANAPHYLAXIS
Exercise: anaphylaxis associated with exercise may be food dependent or food independent; nonsteroidal antiinflammatory drugs and other listed cofactors may also be relevant
Acute infection such as an upper respiratory tract infection
Fever
Emotional stress
Disruption of routine—for example, travel and jet lag
Premenstrual status in women and girls

*Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings

†Patients taking β-adrenergic blockers or ACE inhibitors seem to be at increased risk for severe anaphylaxis. In addition, those taking β-adrenergic blockers may not respond optimally to epinephrine treatment and may need glucagon, a polypeptide with non–catecholamine-dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.

Table 149-4 Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any *1* of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (e.g., *generalized* hives, pruritus or flushing, swollen lips/tongue/uvula) *AND AT LEAST 1 OF THE FOLLOWING:*
   a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a **likely** allergen for that patient* (minutes to several hours):
   a. Involvement of the skin/mucosal tissue (e.g., *generalized* hives, itch/flush, swollen lips/tongue/uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. *Persistent* gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP following exposure to ***known** allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP
   b. Adults: systolic BP <90 mm Hg or >30% drop from patient's baseline

Table 160-2 Classification of Raynaud Phenomenon

Isolated Raynaud phenomenon
Occupational Raynaud phenomenon:
Cold injury
Vibrating tools
Polyvinyl chloride exposure
Secondary Raynaud phenomenon:
Systemic sclerosis
Mixed connective tissue disease
Sjögren syndrome
Systemic lupus erythematosus
Polymyositis/dermatomyositis
Rheumatoid arthritis
Arteritis
Antiphospholipid antibody syndrome
Primary biliary cirrhosis
Carpal tunnel syndrome
Cryoglobulinemia
Leukemia
Vasospastic disorders (migraine, Prinzmetal angina)
Infection:
Hepatitis B and C (cryoglobulinemia)
Cytomegalovirus (?)
Obstructive vascular disease:
Thromboangiitis obliterans
Thoracic outlet syndrome (cervical rib)
Metabolic syndrome:
Hypothyroid
Carcinoid syndrome
Drug-induced:
Antimigraine medications
β-Blocker
Bleomycin
Interferons
Ergotamine derivatives

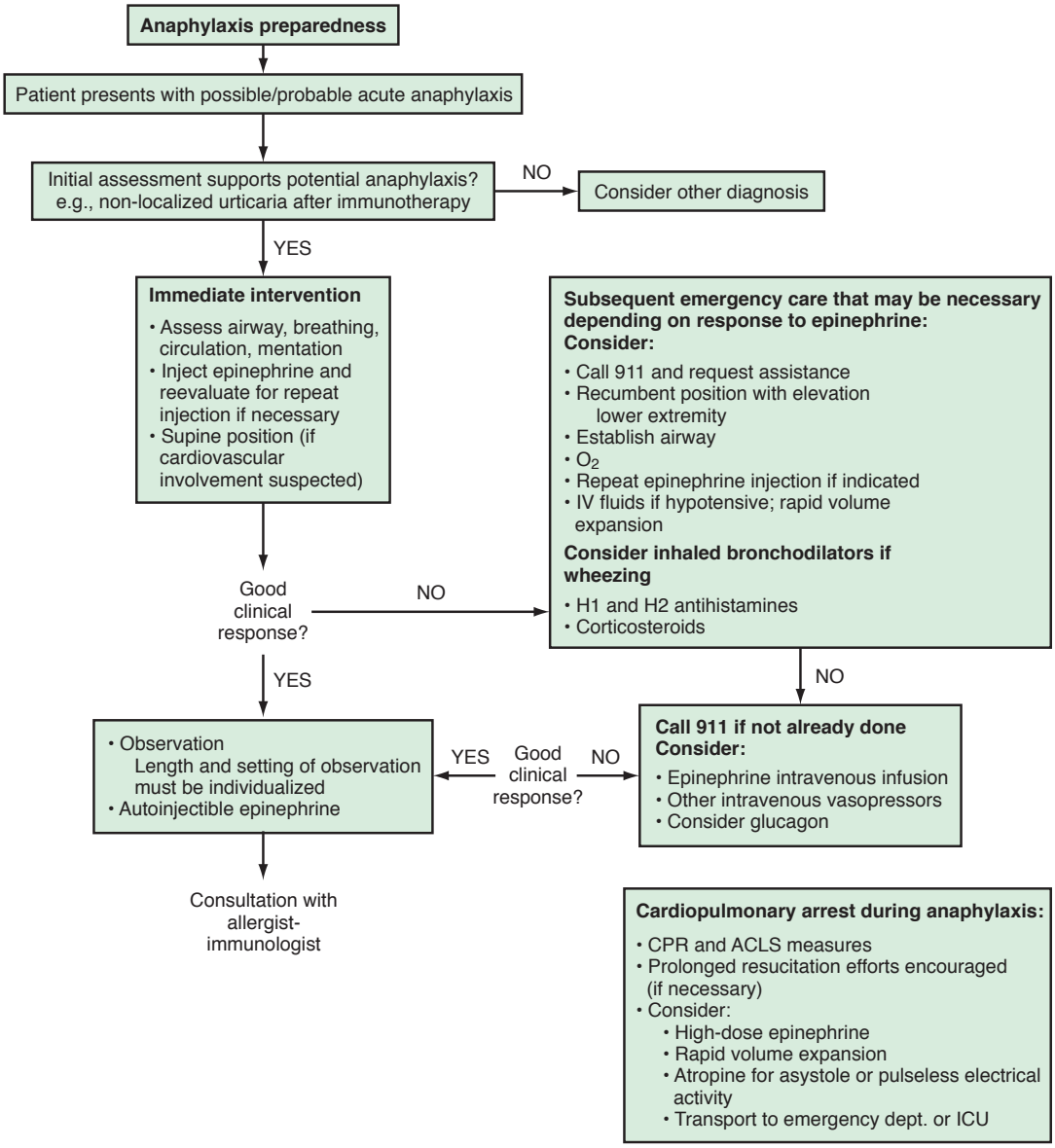


Figure 149-1 Algorithm for the treatment of anaphylactic event in the outpatient setting. IV, Intravenous. *(From Lieberman P, Nicklas RA, Oppenheimer J, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update,* J Allergy Clin Immunol *126:477–480 e471–442, 2010 [Fig. E2].)*

Table 149-5 Management of a Patient with Anaphylaxis

TREATMENT	MECHANISM(S) OF EFFECT	DOSAGE(S)	COMMENTS; ADVERSE REACTIONS
PATIENT EMERGENCY MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1, β_1, β_2 adrenergic effects	0.01 mg/kg up to 0.5 mg IM in lateral thigh Weight 8-25 kg: Adrenaclick, Auvi-Q, EpiPen Jr (0.15 mg) IM Weight >25 kg: Adrenaclick, Auvi-Q, EpiPen (0.3 mg) IM	Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid–5 mg/5 mL 0.25 mg/kg up to 10 mg PO	Hypotension, tachycardia, and somnolence
Alt: diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO or IM	Hypotension, tachycardia, somnolence, and paradoxical excitement
Transport **to an Emergency Facility**			
EMERGENCY PERSONNEL MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1, β_1, β_2 adrenergic effects	0.01 mg/kg up to 0.5 mg IM in lateral thigh Epinephrine autoinjector: 0.15 mg for 8-25kg, 0.3 mg for >25 kg 0.01 mL/kg/dose of 1:1,000 solution up to 0.5 mL IM May repeat every 10-15 min For severe hypotension: 0.01 mL/kg/dose of 1:10,000 slow IV push	Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor
Supplemental oxygen and airway management			
Volume expanders			
Crystalloids (normal saline or Ringer lactate)		30 mL/kg in 1st hr	Rate titrated against blood pressure response If tolerated, place patient supine with legs raised
Colloids (hydroxyethyl starch)		10 mL/kg rapidly followed by slow infusion	Rate titrated against blood pressure response If tolerated, place patient supine with legs raised
Antihistamines			
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid–5 mg/5 mL 0.25 mg/kg up to 10 mg PO	Hypotension, tachycardia, and somnolence
Alt: diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO, IM, or IV	Hypotension, tachycardia, somnolence, and paradoxical excitement
Ranitidine	Antihistamine (competitive of H_2 receptor)	1 mg/kg up to 50 mg IV Should be administered slowly	Headache, mental confusion
Alt: cimetidine	Antihistamine (competitive of H_2 receptor	4 mg/kg up to 200 mg IV Should be administered slowly	Headache, mental confusion
Corticosteroids			
Methylprednisolone	Antiinflammatory	Solu-Medrol (IV) 1-2 mg/kg up to 125 mg IV Depo-Medrol (IM) 1 mg/kg up to 80 mg IM	Hypertension, edema, nervousness, and agitation
Prednisone	Antiinflammatory	1 mg/kg up to 75 mg PO	Hypertension, edema, nervousness, and agitation
Nebulized albuterol	β-Agonist	(0.83 mg/mL [3 mL]) via mask with O_2	Palpitations, nervousness, central nervous system stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat
POSTEMERGENCY MANAGEMENT			
Antihistamine		Cetirizine (5-10 mg qd) or loratadine (5-10 mg qd) for 3 days	
Corticosteroids		*Optional:* Oral prednisone (1 mg/kg up to 75 mg) daily for 3 days	
Preventive treatment			
Prescription for epinephrine autoinjector and antihistamine			
Provide written plan outlining patient emergency management (may download form from http://www.foodallergy.org)			
Follow-up evaluation to determine/confirm etiology			
Immunotherapy for insect sting allergy			
Patient education			
Instruction on avoidance of causative agent			
Information on recognizing early signs of anaphylaxis			
Stress early treatment of allergic symptoms to avoid systemic anaphylaxis			
Encourage wearing medical identification jewelry			

IM, intramuscularly; IV, intravenously; PO, by mouth.

Table 151-1 Adverse Food Reactions

FOOD INTOLERANCE (NON–IMMUNE SYSTEM-MEDIATED, NONTOXIC, NONINFECTIOUS)
Host factors
Enzyme deficiencies—lactase (primary or secondary), sucrase/isomaltase, hereditary fructose intolerance, galactosemia
Gastrointestinal disorders—inflammatory bowel disease, irritable bowel syndrome, pseudoobstruction, colic
Idiosyncratic reactions—caffeine in soft drinks ("hyperactivity")
Psychologic—food phobias, obsessive/compulsive disorder
Migraines (rare)
Food factors (toxic or infectious or pharmacologic)
Infectious organisms—*Escherichia coli, Staphylococcus aureus, Clostridium perfringens, Shigella,* botulism, *Salmonella, Yersinia, Campylobacter*
Toxins—histamine (scombroid poisoning), saxitoxin (shellfish)
Pharmacologic agents—caffeine, theobromine (chocolate, tea), tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)
Contaminants—heavy metals, pesticides, antibiotics
FOOD ALLERGY
IgE-mediated
Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial
Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis
Respiratory—acute rhinoconjunctivitis, bronchospasm
Generalized—anaphylactic shock, exercise induced anaphylaxis
Mixed IgE- and non–IgE-mediated
Cutaneous—atopic dermatitis, contact dermatitis
Gastrointestinal—allergic eosinophilic esophagitis and gastroenteritis
Respiratory—asthma
Non–IgE-mediated
Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)
Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease, food protein induced enteropathy
Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)
Unclassified

IgE, immunoglobulin E.

Table 151-2 Differential Diagnosis of Adverse Food Reactions

GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)
Structural abnormalities (pyloric stenosis, Hirschsprung disease, reflux)
Enzyme deficiencies (primary or secondary):
Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase
Galactosemia
Malignancy with obstruction
Other: pancreatic insufficiency (cystic fibrosis), peptic disease
CONTAMINANTS AND ADDITIVES
Flavorings and preservatives—rarely cause symptoms:
Sodium metabisulfite, monosodium glutamate, nitrites
Dyes and colorings—very rarely cause symptoms (urticaria, eczema):
Tartrazine
Toxins:
Bacterial, fungal (aflatoxin), fish-related (scombroid, ciguatera)
Infectious organisms:
Bacteria (*Salmonella, Escherichia coli, Shigella*)
Virus (rotavirus, enterovirus)
Parasites (*Giardia, Akis simplex* [in fish])
Accidental contaminants:
Heavy metals, pesticides
Pharmacologic agents:
Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese)
PSYCHOLOGIC REACTIONS
Food phobias

Table 151-3 Natural History of Food Allergy and Cross-Reactivity Between Common Food Allergies

FOOD	USUAL AGE AT ONSET OF ALLERGY	CROSS REACTIVITY	USUAL AGE AT RESOLUTION
Hen's egg white	0-1 yr	Other avian eggs	7 yr (75% of cases resolve)*
Cow's milk	0-1 yr	Goat's milk, sheep's milk, buffalo milk	5 yr (76% of cases resolve)*
Peanuts	1-2 yr	Other legumes, peas, lentils; coreactivity with tree nuts	Persistent (20% of cases resolve)
Tree nuts	1-2 yr; in adults, onset occurs after cross reactivity to birch pollen	Other tree nuts; coreactivity with peanuts	Persistent (9% of cases resolve)
Fish	Late childhood and adulthood	Other fish (low cross-reactivity with tuna and swordfish)	Persistent†
Shellfish	Adulthood (in 60% of patients with this allergy)	Other shellfish	Persistent
Wheat*	6-24 mo	Other grains containing gluten (rye, barley)	5 yr (80% of cases resolve)
Soybeans*	6-24 mo	Other legumes	2 yr (67% of cases resolve)
Kiwi	Any age	Banana, avocado, latex	Unknown
Apples, carrots, and peaches§	Late childhood and adulthood	Birch pollen, other fruits, nuts	Unknown

*Recent studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kU_A/L.
†Fish allergy that is acquired in childhood can resolve.
§Allergy to fresh apples, carrots, and peaches (**oral allergy syndrome**) is commonly caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.
Modified from Lack G: Food allergy, N Engl J Med *359:1252–1260, 2008, Table 1.*

Table 151-4 Prevention of Food Allergy

Exclusive breast feeding for 4-6 mo
Introduce solid (complementary) foods after 4-6 mo of exclusive breast feeding
Introduce low-risk complementary foods 1 at a time
Introduce potentially highly allergenic foods (fish, eggs, peanut products, milk, wheat) soon after the lower-risk foods (no need to avoid or delay)
Don't avoid allergenic foods during pregnancy or nursing
Soy-based formulas do not prevent allergic disease

Table 154-1 Multidisciplinary Treatment of Rheumatic Diseases in Childhood

Accurate diagnosis and education of family	Pediatric rheumatologist Pediatrician Nurse: • Disease-related education • Medication administration (injection teaching) • Safety monitoring Social worker: • Facilitation of school services • Resource identification (community, government, financial, advocacy groups, vocational rehabilitation)
Physical medicine and rehabilitation	Physical therapy: • Addressing deficits in joint or muscle mobility, limb length discrepancies, gait abnormalities, weakness Occupational therapy: • Splinting to reduce joint contractures/deformities and lessen stress on joints; adaptive devices for activities of daily living
Consultant team	Ophthalmology: • Eye screening for uveitis (see Table 155-4) • Screening for medication-related ocular toxicity (hydroxychloroquine, glucocorticoids) Nephrology Orthopedics Dermatology Gastroenterology
Physical and psychosocial growth and development	Nutrition: • Addressing undernourishment from systemic illness, obesity/overnourishment from glucocorticoids School integration: • Individualized Educational Plan (IEP) or 504 plan Peer group relationships Individual and/or family counseling
Coordination of care	Involvement of patient and family as active team members Communication among healthcare providers Involvement of school (school nurse) and community (social worker) resources

Table 151-5 Symptoms of Food-Induced Allergic Reactions

TARGET ORGAN	IMMEDIATE SYMPTOMS	DELAYED SYMPTOMS
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper respiratory	Nasal congestion Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough, dyspnea, and wheezing
GI (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	
GI (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	
Miscellaneous	Uterine contractions Sense of "impending doom"	

Note: This table is presented as Table IV in the Guidelines.
GI, gastrointestinal.
From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table IV, p. S19).*

Table 151-8 ACIP and AAP Red Book Recommendations for Administering Vaccines to Patients with Egg Allergy

VACCINE	ACIP	AAP RED BOOK
MMR/MMRV	May be used	May be used
Influenza	Receive with some precautions*	Receive with some precautions*
Rabies	Use caution	No specific recommendation
Yellow fever	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices.
From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table V, p S31).*
*In 2012, recommendations changed to suggest those with mild egg allergy receive the inactivated influenza vaccine in the primary care setting with a 30 minute observation and preparedness to treat anaphylaxis. Those with severe egg allergy are referred to an allergist.

Table 151-6 Food Protein-Induced Gastrointestinal Syndromes

	FPIES	PROCTOCOLITIS	ENTEROPATHY	EOSINOPHILIC GASTROENTEROPATHIES*
Age at onset	1 day–1 year	1 day–6 months	Dependent of age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
Food proteins implicated				
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy, egg white, wheat, peanut
Less common	Rice, chicken, turkey, fish, pea	Egg, corn, chocolate	Wheat, egg	Meats, corn, rice, fruits, vegetables, fish
Multiple food hypersensitivities	>50% both cow's milk and soy	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breast feeding	Formula	Formula
Atopic background				
Family history of atopy	40-70%	25%	Unknown	~50% (often history of eosinophilic esophagitis)
Personal history of atopy	30%	22%	22%	~50%
Symptoms				
Emesis	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Laboratory findings				
Anemia	Moderate	Mild	Moderate	Mild-moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild-severe
Methemoglobinemia	May be present	No	No	No
Allergy evaluation				
Food prick skin test	Negative†	Negative	Negative	Positive in ~50%
Serum food allergen IgE	Negative†	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
Biopsy findings				
Colitis	Prominent	Focal	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation and basal zone hyperplasia
Food challenge	Vomiting in 2-4 hr; diarrhea in 5-8 hr	Rectal bleeding in 6-72 hr	Vomiting, diarrhea, or both in 40-72 hr	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge in 1.5-2 yr	Protein elimination, symptoms clear in 3 days with casein hydrolysate, resume/ continue breastfeeding on maternal antigen-restricted diet	Protein elimination, symptoms clear in 1-3 wk, rechallenge and biopsy in 1-2 yr	Protein elimination, good response to casein hydrolysate, excellent response to elemental diet, symptoms clear within 2-3 wk, excellent acute response to steroids; rechallenge and biopsy in 1-2 yr
Natural history	Cow's milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr	Resolved by 9-12 months	Most cases resolve in 2-3 yr	Typically a prolonged, relapsing course
Reintroduction of the food	Inpatient food challenge	At home, gradually advancing from 1 oz to full feedings over 2 weeks	Home, gradually advancing	Home, gradually advancing

*Eosinophilic gastroenteropathies encompass esophagitis, gastritis, gastroenterocolitis.
†If positive, may be a risk factor for persistent disease.
FPIES, food protein-induced enterocolitis syndrome.
From Nowak-Wegrzyn A, Muraro A: Food protein-induced enterocolitis syndrome. Curr Opin Allergy Immunol *9:371-377, 2009 (Table 1, p. 372).*

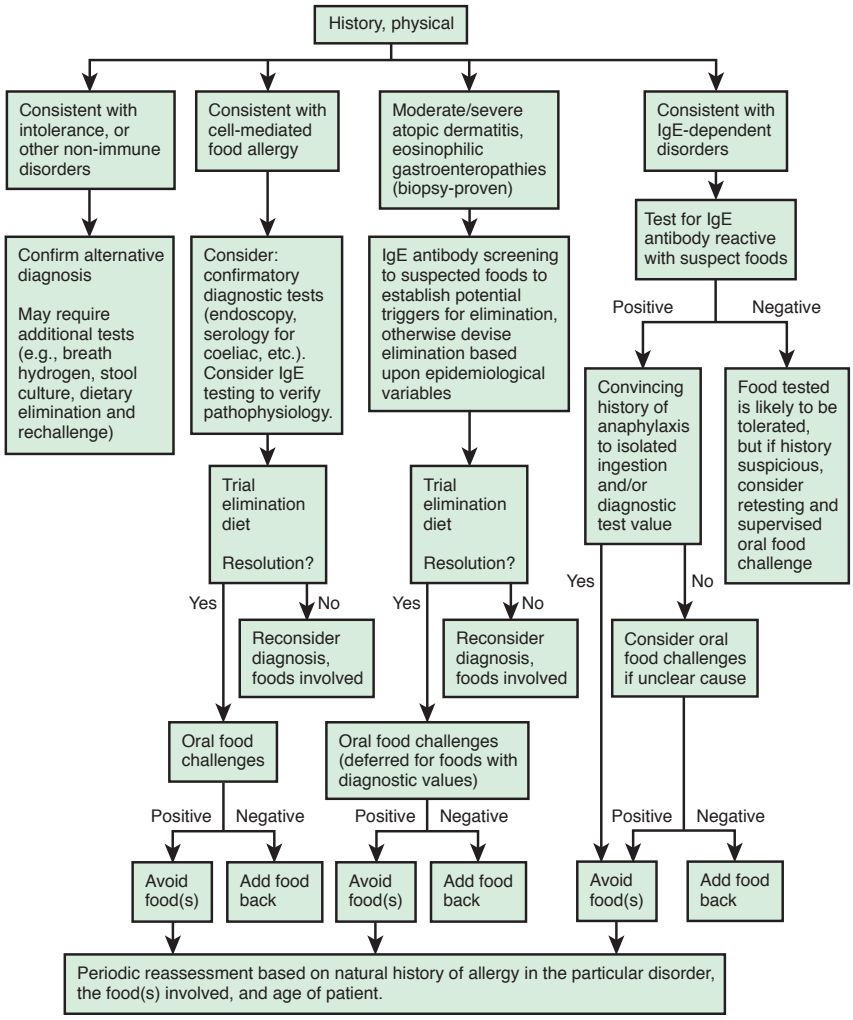


Figure 151-1 General scheme for diagnosis of food allergy. *(From Sicherer SH: Food allergy,* Lancet *360:701–710, 2002.)*

Table 151-7 Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy

FOOD FAMILY	RISK OF ALLERGY TO ≥1 MEMBER (%; APPROXIMATE)	FEATURE(S)
Legumes	5	Main causes of reactions are peanut, soybean, lentil, lupine, and garbanzo (chickpea)
Tree nuts (e.g., almond, cashew, hazelnut, walnut, brazil)	35	Reactions are often severe
Fish	50	Reactions can be severe
Shellfish	75	Reactions can be severe
Grains	20	
Mammalian milks	90	Cow's milk is highly cross reactive with goat's or sheep's milk (92%) but not with mare's milk (4%)
Rosaceae (pitted fruits)	55	Risk of reactions to more than three related foods is very low (<10%), symptoms are usually mild (oral allergy syndrome)
Latex-food	35	For individuals allergic to latex, banana, kiwi, fig, chestnut, and avocado are the main causes of reactions
Food-latex	11	Individuals allergic to banana, kiwi, fig, chestnut, and avocado may be at an increased risk of reactions to latex

Modified from Sicherer SH: Food allergy, Lancet *360:701–710, 2002.*

Rheumatic Diseases of Childhood

Table 153-1 Symptoms Suggestive of Rheumatic Disease

SYMPTOM	RHEUMATIC DISEASE(S)	POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS
Fevers	Systemic JIA, SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD	Malignancies, infections and post-infectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP
Arthralgias	JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma, sarcoidosis	Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overuse syndromes
Weakness	JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma	Muscular dystrophies, metabolic and other myopathies, hypothyroidism
Chest pain	Juvenile rheumatoid arthritis, SLE (with associated pericarditis or costochondritis)	Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation
Back pain	Enthesitis related arthritis, juvenile ankylosing spondylitis	Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury
Fatigue	SLE, JDM, MCTD, vasculitis, JIA	Pain syndromes, chronic infections, chronic fatigue syndrome, depression

HSP, Henoch-Schönlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus.

Table 153-2 Signs Suggestive of Rheumatic Disease

SIGN	RHEUMATIC DISEASES	COMMENTS	NONRHEUMATIC CAUSES
Malar rash	SLE, JDM	SLE classically spares nasolabial folds	Sunburn, parvovirus B19 (fifth disease), Kawasaki disease
Oral ulcers	SLE, Behçet disease	Behçet disease also associated with genital ulcers	HSV infection, PFAPA syndrome
Purpuric rash	Vasculitis, e.g., ANCA-associated vasculitis, HSP	HSP typically starts as small lesions on lower extremities and buttocks that coalesce	Meningococcemia, thrombocytopenia, clotting disorders
Gottron papules	JDM	Look for associated heliotrope rash, periungual telangiectasias	Psoriasis, eczema
Arthritis	Juvenile idiopathic arthritis, SLE, vasculitis, HSP, MCTD, scleroderma, acute rheumatic fever, reactive arthritis	Chronic joint swelling (>6 wk) required for diagnosis of chronic arthritis of childhood; MCTD associated with diffuse puffiness of hands	Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes

ANCA, antineutrophilic cytoplasmic antibody; HSP, Henoch-Schönlein purpura; HSV, herpes simplex virus; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; SLE, systemic lupus erythematosus.

Table 153-3 Autoantibody Specificity and Disease Associations

ANTIBODY	DISEASE	PREVALENCE (%)	SPECIFICITY
Antinuclear antibody (ANA)	SLE, juvenile rheumatoid arthritis, dermatomyositis, scleroderma, psoriatic arthritis, MCTD	—	Associated with increased risk of uveitis in JIA and psoriatic arthritis Up to 30% of children testing positive for ANAs have no underlying rheumatic disease
Double-stranded DNA (dsDNA)	SLE	60-70	High specificity for SLE; associated with lupus nephritis
Smith (Sm)	SLE	20-30	Highly specific for SLE; associated with lupus nephritis
Smooth muscle (Sm)	Autoimmune hepatitis	—	—
Pm-Scl (polymyositis-scleroderma)	Sclerodermatomyositis	—	—
SSA (Ro)	SLE, Sjögren syndrome	25-30	Associated with neonatal lupus syndrome, subacute cutaneous lupus, thrombocytopenia
SSB (La)	SLE, Sjögren syndrome	25-30	Usually coexists with anti-SSA antibody
Ribonuclease protein (RNP)	MCTD, SLE	30-40	Suggestive of MCTD unless meets criteria for SLE
Histone	Drug-induced lupus, SLE	—	—
Centromere	Limited cutaneous systemic sclerosis	70	Nonspecific for systemic sclerosis
Topoisomerase I (Scl-70)	Systemic sclerosis	—	Rare in childhood
Antineutrophil cytoplasmic antibodies (ANCAs)	Vasculitis	—	—
Cytoplasmic (cANCAs)/ PR3-ANCA		—	cANCAs associated with granulomatosis with polyangiitis (Wegener), cystic fibrosis
Perinuclear (pANCAs)/ MPO-ANCA		—	pANCAs associated with microscopic polyangiitis, polyarteritis nodosa, SLE, inflammatory bowel disease, cystic fibrosis, primary sclerosing cholangitis, Henoch-Schönlein purpura, Kawasaki disease, Churg-Strauss syndrome
Anticitrullinated protein (ACPA) also called anti-cyclic citrullinated protein (anti-CCP)	RF positive JIA	50-90	Specific for JIA (RF+), may be positive before RF

MCTD, mixed connective tissue disease; MPO-ANCA, antimyeloperoxidase; PR3-ANCA, antiproteinase 3; RF, rheumatoid factor; SLE, systemic lupus erythematosus.
Modified from Aggerwal A: Clinical application of tests used in rheumatology, Indian J Pediatr *69:889–892, 2002.*

Table 153-4 Evaluation Based on Suspected Diagnosis

SUSPECTED RHEUMATIC DISEASE(S)	INITIAL EVALUATION	FURTHER EVALUATION	SUBSPECIALTY EVALUATION
SLE, MCTD	CBC, ESR, ANA, ALT, AST, CPK, creatinine, albumin, total protein, urinalysis, BP, thyroid profile	If ANA test result is positive: anti–SSA (Ro), anti–SSB (La), anti-Smith, and anti-RNP Abs; anti-dsDNA Ab, C3, C4, Coombs, spot urine protein/creatinine ratio, CXR	Antiphospholipid Abs, lupus anticoagulant, anti–β_2-glycoprotein, echocardiogram; consider renal biopsy, PFTs, bronchoscopy with lavage, HRCT of chest; consider lung biopsy
JDM	CBC, CPK, ALT, AST, LDH, aldolase, ANA; check gag reflex	Consider MRI of muscle	Consider electromyography and possible muscle biopsy, PFTs, swallowing study, serum neopterin
JIA	CBC, ESR, creatinine, ALT, AST, consider anti–streptolysin O/anti–DNAase B for streptococcus-induced arthritis, Epstein-Barr virus titers, Lyme titer, parvovirus B19 titer, plain radiograph of joints	Consider Ab titers to unusual infectious agents, purified protein derivative, RF, ANA, HLA-B27, anti-CCP	MRI
Granulomatosis with polyangiitis (Wegener granulomatosis)	CBC, ANCA, AST, ALT, albumin, creatinine, ESR, urinalysis, CXR, BP	Spot urine protein/creatinine ratio, anti–myeloperoxidase and anti–proteinase-3 Abs, PFTs	Bronchoscopy with lavage, HRCT chest; consider lung and kidney biopsies
Sarcoidosis	CBC, electrolytes, AST, ALT, albumin, creatinine, calcium, phosphorous, ACE, BP	CXR, PFTs	Consider testing for Blau syndrome in infants (see Chapter 159); HRCT of chest; consider renal and lung biopsy
Localized scleroderma	Skin biopsy, CBC, ESR		Serum immunoglobulin G, ANA, RF, single-stranded DNA Ab, antihistone Ab, CPK
Systemic scleroderma	ANA, CBC, ESR, BP, AST, ALT, CPK, creatinine, CXR	Anti-Scl70, PFTs	HRCT of chest, echocardiogram, upper gastrointestinal radiography series

Ab, antibody; ACE, angiotensin-converting enzyme (normally elevated in childhood; interpret with caution); ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-dsDNA Ab, anti–double stranded DNA antibody; AST, aspartate aminotransferase; BP, blood pressure; CBCD, complete blood count with differential; CCP, cyclic citrullinated protein; CPK, creatine phosphokinase; CXR, chest radiograph; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HRCT, high-resolution CT; LDH, lactate dehydrogenase; PFTs, pulmonary function tests; RF, rheumatoid factor.

Table 155-5 Frequency of Ophthalmologic Examination in Patients with Juvenile Idiopathic Arthritis

TYPE	ANTINUCLEAR ANTIBODY TEST RESULT	AGE AT ONSET (Yr)	DURATION OF DISEASE (Yr)	RISK CATEGORY	EYE EXAMINATION FREQUENCY (Mo)
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	NA	Low	12
Systemic disease	NA	NA	NA	Low	12

From Cassidy J, Kivlin J, Lindsley C, et al: Section on Rheumatology; Section on Ophthalmology: Ophthalmologic examinations in children with juvenile rheumatoid arthritis, Pediatrics *117:1843–1845, 2006.*

Table 154-2 Therapeutics for Childhood Rheumatic Diseases*

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Nonsteroidal antiinflammatory drugs (NSAIDs)‡	Etodolac[a]	PO once-daily dose: 20-30 kg: 400 mg 31-45 kg: 600 mg 46-60 kg: 800 mg >60 kg: 1,000 mg	JIA Spondyloarthropathy Pain Serositis Cutaneous vasculitis Uveitis	GI intolerance (abdominal pain, nausea), gastritis, hepatitis, tinnitus, anemia, pseudoporphyria, aseptic meningitis, headache, renal disease	CBC, LFTs, BUN/creatinine, urinalysis at baseline, then every 6-12 mo
	Ibuprofen[a]	40 mg/kg/day PO divided 3 times daily Max 2400 mg per day			
	Naproxen[a]	15 mg/kg/day PO in 2 divided doses Maximum 1,000 mg per day			
	Celecoxib[a]	10-25 kg: 50 mg PO twice daily >25 kg: 100 mg PO twice daily			
	Meloxicam[a]	0.125 mg/kg, maximum 7.5 mg, PO once daily			
Disease modifying antirheumatic drugs (DMARDs)	Methotrexate[a]	10-20 mg/m^2/wk (0.35-0.65 mg/kg/wk) PO 20-30 mg/m^2/wk (0.65-1 mg/kg/wk) SC; higher doses better absorbed by SC injection	JIA Uveitis	GI intolerance (nausea, vomiting), hepatitis, myelosuppression, mucositis, teratogenesis, lymphoma, interstitial pneumonitis	CBC, LFTs at baseline, monthly × 3, then every 8-12 wk
	Leflunomide	PO once daily: 10 to <20 kg: 10 mg 20-40 kg: 15 mg >40 kg: 20 mg	JIA	hepatitis, hepatic necrosis, cytopenias, mucositis, teratogenesis, peripheral neuropathy	CBC, LFTs, at baseline, monthly × 6, then every 8-12 wk
	Hydroxychloroquine	5-6 mg/kg PO once daily; do not exceed 6.5 mg/kg/daily Maximum dose 400 mg daily	SLE JDMS Antiphospholipid antibody syndrome	Retinal toxicity, GI intolerance, rash, skin discoloration, anemia, cytopenias, myopathy, CNS stimulation, death (overdose)	Ophthalmologic screening every 6-12 mo
	Sulfasalazine[a]	30-50 mg/kg/day divided in twice-daily doses Adult maximum 3 g/day	Spondyloarthropathy, JIA	GI intolerance, rash, hypersensitivity reactions, Stevens-Johnson syndrome, cytopenias, hepatitis, headache	CBC, LFTs, BUN/creatinine, urinalysis at baseline, every other wk × 3 mo, monthly × 3, then every 3 mo
Tumor necrosis factor α (TNF-α) antagonists	Adalimumab[a]	SC once every other wk: 15 to <30 kg: 20 mg ≥30 kg: 40 mg	JIA, spondyloarthropathy, psoriatic arthritis, uveitis	Injection site reaction, infection, rash, cytopenias, lupus-like syndrome, potential increased malignancy risk	TB test; anti-dsDNA, CBC
	Etanercept[a]	0.8 mg/kg SC once weekly (maximum 50 mg/dose) or 0.4 mg/kg SC twice weekly (maximum 25 mg/dose)	JIA	Injection site reactions, infections, rash, demyelinating disorders, cytopenias, potential increased malignancy risk	TB test; CBC
	Infliximab	5-10 mg/kg IV q4-8wk	JIA Spondyloarthropathy Uveitis Sarcoidosis	Infusion reactions, hepatitis, potential increased malignancy risk	TB test; anti-dsDNA, LFTs

*Consult a clinical pharmacology reference for current dosing and monitoring guidelines, and complete list of known adverse effects.

Continued

Table 154-2 Therapeutics for Childhood Rheumatic Diseases—cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Modulate T-cell activation	Abatacept[a]	IV every 2 wk × 3 doses, then monthly for ≥6 yr of age: <75 kg: 10 mg/kg 75-100 kg: 750 mg >100 kg: 1,000 mg	JIA	Infection, headache, potential increased malignancy risk	
Anti-CD20 (B cell) antibody	Rituximab	575 mg/m^2, maximum 1,000 mg, IV on days 1 and 15	SLE	Infusion reactions, lymphopenia, reactivation hepatitis B, rash, serum sickness, arthritis, PML	CBC, BMP; consider monitoring quantitative IgG
Anti-BLyS antibody	Belimumab[e]	10 mg/kg IV every 2 wk × 3 doses, then every 4 wk	SLE	Infusion reactions, infection, depression	
Interleukin 1 antagonist	Anakinra	1-2 mg/kg/daily Adult maximum 100 mg	Systemic JIA CAPS	Injection site reactions, infection	CBC
	Canakinumab[b]	Given SC every 8 wk (CAPS) every 4 wk (Systemic JIA): 15-40 kg: 2 mg/kg (up to 3 mg/kg if needed) >40 kg: 150 mg	CAPS Systemic JIA	Injection site reaction, infection, diarrhea, nausea, vertigo, headache	
Interleukin-6 antagonist	Tocilizumab[a]	≥2 yr and ≥30 kg, 8 mg/kg/dose every 2 wk; ≥2 yr and ≤30 kg, 12 mg/kg/dose every 2 wk	Systemic JIA	Infusion reactions, elevated LFTs, elevated lipids, thrombocytopenia, infections	CBC, LFTs, platelet count, serum lipid profile
Intravenous immunoglobulin	IVIG[c]	1,000-2,000 mg/kg IV infusion For JDMS, give monthly	Kawasaki disease JDMS SLE	Infusion reaction, aseptic meningitis, renal failure	Serum creatinine, BUN, IgG level
Cytotoxic	Cyclophosphamide	0.5-1 g/m^2 IV (maximum 1.5 g) monthly for 6-mo induction, then every 2-3 mo Oral regimen: 1-2 mg/kg/daily; maximum 150 mg/daily	SLE Vasculitis JDMS Pulmonary hemorrhage	Nausea, vomiting, myelosuppression, mucositis, hyponatremia, alopecia, hemorrhagic cystitis, gonadal failure, teratogenesis, secondary malignancy	CBC
Immunosuppressive	Mycophenolate mofetil	Oral suspension: maximum 1,200 mg/m^2/day PO (up to 2 g/day) divided twice daily Capsules: maximum 1,500 mg/day PO for BSA 1.25-1.5 m^2, 2 g/day PO for BSA >1.5 m^2 divided twice daily	SLE Uveitis	GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML	CBC, BMP

Table 154-2 Therapeutics for Childhood Rheumatic Diseases—cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Glucocorticoids	Prednisone[a,d-f]	0.05-2 mg/kg/day PO given in 1-4 divided doses; maximum varies by individual (80 mg/daily) Adverse effects are dose dependent; lowest effective dose should be used	SLE JDMS Vasculitis JIA Uveitis Sarcoidosis	Cushing syndrome, osteoporosis, increased appetite, weight gain, striae, hypertension, adrenal suppression, hyperglycemia, infection, avascular necrosis	Blood glucose, potassium Blood pressure
	Methylprednisolone[a,d-g]	0.5-1.7 mg/kg/day or 5-25 mg/m^2/day IM/IV in divided doses q6-12h For severe manifestations: 30 mg/kg/dose (maximum 1 g) daily for 1-5 days	SLE JDMS Vasculitis Sarcoidosis Localized scleroderma		
	Intraarticular	Dose varies by joint and formulation	JIA	Subcutaneous atrophy, skin hypopigmentation, calcification, infection	
	Prednisolone ophthalmic suspension	1-2 drops into eye up to every hr while awake Needs monitoring by ophthalmologist	Uveitis	Ocular hypertension, glaucoma, nerve damage, cataract, infection	Ophthalmologic exam

Blys, B-lymphocyte stimulator; BMP, basic metabolic panel; BSA, body surface area; BUN, blood urea nitrogen; CAPS, cryopyrin-associated periodic syndrome; CBC, complete blood count; CNS, central nervous system; dsDNA, double-stranded DNA; GI, gastrointestinal; Ig, immunoglobulin; IM, intramuscular(ly); IV, intravenous(ly); IVIG, intravenous immunoglobulin; JDMS, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LFTs, liver function tests; PML, progressive multifocal leukoencephalopathy; PO, by mouth; SC, subcutaneous(ly); SLE, systemic lupus erythematosus; TB, tuberculosis.

†Therapeutics used in practice may not have a FDA-approved indication. Individual therapeutics annotated with FDA-approved indication as follows: a, JIA; b, CAPS; c, Kawasaki disease; d, sarcoidosis; e, SLE; f, uveitis; g, dermatomyositis.

‡Many more products available in this class.

Table 155-1 Criteria for the Classification of Juvenile Rheumatoid Arthritis

Age at onset: <16 yr
Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joint
Duration of disease: ≥6 wk
Onset type defined by type of articular involvement in the 1st 6 mo after onset:
- Polyarthritis: ≥5 inflamed joints
- Oligoarthritis: ≤4 inflamed joints
- Systemic-onset disease: arthritis with rash and a characteristic quotidian fever

Exclusion of other forms of juvenile arthritis

Modified from Cassidy JT, Levison JE, Bass JC, et al: A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis, Arthritis Rheum *29:174–181, 1986.*

Table 154-3 Summary of Biologic Therapies Studied in Juvenile Idiopathic Arthritis and Their Method of Action

DRUG	METHOD OF ACTION
Etanercept	Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α
Infliximab	Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action
Adalimumab	A humanized IgG_1 monoclonal antibody that binds to TNF-α
Abatacept	Soluble, fully human fusion protein of the extracellular domain of (CTLA-4, linked to a modified Fc portion of the human IgG_1. It acts as a costimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation
Tocilizumab	A humanized anti–human IL-6 receptor monoclonal antibody
Anakinra	An IL-1 receptor antagonist (IL-1RA)

CTLA, cytotoxic T lymphocyte–associated antigen; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.

From Beresford MW, Baildam EM: New advances in the management of juvenile idiopathic arthritis—2: the era of biologicals, Arch Dis Child Educ Pract Ed *94:151–156, 2009.*

Table 155-2 International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA)

CATEGORY	DEFINITION	EXCLUSIONS
Systemic	Arthritis in ≥1 joint with, or preceded by, fever of at least 2 wk in duration that is documented to be daily ("quotidian"*) for at least 3 days and accompanied by ≥1 of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly or splenomegaly or both 4. Serositis†	a. Psoriasis or a history of psoriasis in the patient or a 1st-degree relative b. Arthritis in an HLA-B27–positive boy beginning after the 6th birthday c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis, or a history of one of these disorders in a 1st-degree relative d. Presence of immunoglobulin M RF on at least 2 occasions at least 3 mo apart
Oligoarthritis	Arthritis affecting 1-4 joints during the 1st 6 mo of disease. Two subcategories are recognized: 1. Persistent oligoarthritis—affecting ≤4 joints throughout the disease course 2. Extended oligoarthritis—affecting >4 joints after the 1st 6 mo of disease	a, b, c, d (above) plus e. Presence of systemic JIA in the patient
Polyarthritis (RF-negative)	Arthritis affecting ≥5 joints during the 1st 6 mo of disease; a test for RF is negative	a, b, c, d, e
Polyarthritis (RF-positive)	Arthritis affecting ≥5 joints during the 1st 6 mo of disease; ≥2 tests for RF at least 3 mo apart during the 1st 6 mo of disease are positive	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in a 1st-degree relative	b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis,‖ or arthritis or enthesitis with at least 2 of the following: 1. Presence of or a history of sacroiliac joint tenderness or inflammatory lumbosacral pain or both¶ 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male >6 yr old 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a 1st-degree relative	a, d, e
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in ≥2 of the above categories.	

RF, rheumatoid factor.
**Quotidian fever* is defined as a fever that rises to 39°C (102.2°F) once a day and returns to 37°C (98.6°F) between fever peaks.
†*Serositis* refers to pericarditis, pleuritis, or peritonitis, or some combination of the 3.
‡*Dactylitis* is swelling of ≥1 digits, usually in an asymmetric distribution, that extends beyond the joint margin.
§A minimum of 2 pits on any 1 or more nails at any time.
‖*Enthesitis* is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.
¶*Inflammatory lumbosacral pain* refers to lumbosacral pain at rest with morning stiffness that improves on movement.
From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

Table 155-3 Characteristics of the American College of Rheumatology (ACR) and International League of Associations for Rheumatology (ILAR) Classifications of Childhood Chronic Arthritis

PARAMETER	ACR (1977)	ILAR (1997)
Term	Juvenile rheumatoid arthritis (JRA)	Juvenile idiopathic arthritis (JIA)
Minimum duration	≥6 wk	≥6 wk
Age at onset	<16 yr	<16 yr
≤4 joints in 1st 6 mo after presentation	• Pauciarticular	• Oligoarthritis: a. Persistent: <4 joints for course of disease b. Extended: >4 joints after 6 mo
>4 joints in 1st 6 mo after presentation	• Polyarticular	• Polyarthritis rheumatoid factor–negative • Polyarthritis rheumatoid factor–positive
Fever, rash, arthritis	• Systemic-onset	• Systemic
Other categories included	Exclusion of other forms	• Psoriatic arthritis • Enthesitis-related arthritis • Undifferentiated: a. Fits no other category b. Fits more than 1 category
Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis	No (see Chapter 156)	Yes

Table 155-4 Overview of the Main Features of the Subtypes of Juvenile Idiopathic Arthritis

INTERNATIONAL LEAGUE OF ASSOCIATIONS FOR RHEUMATOLOGY SUBTYPE	PEAK AGE OF ONSET (Yr)	FEMALE:MALE RATIO	PERCENTAGE OF ALL JIA CASES	ARTHRITIS PATTERN	EXTRAARTICULAR FEATURES	LABORATORY INVESTIGATIONS	NOTES ON THERAPY
Systemic arthritis	1-5	1:1	5-15	Polyarticular, often affecting knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis; pleuritis	Anemia; WBC ↑↑; ESR ↑↑; CRP ↑↑; ferritin ↑; platelets ↑↑ (normal or ↓ in MAS)	Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-1 or IL-6 inhibitors in resistant cases or as first-line therapy
Oligoarthritis	2-4	3:1	40-50 (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in ≈30% of cases	ANA positive in ≈60%; other test results usually normal; may have mildly ↑ ESR/CRP	NSAIDs and intraarticular steroids; MTX occasionally required
Polyarthritis: RF-negative	2-4 and 10-14	3:1 and 10:1	20-35	Symmetric or asymmetric; small and large joints; cervical spine; temporomandibular joint	Uveitis in ≈10%	ANA positive in 40%; RF negative; ESR ↑ or ↑↑; CRP ↑/normal; mild anemia	Standard therapy with MTX and NSAIDs; then, if nonresponsive, anti-TNF agents or other biologics, including abatacept, indicated as first-line therapy
RF-positive	9-12	9:1	<10	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive; ESR ↑↑; CRP ↑/normal; mild anemia	Long-term remission unlikely; early aggressive therapy is warranted
Psoriatic arthritis	2-4 and 9-11	2:1	5-10	Asymmetric arthritis of small or medium-sized joints	Uveitis in 10%; psoriasis in 50%	ANA positive in 50%; ESR ↑; CRP ↑/normal; mild anemia	NSAIDs and intraarticular steroids; MTX, anti-TNF agents
Enthesitis-related arthritis	9-12	1:7	5-10	Predominantly lower limb joints affected; sometimes axial skeleton (but less than in adult, ankylosing spondylitis)	Acute anterior uveitis; association with reactive arthritis and inflammatory bowel disease	80% of patients positive for HLA-B27	NSAIDs and intra-articular steroids; consider sulfasalazine as alternative to MTX; anti-TNF agents

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

Table 155-7 Conditions Causing Arthritis or Extremity Pain

RHEUMATIC AND INFLAMMATORY DISEASES
Juvenile idiopathic arthritis
Systemic lupus erythematosus
Juvenile dermatomyositis
Polyarteritis nodosa
Scleroderma
Sjögren syndrome
Behçet disease
Overlap syndromes
Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis
Sarcoidosis
Kawasaki syndrome
Henoch-Schönlein purpura
Chronic recurrent multifocal osteomyelitis

SERONEGATIVE SPONDYLOARTHROPATHIES
Juvenile ankylosing spondylitis
Inflammatory bowel disease
Psoriatic arthritis
Reactive arthritis associated with urethritis, iridocyclitis, and mucocutaneous lesions

INFECTIOUS ILLNESSES
Bacterial arthritis (septic arthritis, *Staphylococcus aureus, Kingella kingae,* pneumococcus, gonococcus, *Haemophilus influenzae*)
Lyme disease
Viral illness (parvovirus, rubella, mumps, Epstein-Barr virus, hepatitis B, Chikungunya virus)
Fungal arthritis
Mycobacterial infection
Spirochetal infection
Endocarditis

REACTIVE ARTHRITIS
Acute rheumatic fever
Reactive arthritis (postinfectious caused by *Shigella, Salmonella, Yersinia, Chlamydia,* or meningococcus)
Serum sickness
Toxic synovitis of the hip
Postimmunization

IMMUNODEFICIENCIES
Hypogammaglobulinemia
Immunoglobulin A deficiency
Human immunodeficiency virus

CONGENITAL AND METABOLIC DISORDERS
Gout
Pseudogout
Mucopolysaccharidoses
Thyroid disease (hypothyroidism, hyperthyroidism)
Hyperparathyroidism
Vitamin C deficiency (scurvy)
Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome)
Fabry disease
Farber disease
Amyloidosis (familial Mediterranean fever)

BONE AND CARTILAGE DISORDERS
Trauma
Patellofemoral syndrome
Hypermobility syndrome
Osteochondritis dissecans
Avascular necrosis (including Legg-Calvé-Perthes disease)
Hypertrophic osteoarthropathy
Slipped capital femoral epiphysis
Osteolysis
Benign bone tumors (including osteoid osteoma)
Histiocytosis
Rickets

NEUROPATHIC DISORDERS
Peripheral neuropathies
Carpal tunnel syndrome
Charcot joints

NEOPLASTIC DISORDERS
Leukemia
Neuroblastoma
Lymphoma
Bone tumors (osteosarcoma, Ewing sarcoma)
Histiocytic syndromes
Synovial tumors

HEMATOLOGIC DISORDERS
Hemophilia
Hemoglobinopathies (including sickle cell disease)

MISCELLANEOUS DISORDERS
Autoinflammatory diseases
Recurrent multifocal osteomyelitis
Pigmented villonodular synovitis
Plant-thorn synovitis (foreign-body arthritis)
Myositis ossificans
Eosinophilic fasciitis
Tendinitis (overuse injury)
Raynaud phenomenon

PAIN SYNDROMES
Fibromyalgia
Growing pains
Depression (with somatization)
Reflex sympathetic dystrophy
Regional myofascial pain syndromes

Table 155-6 Main Clinical, Laboratory, and Pathologic Features of Macrophage Activation Syndrome

LABORATORY CRITERIA
1. Cytopenias
2. Abnormal liver function tests
3. Coagulopathy (hypofibrinogenemia)
4. Decreased erythrocyte sedimentation rate
5. Hypertriglyceridemia
6. Hyponatremia
7. Hypoalbuminemia
8. Hyperferritinemia
9. Elevated sCD25 and sCD163

CLINICAL CRITERIA
1. Nonremitting fever
2. Hepatomegaly
3. Splenomegaly
4. Lymphadenopathy
5. Hemorrhages
6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)

HISTOPATHOLOGIC CRITERIA
1. Macrophage hemophagocytosis in the bone marrow aspirate
2. Increased CD163 staining of the bone marrow

Table 156-2 Etiologic Microorganisms of Reactive Arthritis

PROBABLE	POSSIBLE
Chlamydia trachomatis	*Neisseria gonorrhoeae*
Shigella flexneri	*Mycoplasma fermentans*
Salmonella enteritidis	*Mycoplasma genitalium*
Salmonella typhimurium	*Ureaplasma urealyticum*
Yersinia enterocolitica	*Escherichia coli*
Yersinia pseudotuberculosis	*Cryptosporidium*
Campylobacter jejuni	*Entamoeba histolytica*
	Giardia lamblia
	Brucella abortus
	Clostridium difficile
	Streptococcus pyogenes
	Chlamydia pneumoniae
	Chlamydia psittaci

From Kim PS, Klausmeier TL, Orr DP: Reactive arthritis: a review. J Adolesc Health *44:309–315, 2009, Table 2, p. 311.*

Table 155-8 Pharmacologic Treatment of Juvenile Idiopathic Arthritis (JIA)

TYPICAL MEDICATIONS	TYPICAL DOSES	JIA SUBTYPE	SIDE EFFECT(S)
NONSTEROIDAL ANTIINFLAMMATORY DRUGS			
Naproxen	15 mg/kg/day PO divided bid (maximum dose 500 mg bid)	Polyarthritis Systemic Oligoarthritis	Gastritis, renal and hepatic toxicity, pseudoporphyria
Ibuprofen	40 mg/kg/day PO divided tid (maximum dose 800 mg tid)	Same as above	Same as above
Meloxicam	0.125 mg/kg PO once daily (maximum dose 15 mg daily)	Same as above	Same as above
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS			
Methotrexate	0.5-1 mg/kg PO or SC weekly (maximum dose 25 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Nausea, vomiting, oral ulcerations, hepatic toxicity, blood count dyscrasias, immunosuppression, teratogenicity
Sulfasalazine	Initial 12.5 mg/kg PO daily; increase by 10 mg/kg/day Maintenance: 40-50 mg/kg divided bid (maximum dose 2 g/day)	Polyarthritis	GI upset, allergic reaction, pancytopenia, renal and hepatic toxicity, Stevens-Johnson syndrome
Leflunomide*	10-20 mg PO daily	Polyarthritis	GI upset, hepatic toxicity, allergic rash, alopecia (reversible), teratogenicity (needs washout with cholestyramine)
BIOLOGIC AGENTS			
Anti–Tumor Necrosis Factor-α			
Etanercept	0.8 mg/kg SC weekly or 0.4 mg/kg SC twice weekly (maximum dose 50 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Immunosuppressant, concern for malignancy, demyelinating disease, lupus-like reaction, injection site reaction
Infliximab*	3-10 mg/kg IV q4-8wk	Same as above	Same as above, infusion reaction
Adalimumab	<30 kg: 20 mg SC every other week >30 kg: 40 mg SC every other week	Same as above	Same as above
Anticytotoxic T-Lymphocyte–Associated Antigen-4 Immunoglobulin			
Abatacept	<75 kg: 10 mg/kg/dose IV q4wk 75-100 kg: 750 mg/dose IV q4wk >100 kg: 1,000 mg/dose IV q4wk	Polyarthritis	Immunosuppressant, concern for malignancy, infusion reaction
Anti-CD20			
Rituximab*	750 mg/m2 IV 2 wk × 2 (maximum dose 1,000 mg)	Polyarthritis	Immunosuppressant, infusion reaction, progressive multifocal encephalopathy
Interleukin-1 Inhibitors			
Anakinra*	1-2 mg/kg SC daily (maximum dose 100 mg/day)	Systemic	Immunosuppressant, GI upset, injection site reaction
Canakinumab	15-40 kg: 2 mg/kg/dose SC q8wk >40 kg: 150 mg SC q8wk	Systemic	Immunosuppressant, headache, GI upset, injection site reaction
Rilonacept*	2.2 mg/kg/dose SC weekly (maximum dose 160 mg)	Systemic	Immunosuppressant, allergic reaction, dyslipidemia, injection site reaction
Interleukin-6 Receptor Antagonist			
Tocilizumab	<30 kg: 12 mg/kg/dose q2wk >30 kg: 8 mg/kg/dose q2wk (maximum dose 800 mg)	Systemic Polyarthritis	Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction

bid, Twice daily; GI, gastrointestinal; IV, intravenous; PO, oral; SC, subcutaneous; tid, 3 times daily.
*Not indicated by the U.S. Food and Drug Administration for use in JIA.

Table 156-1 Overlapping Characteristics of the Spondyloarthritides

CHARACTERISTIC	JUVENILE ANKYLOSING SPONDYLITIS	JUVENILE PSORIATIC ARTHRITIS	INFLAMMATORY BOWEL DISEASE	REACTIVE ARTHRITIS
Enthesitis	+++	+	+	++
Axial arthritis	+++	++	++	+
Peripheral arthritis	+++	+++	+++	+++
HLA-B27 positive	+++	+	+++	+++
Antinuclear antibody positive	–	++	–	–
Rheumatoid factor positive	–	–	–	–
Systemic disease:				
Eyes	+	+	+	+
Skin	–	+++	+	+
Mucous membranes	–	–	+	+
Gastrointestinal tract	–	–	++++	+++

Frequency of characteristics: –, absent; +, <25%; ++, 25-50%; +++, 50-75%, ++++, 75% or more.
From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders.*

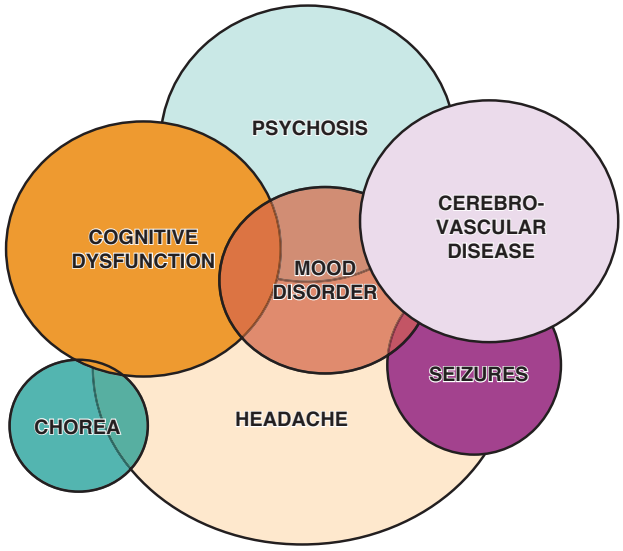


Figure 158-2 Overlapping neuropsychiatric symptoms in pediatric SLE. Patients with pediatric SLE most commonly have more than 1 neuropsychiatric symptom—in particular for seizures. *(From Silverman E, Eddy A: Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders/Elsevier,* Fig. 21-17, *p. 329.)*

Table 158-2 American College of Rheumatology 1997 Revised Classification Criteria for Systemic Lupus Erythematosus*

Malar rash
Discoid rash
Photosensitivity
Oral or nasal ulcers
Arthritis
Nonerosive, ≥2 joints
Serositis
Pleuritis, pericarditis or peritonitis
Renal manifestations†
Consistent renal biopsy
Persistent proteinuria or renal casts
Seizure or psychosis
Hematologic manifestations†
Hemolytic anemia
Leukopenia (<4,000 leukocytes/mm^3)
Lymphopenia (<1,500 leukocytes/mm^3)
Thrombocytopenia (<100,000 thrombocytes/mm^3)
Immunologic abnormalities†
Positive anti–double-stranded or anti-Smith antibody
False-positive rapid plasma regain test result, positive lupus anticoagulant test result, or elevated anticardiolipin immunoglobulin (Ig) G or IgM antibody
Positive antinuclear antibody test result

*The presence of 4 of 11 criteria establishes the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.
†Each of these criteria counts as a single criterion whether 1 or more definitions are satisfied.
Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum *40:1725, 1997.*

Table 158-3 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus*

CLINICAL CRITERIA	IMMUNOLOGIC CRITERIA
Acute cutaneous lupus	**Positive antinuclear antibody**
Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus	**Positive double-stranded DNA antibody**
Chronic cutaneous lupus	**Positive anti-Smith antibody**
Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematous tumidus, chilblains lupus, discoid lupus/lichen planus overlap	**Antiphospholipid antibody positivity**
Oral or nasal ulcers	Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium to high titer anticardiolipin antibody level (IgA, IgG, IgM), or positive anti–B_2-glycoprotein I antibody (IgA, IgG, IgM)
Nonscarring alopecia	**Low complement**
Synovitis (≥2 joints)	Low C3, C4, or Ch50 level
Serositis	**Positive direct Coombs test** (in the absence of hemolytic anemia)
Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis	
Renal	
Presence of red blood cell casts or urine protein/creatinine ratio representing >500 mg protein/24 hours	
Neurologic	
Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state	
Hemolytic anemia	
Leukopenia (<4,000/mm^3) or lymphopenia (<1,000/mm^3)	
Thrombocytopenia (<100,000/mm^3)	

*The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE. Biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA also satisfies the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.
Adapted from Petri M: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, Arthritis Rheum *64(8):2677–2686, 2012.*

Table 158-4 Medications Associated with Drug-Induced Lupus

DEFINITE ASSOCIATION Minocycline, procainamide, hydralazine, isoniazid, penicillamine, diltiazem, interferon-α, methyldopa, chlorpromazine, etanercept, infliximab, adalimumab
PROBABLE ASSOCIATION Phenytoin, ethosuximide, carbamazepine, sulfasalazine, amiodarone, quinidine, rifampin, nitrofurantoin, beta blockers, lithium, captopril, interferon-γ, hydrochlorothiazide, glyburide, docetaxel, penicillin, tetracycline, statins, gold, valproate, griseofulvin, gemfibrozil, propylthiouracil

Table 158-6 Morbidity in Childhood Lupus

Renal	Hypertension, dialysis, transplantation
Central nervous system	Organic brain syndrome, seizures, psychosis, neurocognitive dysfunction
Cardiovascular	Atherosclerosis, myocardial infarction, cardiomyopathy, valvular disease
Immune	Recurrent infection, functional asplenia, malignancy
Musculoskeletal	Osteopenia, compression fractures, avascular necrosis
Ocular	Cataracts, glaucoma, retinal detachment, blindness
Endocrine	Diabetes, obesity, growth failure, infertility, fetal wastage

Table 159-2 Clinical Features of Juvenile Dermatomyositis During the Course of the Disease

FEATURE	%
Muscle weakness	90-100
Dysphagia or dysphonia	13-40
Muscle atrophy	10
Muscle pain and tenderness	30-83
Skin lesions	85-100
Heliotrope rash of eyelids	66-83
Gottron papules	57-91
Erythematous rash of malar/facial area	42-100
Periungual capillary changes	80
Photosensitive rash	5-42
Ulcerations	22-30
Calcinosis	12-30
Lipodystrophy	11-14
Raynaud phenomenon	2-15
Arthritis and arthralgia	22-58
Joint contractures	26-27
Fever	16-46
Gastrointestinal signs and symptoms	8-22
Restrictive pulmonary disease	4-32
Interstitial lung disease	1-7
Cardiac involvement	0-3

Table 158-5 Autoantibodies Commonly Associated with Systemic Lupus Erythematosus (SLE)

ANTIBODY	CLINICAL ASSOCIATION
Anti–double-stranded DNA	Correlates with disease activity, especially nephritis, in some with SLE
Anti-Smith antibody	Specific for the diagnosis of SLE
Antiribonucleoprotein antibody	Increased risk for Raynaud phenomenon and pulmonary hypertension High titer may suggest diagnosis of mixed connective tissue disorder
Anti-Ro antibody (anti-SSA antibody) Anti-La antibody (anti-SSB antibody)	Associated with sicca syndrome May suggest diagnosis of Sjögren syndrome Increased risk of neonatal lupus in offspring (congenital heart block) May be associated with cutaneous and pulmonary manifestations of SLE May be associated with isolated discoid lupus
Antiphospholipid antibodies (including anticardiolipin antibodies)	Increased risk for venous and arterial thrombotic events
Antihistone antibodies	Present in a majority of patients with drug-induced lupus May be present in SLE

Table 158-1 Potential Clinical Manifestations of Systemic Lupus Erythematosus

TARGET ORGAN	POTENTIAL CLINICAL MANIFESTATIONS
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, tendonitis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neurologic	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex) , chorea, optic neuritis, cranial nerve palsies, acute confusional states, dural sinus thrombosis
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis

Table 159-3 Phenotypic Characteristics of the Clinical Subgroups of Juvenile Myositis*

CHARACTERISTIC	JDM	JPM	JCTM
Demographics			
Median age at diagnosis (yr)	Youngest (7.4 yr)	Oldest (12.1 yr)	Intermediate (10.2 yr)
Race	Predominantly white (71.2%)	Black (39.4%)	Black or other (49.0%)
Severity at onset	Mild or moderate severity	**Severe or very severe onset**	Mild or moderate severity
Median delay to diagnosis (mo)	4 mo	3.5 mo	Longer delay (7 mo)
Clinical features	Gottron papules Heliotrope rash **Periungual capillary abnormalities** **Malar rash** *Photosensitivity* *Linear extensor erythema*† Cuticular overgrowth Mucous membrane involvement "V-sign" and "shawl-sign" rashes Skin ulcerations Dyspnea on exertion	*Weight loss* Falling episodes Raynaud phenomenon Abnormal PFT Dyspnea on exertion Cardiac abnormalities on EKG or ECHO	Gottron papules Heliotrope rash **Malar rash** **Raynaud phenomenon** **Interstitial lung disease** **Arthralgia** *Linear extensor erythema*† *Mucous membrane involvement* *Arthritis* *Photosensitivity* *Sclerodactyly* *Periungual capillary abnormalities*† Cuticular overgrowth Abdominal pain, GI bleeding Dyspnea on exertion Weight loss
Autoantibodies	Intermediate ANA titer (median, 1:320) *Anti-p155/140*† Anti-MJ Anti-Mi-2	Intermediate ANA titer (median, 1:320) Anti-SRP Anti-aminoacyl-tRNA synthetase (anti–Jo-1)	Highest ANA titer (median, 1:1280) **Anti-U1-RNP** Anti-PM-Sc1 Anti-Ro Anti-SM Anti-La All other U-RNP autoantibodies
Laboratory features	*Lowest CK level (median, 829 U/L)*	**Highest CK level (median, 5027 U/L)** Highest levels of aldolase and ALT	Intermediate CK level (median 1208 U/L)
Outcome	Low mortality (2.4%) Calcinosis (34.0%)	Medium mortality (6.3%) **Frequently hospitalized (71.9%)** Wheelchair use	Highest mortality (14.6%)

ALT, alanine aminotransferase; ANA, antinuclear antibody; CK, creatine kinase; ECHO, echocardiogram; EKG, electrocardiogram; GI, gastrointestinal; JCTM, juvenile myositis overlapping with another autoimmune or connective tissue disease; JDM, juvenile dermatomyositis; JPM, juvenile polymyositis; PFT, pulmonary function test; tRNA, transfer RNA.

*__Bold__ indicates significant in logistic regression; *italics* indicates top variables entered in pruned-down random forest models. Other variables included in this table were significant in univariable analysis to $p \leq 0.01$.

†Removed from logistic regression analyses because variable was either 100% or 0% in 1 of the compared subgroups. Gottron papules and heliotrope rash, which were part of the definition of cases of dermatomyositis, were not entered into multivariable analyses.

Modified from Shah M, Mamyrova G, Targoff IN, et al: The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore) *92:25–41, 2013, Table 9, p. 36.*

Table 160-3 Provisional Criteria for the Classification of Juvenile Systemic Sclerosis (SSc)

MAJOR CRITERION (REQUIRED)* Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints
MINOR CRITERIA (AT LEAST 2 REQUIRED) Cutaneous: sclerodactyly Peripheral vascular: Raynaud phenomenon, nailfold capillary abnormalities (telangiectasias), digital tip ulcers Gastrointestinal: dysphagia, gastroesophageal reflux Cardiac: Arrhythmias, heart failure Renal: Renal crisis, new-onset arterial hypertension Respiratory: pulmonary fibrosis (high-resolution computed tomography/radiography), decreased diffusing capacity for carbon monoxide, pulmonary arterial hypertension Neurologic: neuropathy, carpal tunnel syndrome Musculoskeletal: tendon friction rubs, arthritis, myositis Serologic: antinuclear antibodies—SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin or anti-RNA polymerase I or III

*Diagnosis requires at least 1 major and at least 2 minor criteria.

Table 159-1 Diagnostic Criteria for Juvenile Dermatomyositis

Classic rash	Heliotrope rash of the eyelids Gottron papules
Plus 3 of the following:	
Weakness	Symmetric Proximal
Muscle enzyme elevation (≥1)	Creatine kinase Aspartate aminotransferase Lactate dehydrogenase Aldolase
Electromyographic changes	Short, small polyphasic motor unit potentials Fibrillations Positive sharp waves Insertional irritability Bizarre, high-frequency repetitive discharges
Muscle biopsy	Necrosis Inflammation

Table 160-1 Classification of Pediatric Scleroderma (Morphea)

LOCALIZED SCLERODERMA

Plaque Morphea

Confined to dermis, occasionally superficial panniculus

Well-circumscribed circular area of induration, often a central waxy, ivory-colored area surrounded by a violaceous halo; unilateral

Generalized Morphea

Involves dermis primarily, occasionally panniculus

Defined as confluence of individual morphea plaques or lesions in 3 or more anatomic sites; more likely to be bilateral

Bullous Morphea

Bullous lesions that can occur with any of the subtypes of morphea

Linear Scleroderma

Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral

Limbs/trunk:

One or more linear streaks of the extremities or trunk

Flexion contracture occurs when lesion extends over a joint; limb length discrepancies

En coup de sabre:

Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches

Parry Romberg syndrome:

Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement

Deep Morphea

Involves deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral

Subcutaneous morphea:

Primarily involves the panniculus or subcutaneous tissue

Plaques are hyperpigmented and symmetric

Eosinophilic fasciitis:

Fasciitis with marked blood eosinophilia

Fascia is the primary site of involvement; typically involves extremities

Classic description is "peau d'orange" or orange peel texture, but early disease manifests as edema (see Fig. 160-2)

Morphea profunda:

Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk

Disabling pansclerotic morphea of childhood:

Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing finger tips and toes

SYSTEMIC SCLEROSIS

Diffuse

Most common type in childhood

Symmetric thickening and hardening of the skin (sclerosis) with fibrous and degenerative changes of viscera

Limited

Rare in childhood

Previously known as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome

Table 161-1 Criteria of the International Study Group for the Diagnosis of Behçet disease

CRITERION	DESCRIPTION
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration recurring at least 3 times in one 12 mo period, observed by physician or patient
Plus 2 of the following:	
Recurrent genital ulcers	Aphthous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, cells in vitreous on slit-lamp examination, or retinal vasculitis observed by an ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions, or acneiform nodules observed by physician in postadolescent patient not on corticosteroid treatment
Pathergy	Skin reaction to a needle prick observed by physician at 24-48 hr

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Table 162-1 Proposed Criteria for Pediatric Sjögren Syndrome

I. CLINICAL SYMPTOMS
   1. Oral: recurrent parotitis or enlargement of parotid gland, dry mouth (xerostomia)
   2. Ocular: dry eyes (xerophthalmia) recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca
   3. Other mucosal: recurrent vaginitis
   4. Systemic: fever, non-inflammatory arthralgias, hypokalemic paralysis, abdominal pain

II. IMMUNOLOGIC ABNORMALITIES: presence of at least 1 of the following antibodies: anti-SSA, anti-SSB, high titer antinuclear antibody, rheumatoid factor

III. OTHER ABNORMALITIES OR INVESTIGATIONS
   1. Biochemical: elevated serum amylase
   2. Hematologic: leukopenia, high sedimentation rate
   3. Immunologic: polyclonal hyperimmunoglobulinemia
   4. Renal: renal tubular acidosis
   5. Histologic proof of lymphocytic infiltration of salivary glands or other organs (i.e., liver)
   6. Objective documentation of ocular dryness (Bengal red staining or Schirmer test)
   7. Positive findings of parotid gland scintigraphy

IV. Exclusion of all other autoimmune diseases

Diagnosis requires ≥4 criteria.

Table 163-1 Differential Diagnosis of Familial Autoinflammatory Syndromes

		Mevalonate Kinase Deficiency (MKD)			Cryopyrin-Associated Periodic Syndrome (CAPS)			
	FAMILIAL MEDITERRANEAN FEVER (FMF)	HYPERIMMUNOGLOBULIN D SYNDROME (HIDS)	MEVALONIC ACIDURIA	TUMOR NECROSIS FACTOR RECEPTOR–ASSOCIATED PERIODIC SYNDROME (TRAPS)	FAMILIAL COLD AUTOINFLAMMATORY SYNDROME (FCAS)	MUCKLE-WELLS SYNDROME (MWS)	CHRONIC INFANTILE NEUROLOGIC CUTANEOUS AND ARTICULAR SYNDROME (CINCA)	DEFICIENCY OF IL-1 RECEPTOR ANTAGONIST (DIRA)
Mode of Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
Age at Onset (yr)	<20	<1	<1	<20	<1	<20	<1	Birth, <4 wk
Duration of attack (days)*	<2	4-6	4-5	>14	<2	1-2	?	Continuous
Cutaneous Involvement	Erysipelas-like erythema	Maculopapular rash	Morbilliform rash	Migratory rash, overlying area of myalgia	Cold-induced urticaria-like lesions	Urticaria-like rash	Urticaria-like lesions	Generalized pustulosis
Musculoskeletal Involvement	Monoarthritis common	Arthralgia, occasional oligoarthritis	Arthralgia common	Severe myalgia common; occasional frank monoarthritis	Arthralgia common; occasional mild myalgia	Lancing limb pain, arthralgia common; arthritis can occur	Epiphyseal bone formation	Sterile pustulous osteomyelitis
Abdominal Involvement	Sterile peritonitis common	Splenomegaly, severe pain common	Splenomegaly, pain may occur	Severe pain common	None	May occur	Hepatosplenomegaly	
Eye Involvement	Uncommon	Uncommon	Uncommon	Conjunctivitis and periorbital edema common	Conjunctivitis	Conjunctivitis; sometimes optic nerve elevation	Papilledema with possible loss of vision, uveitis	
Distinguishing Clinical Symptoms	Erysipelas-like erythema	Prominent cervical lymphadenopathy	Dysmorphic features, neurologic symptoms	Migratory nature of myalgia and rash, periorbital edema	Cold-induced urticaria-like lesions	Sensorineural hearing loss	Chronic aseptic meningitis, sensorineural hearing loss, arthropathy	
Gene Involved	*MEFV*	*MVK*	*MVK*	*TNFRSF1A*	*CIAS1 = NLRP3*	*CIAS1 = NLRP3*	*CIAS1 = NRLP3*	*IL-1RN*
Protein Involved	Pyrin (marenostrin)	Mevalonate kinase	Mevalonate kinase	Type 1 tumor necrosis factor receptor	Cryopyrin	Cryopyrin	Cryopyrin	IL-1RA

Note: For details on Blau syndrome, DIRA, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, see text.
*Duration may vary; this is a typical duration.
Modified from Hull KM, Shoham N, Chae JJ, et al: The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations, Curr Opin Rheumatol *15:61–69, 2003.*

Table 163-1 Differential Diagnosis of Familial Autoinflammatory Syndromes

		Mevalonate Kinase Deficiency (MKD)			Cryopyrin-Associated Periodic Syndrome (CAPS)			
	FAMILIAL MEDITERRANEAN FEVER (FMF)	HYPERIMMUNOGLOBULIN D SYNDROME (HIDS)	MEVALONIC ACIDURIA	TUMOR NECROSIS FACTOR RECEPTOR–ASSOCIATED PERIODIC SYNDROME (TRAPS)	FAMILIAL COLD AUTOINFLAMMATORY SYNDROME (FCAS)	MUCKLE-WELLS SYNDROME (MWS)	CHRONIC INFANTILE NEUROLOGIC CUTANEOUS AND ARTICULAR SYNDROME (CINCA)	DEFICIENCY OF IL-1 RECEPTOR ANTAGONIST (DIRA)
Mode of Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
Age at Onset (yr)	<20	<1	<1	<20	<1	<20	<1	Birth, <4 wk
Duration of attack (days)*	<2	4-6	4-5	>14	<2	1-2	?	Continuous
Cutaneous Involvement	Erysipelas-like erythema	Maculopapular rash	Morbilliform rash	Migratory rash, overlying area of myalgia	Cold-induced urticaria-like lesions	Urticaria-like rash	Urticaria-like lesions	Generalized pustulosis
Musculoskeletal Involvement	Monoarthritis common	Arthralgia, occasional oligoarthritis	Arthralgia common	Severe myalgia common; occasional frank monoarthritis	Arthralgia common; occasional mild myalgia	Lancing limb pain, arthralgia common; arthritis can occur	Epiphyseal bone formation	Sterile pustulous osteomyelitis
Abdominal Involvement	Sterile peritonitis common	Splenomegaly, severe pain common	Splenomegaly, pain may occur	Severe pain common	None	May occur	Hepatosplenomegaly	
Eye Involvement	Uncommon	Uncommon	Uncommon	Conjunctivitis and periorbital edema common	Conjunctivitis	Conjunctivitis; sometimes optic nerve elevation	Papilledema with possible loss of vision, uveitis	
Distinguishing Clinical Symptoms	Erysipelas-like erythema	Prominent cervical lymphadenopathy	Dysmorphic features, neurologic symptoms	Migratory nature of myalgia and rash, periorbital edema	Cold-induced urticaria-like lesions	Sensorineural hearing loss	Chronic aseptic meningitis, sensorineural hearing loss, arthropathy	
Gene Involved	*MEFV*	*MVK*	*MVK*	*TNFRSF1A*	*CIAS1 = NLRP3*	*CIAS1 = NLRP3*	*CIAS1 = NRLP3*	*IL-1RN*
Protein Involved	Pyrin (marenostrin)	Mevalonate kinase	Mevalonate kinase	Type 1 tumor necrosis factor receptor	Cryopyrin	Cryopyrin	Cryopyrin	IL-1RA

Note: For details on Blau syndrome, DIRA, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, see text.
*Duration may vary; this is a typical duration.
Modified from Hull KM, Shoham N, Chae JJ, et al: The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations, Curr Opin Rheumatol *15:61–69, 2003.*

Table 163-2 Clinical Grouping of Autoinflammatory Diseases by Fever and Skin Manifestations

1. Nonspecific maculopapular rashes with recurrent episodic fever and abdominal pain (the classic "periodic fever syndromes")
   Recurrent fever attacks of short duration (typically <7 days)
   - FMF: familial Mediterranean fever
   - HIDS: mevalonate kinase deficiency/hyperimmunoglobulinemia D with periodic fever syndrome

   Recurrent fever attacks of longer duration (typically >7 days)
   - TRAPS: TNF receptor-associated periodic fever syndrome
2. Neutrophilic urticaria (the cryopyrinopathies)
   Recurrent fever attacks of short duration (typically <24 hr)
   - CAPS/FCAS: familial cold autoinflammatory syndrome
   - CAPS/MWS: Muckle-Wells syndrome

   Continuous low-grade fever
   - CAPS/NOMID: neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA)
3. Granulomatous skin lesions and minimal or low-grade fever attacks
   - Blau syndrome/early-onset sarcoidosis (pediatric granulomatous arthritis)
4. Pustular skin rashes and episodic fever

   With inflammatory bone disease
   - DIRA: deficiency of interleukin-1 receptor agonist
   - Majeed syndrome

   With pyogenic arthritis
   - PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

   With inflammatory bowel disease
   - Early-onset inflammatory bowel disease

   Without other organ involvement
   - DITRA: deficiency of interleukin-36-receptor antagonist
   - CAMPS: CARD14-mediated psoriasis
5. Atypical neutrophilic dermatosis with histiocytic-like infiltrate
   - PRAAS: proteasome associated autoinflammatory syndromes
6. Syndromes with autoinflammation and immunodeficiency
   - PLAID: PLCγ_2-associated antibody deficiency and immune dysregulation
   - APLAID: autoinflammation and PLCγ_2-associated antibody deficiency and immune dysregulation
   - HOIL-1 deficiency

From Almeida de Jesus A, Goldbach-Mansky R: Monogenic autoinflammatory diseases: concept and clinical manifestations. Clin Immunol *147:155-174, 2013, Table 1.*

Table 163-3 Autoinflammatory Bone Disorders

	CRMO	Majeed Syndrome	DIRA	Cherubism	cmo and lupo Mice
Ethnicity	Worldwide, but mostly European	Arabic	European, Puerto Rican, Arabic	Worldwide	Occurs in various backgrounds
Fever	Uncommon	Common	Uncommon	No	Not assessed
Sites of osseous involvement	Metaphyses of long bones > vertebrae, clavicle, sternum, pelvis, others	Similar to CRMO	Anterior rib ends, metaphyses of long bones, vertebrae, others	Mandible > maxilla Rarely ribs	Vertebrae hind > forefeet
Extraosseous manifestations	PPP, psoriasis, IBD, others	Dyserythropoietic anemia, Sweet syndrome, HSM, growth failure	Generalized pustulosis, nail changes, lung disease, vasculitis	Cervical lymphadenopathy	Dermatitis, extramedullary hematopoiesis, splenomegaly
Family history of inflammatory disorders	Psoriasis, PPP, arthritis, IBD, others	Psoriasis in some obligate carriers	No known associations	No known associations	Heterozygotes normal
Inheritance	Not clear	Autosomal recessive	Autosomal recessive	Autosomal dominant; incomplete penetrance	Autosomal recessive
Gene defect	Unknown	*LPIN2*	*IL1RN*	*SH3BP2* ≫ *PTPN11*	*Pstpip2*
Protein name	?	Lipin2	IL-1Ra	SH3BP2	PSTPIP2 (a.k.a. MAYP)
Protein function	?	Fat metabolism: (PAP enzyme activity), ↑ message to oxidative stress, ? role in mitosis	Antagonist of IL-1 receptor	↑ Myeloid cell response to M-CSF and RANKL, ↑ TNF-α expression in macrophages	Macrophage proliferation, macrophage recruitment to sites of inflammation, cytoskeletal function
Cytokine abnormalities	↑ serum TNF-α	Not tested	↑ IL-1α, IL-1β, MIP-1α, TNF-α, IL-8, IL-6 ex vivo monocyte assay; skin reveals ↑ IL-17 staining	↑ serum TNF-α in mouse model	cmo: ↑serum IL-6, MIP-1α, TNF-α, CSF-1, IP-10 Lupo: ↑ serum MIP-1α, IL-4, RANTES, TGF-β

CRMO, chronic recurrent multifocal osteomyelitis; CSF, colony-stimulating factor; DIRA, deficiency of interleukin-1 receptor antagonist; HSM, hepatosplenomegaly; IBD, inflammatory bowel disease; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IP-10, interferon-inducible protein-10; M-CSF, macrophage–colony-stimulating factor; MIP-1α, macrophage inflammatory protein-1α; PAP, phosphatidate phosphatase; PPP, palmer-plantar pustulosis; PSTPIP2, proline-serine-threonine phosphatase interacting protein; RANKL, receptor activator of nuclear factor-κB ligand; RANTES, regulated upon activation, normal T-cell expressed and secreted; SH3BP2, SH3 binding protein 2; TGF, transforming growth factor; TNF-α, tumor necrosis factor α.

From Ferguson PJ, Laxer RM: Autoinflammatory bone disorders. In Cassidy JT, Petty RE, Laxer RM, et al, editors: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2010, Saunders, Table 44-2.*

Table 163-4 Clues That May Assist in the Diagnosis of Autoinflammatory Syndromes

AGE OF ONSET	
At birth	NOMID, DIRA, FCAS
Infancy and 1st yr of life	HIDS, FCAS, NLRP12
Toddler	PFAPA
Late childhood	PAPA
Most common of autoinflammatory syndromes to have onset in adulthood	TRAPS, DITRA
Variable (mostly in childhood)	All others
ETHNICITY AND GEOGRAPHY	
Armenians, Turks, Italian, Sephardic Jews	FMF
Arabs	FMF, DITRA (Arab Tunisian)
Dutch, French, German, Western Europe	HIDS, MWS, NLRP12
United States	FCAS
Can occur in blacks (West Africa origin)	TRAPS
Eastern Canada, Puerto Rico	DIRA
Worldwide	All others
TRIGGERS	
Vaccines	HIDS
Cold exposure	FCAS, NLRP12
Stress, menses	FMF, TRAPS, MWS, PAPA, DITRA
Minor trauma	PAPA, MWS, TRAPS, HIDS
Exercise	FMF, TRAPS
Pregnancy	DITRA
Infections	All, especially DITRA
ATTACK DURATION	
<24 h	FCAS, FMF
1–3 d	FMF, MWS, DITRA (fever)
3–7 d	HIDS, PFAPA
>7 d	TRAPS, PAPA
Almost always "in attack"	NOMID, DIRA
INTERVAL BETWEEN ATTACKS	
3–6 wk	PFAPA, HIDS
>6 wk	TRAPS
Mostly unpredictable	All others
Truly periodic	PFAPA, cyclic neutropenia
USEFUL LABORATORY TESTS	
Acute-phase reactants must be normal between attacks	PFAPA
Urine mevalonic acid in attack	HIDS
IgD > 100 mg/dL	HIDS
Proteinuria (amyloidosis)	FMF, TRAPS, MWS, NOMID
RESPONSE TO THERAPY	
Corticosteroid dramatic	PFAPA
Corticosteroid partial	TRAPS, FCAS, MWS, NOMID, PAPA*
Colchicine	FMF, PFAPA (30% effective)
Cimetidine	PFAPA (30% effective)
Etanercept	TRAPS, FMF arthritis
Anti–IL-1 dramatic	DIRA (anakinra), FCAS, MWS, NOMID, PFAPA
Anti–IL-1 mostly	TRAPS, FMF
Anti–IL-1 partial	HIDS, PAPA

DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

*For intraarticular steroids.

From Hashkes PJ, Toker O: Autoinflammatory syndromes. Pediatr Clin North Am *59:447–470, 2012, Table 2.*

Table 163-5 Differential Diagnosis of Periodic Fever

1 Hereditary (see Table 163-1)
2 Nonhereditary
- a Infectious
  - i Hidden infectious focus (e.g., aortoenteric fistula, Caroli disease)
  - ii Recurrent reinfection (e.g., chronic meningococcemia, host defense defect)
  - iii Specific infection (e.g., Whipple disease, malaria)
- b Noninfectious inflammatory disorder, e.g.:
  - i Adult-onset Still disease
  - ii Juvenile chronic rheumatoid arthritis
  - iii Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
  - iv Schnitzler syndrome
  - v Behçet syndrome
  - vi Crohn disease
  - vii Sarcoidosis
  - viii Extrinsic alveolitis
  - ix Humidifier lung, polymer fume fever
- c Neoplastic
  - i Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)
  - ii Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma)
- d Vascular (e.g., recurrent pulmonary embolism)
- e Hypothalamic
- f Psychogenic periodic fever
- g Factitious or fraudulent

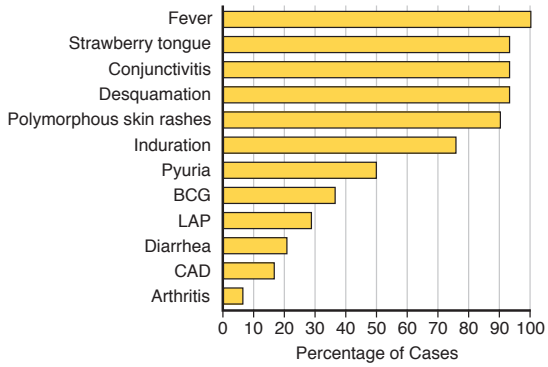


Figure 166-1 Clinical symptoms and signs of Kawasaki disease. A summary of the clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery dilation, defined by an internal diameter >3 mm. *(From Wang CL, Wu YT, Liu CA, et al: Kawasaki disease: infection, immunity and genetics,* Pediatr Infect Dis J *24:998–1004, 2005.)*

Table 166-2 Differential Diagnosis of Kawasaki Disease

VIRAL INFECTIONS
• Adenovirus
• Enterovirus
• Measles
• Epstein-Barr virus
• Cytomegalovirus
BACTERIAL INFECTIONS
• Scarlet fever
• Rocky Mountain spotted fever
• Leptospirosis
• Bacterial cervical lymphadenitis
• Meningococcemia
RHEUMATOLOGIC DISEASE
• Systemic-onset juvenile idiopathic arthritis
• Behçet disease
OTHER
• Toxic shock syndromes
• Staphylococcal scalded skin syndrome
• Drug hypersensitivity reactions
• Stevens-Johnson syndrome

Table 167-5 Classification Criteria for Henoch-Schönlein Purpura*

AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA†
Two of the following criteria must be present:
• Palpable purpura
• Age at onset ≤20 yr
• Bowel angina (postprandial abdominal pain, bloody diarrhea)
• Biopsy demonstrating intramural granulocytes in small arterioles and/or venules
EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CRITERIA‡
Palpable purpura (in absence of coagulopathy or thrombocytopenia) and 1 or more of the following criteria must be present:
• Abdominal pain (acute, diffuse, colicky pain)
• Arthritis or arthralgia
• Biopsy of affected tissue demonstrating predominant immunoglobulin A deposition
• Renal involvement (proteinuria >3 grams/24 hr), hematuria or red cell casts

*Classification criteria are developed for use in research and not validated for clinical diagnosis.

†Developed for use in adult and pediatric populations. Adapted from Mills JA, Michel BA, Bloch DA, et al: The American College of Rheumatology 1990 criteria for classification of Henoch-Schönlein purpura, *Arthritis Rheum* 33:1114–1121, 1990.

Table 166-1 Clinical and Laboratory Features of Kawasaki Disease

EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)*
Fever persisting at least 5 days†
Presence of at least 4 principal features:
Changes in extremities:
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthem
Bilateral bulbar conjunctival injection without exudate
Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Exclusion of other diseases with similar findings‡
OTHER CLINICAL AND LABORATORY FINDINGS
Cardiovascular findings:
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
Coronary artery abnormalities
Aneurysms of medium-size noncoronary arteries
Raynaud phenomenon
Peripheral gangrene
Musculoskeletal system:
Arthritis, arthralgias
Gastrointestinal tract:
Diarrhea, vomiting, abdominal pain
Hepatic dysfunction
Hydrops of gallbladder
Central nervous system:
Extreme irritability
Aseptic meningitis
Sensorineural hearing loss
Genitourinary system:
Urethritis/meatitis
Other findings:
Erythema, induration at bacille Calmette-Guérin inoculation site
Anterior uveitis (mild)
Desquamating rash in groin
LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE
Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1§
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

*Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.

†In the presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4.

‡See differential diagnosis (Table 166-2).

§Some infants present with thrombocytopenia and disseminated intravascular coagulation.

Table 166-3 Treatment of Kawasaki Disease

ACUTE STAGE
- Intravenous immunoglobulin 2 g/kg over 10-12 hr
  and
- Aspirin 80-100 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr

CONVALESCENT STAGE
- Aspirin 3-5 mg/kg once daily orally until 6-8 wk after illness onset if normal coronary findings throughout course

LONG-TERM THERAPY FOR PATIENTS WITH CORONARY ABNORMALITIES
- Aspirin 3-5 mg/kg once daily orally
- Clopidogrel 1 mg/kg/day (maximum: 75 mg/day)
- Most experts add warfarin or low-molecular-weight heparin for those patients at particularly high risk of thrombosis

ACUTE CORONARY THROMBOSIS
- Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under supervision of a pediatric cardiologist

Table 167-1 Common Disease Associations with Antibodies to Neutrophil Cytoplasmic Antigens

ANTIGEN	ANCA PATTERN	DISEASE ASSOCIATION	FREQUENCY (%)
PR3	cANCA	Wegener granulomatosis Churg-Strauss	30 to 90 25 to 50
MPO	pANCA	Microscopic polyarteritis Ulcerative colitis Sclerosing cholangitis Crohn disease	25 to 75 40 to 80 65 to 85 10 to 40
BPI	ANCA	Cystic fibrosis	80 to 90
Actin	pANCA	Autoimmune hepatitis type 1	70 to 75

ANCA, Antibodies directed at neutrophil cytoplasmic antigen; BPI, Bactericidal permeability increasing protein. cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA.

From Cabral D, Benseler S: Granulomatous vasculitis, microscopic polyangiitis and primary angiitis of the central nervous system. In Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors, Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders, Table 34-3, p. 526.*

Table 167-6 Proposed Classification Criteria for Pediatric-Onset Takayasu Arteritis

Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least one of the following criteria:
- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference between arms or legs of >10 mm Hg
- Bruits over the aorta and/or its major branches
- Hypertension (defined by childhood normative data)
- Elevated acute phase reactant (erythrocyte sedimentation rate or C-reactive protein)

Table 167-2 Classification of Childhood Vasculitis

I. Predominantly Large Vessel Vasculitis
- Takayasu arteritis

II. Predominantly Medium Vessel Vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis nodosa
- Kawasaki disease

III. Predominantly Small Vessel Vasculitis
A. Granulomatous:
- Granulomatosis with polyangiitis (Wegener granulomatosis)*
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)*

B. Nongranulomatous:
- Microscopic polyangiitis*
- Henoch-Schönlein purpura
- Isolated cutaneous leukocytoclastic vasculitis
- Hypocomplementemic urticarial vasculitis

IV. Other Vasculitides
- Behçet disease
- Vasculitis secondary to infection (including hepatitis B–associated polyarteritis nodosa), malignancies, and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue disease
- Isolated vasculitis of the central nervous system
- Cogan syndrome
- Unclassified

*Associated with antineutrophil cytoplasmic antibody.

Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis *69:798-806; 2010.*

Table 167-3 Features That Suggest a Vasculitic Syndrome

CLINICAL FEATURES
Fever, weight loss, fatigue of unknown origin
Skin lesions (palpable purpura, vasculitic urticaria, livedo reticularis, nodules, ulcers)
Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)
Arthralgia or arthritis, myalgia, or myositis
Serositis
Hypertension
Pulmonary infiltrates or hemorrhage

LABORATORY FEATURES
Increased erythrocytes sedimentation rate or C-reactive protein level
Leukocytosis, anemia
Eosinophilia
Antineutrophil cytoplasmic antibodies
Elevated factor VIII–related antigen (von Willebrand factor)
Cryoglobulins
Circulating immune complexes
Hematuria, proteinuria, elevated serum creatinine

From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.*

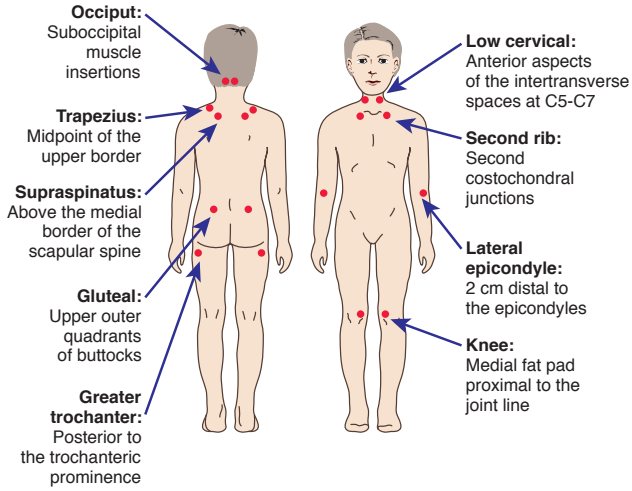


Figure 168-1 Fibromyalgia tender points.

Table 167-4 Clinical and Pathologic Characteristics of Some Vasculitides in Childhood

SYNDROME	FREQUENCY	VESSELS AFFECTED	CHARACTERISTIC PATHOLOGY
POLYARTERITIS			
Polyarteritis nodosa	Rare	Medium-size and small muscular arteries and sometimes arterioles	Focal segmental (often near bifurcations); fibrinoid necrosis; gastrointestinal, renal microaneurysms; lesions at various stages of evolution
Kawasaki disease	Common	Coronary and other muscular arteries	Thrombosis, fibrosis, aneurysms, especially of coronary vessels
LEUKOCYTOCLASTIC VASCULITIS			
Henoch-Schönlein purpura	Common	Arterioles and venules, often small arteries and veins	Leukocytoclasis; mixed cells, eosinophils, immunoglobulin A deposits in affected vessels
Hypersensitivity angitis	Rare	Arterioles and venules	Leukocytoclastic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution
GRANULOMATOUS VASCULITIS			
Granulomatosis with polyangiitis	Rare	Small arteries and veins, occasionally larger vessels	Upper and lower respiratory tract, necrotizing granulomata glomerulonephritis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Rare	Small arteries and veins, often arterioles and venules	Necrotizing extravascular granulomata; lung involvement; eosinophilia
GIANT CELL ARTERITIS			
Takayasu arteries	Uncommon	Large arteries	Granulomatous inflammation, giant cells; aneurysms, dissection
Temporal arteritis	Rare	Medium-size and large arteries	Granulomatous inflammation, giant cell arteries

Table 167-8 EULAR/PReS Classification Criteria for Pediatric-Onset Granulomatosis with Polyangiitis*

Histopathology showing granulomatous inflammation
Upper airway involvement
Laryngeal, tracheal or bronchial involvement
ANCA positivity
Renal involvement
Proteinuria, hematuria, red blood cell casts, necrotizing pauci-immune glomerulonephritis

*Diagnosis requires 3 of 6 criteria.

Table 167-7 Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa*

Histopathology	Necrotizing vasculitis in medium or small arteries
Angiographic abnormalities	Angiography showing aneurysm, stenosis, or occlusion of a medium or small size artery not from a noninflammatory cause
Cutaneous findings	Livedo reticularis, tender subcutaneous nodules, superficial skin ulcers, deep skin ulcers, digital necrosis, nail bed infarctions or splinter hemorrhages
Muscle involvement	Myalgia or muscle tenderness
Hypertension	Systolic or diastolic blood pressure >95th percentile for height
Peripheral neuropathy	Sensory peripheral neuropathy, motor mononeuritis multiplex
Renal involvement	Proteinuria (>300 mg/24 hr equivalent), hematuria or red blood cell casts, impaired renal function (glomerular filtration rate <50% normal)

*The presence of all 5 criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood onset polyarteritis nodosa.

Table 167-9 Differential Diagnostic Features of Small Vessel Vasculitis

FEATURE	HENOCH-SCHÖNLEIN PURPURA	GRANULOMATOSIS WITH POLYANGIITIS	CHURG-STRAUSS SYNDROME	MICROSCOPIC POLYANGIITIS
Signs and symptoms of small vessel vasculitis*	+	+	+	+
Immunoglobulin A–dominant immune deposits	+	–	–	–
Circulating antineutrophil cytoplasmic antibodies	–	+ (PR3)	+ (MPO > PR3)	+ (MPO)
Necrotizing vasculitis	–	+	+	+
Granulomatous inflammation	–	+	+	–
Asthma and eosinophilia	–	–	+	–

MPO, myeloperoxidase-reactive antibodies; PR3, proteinase 3–reactive antibodies; +, presence; –, absent.

*Signs and symptoms of small vessel vasculitis include purpura, other rash, arthralgias, arthritis, and constitutional symptoms.

Table 168-2 Common Musculoskeletal Pain Syndromes in Children by Anatomic Region

ANATOMICAL REGION	PAIN SYNDROMES	
Shoulder	Impingement syndrome	
Elbow	Little League elbow Avulsion fractures Osteochondritis dissecans	Tennis elbow Panner disease
Arm	Localized hypermobility syndrome Complex regional pain syndrome	
Pelvis and hip	Avulsion injuries Legg-Calvé-Perthes syndrome	Slipped capital femoral epiphysis Congenital hip dysplasia
Knee	Osteochondritis dissecans Osgood-Schlatter disease Sinding-Larsen syndrome	Patellofemoral syndrome Malalignment syndromes
Leg	Growing pains Complex regional pain syndrome Localized hypermobility syndrome	Shin splints Stress fractures Compartment syndromes
Foot	Plantar fasciitis Tarsal coalition Stress fractures	Achilles tendonitis Juvenile bunion
Spine	Musculoskeletal strain Spondylolisthesis Spondylolysis	Scoliosis Scheuermann disease (kyphosis) Low back pain
Generalized	Hypermobility syndrome Juvenile fibromyalgia Generalized pain syndrome	

Table 168-1 Potential Indicators of Benign Versus Serious Causes of Musculoskeletal Pain

CLINICAL FINDING	BENIGN CAUSE OF MUSCULOSKELETAL PAIN	SERIOUS CAUSE OF MUSCULOSKELETAL PAIN
Effects of rest versus activity on pain	Relieved by rest and worsened by activity	Relieved by activity and present at rest
Time of day pain occurs	End of the day and nights	Morning*
Objective joint swelling	No	Yes
Joint characteristics	Hypermobile/normal	Stiffness, limited range of motion
Bony tenderness	No	Yes
Muscle strength	Normal	Muscle weakness
Growth	Normal growth pattern or weight gain	Poor growth and/or weight loss
Constitutional symptoms (e.g., fever, malaise)	Fatigue without other constitutional symptoms	Yes
Lab findings	Normal CBC, ESR, CRP	Abnormal CBC, raised ESR and CRP
Radiographic findings	Normal	Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bony destruction

CBC, complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.
*Cancer pain is often severe and worst at night.
Adapted from Malleson PN, Beauchamp RD: Diagnosing musculoskeletal pain in children. CMAJ *165:183–188, 2001.*

Table 168-3 Definition of "Growing Pains"

	INCLUSIONS	EXCLUSIONS
Nature of pain	Intermittent; some pain-free days and nights, deep aching, cramping	Persistent; increasing intensity, pain during the day
Unilateral or bilateral	Bilateral	Unilateral
Location of pain	Anterior thigh, calf, posterior knee—in muscles	Articular, back, or groin pain
Onset of pain	Late afternoon or evening	Pain still present next morning
Physical findings	Normal	Swelling, erythema, tenderness; local trauma or infection; reduced joint range of motion; limping, fever, weight loss, mass
Laboratory findings	Normal	Objective evidence of abnormalities; increased erythrocyte sedimentation rate, C-reactive protein, abnormal complete blood count, radiography, bone scan or MRI

Infectious Diseases

Table 172-3 Currently* Available Vaccines in the United States by Type

PRODUCT	TYPE
Anthrax vaccine adsorbed	Cell-free filtrate of components including protective antigen
Bacille Calmette-Guérin (BCG) vaccine	Live-attenuated mycobacterial strain used to prevent tuberculosis in very limited circumstances
Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine	Toxoids of diphtheria and tetanus and purified and detoxified components from *Bordetella pertussis*
DTaP–hepatitis B–inactivated polio vaccine (DTaP-HepB-IPV)	DTaP with hepatitis B surface antigen (HBsAg) produced through recombinant techniques in yeast with inactivated whole polioviruses
DTaP with IPV and Hib (DTaP-IPV/Hib)	DTaP with inactivated whole polioviruses and Hib polysaccharide conjugated to tetanus toxoid
DTaP and inactivated polio vaccine (DTaP-IPV)	DTaP with inactivated whole polioviruses
Hib conjugate vaccine (Hib)	Polysaccharide conjugated to either tetanus toxoid or meningococcal group B outer membrane protein
Hepatitis A vaccine (HAV)	Inactivated whole virus
Hepatitis A–hepatitis B vaccine (HAV-HBV)	Combined hepatitis A and B vaccine
Hepatitis B vaccine (HBV)	HBsAg produced through recombinant techniques in yeast
Hepatitis B–Hib vaccine (Hib-HBV)	Combined hepatitis B–Hib vaccine; the Hib component is polysaccharide conjugated to meningococcal group B outer membrane protein
Human papillomavirus vaccine (bivalent) (HPV2), (quadrivalent) (HPV4), and 9-valent (HPV9)	The L1 capsid proteins of HPV types 6, 11, 16, and 18 to prevent cervical cancer and genital warts (HPV4) and types 16 and 18 to prevent cervical cancer (HPV2); HPV9 also contains types 31, 33, 45, 52, and 58.
Influenzavirus vaccine inactivated (IIV)	Available either as trivalent (A/H_3N_2, A/H_1N_1, and B) split and purified inactivated vaccines containing the hemagglutinin (H) and neuraminidase (N) of each type or as quadrivalent preparations (which include representative strains from 2 B-lymphocyte clades in addition to the 2 influenza A strains in trivalent inactivated influenza vaccine)
Influenzavirus vaccine live, intranasal (LAIV)	Live-attenuated, temperature-sensitive, cold-adapted trivalent vaccine containing the H and N genes from the wild strains reassorted to have the 6 other genes from the cold-adapted parent, only available as quadrivalent preparation
Japanese encephalitis vaccine	Inactivated whole virus that is purified
Measles, mumps, rubella (MMR) vaccine	Live-attenuated viruses
Measles, mumps, rubella, varicella (MMRV) vaccine	Live-attenuated viruses
Meningococcal conjugate vaccine against serogroups A, C, W135, and Y (MCV4)	Polysaccharide from each serogroup conjugated to diphtheria toxoid or CRM 197
Meningococcal conjugate vaccine against serogroups C and Y and Hib conjugate vaccine	Polysaccharide from each serogroup conjugated to diphtheria toxoid and Hib polysaccharide conjugated to tetanus toxoid
Meningococcal polysaccharide vaccine against serogroups A, C, W135, and Y (MPSV4)	Polysaccharides from each of the serogroups
Pneumococcal conjugate vaccine (13 valent) (PCV13)	Pneumococcal polysaccharides conjugated to a nontoxic form of diphtheria toxin CRM197 Contains 13 serotypes that accounted for >80% of invasive disease in young children prior to vaccine licensure
Pneumococcal polysaccharide vaccine (23 valent) (PPSV23)	Pneumococcal polysaccharides of 23 serotypes responsible for 85-90% of bacteremic disease in the United States
Poliomyelitis (inactivated, enhanced potency) (IPV)	Inactivated whole virus
Rabies vaccines (human diploid and purified chick embryo cell)	Inactivated whole virus
Rotavirus vaccines (RV5 and RV1)	Bovine rotavirus pentavalent vaccine (RV5) live reassortment attenuated virus, and human live-attenuated virus (RV1)
Smallpox vaccine	Vaccinia virus, an attenuated poxvirus that provides cross-protection against smallpox
Tetanus and diphtheria toxoids, adsorbed (Td, adult use)	Tetanus toxoid plus a reduced quantity of diphtheria toxoid compared to diphtheria toxoid used for children <7 yr of age
Tetanus and diphtheria toxoids adsorbed plus acellular pertussis (Tdap) vaccine	Tetanus toxoid plus a reduced quantity of diphtheria toxoid plus acellular pertussis vaccine to be used in adolescents and adults and in children 7 through 9 yr of age who have not been appropriately immunized with DTaP
Typhoid vaccine (polysaccharide)	Vi capsular polysaccharide of *Salmonella typhi*
Typhoid vaccine (oral)	Live-attenuated Ty21a strain of *S. typhi*
Varicella vaccine	Live-attenuated Oka strain
Yellow fever vaccine	Live-attenuated 17D strain

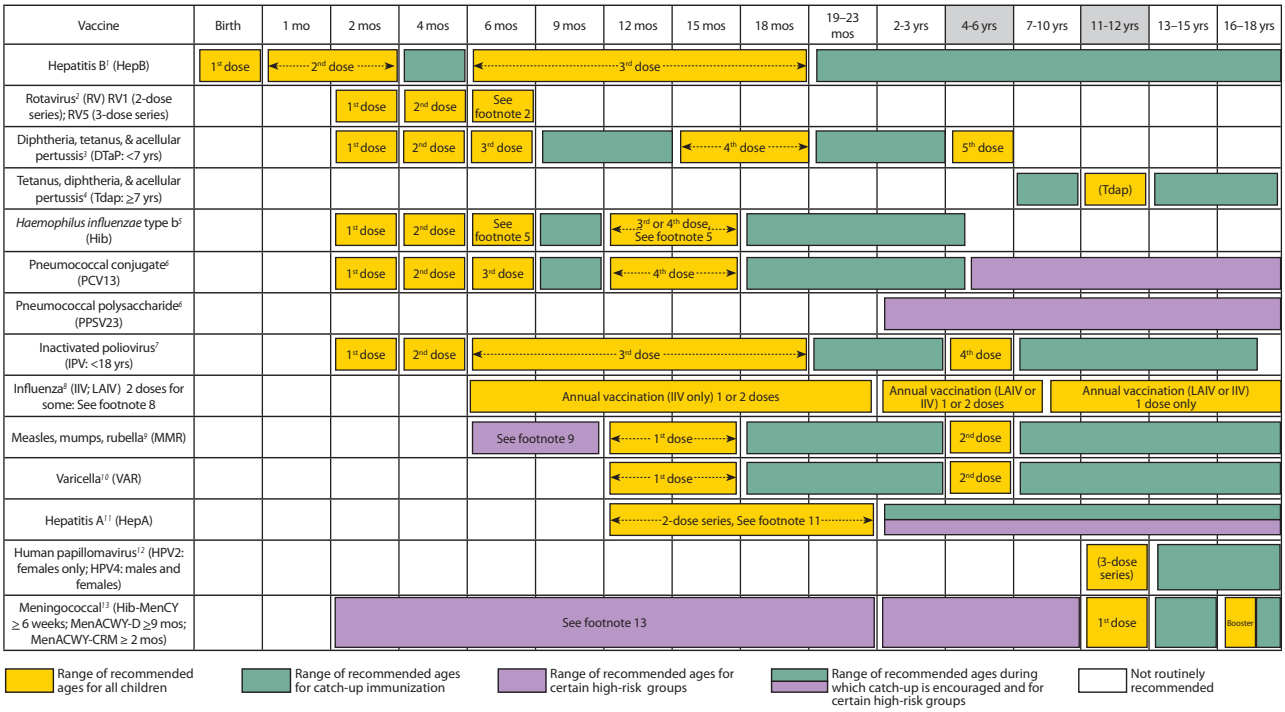
*As of January 2015.

Data from Centers for Disease Control and Prevention: U.S. vaccine names. http://www.cdc.gov/vaccines/about/terms/USvaccines.html

Table 172-2 Immunoglobulin and Animal Antisera Preparations

PRODUCT	MAJOR INDICATIONS
Immunoglobulin for intramuscular injection	Replacement therapy in primary immunodeficiency disorders Hepatitis A prophylaxis Measles prophylaxis
Intravenous immunoglobulin (IVIG)	Replacement therapy in primary immune-deficiency disorders Kawasaki disease Pediatric HIV infection Hypogammaglobulinemia in chronic B-lymphocyte lymphocytic leukemia Immune-mediated thrombocytopenia Hematopoietic cell transplantation in adults to prevent graft-versus-host disease and infection May be useful in a variety of other conditions
Hepatitis B immunoglobulin (IM)	Postexposure prophylaxis Prevention of perinatal infection in infants born to hepatitis B surface antigen–positive mothers
Rabies immunoglobulin (IM)	Postexposure prophylaxis
Tetanus immunoglobulin (IM)	Wound prophylaxis Treatment of tetanus
Varicella-zoster immunoglobulin (IM) or IVIG	Postexposure prophylaxis of susceptible people at high risk for complications from varicella
Cytomegalovirus IVIG	Prophylaxis of disease in seronegative transplant recipients
Subcutaneous immunoglobulin	Treatment of patients with primary immunodeficiencies
Vaccinia immunoglobulin (IV)	Prevent or modify serious adverse events following smallpox vaccination caused by vaccinia replication
Botulism IVIG human	Treatment of infant botulism
Diphtheria antitoxin, equine	Treatment of diphtheria
Heptavalent botulinum antitoxin against all 7 (A-G) botulinum toxin types	Treatment of food and wound botulism
Palivizumab (monoclonal antibody) (IM)	Prophylaxis for infants against respiratory syncytial virus (see Chapter 260)

Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 years – United States, 2015.
(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 172-3]).
These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 172-2. To determine minimum intervals between doses, see the catch-up schedule (Figure 172-3). School entry and adolescent vaccine age groups are shaded.



This schedule includes recommendations in effect as of January 1, 2015. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2015

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

Additional information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see *MMWR, General Recommendations on Immunization and Reports* / Vol. 60 / No. 2; Table 1. *Recommended and minimum ages and intervals between vaccine doses* available online at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/destinations/list.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, *"Vaccination of persons with primary and secondary immunodeficiencies,"* in *General Recommendations on Immunization* (ACIP), available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.; and American Academy of Pediatrics. "Immunization in Special Clinical Circumstances," in Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. *Red Book: 2012 report of the Committee on Infectious Diseases. 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics.

1. Hepatitis B (HepB) vaccine. (Minimum age: birth)

Routine vaccination:

At birth:

- Administer monovalent HepB vaccine to all newborns before hospital discharge.
- For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series at age 9 through 18 months (preferably at the next well-child visit).
- If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

Doses following the birth dose:

- The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
- Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered **no earlier than age 24 weeks**.
- Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

Catch-up vaccination:

- Unvaccinated persons should complete a 3-dose series.
- A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
- For other catch-up guidance, see Figure 172-3.

2. Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])

Routine vaccination:

Administer a series of RV vaccine to all infants as follows:

1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

Catch-up vaccination:

- The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
- The maximum age for the final dose in the series is 8 months, 0 days.
- For other catch-up guidance, see Figure 172-3.

3. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]: 4 years)

Routine vaccination:

- Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose. However, the fourth dose of DTaP need not be repeated if it was administered at least 4 months after the third dose of DTaP.

Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 yr—United States, 2015. *(From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html)*

Continued

3. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (cont'd)

Catch-up vaccination:

- The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
- For other catch-up guidance, see Figure 172-3.

4. Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for both Boostrix and Adacel)

Routine vaccination:

- Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
- Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
- Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks' gestation) regardless of time since prior Td or Tdap vaccination.

Catch-up vaccination:

- Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 dose (preferably the first) in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
- Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoid (Td) booster doses every 10 years thereafter.
- Inadvertent doses of DTaP vaccine:
  - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
  - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
- For other catch-up guidance, see Figure 172-3.

5. *Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])

Routine vaccination:

- Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
- The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
- One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
- For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to *MMWR* February 28, 2014 / 63(RR01);1-13, available at http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Catch-up vaccination:

- If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
- If both doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later.
- If first dose is administered before the first birthday and second dose administered at younger than 15 months, a third (and final) dose should be given 8 weeks later.
- For unvaccinated children aged 15 months or older, administer only 1 dose.
- For other catch-up guidance, see Figure 172-3. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also *MMWR* February 28, 2014 / 63(RR01);1-13, available at http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Vaccination of persons with high-risk conditions:

- Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
- For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
- Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
- A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
- Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.

** Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

6. Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)

Routine vaccination with PCV13:

- Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
- For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

Catch-up vaccination with PCV13:

- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up guidance, see Figure 172-3.

Vaccination of persons with high-risk conditions with PCV13 and PPSV23:

- All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
- For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; solid organ transplantation; or congenital immunodeficiency:
  1. Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  2. Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
  4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
  5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
- For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; generalized malignancy; solid organ transplantation; or multiple myeloma:
  1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
  2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
  3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
- For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
- A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

7. Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)

Routine vaccination:

- Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

Catch-up vaccination:

- In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk of imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
- If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. IPV is not routinely recommended for U.S. residents aged 18 years or older.
- For other catch-up guidance, see Figure 172-3.

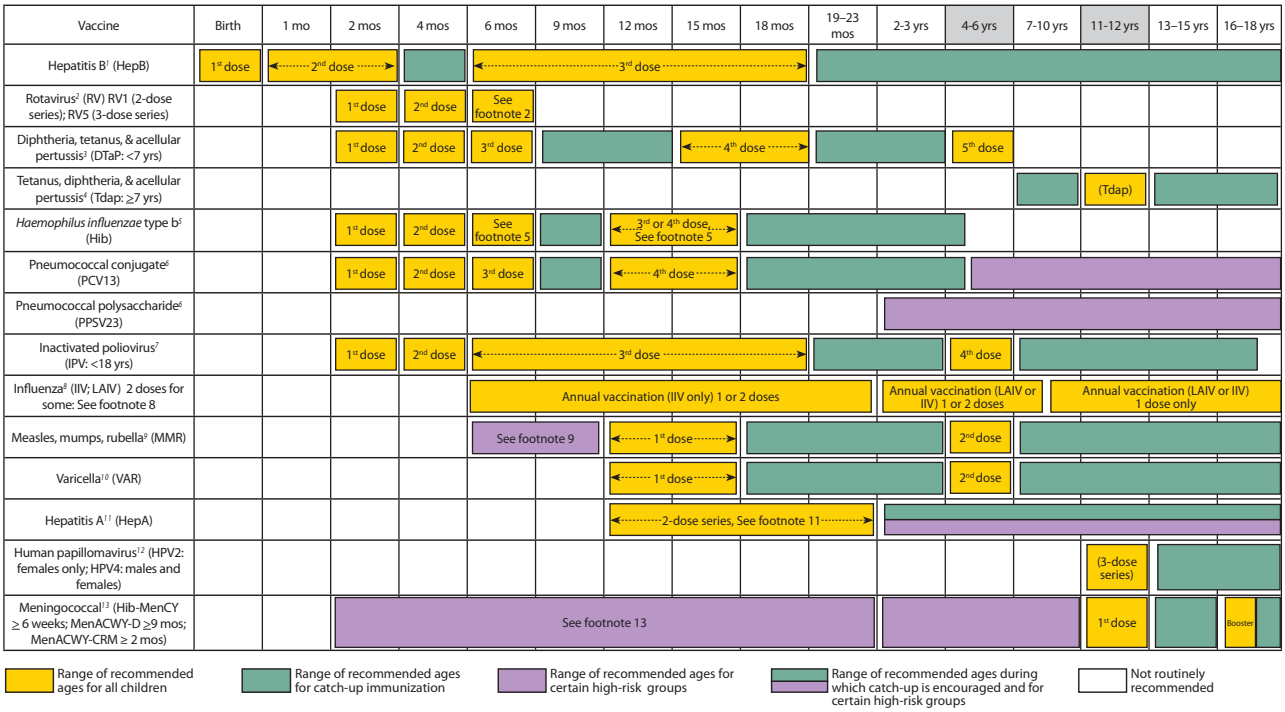
8. Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 2 years for live, attenuated influenza vaccine [LAIV])

Routine vaccination:

- Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) persons who have experienced severe allergic reactions to LAIV, any of its components, or to a previous dose of any other influenza vaccine; 2) children 2 through 17 years receiving aspirin or aspirin-containing products; 3) persons who are allergic to eggs; 4) pregnant women; 5) immunosuppressed persons; 6) children 2 through 4 years of age with asthma or who had wheezing in the past 12 months; or 7) persons who have taken influenza antiviral medications in the previous 48 hours. For all other contraindications and precautions to use of LAIV, see *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.

Figure 172-2, cont'd

Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 years – United States, 2015.
(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 172-3]).
These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 172-2. To determine minimum intervals between doses, see the catch-up schedule (Figure 172-3). School entry and adolescent vaccine age groups are shaded.



This schedule includes recommendations in effect as of January 1, 2015. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2015

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

Additional information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see *MMWR, General Recommendations on Immunization and Reports* / Vol. 60 / No. 2; Table 1. *Recommended and minimum ages and intervals between vaccine doses* available online at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/destinations/list.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, *"Vaccination of persons with primary and secondary immunodeficiencies,"* in *General Recommendations on Immunization* (ACIP), available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.; and American Academy of Pediatrics. "Immunization in Special Clinical Circumstances," in Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. *Red Book: 2012 report of the Committee on Infectious Diseases. 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics.

1. Hepatitis B (HepB) vaccine. (Minimum age: birth)

Routine vaccination:

At birth:

- Administer monovalent HepB vaccine to all newborns before hospital discharge.
- For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series at age 9 through 18 months (preferably at the next well-child visit).
- If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

Doses following the birth dose:

- The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
- Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered **no earlier than age 24 weeks**.
- Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

Catch-up vaccination:

- Unvaccinated persons should complete a 3-dose series.
- A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
- For other catch-up guidance, see Figure 172-3.

2. Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])

Routine vaccination:

Administer a series of RV vaccine to all infants as follows:

1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

Catch-up vaccination:

- The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
- The maximum age for the final dose in the series is 8 months, 0 days.
- For other catch-up guidance, see Figure 172-3.

3. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]: 4 years)

Routine vaccination:

- Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose. However, the fourth dose of DTaP need not be repeated if it was administered at least 4 months after the third dose of DTaP.

Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 yr—United States, 2015. *(From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html)*

Continued

3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (cont'd)**
Catch-up vaccination:
- The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
- For other catch-up guidance, see Figure 172-3.

4. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for both Boostrix and Adacel)**
Routine vaccination:
- Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
- Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
- Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks' gestation) regardless of time since prior Td or Tdap vaccination.

Catch-up vaccination:
- Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 dose (preferably the first) in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
- Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoid (Td) booster doses every 10 years thereafter.
- Inadvertent doses of DTaP vaccine:
  - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
  - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
- For other catch-up guidance, see Figure 172-3.

5. ***Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])**
Routine vaccination:
- Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
- The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
- One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
- For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to *MMWR* February 28, 2014 / 63(RR01);1-13, available at http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Catch-up vaccination:
- If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
- If both doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later.
- If first dose is administered before the first birthday and second dose administered at younger than 15 months, a third (and final) dose should be given 8 weeks later.
- For unvaccinated children aged 15 months or older, administer only 1 dose.
- For other catch-up guidance, see Figure 172-3. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also *MMWR* February 28, 2014 / 63(RR01);1-13, available at http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Vaccination of persons with high-risk conditions:
- Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
- For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
- Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
- A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
- Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.

** Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

6. **Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)**
Routine vaccination with PCV13:
- Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
- For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

Catch-up vaccination with PCV13:
- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up guidance, see Figure 172-3.

Vaccination of persons with high-risk conditions with PCV13 and PPSV23:
- All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
- For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; solid organ transplantation; or congenital immunodeficiency:
  1. Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  2. Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
  4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
  5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
- For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; generalized malignancy; solid organ transplantation; or multiple myeloma:
  1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
  2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
  3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
- For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
- A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

7. **Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)**
Routine vaccination:
- Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

Catch-up vaccination:
- In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk of imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
- If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. IPV is not routinely recommended for U.S. residents aged 18 years or older.
- For other catch-up guidance, see Figure 172-3.

8. **Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 2 years for live, attenuated influenza vaccine [LAIV])**
Routine vaccination:
- Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) persons who have experienced severe allergic reactions to LAIV, any of its components, or to a previous dose of any other influenza vaccine; 2) children 2 through 17 years receiving aspirin or aspirin-containing products; 3) persons who are allergic to eggs; 4) pregnant women; 5) immunosuppressed persons; 6) children 2 through 4 years of age with asthma or who had wheezing in the past 12 months; or 7) persons who have taken influenza antiviral medications in the previous 48 hours. For all other contraindications and precautions to use of LAIV, see *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.

Figure 172-2, cont'd

8. Influenza vaccines (cont'd)

For children aged 6 months through 8 years:

- For the 2014-15 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. Some children in this age group who have been vaccinated previously will also need 2 doses. For additional guidance, follow dosing guidelines in the 2014-15 ACIP influenza vaccine recommendations, *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.
- For the 2015–16 season, follow dosing guidelines in the 2015 ACIP influenza vaccine recommendations.

For persons aged 9 years and older:

- Administer 1 dose.

9. Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)

Routine vaccination:

- Administer a 2-dose series of MMR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:

- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

10. Varicella (VAR) vaccine. (Minimum age: 12 months)

Routine vaccination:

- Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:

- Ensure that all persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007 / 56 [No. RR-4], available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. Hepatitis A (HepA) vaccine. (Minimum age: 12 months)

Routine vaccination:

- Initiate the 2-dose HepA vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

Catch-up vaccination:

- The minimum interval between the two doses is 6 months.

Special populations:

- Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. The first dose should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

12. Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for HPV2 [Cervarix] and HPV4 [Gardasil])

Routine vaccination:

- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11 through 12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series may be started at age 9 years.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks); administer the third dose 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of 12 weeks).

Catch-up vaccination:

- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see Routine vaccination above) for vaccine series catch-up.

13. Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACWY-D [Menactra], 2 months for MenACWY-CRM [Menveo])

Routine vaccination:

- Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of Menactra or Menveo with at least 8 weeks between doses.
- For children aged 2 months through 18 years with high-risk conditions, see below.

Catch-up vaccination:

- Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up guidance, see Figure 172-3.

Vaccination of persons with high-risk conditions and other persons at increased risk of disease:

- Children with anatomic or functional asplenia (including sickle cell disease):
  1. Menveo
     - *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
     - *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  2. MenHibrix
     - *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
     - If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
  3. Menactra
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until 2 years of age and at least 4 weeks after the completion of all PCV13 doses.
- Children with persistent complement component deficiency:
  1. Menveo
     - *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
     - *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  2. MenHibrix
     - *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
     - If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
  3. Menactra
     - *Children 9 through 23 months:* Administer 2 primary doses at least 12 weeks apart.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
- For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, administer an age-appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.
- For children at risk during a community outbreak attributable to a vaccine serogroup, administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.
- For booster doses among persons with high-risk conditions, refer to *MMWR* 2013 / 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.

For other catch-up recommendations for these persons, and complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see MMWR March 22, 2013 / 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

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Figure 172-2, cont'd

FIGURE 172-3. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind —United States, 2015.
The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Children age 4 months through 6 years					
Hepatitis B[1]	Birth	4 weeks	8 weeks *and* at least 16 weeks after first dose. Minimum age for the final dose is 24 weeks.		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, and acellular pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[5]	6 weeks	4 weeks if first dose was administered before the 1st birthday. 8 weeks (as final dose) if first dose was administered at age 12 through 14 months. No further doses needed if first dose was administered at age 15 months or older.	4 weeks[5] if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel) or unknown. 8 weeks *and* age 12 through 59 months (as final dose)[5] • if current age is younger than 12 months **and** first dose was administered at age 7 through 11 months; OR • if current age is 12 through 59 months **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months; OR • if both doses were PRP-OMP (PedvaxHIB; Comvax) **and** were administered before the 1st birthday. No further doses needed if previous dose was administered at age 15 months or older.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal[6]	6 weeks	4 weeks if first dose administered before the 1st birthday. 8 weeks (as final dose for healthy children) if first dose was administered at the 1st birthday or after. No further doses needed for healthy children if first dose administered at age 24 months or older.	4 weeks if current age is younger than 12 months and previous dose given at <7months old. 8 weeks (as final dose for healthy children) if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months. No further doses needed for healthy children if previous dose administered at age 24 months or older.	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus[7]	6 weeks	4 weeks[7]	4 weeks[7]	6 months[7] (minimum age 4 years for final dose).	
Meningococcal[13]	6 weeks	8 weeks[13]	See footnote 13	See footnote 13	
Measles, mumps, rubella[9]	12 months	4 weeks			
Varicella[10]	12 months	3 months			
Hepatitis A[11]	12 months	6 months			
Children and adolescents age 7 through 18 years					
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis[4]	7 years[4]	4 weeks	4 weeks if first dose of DTaP/DT was administered before the 1st birthday. 6 months (as final dose) if first dose of DTaP/DT was administered at or after the 1st birthday.	6 months if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus[12]	9 years	Routine dosing intervals are recommended.[12]			
Hepatitis A[11]	Not applicable (N/A)	6 months			
Hepatitis B[1]	N/A	4 weeks	8 weeks **and** at least 16 weeks after first dose.		
Inactivated poliovirus[7]	N/A	4 weeks	4 weeks[7]	6 months[7]	
Meningococcal[13]	N/A	8 weeks[13]			
Measles, mumps, rubella[9]	N/A	4 weeks			
Varicella[10]	N/A	3 months if younger than age 13 years. 4 weeks if age 13 years or older.			

NOTE: The above recommendations must be read along with the footnotes of this schedule in Fig. 172-2.

Figure 172-3 Catch-up immunization schedule for persons aged 4 mo through 18 yr who start late or who are more than 1 mo old–United States, 2015. *(From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-pr.pdf)*

Table 172-6 Combination Vaccines Licensed and Available in the United States

VACCINE PRODUCT (MANUFACTURER)*	TRADE NAME (YEAR LICENSED)	COMPONENTS	Recommended Ages	
			PRIMARY SERIES	BOOSTER DOSE
Hib-HepB†‡ (Merck & Co, Inc.)	Comvax (1996)	PRP-OMP + HepB vaccine	2, 4 mo of age	12 through 15 mo of age
MenCY/Hib (GlaxoSmithKline)	MenHibRix (2013)	MenCY + PRP-T	2, 4, 6 mo of age	12 through 15 mo of age
DTaP-IPV/Hib (Sanofi Pasteur)	Pentacel (2008)	DTaP-IPV + PRP-T	2, 4, 6 mo of age	15 through 18 mo of age
DTaP-HepB-IPV (GlaxoSmithKline)	Pediarix (2002)	DTaP + HepB + IPV	2, 4, 6 mo of age	
DTaP-IPV (GlaxoSmithKline)	Kinrix (2008)	DTaP + IPV		4 through 6 yr of age: • booster for 5th dose of DTaP • booster for 4th dose of IPV
HepA-HepB (GlaxoSmithKline)	Twinrix (2001)	HepA + HepB	>18 yr of age; 0, 1, and 6 mo schedule	
MMRV (Merck & Co, Inc.)	ProQuad (2005)	MMR + varicella	12 through 15 mo of age	4 through 6 yr of age

*Dash (-) indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products are mixed or reconstituted by user.
†If a PRP-OMP vaccine is not administered as both doses in the primary series or if there is uncertainty about which products were administered previously, a 3rd dose of Hib conjugate vaccine is needed to complete the primary series.
‡Preferred for American Indian/Alaska Native children.
DTap, diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; IPV/Hib, trivalent inactivated polio vaccine and *Haemophilus influenzae* type b vaccine; MMRV, measles-mumps-rubella and varicella vaccine.

Table 172-8 Recommended Immunizations for Travelers to Developing Countries*

IMMUNIZATIONS	Length of Travel		
	BRIEF, <2 WK	INTERMEDIATE, 2 WK-3 MO	LONG-TERM RESIDENTIAL, >3 MO
Review and complete age-appropriate childhood and adolescent schedule (see text for details)	+	+	+
• DTaP, poliovirus, pneumococcal, and *Haemophilus influenzae* type b vaccines may be given at 4-wk intervals if necessary to complete the recommended schedule before departure • Measles: 2 additional doses given if <12 mo of age at 1st dose • Rotavirus • Varicella • HPV • Hepatitis B† • Tdap • MCV4			
Yellow fever‡	+	+	+
Hepatitis A§	+	+	+
Typhoid fever‖	±	+	+
Meningococcal disease¶	±	±	±
Rabies**	±	+	+
Japanese encephalitis††	±	±	+

*See disease-specific chapters in the Red Book for details. For further sources of information, see text.
†If there is insufficient time to complete 6 mo primary series, accelerated series can be given.
‡For regions with endemic infection, see Health Information for International Travel (http://www.cdc.gov/travel).
§Indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection.
‖Indicated for travelers who will consume food and liquids in areas of poor sanitation.
¶Recommended for regions of Africa with endemic infection and during local epidemics, and required for travel to Saudi Arabia for the Hajj.
**Indicated for people with high risk for animal exposure (especially to dogs) and for travelers to countries with endemic infection.
††For regions with endemic infection (see Health Information for International Travel). For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.
+, Recommended; ±, consider; DTaP, diphtheria and tetanus toxoids and acellular pertussis.
Modified Pickering LK, Baker CJ, Kimberlin DW, Long SL, editors: Red Book 2012: report of the Committee on Infectious Diseases, *Elk Grove Village, IL, 2012,*

Table 172-7 Vaccines Recommended for Children and Adolescents with Underlying Conditions or at High Risk

VACCINES	CONDITIONS

PCV13 (and PPSV23 in certain conditions)	• Immunocompetent children with:
	  • Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure)
	  • Chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy)
	  • Diabetes mellitus
	  • Cerebrospinal fluid leaks
	  • Cochlear implant
	• Anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia or splenic dysfunction)
	• Immunocompromising conditions: HIV infection; chronic renal failure and nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease or solid organ transplantation; congenital immunodeficiency

MCV4	• Anatomic or functional asplenia (including sickle cell disease) • Persistent complement component deficiency • Residents of or travelers to countries in African meningitis belt or pilgrims on the Haj • During outbreaks caused by a vaccine serogroup
Hib	• Anatomic or functional asplenia (including sickle cell disease) • Immunocompromising conditions: HIV disease; immunosuppressive therapy for malignant neoplasms; immunoglobulin deficiency including immunoglobulin G_2 subclass deficiency or early complement deficiency; recipients of a hematopoietic stem cell transplant (HSCT)

Table 172-9 Vaccination of Persons with Primary and Secondary Immune Deficiencies

PRIMARY

CATEGORY	SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
B lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[†] Smallpox LAIV BCG Ty21a (live typhoid) YF	Pneumococcal Consider measles and varicella vaccination	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response (e.g., PPSV, MPSV) IVIG interferes with the immune response to measles vaccine and possibly varicella vaccine
	Less-severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[†] BCG YF Other live vaccines appear to be safe	Pneumococcal	All vaccines probably effective Immune response may be attenuated
T lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines[‡§‖]	Pneumococcal	Vaccines may be ineffective
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[‡§‖]	Pneumococcal Meningococcal Hib (if not administered in infancy)	Effectiveness of any vaccine depends on degree of immune suppression
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal	All routine vaccines probably effective
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency	Live bacterial vaccines[‡]	Pneumococcal[¶]	All inactivated vaccines safe and probably effective Live viral vaccines probably safe and effective

SECONDARY

SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
HIV/AIDS	OPV[†] Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons	Pneumococcal Consider Hib (if not administered in infancy) and meningococcal vaccination	MMR, varicella, rotavirus, and all inactivated vaccines, including inactivated influenza, may be effective[#]
Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status[‡§]	Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression
Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines probably effective
Chronic renal disease	LAIV	Pneumococcal Hepatitis B**	All routine vaccines probably effective

*Other vaccines that are universally or routinely recommended should be given if not contraindicated.

[†]OPV is no longer recommended for routine use in the United States.

[‡]Live bacterial vaccines: BCG and oral Ty21a *Salmonella typhi* vaccine.

[§]Live viral vaccines: MMR, MMRV, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

[‖]Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

[¶]Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.

[#]HIV-infected children should receive immunoglobulin after exposure to measles and may receive varicella, measles, and YF vaccine if CD4+ lymphocyte count is greater than 15%. (For YF vaccine, CD4+ T-lymphocyte count between 15% and 24% is a precaution.)

**Indicated based on the risk from dialysis-based bloodborne transmission.

BCG, bacille Calmette-Guérin vaccine; Hib, *Haemophilus influenzae* type b vaccine; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IVIG, intravenous immunoglobulin; LAIV, live-attenuated influenza vaccine; MMR, measles, mumps, rubella vaccine; MPSV, quadrivalent meningococcal polysaccharide vaccine; OPV, oral poliovirus vaccine (live); PPSV, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency disease; YF, yellow fever.

Table 174-1 Infectious Diseases in the Childcare Setting

DISEASE	INCREASED INCIDENCE WITH CHILDCARE
RESPIRATORY TRACT INFECTIONS	
Otitis media	Yes
Sinusitis	Probably
Pharyngitis	Probably
Pneumonia	Yes
GASTROINTESTINAL TRACT INFECTIONS	
Diarrhea (rotavirus, calicivirus, astrovirus, enteric adenovirus, *Giardia lamblia, Cryptosporidium, Shigella, Escherichia coli* O157:H7, and *Clostridium difficile*)	Yes
Hepatitis A	Yes
SKIN DISEASES	
Impetigo	Probably
Scabies	Probably
Pediculosis	Probably
Tinea (ringworm)	Probably
INVASIVE BACTERIA INFECTIONS	
Haemophilus influenzae type b	No*
Neisseria meningitidis	Probably
Streptococcus pneumoniae	Yes
ASEPTIC MENINGITIS	
Enteroviruses	Probably
HERPESVIRUS INFECTIONS	
Cytomegalovirus	Yes
Varicella-zoster virus	Yes
Herpes simplex virus	Probably
BLOOD-BORNE INFECTIONS	
Hepatitis B	Few case reports
HIV	No cases reported
Hepatitis C	No cases reported
VACCINE-PREVENTABLE DISEASES	
Measles, mumps, rubella, diphtheria, pertussis, tetanus	Not established
Polio	No
H. influenzae type b	No*
Varicella	Yes
Rotavirus	Yes

*Not in the postvaccine era; yes in the prevaccine era

Table 172-10 Standards for Child and Adolescent Immunization Practices

AVAILABILITY OF VACCINES
Vaccination services are readily available.
Vaccinations are coordinated with other healthcare services and provided in a medical home when possible.
Barriers to vaccination are identified and minimized.
Patient costs are minimized.

ASSESSMENT OF VACCINATION STATUS
Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.
Healthcare professionals assess for and follow only medically accepted contraindications.

EFFECTIVE COMMUNICATION ABOUT VACCINE BENEFITS AND RISKS
Parents or guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.

PROPER STORAGE AND ADMINISTRATION OF VACCINES AND DOCUMENTATION OF VACCINATIONS
Healthcare professionals follow appropriate procedures for vaccine storage and handling.
Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.
Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.
Healthcare professionals simultaneously administer as many indicated vaccine doses as possible.
Vaccination records for patients are accurate, complete, and easily accessible.
Healthcare professionals report adverse events following vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).
All personnel who have contact with patients are appropriately vaccinated.

IMPLEMENTATION OF STRATEGIES TO IMPROVE VACCINATION COVERAGE
Systems are used to remind parents or guardians, patients, and healthcare professionals when vaccinations are due and to recall those who are overdue.
Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.
Healthcare professionals practice community-based approaches.

Table 173-3 Common Surgical Procedures for Which Perioperative Prophylactic Antibiotics Are Recommended

SURGICAL PROCEDURE	LIKELY PATHOGENS	RECOMMENDED DRUGS	NON–β-LACTAM ALTERNATIVE
CLEAN WOUNDS			
Cardiac surgery (e.g., open heart surgery) Vascular surgery Neurosurgery Orthopedic surgery (e.g., joint replacement)	Skin flora, enteric Gram-negative bacilli	Cefazolin or cefuroxime	Clindamycin or vancomycin
CLEAN CONTAMINATED WOUNDS			
Head and neck surgery involving the oral cavity or pharynx	Skin flora, oral anaerobes, oral streptococci	Cefazolin + metronidazole, ampicillin-sulbactam	Clindamycin
Gastrointestinal and genitourinary surgery	Enteric Gram-negative bacilli, anaerobes, Gram-positive cocci	Cefazolin + metronidazole, cefotetan or piperacillin-tazobactam If colon is involved, consider bacterial reduction with PO neomycin and erythromycin	Clindamycin
CONTAMINATED WOUNDS			
Traumatic wounds (e.g., compound fracture)	Skin flora	Cefazolin	Clindamycin, vancomycin
DIRTY WOUNDS			
Appendectomy, penetrating abdominal wounds, colorectal surgery	Enteric Gram-negative bacilli, anaerobes, Gram-positive cocci	Cefazolin + metronidazole, cefoxitin, cefotetan or ampicillin-sulbactam	Clindamycin + aminoglycoside

Table 174-2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare—cont'd

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
Measles	Exclusion until 4 days after beginning of rash and when the child is able to participate	Immunize exposed children without evidence of immunity within 72 hr of exposure Children who do not receive vaccine within 72 hr or who remain unimmunized after exposure should be excluded until at least 2 wk after onset of rash in the last case of measles
Mumps	Exclusion until 5 days after onset of parotid gland swelling	In outbreak setting, people without documentation of immunity should be immunized or excluded Immediate readmission may occur following immunization Unimmunized people should be excluded for ≥26 days following onset of parotitis in last case
Pediculosis capitis (head lice)	Treatment at end of program day and readmission on completion of 1st treatment	Household and close contacts should be examined and treated if infested No exclusion is necessary
Pertussis	Exclusion until 5 days of appropriate antimicrobial therapy course have been completed	Immunization and chemoprophylaxis should be administered as recommended for household contacts Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy course Untreated adults should be excluded until 21 days after onset of cough
Rubella	Exclusion until 6 days after onset of rash for postnatal infection	Pregnant contacts should be evaluated
Salmonella serotype Typhi infection	Exclusion until diarrhea resolves 3 Negative stool culture results required before readmission	Stool cultures should be performed for attendees and staff; infected people should be excluded on the basis of age
Non–serotype Typhi *Salmonella* infection	Exclusion until diarrhea resolves. Negative stool culture results not required for non–serotype Typhi *Salmonella* species	Symptomatic contacts should be excluded until symptoms resolve Stool cultures are not required for asymptomatic contacts Antimicrobial therapy is not recommended for asymptomatic infection or uncomplicated diarrhea or for contacts
Scabies	Exclusion until after treatment given	Close contacts with prolonged skin-to-skin contact should have prophylactic therapy Bedding and clothing in contact with skin of infected people should be laundered
Shiga toxin–producing *Escherichia coli*, including *E. coli* O157:H7, or *Shigella* infection	Exclusion until diarrhea resolves and results of 2 stool cultures are negative for these organisms, depending on state regulations	Meticulous hand hygiene; stool cultures should be performed for contacts Center(s) with cases should be closed to new admissions during *E. coli* O157:H7 outbreak
Staphylococcus aureus skin infections	Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing	Meticulous hand hygiene Cultures of contacts are not recommended
Streptococcal pharyngitis	Exclusion until 24 hr after treatment has been initiated and the child is able to participate in activities	Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive
Tuberculosis	For active disease, exclusion until determined to be noninfectious by physician or health department authority May return to activities after therapy is instituted, symptoms have diminished, and adherence to therapy is documented No exclusion for latent tuberculosis infection	Local health department personnel should be informed for contact investigation
Varicella	Exclusion until all lesions have dried and crusted, usually 6 days after onset of rash in immunocompetent people; may be longer in immunocompromised people	Varicella vaccine should be administered by 3-5 days after exposure, and varicella-zoster Ig should be administered up to 96 hr after exposure when indicated

HAV, hepatitis A virus; Ig, immunoglobulin.

Table 174-2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
HAV infection	Serologic testing to confirm HAV infection in suspected cases Exclusion until 1 wk after onset of jaundice	If ≥1 case is confirmed in child or staff attendees or ≥2 cases in households of staff or attendees, HAV vaccine or Ig should be administered within 14 days of exposure to unimmunized staff and attendees In centers without diapered children, HAV vaccine or Ig should be given to unimmunized classroom contacts of index case Asymptomatic Ig recipients may return after receipt of Ig
Impetigo	Exclusion until 24 hr after treatment has been initiated Lesions on exposed skin covered with watertight dressing	No intervention needed unless additional lesions develop

Table 174-3 General Recommendations for Exclusion of Children in Out-of-Home Childcare

SYMPTOM(S)	MANAGEMENT
Illness preventing participation in activities, as determined by childcare staff	Exclusion until illness resolves and able to participate in activities
Illness that requires care greater than staff can provide without compromising health and safety of others	Exclusion or placement in care environment where appropriate care can be provided without compromising care of others
Severe illness suggested by fever with behavior changes, lethargy, irritability, persistent crying, difficulty breathing, progressive rash	Medical evaluation and exclusion until symptoms have resolved
Rash with fever or behavioral change	Medical evaluation and exclusion until illness is determined not to be communicable
Persistent abdominal pain (≥2 hr) or intermittent abdominal pain associated with fever, dehydration, or other systemic signs and symptoms	Medical evaluation and exclusion until symptoms have resolved
Vomiting ≥2 times in preceding 24 hr	Exclusion until symptoms have resolved, unless vomiting is determined to be caused by a noncommunicable condition and child is able to remain hydrated and participate in activities
Diarrhea or stools containing blood or mucus	Medical evaluation and exclusion until symptoms have resolved
Oral lesions	Exclusion until child or staff member is considered to be noninfectious (lesions crusted and dry)

Table 175-1 Travel Vaccinations for Children

VACCINE	PRIMARY SERIES	AGE AT VACCINATION	BOOSTER/COMMENTS
HEPATITIS A			
Havrix, Vaqta	0.5 mL IM × 2 doses ≥6 mo apart	>1 yr	No booster; see text about off-label administration (age 6-11 mo)
Immunoglobulin (Ig)	Travel <2 mo: 0.02 mL/kg IM once Travel >2 mo: 0.06 mL/kg IM once	Birth	See text about restrictions with live virus vaccinations (i.e., MMR) following Ig administration
INFLUENZA			
Inactivated	6-35 mo: 0.25 mL IM, 1 or 2 doses 3-8 yr: 0.5 mL IM, 1 or 2 doses >9 yr: 0.5 mL IM once	>6 mo	New vaccine yearly In children 6 mo-9 yr, 2 doses should be given ≥1 mo apart if no prior vaccination
Live-attenuated	0.25 mL in each nostril, 1 or 2 doses	>2 yr	New vaccine yearly
JAPANESE B ENCEPHALITIS			
Ixiaro (inactivated)	2 mo-2 yr: 0.25 mL IM on days 0 and 28	2 mo to <3 yr	Booster 1-2 yr after primary series
	>3 yr: 0.5 mL IM on days 0 and 28	>3 yr	Booster 1-2 yr after primary series
MEASLES			
MMR	Recommended schedule: 12-15 mo and 4-6 yr If >12 mo and traveling internationally, 2nd MMR dose can be administered 4 wk later	>6-11 mo: 1 dose recommended if traveling to measles-endemic area	See text. MMR at 6-11 mo does not count toward primary series; MMR should be administered simultaneously with other recommended/required live-virus travel vaccines (yellow fever)
MENINGOCOCCAL DISEASE			
Conjugate A/C/Y/W-135	0.5 mL IM 9-23 mo: 2 doses, 3 mo apart	9-23 mo	Booster 3 yr after primary series
	0.5 mL IM once	>2–6 yr	Booster after 3 yr (age 2-6 yr)
		>7 yr	Booster after 5 yr (age >7 yr) Children with functional/anatomic asplenia receive 2 dose primary series, 2 mo apart; conjugate vaccine recommended over polysaccharide A/C/Y/W-135
Polysaccharide A/C/Y/W-135	0.5 mL SC once	>2 yr	<4 yr of age: every 2 yr >4 yr of age: every 3-5 yr
RABIES			
	Preexposure: 1.0 mL IM × 3 doses, days 0, 7, and 21 or 28 days	Any age	See text for follow-up vaccination if bitten
TYPHOID			
Intramuscular Vi	0.5 mL IM once	≥2 yr	Every 2-3 yr
Oral Ty21	4 doses: 1 capsule PO every other day	≥6 yr	Every 5 yr; see text for administration
YELLOW FEVER			
	0.5 mL SC once	>9 mo	Every 10 yr (see text)

A/C/Y/W-135, serogroup A, C, Y, and W^{135} meningococcal vaccine.

Table 177-1 Febrile Patients at Increased Risk for Serious Bacterial and Viral Infections

RISK GROUP	DIAGNOSTIC CONSIDERATIONS
IMMUNOCOMPETENT PATIENTS	
Neonates (<28 days)	Sepsis and meningitis caused by group B *Streptococcus*, *Escherichia coli*, *Listeria monocytogenes;* neonatal herpes simplex virus infection, enteroviruses, parechovirus
Infants 1-3 mo	Serious bacterial disease in 5-15%, including bacteremia in 5%; urinary tract infection most common serious bacterial infection; *E. coli* most common pathogen; enterovirus, parechovirus, influenza
Infants and children 3-36 mo	Occult bacteremia in <0.5% of children immunized with both *Haemophilus influenzae* type b and pneumococcal conjugate vaccines; urinary tract infections
Hyperpyrexia (>40°C [104°F])	Meningitis, bacteremia, pneumonia, heatstroke, hemorrhagic shock-encephalopathy syndrome
Fever with petechiae	Bacteremia and meningitis caused by *Neisseria meningitidis, H. influenzae* type b, and *Streptococcus pneumoniae* Rickettsial disease Viral exanthem
IMMUNOCOMPROMISED PATIENTS	
Sickle cell disease	Sepsis, pneumonia, and meningitis caused by *S. pneumoniae*, osteomyelitis caused by *Salmonella* and *Staphylococcus aureus*
Asplenia	Bacteremia and meningitis caused by *N. meningitidis, H. influenzae* type b, *S. pneumoniae*, and *Capnocytophaga* sp.
Complement or properdin deficiency	Sepsis caused by *N. meningitidis*
Agammaglobulinemia	Bacteremia, sinopulmonary infections
AIDS	*S. pneumoniae, H. influenzae* type b, and *Salmonella* infections
Congenital heart disease	Infective endocarditis; brain abscess with right-to-left shunting
Central venous line	*S. aureus*, coagulase-negative staphylococci, *Candida*
Malignancy	Bacteremia with gram-negative enteric bacteria, *S. aureus*, and coagulase-negative staphylococci; fungemia with *Candida* and *Aspergillus*

Table 176-1 Fevers Prone to Relapse

INFECTIOUS CAUSES
Relapsing fever *(Borrelia recurrentis)*
Trench fever *(Bartonella quintana)*
Q fever *(Coxiella burnetii)*
Typhoid fever *(Salmonella typhi)*
Syphilis *(Treponema pallidum)*
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Blastomycosis
Melioidosis *(Pseudomonas pseudomallei)*
Lymphocytic choriomeningitis (LCM) infection
Dengue fever
Yellow fever
Chronic meningococcemia
Colorado tick fever
Leptospirosis
Brucellosis
Oroya fever *(Bartonella bacilliformis)*
Acute rheumatic fever
Rat bite fever *(Spirillum minus)*
Visceral leishmaniasis
Lyme disease *(Borrelia burgdorferi)*
Malaria
Babesiosis
Noninfluenza respiratory viral infection
Epstein-Barr virus infection

NONINFECTIOUS CAUSES
Behçet disease
Crohn disease
Weber-Christian disease (panniculitis)
Leukoclastic angiitis syndromes
Sweet syndrome
Systemic lupus erythematosus and other autoimmune disorders

PERIODIC FEVER SYNDROMES (see Chapter 163)
Familial Mediterranean fever
Cyclic neutropenia
Periodic fever, aphthous stomatitis, pharyngitis, adenopathy (PFAPA)
Hyperimmunoglobulin D syndrome
Hibernian fever (tumor necrosis factor superfamily immunoglobulin A–associated syndrome [TRAPS])
Muckle-Wells syndrome
Others

Table 176-2 Evaluation of Acute Fever

Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates), travel, medications, other underlying disorders, immunizations
Physical examination: complete, with focus on localizing symptoms
Laboratory studies on a case-by-case basis:
- Rapid antigen testing
- Nasopharyngeal: respiratory viruses by polymerase chain reaction
- Throat: group A *Streptococcus*
- Stool: rotavirus
- Blood: complete blood count, blood culture, C-reactive protein, sedimentation rate, procalcitonin
- Urine: urinalysis, culture
- Stool: Hemoccult, culture
- Cerebrospinal fluid: cell count, glucose, protein, Gram stain, culture
- Chest radiograph or other imaging studies on a case-by-case basis

Table 177-3 Management of Fever Without Localizing Signs

GROUP	MANAGEMENT
Any toxic-appearing child 0-36 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child <1 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child 1-3 mo and temperature ≥38°C (100.4°F)	Two-step process 1. Determine risk based on history, physical examination, and laboratory studies. Low risk: • Uncomplicated medical history • Normal physical examination • Normal laboratory studies • Urine: negative leukocyte esterase, nitrite and <10 WBC/HPF • Peripheral blood: 5,000-15,000 WBC/mm^3; <1,500 bands or band: total neutrophil ratio <0.2 • Stool studies if diarrhea (no RBC and <5 WBC/HPF) • CSF cell count (<8 WBC/μL) and negative Gram stain • Chest radiograph without infiltrate 2. If child fulfills all low-risk criteria, administer no antibiotics, ensure follow-up in 24 hr and access to emergency care if child deteriorates. Daily follow-up should occur until blood, urine, and CSF cultures are final. If any cultures are positive, child returns for further evaluation and treatment. If child does not fulfill all low-risk criteria, hospitalize and administer parenteral antibiotics until all cultures are final and definitive diagnosis determined and treated
Child 3-36 mo and temperature 38-39°C (100.4-102.2°F)	Reassurance that diagnosis is likely self-limiting viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and new signs and symptoms
Child 3-36 mo and temperature >39°C (102.2°F)	Two-step process: 1. Determine immunization status 2. If received conjugate pneumococcal and *Haemophilus influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all girls, all boys <6 mo old, all uncircumcised boys <2 yr, all children with recurrent urinary tract infections If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines (see Baraff et al. *Ann Emerg Med* 22:1198-1210, 1993.)

*Other tests may include chest radiograph, stool studies, herpes simplex polymerase chain reaction.
CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

Table 177-4 Summary of Definitions and Major Features of the 4 Subtypes of Fever of Unknown Origin

FEATURE	CLASSIC FUO	HEALTHCARE-ASSOCIATED FUO	IMMUNE-DEFICIENT FUO	HIV-RELATED FUO
Definition	>38°C (100.4°F), >3 wk, >2 visits or 1 wk in hospital	≥38°C (100.4°F), >1 wk, not present or incubating on admission	≥38°C (100.4°F), >1 wk, negative cultures after 48 hr	≥38°C (100.4°F), >3 wk for outpatients, >1 wk for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Healthcare-associated infections, postoperative complications, drug fever	Majority caused by infections, but cause documented in only 40-60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower-limb deep veins	Wounds, drains, devices, sinuses, urine	Skin folds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

CMV, cytomegalovirus; CXR, chest radiograph; FUO, fever of unknown origin.
Adapted from Mandell GL, Bennett, JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, *ed 7, Philadelphia, 2010, Churchill Livingstone/Elsevier, p. 780, Table 51-1.*

Table 177-5 Diagnostic Considerations of Fever of Unknown Origin in Children

ABSCESSES
Abdominal
Brain
Dental
Hepatic
Pelvic
Perinephric
Rectal
Subphrenic
Psoas

BACTERIAL DISEASES
Actinomycosis
Bartonella henselae (cat-scratch disease)
Brucellosis
Campylobacter
Francisella tularensis (tularemia)
Listeria monocytogenes (listeriosis)
Meningococcemia (chronic)
Mycoplasma pneumoniae
Rat bite fever (*Streptobacillus moniliformis;* streptobacillary form of rat bite fever)
Salmonella
Tuberculosis
Whipple disease
Yersiniosis

LOCALIZED INFECTIONS
Cholangitis
Infective endocarditis
Mastoiditis
Osteomyelitis
Pneumonia
Pyelonephritis
Sinusitis

SPIROCHETES
Borrelia burgdorferi (Lyme disease)
Relapsing fever *(Borrelia recurrentis)*
Leptospirosis
Rat bite fever (*Spirillum minus;* spirillary form of rat bite fever)
Syphilis

FUNGAL DISEASES
Blastomycosis (extrapulmonary)
Coccidioidomycosis (disseminated)
Histoplasmosis (disseminated)
Chlamydia
Lymphogranuloma venereum
Psittacosis

RICKETTSIA
Ehrlichia canis
Q fever
Rocky Mountain spotted fever
Tick-borne typhus

VIRUSES
Cytomegalovirus
Hepatitis viruses
HIV
Epstein-Barr virus

PARASITIC DISEASES
Amebiasis
Babesiosis
Giardiasis
Malaria
Toxoplasmosis
Trichinosis
Trypanosomiasis
Visceral larva migrans *(Toxocara)*

RHEUMATOLOGIC DISEASES
Behçet disease
Juvenile dermatomyositis
Juvenile idiopathic arthritis
Rheumatic fever
Systemic lupus erythematosus

HYPERSENSITIVITY DISEASES
Drug fever
Hypersensitivity pneumonitis
Serum sickness
Weber-Christian disease

NEOPLASMS
Atrial myxoma
Cholesterol granuloma
Hodgkin disease
Inflammatory pseudotumor
Leukemia
Lymphoma
Pheochromocytoma
Neuroblastoma
Wilms tumor

GRANULOMATOUS DISEASES
Crohn disease
Granulomatous hepatitis
Sarcoidosis
Angiitis

FAMILIAL AND HEREDITARY DISEASES
Anhidrotic ectodermal dysplasia
Autonomic neuropathies
Fabry disease
Familial dysautonomia
Familial Hibernian fever
Familial Mediterranean fever and the many other autoinflammatory diseases (see Chapter 163)
Hypertriglyceridemia
Ichthyosis
Sickle cell crisis
Spinal cord/brain injury

MISCELLANEOUS
Addison disease
Castleman disease
Chronic active hepatitis
Cyclic neutropenia
Diabetes insipidus (nonnephrogenic and nephrogenic)
Factitious fever
Hemophagocytic syndromes
Hypothalamic-central fever
Infantile cortical hyperostosis
Inflammatory bowel disease
Kawasaki disease
Kikuchi-Fujimoto disease
Metal fume fever
Pancreatitis
Periodic fever syndromes
Poisoning
Pulmonary embolism
Thrombophlebitis
Thyrotoxicosis, thyroiditis

Table 177-6 Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Unknown Origin

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration	Disseminated histoplasmosis, SLE, IBD, Behcet syndrome, periodic fever syndromes
	Tender tooth	Periapical abscess
Fundi or conjunctivae	Choroid tubercle	Disseminated granulomatosis*
	Petechiae, Roth spot	Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
Rectum	Perirectal fluctuance, tenderness	Abscess
	Prostatic tenderness, fluctuance	Abscess
Genitalia	Testicular nodule	Periarteritis nodosa, cancer
	Epididymal nodule	Disseminated granulomatosis
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, granulomatosis with polyangiitis, and syphilis.
From Mandell GL, Bennett, JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, *ed 7, Philadelphia, 2010, Churchill Livingstone/Elsevier, p. 785, Table 51-8.*

Table 177-2 Low-Risk Criteria in a Child 1-3 Months Old with Fever

BOSTON CRITERIA
Infants are at low risk if they appear well, have a normal physical examination, and have a caretaker reachable by telephone and if laboratory tests are as follows:
- CBC: <20,000 WBC/μL
- Urine: negative leukocyte esterase
- CSF: leukocyte count less than 10×10^6/L

PHILADELPHIA PROTOCOL
Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows:
- CBC: <15,000 WBC/μL; band: total neutrophil ratio <0.2
- Urine: <10 WBC/HPF; no bacteria on Gram stain
- CSF: <8 WBC/μL; no bacteria on Gram stain
- Chest radiograph: no infiltrate
- Stool: no RBC; few to no WBC

PITTSBURGH GUIDELINES
Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows:
- CBC: 5,000-15,000 WBC/μL; peripheral absolute band count <1,500/μL
- Urine (enhanced urinalysis): 9 WBC/μL and no bacteria on Gram stain
- CSF: 5 WBC/μL and negative Gram stain; if bloody tap, then WBC:RBC ≤1 : 500
- Chest radiograph: no infiltrate
- Stool: 5 WBC/HPF with diarrhea

ROCHESTER CRITERIA
Infants are at low risk if they appear well and have a normal physical examination and if laboratory findings are as follows:
- CBC: 5,000-15,000 WBC/μL; absolute band count ≤1,500/μL
- Urine: <10 WBC/HPF at 40×
- Stool: <5 WBC/HPF if diarrhea

CBC, complete blood count; CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

Table 178-3 Possible Causes of Fever in Neutropenic Patients Not Responding to Broad-Spectrum Antibiotics

CAUSES	APPROXIMATE FREQUENCY IN HIGH-RISK PATIENTS (%)
Fungal infections susceptible to empirical therapy	40
Fungal infections resistant to empirical antifungal therapy	5
Bacterial infections (with cryptic foci, biofilms, and resistant organisms)	10
Toxoplasma gondii, mycobacteria, or fastidious pathogens *(Legionella, Mycoplasma, Chlamydophila pneumoniae, Bartonella)*	5
Viral infections (herpesviruses, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, varicella-zoster virus, herpes simplex virus, parainfluenza virus, respiratory syncytial virus, influenzaviruses)	5
Graft-versus-host disease after hematopoietic stem cell transplantation	10
Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens)	25

Table 178-2 Most Common Causes of Infections in Immunocompromised Children

BACTERIA, AEROBIC*
Acinetobacter
Bacillus
Burkholderia cepacia
Citrobacter
Corynebacterium
Enterobacter spp.
Enterococcus faecalis
Enterococcus faecium
Escherichia coli
Klebsiella spp.
Listeria monocytogenes
Mycobacterium spp.
Neisseria meningitidis
Nocardia
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus, coagulase-negative
Streptococcus pneumoniae
Streptococcus, viridans group
BACTERIA, ANAEROBIC*
Bacillus
Clostridium
Fusobacterium
Peptococcus
Peptostreptococcus
Propionibacterium
Veillonella
FUNGI*
Aspergillus
Candida albicans
Other *Candida* spp.
Cryptococcus neoformans
Fusarium spp.
Pneumocystis jiroveci
Zygomycoses *(Mucor, Rhizopus, Rhizomucor)*
VIRUSES*
Adenoviruses
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Human herpesvirus 6
Polyomavirus (BK)
Respiratory and enteric community-acquired viruses
Varicella-zoster virus
PROTOZOA*
Cryptosporidium parvum
Giardia lamblia
Toxoplasma gondii

*Listed alphabetically.

Table 178-1 Major Causes of Increased Risk for Infection in Immunocompromised Hosts

PRIMARY IMMUNODEFICIENCIES
Antibody deficiency (B-cell defects; see Chapter 124)
• X-linked agammaglobulinemia
• Common variable immunodeficiency
• Selective immunoglobulin IgA deficiency
• IgG subclass deficiencies
• Hyper-IgM syndrome
• Transient hypogammaglobulinemia of infancy
Cell-mediated deficiency (T-cell defects)
• Thymic dysplasia (DiGeorge syndrome)
• Defective T-cell receptor
• Defective cytokine production
• T-cell activation defects
• CD8 lymphocytopenia
• Chronic mucocutaneous candidiasis
Combined B- and T-cell defects (see Chapter 126)
• Severe combined immunodeficiency
• Combined immunodeficiency
• Omenn syndrome
• Thrombocytopenia and eczema (Wiskott-Aldrich syndrome)
• Ataxia-telangiectasia
• Hyper-IgE syndrome
Phagocyte defects (see Chapter 130)
• Leukocyte adhesion deficiency
• Chédiak-Higashi syndrome
• Myeloperoxidase deficiency
• Chronic granulomatous disease
Leukopenia (see Chapter 131)
• Congenital neutropenia (Kostmann syndrome)
• Shwachman-Diamond syndrome
Disorders of the complement system (see Chapter 133)
SECONDARY IMMUNODEFICIENCIES
HIV (see Chapter 276)
Malignancies (and cancer chemotherapy)
Transplantation (see Chapters 135, 339, 368, 443, 444, and 536)
• Bone marrow and hematopoietic stem cell
• Solid organ
Burns
Sickle cell disease
Cystic fibrosis (see Chapter 403)
Diabetes mellitus
Immunosuppressive drugs
Asplenia including heterotaxy syndrome
Implanted foreign body
Malnutrition

Table 178-4 Host Defense Defects and Common Pathogens by Time After Bone Marrow Transplantation/Hematopoietic Stem Cell Transplantation

TIME PERIOD	HOST DEFENSE DEFECTS	CAUSES	COMMON PATHOGENS
Pretransplant	Neutropenia Abnormal anatomic barriers	Underlying disease Prior chemotherapy	Aerobic Gram-negative bacilli
Preengraftment	Neutropenia Abnormal anatomic barriers	Chemotherapy Radiation Indwelling catheters	Aerobic Gram-positive cocci Aerobic Gram-negative bacilli *Candida* *Aspergillus* Herpes simplex virus (in previously infected patients) Community-acquired viral pathogens
Postengraftment	Abnormal cell-mediated immunity Abnormal anatomic barriers	Chemotherapy Immunosuppressive medications Radiation Indwelling catheters Unrelated cord blood donor	Gram-positive cocci Aerobic Gram-negative bacilli Cytomegalovirus Adenoviruses Community-acquired viral pathogens *Pneumocystis jiroveci*
Late posttransplant	Delayed recovery of immune function (cell-mediated, humoral, and abnormal anatomic barriers)	Time required to develop donor-related immune function Graft-versus-host disease	Varicella-zoster virus *Streptococcus pneumoniae*

Table 178-6 Timing of Infectious Complications Following Solid-Organ Transplantation

EARLY PERIOD (0-30 DAYS)
Bacterial Infections
Gram-negative enteric bacilli
- Small bowel, liver, neonatal heart

Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
- Cystic fibrosis lung

Gram-positive organisms
- All transplant types

Fungal Infections
All transplant types
Viral Infections
Herpes simplex virus
- All transplant types

Nosocomial respiratory viruses
- All transplant types

MIDDLE PERIOD (1-6 MO)
Viral Infections
Cytomegalovirus
- All transplant types
- Seronegative recipient of seropositive donor

Epstein-Barr virus
- All transplant types (small bowel highest risk group)
- Seronegative recipient

Varicella-zoster virus
- All transplant types
- Opportunistic infections

Pneumocystis jiroveci
- All transplant types

Toxoplasma gondii
- Seronegative recipient of cardiac transplant from a seropositive donor

Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
- Cystic fibrosis lung

Gram-negative enteric bacilli
- Small bowel

LATE PERIOD (>6 MO)
Viral Infections
Epstein-Barr virus
- All transplant types, but less risk than middle period

Varicella-zoster virus
- All transplant types

Community-acquired viral infections
- All transplant types

Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
- Cystic fibrosis lung
- Lung transplants with chronic rejection

Gram-negative bacillary bacteremia
- Small bowel

Fungal Infections
Aspergillus
- Lung transplants with chronic rejection

Table 178-5 Risk Factors for Infections Following Solid-Organ Transplantation in Children

PRETRANSPLANTATION FACTORS
Age of patient
Underlying disease, malnutrition
Specific organ transplanted
Previous exposures to infectious agents
Previous immunizations
Presence of infection in the donor

INTRAOPERATIVE FACTORS
Duration of transplant surgery
Exposure to blood products
Technical problems
Organisms transmitted with donor organ

POSTTRANSPLANTATION FACTORS
Immunosuppression
Induction immunosuppression
Maintenance immunosuppression
Augmented treatment for rejection
Indwelling catheters
Nosocomial exposures
Community exposures

Table 180-3 Antibacterial Medications (Antibiotics)*

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Amikacin sulfate Amikin Injection: 50 mg/mL, 250 mg/mL	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days: weight 1,200-2,000 g: 7.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 10 mg/kg q 12 hr IV or IM; postnatal age >7 days: weight 1,200-2,000 g IV or IM: 7.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 10 mg/kg q 8 hr IV or IM Children: 15-25 mg/kg/24 hr divided q 8-12 hr IV or IM Adults: 15 mg/kg/24 hr divided q 8-12 hr IV or IM	*Cautions:* Anaerobes, *Streptococcus* (including *S. pneumoniae*) are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 25-40 mg/L; trough <10 mg/L
Amoxicillin Amoxil, Polymox Capsule: 250, 500 mg Tablet: chewable: 125, 250 mg Suspension: 125 mg/5 mL, 250 mg/5 mL Drops: 50 mg/mL	**Penicillinase-susceptible β-lactam: Gram-positive pathogens except *Staphylococcus; Salmonella, Shigella, Neisseria, E. coli,* and *Proteus mirabilis*** Children: 20-50 mg/kg/24 hr divided q 8-12 hr PO. Higher dose of 80-90 mg/kg 24 hr PO for otitis media Adults: 250-500 mg q 8-12 hr PO Uncomplicated gonorrhea: 3 g with 1 g probenecid PO	*Cautions:* Rash, diarrhea, abdominal cramping. Drug eliminated renally *Drug interaction:* Probenecid
Amoxicillin-clavulanate Augmentin Tablet: 250, 500, 875 mg Tablet, chewable: 125, 200, 250, 400 mg Suspension: 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL, 400 mg/5 mL	**β-Lactam (amoxicillin) combined with β-lactamase inhibitor (clavulanate) enhances amoxicillin activity against penicillinase-producing bacteria. *S. aureus* (not methicillin-resistant organism), *Streptococcus, Haemophilus influenzae, Moraxella catarrhalis, E. coli, Klebsiella, Bacteroides fragilis*** Neonates: 30 mg/kg/24 hr divided q 12 hr PO Children: 20-45 mg/kg 24 hr divided q 8-12 hr PO. Higher dose 80-90 mg/kg/24 hr PO for otitis media	*Cautions:* Drug dosed on amoxicillin component. May cause diarrhea, rash. Drug eliminated renally *Drug interaction:* Probenecid *Comment:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae*
Ampicillin Polycillin, Omnipen Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL Injection	**β-Lactam with same spectrum of antibacterial activity as amoxicillin** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 50 mg/kg/24 hr IV or IM q 12 hr (meningitis: 100 mg/kg/24 hr divided q 12 hr IV or IM); weight >2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr divided q 8 hr IV or IM). Postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV or IM q 12 hr (meningitis: 100 mg/kg/24 hr divided q 12 hr IV or IM); weight 1,200-2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr divided q 8 hr IV or IM); weight >2,000 g: 100 mg/kg/24 hr divided q 6 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6 hr IV or IM) Children: 100-200 mg/kg/24 hr divided q 6 hr IV or IM (meningitis: 200-400 mg/kg/24 hr divided q 4-6 hr IV or IM) Adults: 250-500 mg q 4-8 hr IV or IM	*Cautions:* Less bioavailable than amoxicillin, causing greater diarrhea *Drug interaction:* Probenecid
Ampicillin-sulbactam Unasyn Injection	**β-Lactam (ampicillin) and β-lactamase inhibitor (sulbactam) enhances ampicillin activity against penicillinase-producing bacteria: *S. aureus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis*** Children: 100-200 mg/kg/24 hr divided q 4-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max daily dose: 8 g)	*Cautions:* Drug dosed on ampicillin component. May cause diarrhea, rash. Drug eliminated renally *Note:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae* *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Azithromycin Zithromax Tablet: 250 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Azalide antibiotic with activity against *S. aureus*, *Streptococcus*, *H. influenzae*, *Mycoplasma*, *Legionella*, *Chlamydia trachomatis*** Children: 10 mg/kg PO on day 1 (max dose: 500 mg) followed by 5 mg/kg PO q 24 hr for 4 days Group A streptococcus pharyngitis: 12 mg/kg/24 hr PO (max dose: 500 mg) for 5 days. Adults: 500 mg PO day 1 followed by 250 mg for 4 days Uncomplicated *C. trachomatis* infection: single 1 g dose PO	*Note:* Very long half-life permitting once-daily dosing. No metabolic-based drug interactions (unlike erythromycin and clarithromycin), limited gastrointestinal distress. Shorter-course regimens (e.g., 1-3 days) under investigation. 3 day, therapy (10 mg/kg/24 hr × 3 days) and single-dose therapy (30 mg/kg): use with increasing frequency (not for streptococcus pharyngitis)
Aztreonam Azactam Injection	**β-Lactam (monobactam) antibiotic with activity against Gram-negative aerobic bacteria, *Enterobacteriaceae*, and *Pseudomonas aeruginosa*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 90 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age >7 days weight <1,200 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight 1,200-2,000 g: 90 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 120 mg/kg/24 hr divided q 6-8 hr IV or IM Children: 90-120 mg/kg/24 hr divided q 6-8 hr IV or IM. For cystic fibrosis up to 200 mg/kg/24 hr IV Adults: 1-2 g IV or IM q 8-12 hr (max dose: 8 g/24 hr)	*Cautions:* Rash, thrombophlebitis, eosinophilia. Renally eliminated *Drug interaction:* Probenecid
Carbenicillin Geopen Injection Geocillin oral tablet	**Extended-spectrum penicillin (remains susceptible to penicillinase destruction) active against *Enterobacter*, indole-positive *Proteus*, and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 225 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 300 mg/kg/24 hr divided q 6 hr IV or IM; >7 days: 300-400 mg/kg/24 hr divided q 6 hr IV or IM Children: 400-600 mg/kg/24 hr divided q 4-6 hr IV or IM	*Cautions:* Painful given intramuscularly; rash; each gram contains 5.3 mEq sodium. Interferes with platelet aggregation at high doses, increases in liver transaminase levels. Renally eliminated. Oral tablet for treatment of urinary tract infection only *Drug interaction:* Probenecid
Cefaclor Ceclor Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL, 375 mg/5 mL	**Second-generation cephalosporin active against *S. aureus*, *Streptococcus* including *S. pneumoniae*, *H. influenzae*, *E. coli*, *Klebsiella*, and *Proteus*** Children: 20-40 mg/kg/24 hr divided q 8-12 hr PO (max dose: 2 g) Adults: 250-500 mg q 6-8 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia) with high incidence of serum sickness reaction. Renally eliminated *Drug interaction:* Probenecid
Cefadroxil Duricef, Ultracef Capsule: 500 mg Tablet: 1,000 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL	**First-generation cephalosporin active against *S. aureus*, *Streptococcus*, *E. coli*, *Klebsiella*, and *Proteus*** Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g) Adults: 250-500 mg q 8-12 hr PO	*Cautions:* β-lactam safety profile (rash, eosinophilia). Renally eliminated. Long half-life permits q 12-24 hr dosing *Drug interaction:* Probenecid
Cefazolin Ancef, Kefzol Injection	**First-generation cephalosporin active against *S. aureus*, *Streptococcus*, *E. coli*, *Klebsiella*, and *Proteus*** Neonates: Postnatal age ≤7 days 40 mg/kg/24 hr divided q 12 hr IV or IM; >7 days 40-60 mg/kg/24 hr divided q 8 hr IV or IM Children: 50-100 mg/kg/24 hr divided q 8 hr IV or IM Adults: 0.5-2g q 8 hr IV or IM (max dose: 12 g/24 hr)	*Caution:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS *Drug interaction:* Probenecid
Cefdinir Omnicef Capsule: 300 mg Oral suspension: 125 mg/5 mL	**Extended-spectrum, semisynthetic cephalosporin** Children 6 mo-12 yr: 14 mg/kg/24 hr in 1 or 2 doses PO (max dose: 600 mg/24 hr) Adults: 600 mg q 24 hr PO	*Cautions:* Reduce dosage in renal insufficiency (creatinine clearance <60 mL/min). Avoid taking concurrently with iron-containing products and antacids because absorption is markedly decreased; take at least 2 hr apart *Drug interaction:* Probenecid
Cefepime Maxipime Injection	**Expanded-spectrum, fourth-generation cephalosporin active against many Gram-positive and Gram-negative pathogens, including *P. aeruginosa* many multidrug-resistant pathogens** Children: 100-150 mg/kg/24 hr q 8-12 hr IV or IM Adults: 2-4 g/24 hr q 12 hr IV or IM	*Adverse events:* Diarrhea, nausea, vaginal candidiasis Cautions: β-lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Cefixime Suprax Tablet: 200, 400 mg Suspension: 100 mg/5 mL	**Third-generation cephalosporin active against streptococci, *H. influenzae, M. catarrhalis, Neisseria gonorrhoeae, Serratia marcescens*, and *Proteus vulgaris*. No antistaphylococcal or antipseudomonal activity** Children: 8 mg/kg/24 hr divided q 12-24 hr PO Adults: 400 mg/24 hr divided q 12-24 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS *Drug interaction:* Probenecid
Cefoperazone sodium Cefobid Injection	**Third-generation cephalosporin active against many Gram-positive and Gram-negative pathogens** Neonates: 100 mg/kg/24 hr divided q 12 hr IV or IM Children: 100-150 mg/kg/24 hr divided q 8-12 hr IV or IM Adults: 2-4 g/24 hr divided q 8-12 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin with limited potency reflected by weak antipseudomonal activity. Variable Gram-positive activity. Primarily hepatically eliminated in bile *Drug interaction:* Disulfiram-like reaction with alcohol
Cefotaxime sodium Claforan Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Neonates: ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; >7 days: weight <1,200 g 100 mg/kg/24 hr divided q 12 hr IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6-8 hr IV) Adults: 1-2 g q 8-12 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Each gram of drug contains 2.2 mEq sodium. Active metabolite *Drug interaction:* Probenecid
Cefotetan disodium Cefotan Injection	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter*** Children: 40-80 mg/kg/24 hr divided IV or IM q 12 hr Adults: 2-4 g/24 hr divided q 12 hr IV or IM (max dose: 6 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin, poor CNS penetration; β-lactam safety profile (rash, eosinophilia), disulfiram-like reaction with alcohol. Renally eliminated (~20% in bile)
Cefoxitin sodium Mefoxin Injection	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter*** Neonates: 70-100 mg/kg/24 hr divided q 8-12 hr IV or IM Children: 80-160 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* Poor CNS penetration; β-lactam safety profile (rash, eosinophilia). Renally eliminated. Painful given intramuscularly *Drug interaction:* Probenecid
Cefpodoxime proxetil Vantin Tablet: 100 mg, 200 mg Suspension: 50 mg/5 mL, 100 mg/5 mL	**Third-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, N. gonorrhoeae, E. coli, Klebsiella*, and *Proteus*. No antipseudomonal activity** Children: 10 mg/kg/24 hr divided q 12 hr PO Adults: 200-800 mg/24 hr divided q 12 hr PO (max dose: 800 mg/24 hr) Uncomplicated gonorrhea: 200 mg PO as single-dose therapy	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability when taken with food *Drug interaction:* Probenecid; antacids and H-2 receptor antagonists may decrease absorption
Ceftaroline fosamil Teflaro Injection	**Fifth-generation cephalosporin active against *S. aureus* (including MRSA when used for skin and soft-tissue infection), *Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae, H. influenzae*, and *Klebsiella oxytoca*** *Children: 24 mg/kg/24 hr divided q 8 hr IV (<6 mo of age); 36 mg/kg/24 hr divided q 8 hr IV (weight ≤33 kg); 400 mg q 8 hr IV (weight >33 kg) Adults: 600 mg q 12 hr IV *Suggested dose; safety and effectiveness in pediatric patients have not yet been established	*Caution:* β-Lactam safety profile (rash, eosinophilia) *Drug interaction:* Probenecid
Cefprozil Cefzil Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella*, and *Proteus*** Children: 30 mg/kg/24 hr divided q 8-12 hr PO Adults: 500-1,000 mg/24 hr divided q 12 hr PO (max dose: 1.5 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Good bioavailability; food does not affect bioavailability *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Ceftazidime Fortaz, Ceptaz, Tazicef, Tazidime Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens, including *P. aeruginosa*** Neonates: Postnatal age ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; >7 days weight ≤1,200 g: 100 mg/kg/24 hr divided q 12 hr IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM Children: 150 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr IV divided q 8 hr) Adults: 1-2 g q 8-12 hr IV or IM (max dose: 8-12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use *Drug interaction:* Probenecid
Ceftizoxime Cefizox Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Ceftriaxone sodium Rocephin Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Neonates: 50-75 mg/kg q 24 hr IV or IM Children: 50-75 mg/kg q 24 hr IV or IM (meningitis: 75 mg/kg dose 1 then 80-100 mg/kg/24 hr divided q 12-24 hr IV or IM) Adults: 1-2 g q 24 hr IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Eliminated via kidney (33-65%) and bile; can cause sludging. Long half-life and dose-dependent protein binding favors q 24 hr rather than q 12 hr dosing. Can add 1% lidocaine for IM injection *Drug interaction:* Probenecid. In neonates, coadministration with calcium-containing products can result in severe precipitation and attendant embolic complications
Cefuroxime (cefuroxime axetil for oral administration) Ceftin, Kefurox, Zinacef Injection Suspension: 125 mg/5 mL Tablet: 125, 250, 500 mg	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella*, and *Proteus*** Neonates: 40-100 mg/kg/24 hr divided q 12 hr IV or IM Children: 200-240 mg/kg/24 hr divided q 8 hr IV or IM; PO administration: 20-30 mg/kg/24 hr divided q 8 hr PO Adults: 750-1,500 mg q 8 hr IV or IM (max dose: 6 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Food increases PO bioavailability *Drug interaction:* Probenecid
Cephalexin Keflex, Keftab Capsule: 250, 500 mg Tablet: 500 mg, 1 g Suspension: 125 mg/5 mL, 250 mg/5 mL, 100 mg/mL drops	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*** Children: 25-100 mg/kg/24 hr divided q 6-8 hr PO Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Cephradine Velosef Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*** Children: 50-100 mg/kg/24 hr divided q 6-12 hr PO Adults: 250-500 mg q 6-12 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Chloramphenicol Chloromycetin Injection Capsule: 250 mg Ophthalmic, otic solutions Ointment	**Broad-spectrum protein synthesis inhibitor active against many Gram-positive and Gram-negative bacteria, *Salmonella*, vancomycin-resistant *Enterococcus faecium, Bacteroides*, other anaerobes, *Mycoplasma, Chlamydia*, and *Rickettsia*; usually inactive against *Pseudomonas*** Neonates: Initial loading dose 20 mg/kg followed 12 hr later by: postnatal age ≤7 days: 25 mg/kg/24 hr q 24 hr IV; >7 days: weight ≤2,000 g: 25 mg/kg/24 hr q 24 hr IV; weight >2,000 g: 50 mg/kg/24 hr divided q 12 hr IV Children: 50-75 mg/kg/24 hr divided q 6-8 hr IV or PO (meningitis: 75-100 mg/kg/24 hr IV divided q 6 hr) Adults: 50 mg/kg/24 hr divided q 6 hr IV or PO (max dose: 4 g/24 hr)	*Cautions:* Gray-baby syndrome (from too-high dose in neonate), bone marrow suppression aplastic anemia (monitor hematocrit, free serum iron) *Drug interactions:* Phenytoin, phenobarbital, rifampin may decrease levels *Target serum concentrations:* Peak 20-30 mg/L; trough 5-10 mg/L

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Ciprofloxacin Cipro Tablet: 100, 250, 500, 750 mg Injection Ophthalmic solution and ointment Otic suspension Oral suspension: 250 and 500 mg/5 mL	**Quinolone antibiotic active against *P. aeruginosa, Serratia, Enterobacter, Shigella, Salmonella, Campylobacter, N. gonorrhoeae, H. influenzae, M. catarrhalis,* some *S. aureus*, and some *Streptococcus*** Neonates: 10 mg/kg q 12 hr PO or IV Children: 15-30 mg/kg/24 hr divided q 12 hr PO or IV; cystic fibrosis: 20-40 mg/kg/24 hr divided q 8-12 hr PO or IV Adults: 250-750 mg q 12 hr; 200-400 mg IV q 12 hr PO (max dose: 1.5 g/24 hr)	*Cautions:* Concerns of joint destruction in juvenile animals not seen in humans; tendonitis, superinfection, dizziness, confusion, crystalluria, some photosensitivity *Drug interactions:* Theophylline; magnesium-, aluminum-, or calcium-containing antacids; sucralfate; probenecid; warfarin; cyclosporine
Clarithromycin Biaxin Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Macrolide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Legionella, Mycoplasma,* and *C. trachomatis*** Children: 15 mg/kg/24 hr divided q 12 hr PO Adults: 250-500 mg q 12 hr PO (max dose: 1 g/24 hr)	*Cautions:* Adverse events less than erythromycin; gastrointestinal upset, dyspepsia, nausea, cramping *Drug interactions:* Same as erythromycin: astemizole carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus
Clindamycin Cleocin Capsule: 75, 150, 300 mg Suspension: 75 mg/5 mL Injection Topical solution, lotion, and gel Vaginal cream	**Protein synthesis inhibitor active against most Gram-positive aerobic and anaerobic cocci except *Enterococcus*** Neonates: Postnatal age ≤7 days weight <2,000 g; 10 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; >7 days weight <1,200 g: 10 mg/kg/24 hr IV or IM divided q 12 hr; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 20 mg/kg/24 hr divided q 8 hr IV or IM Children: 10-40 mg/kg/24 hr divided q 6-8 hr IV, IM, or PO Adults: 150-600 mg q 6-8 hr IV, IM, or PO (max dose: 5 g/24 hr IV or IM or 2 g/24 hr PO)	*Cautions:* Diarrhea, nausea, *Clostridium difficile*–associated colitis, rash Administer slow IV over 30-60 min Topically active as an acne treatment
Cloxacillin sodium Tegopen Capsule: 250, 500 mg Suspension: 125 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 50-100 mg/kg/24 hr divided q 6 hr PO Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily hepatically eliminated; requires dose reduction in renal disease. Food decreases bioavailability *Drug interaction:* Probenecid
Colistin (Colistimethate sodium; polymyxin E) Injection Inhalation	**Treatment of multidrug resistant Gram-negative organisms (*Enterobacteriaceae* including extended-spectrum betalactamase and carbapenemase-producing strains)** Children: 2.5-5 mg/kg/day divided in 2-4 divided doses IV Adults: 300 mg/day in 2-4 divided doses IV	*Cautions:* Nephrotoxicity (~3% in young children; higher rates in adolescents and adults); adjust dose for renal insufficiency; neurotoxicity (headaches, paresthesia, ataxia) *Drug interactions:* Should not be administered concomitantly with polymyxins or aminoglycosides
Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMZ) Bactrim, Cotrim, Septra, Sulfatrim Tablet: SMZ 400 mg and TMP 80 mg Tablet DS: SMZ 800 mg and TMP 160 mg Suspension: SMZ 200 mg and TMP 40 mg/5 mL Injection	**Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: *Shigella, Legionella, Nocardia, Chlamydia, Pneumocystis jiroveci*. Dosage based on TMP component** Children: 6-20 mg TMP/kg/24 hr or IV divided q 12 hr PO *Pneumocystis carinii* pneumonia: 15-20 mg TMP/kg/24 hr divided q 12 hr PO or IV *P. carinii* prophylaxis: 5 mg TMP/kg/24 hr or 3 times/wk PO Adults: 160 mg TMP q 12 hr PO	*Cautions:* Drug dosed on TMP (trimethoprim) component. Sulfonamide skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure *Drug interactions:* Protein displacement with warfarin, possibly phenytoin, cyclosporine

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Daptomycin Cubicin	**Disrupts bacterial cell membrane function, causing depolarization leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. Active against enterococci (including glycopeptide-resistant strains), staphylococci (including MRSA), streptococci, and corynebacteria. Approved for skin and soft-tissue infections. Acceptable for bacteremia and right-sided endocarditis with susceptible strains** Adults: In skin and soft-tissue infections, 4 mg/kg daptomycin is given intravenously once daily. For *S. aureus* bacteremia or right-sided endocarditis, the approved dose is 6 mg/kg given intravenously once daily Children: Unknown. Doses of 5-9 mg/kg/day in once-daily dosing have been reported in pediatric clinical trials	*Cautions:* Should not be used for pneumonia as drug inactivated by surfactants. Associated with rash, renal failure, anemia, headache. Is reported to cause myopathy, rhabdomyolysis, and eosinophilic pneumonia *Drug interactions:* Should not be administered with statins
Demeclocycline Declomycin Tablet: 150, 300 mg Capsule: 150 mg	**Tetracycline active against most Gram-positive cocci except *Enterococcus*, many Gram-negative bacilli, anaerobes, *Borrelia burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 8-12 mg/kg/24 hr divided q 6-12 hr PO Adults: 150 mg PO q 6-8 hr Syndrome of inappropriate antidiuretic hormone secretion: 900-1,200 mg/24 hr or 13-15 mg/kg/24 hr divided q 6-8 hr PO with dose reduction based on response to 600-900 mg/24 hr	*Cautions:* Teeth staining, possibly permanent (if administered <8 yr of age) with prolonged use; photosensitivity, diabetes insipidus, nausea, vomiting, diarrhea, superinfections *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc- and iron-containing food, milk, dairy products may decrease absorption
Dicloxacillin Dynapen, Pathocil Capsule: 125, 250, 500 mg Suspension: 62.5 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 12.5-100 mg/kg/24 hr divided q 6 hr PO Adults: 125-500 mg q 6 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily renally (65%) and bile (30%) elimination. Food may decrease bioavailability *Drug interaction:* Probenecid
Doripenem Doribax Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes** Children: dose unknown. Adults: 500 mg q 8 hr IV	*Cautions:* β-Lactam safety profile; does not undergo hepatic metabolism. Renal elimination (70-75%); dose adjustment for renal failure *Drug interactions:* Valproic acid, probenecid
Doxycycline Vibramycin, Doxy Injection Capsule: 50, 100 mg Tablet: 50, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL	**Tetracycline antibiotic active against most Gram-positive cocci except *Enterococcus*, many Gram-negative bacilli, anaerobes, *B. burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 2-5 mg/kg/24 hr divided q 12-24 hr PO or IV (max dose: 200 mg/24 hr) Adults: 100-200 mg/24 hr divided q 12-24 hr PO or IV	*Cautions:* Teeth staining, possibly permanent (<8 yr of age) with prolonged use; photosensitivity, nausea, vomiting, diarrhea, superinfections *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc-, iron-, kaolin-, and pectin-containing products, food, milk, dairy products may decrease absorption. Carbamazepine, rifampin, barbiturates may decrease half-life
Erythromycin E-Mycin, Ery-Tab, Eryc, Ilosone Estolate 125, 500 mg Tablet EES: 200 mg Tablet base: 250, 333, 500 mg Suspension: estolate 125 mg/5 mL, 250 mg/5 mL, EES 200 mg/5 mL, 400 mg/5 mL Estolate drops: 100 mg/mL. EES drops: 100 mg/2.5 mL. Available in combination with sulfisoxazole (Pediazole), dosed on erythromycin content	**Bacteriostatic macrolide antibiotic most active against Gram-positive organisms, *Corynebacterium diphtheriae*, and *Mycoplasma pneumoniae*** Neonates: Postnatal age ≤7 days: 20 mg/kg/24 hr divided q 12 hr PO; >7 days weight <1,200 g: 20 mg/kg/24 hr divided q 12 hr PO; weight >1,200 g: 30 mg/kg/24 hr divided q 8 hr PO (give as 5 mg/kg/dose q 6 hr to improve feeding intolerance) Children: Usual max dose 2 g/24 hr Base: 30-50 mg/kg/24 hr divided q 6-8 hr PO Estolate: 30-50 mg/kg/24 hr divided q 8-12 hr PO Stearate: 20-40 mg/kg/24 hr divided q 6 hr PO Lactobionate: 20-40 mg/kg/24 hr divided q 6-8 hr IV Gluceptate: 20-50 mg/kg/24 hr divided q 6 hr IV; usual max dose 4 g/24 hr IV Adults: Base: 333 mg PO q 8 hr; estolate/stearate/base: 250-500 mg q 6 hr PO	*Cautions:* Motilin agonist leading to marked abdominal cramping, nausea, vomiting, diarrhea. Associated with hypertrophic pyloric stenosis in young infants. Many different salts with questionable tempering of gastrointestinal adverse events. Rare cardiac toxicity with IV use. Dose of salts differ. Topical formulation for treatment of acne *Drug interactions:* Antagonizes hepatic CYP 3A4 activity: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus, carbamazepine

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Gentamicin Garamycin Injection Ophthalmic solution, ointment, topical cream	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *E. coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 2.5 mg/kg q 12-18 hr IV or IM; weight <2,000 g: 2.5 mg/kg q 12 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 8 hr IV or IM Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV once daily Intrathecal: Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr intrathecal; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM	Cautions: Anaerobes, *S. pneumoniae,* and other *Streptococcus* are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 6-12 mg/L; trough >2 mg/L with intermittent daily dose regimens only
Imipenem-cilastatin Primaxin Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *Stenotrophomonas maltophilia*** Neonates: Postnatal age ≤7 days weight <1,200 g: 20 mg/kg q 18-24 hr IV or IM; weight >1,200 g: 40 mg/kg divided q 12 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 40 mg/kg q 12 hr IV or IM; weight >2,000 g: 60 mg/kg q 8 hr IV or IM Children: 60-100 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 2-4 g/24 hr divided q 6-8 hr IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated *Drug interaction:* Possibly ganciclovir
Linezolid Zyvox Tablet: 400, 600 mg Oral suspension: 100 mg/5 mL Injection: 100 mg/5 mL	**Oxazolidinone antibiotic active against Gram-positive cocci (especially drug-resistant organisms), including *Staphylococcus, Streptococcus, E. faecium,* and *Enterococcus faecalis*. Interferes with protein synthesis by binding to 50S ribosome subunit** Children: 10 mg/kg q 12 hr IV or PO Adults: Pneumonia: 600 mg q 12 hr IV or PO; skin infections: 400 mg q 12 hr IV or PO	*Adverse events:* Myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache *Drug interaction:* Probenecid
Loracarbef Lorabid Capsule: 200 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Carbacephem very closely related to cefaclor (second-generation cephalosporin) active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, E. coli, Klebsiella,* and *Proteus*** Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g) Adults: 200-400 mg q 12 hr PO (max dose: 800 mg/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Meropenem Merrem Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *S. maltophilia*** Children: 60 mg/kg/24 hr divided q 8 hr IV meningitis: 120 mg/kg/24 hr (max dose: 6 g/24 hr) q 8 hr IV Adults: 1.5-3 g q 8 hr IV	*Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem. 80% renal elimination *Drug interaction:* Probenecid
Metronidazole Flagyl, Metro I.V., Topical gel, vaginal gel Injection Tablet: 250, 500 mg	**Highly effective in the treatment of infections caused by anaerobes. Oral therapy of *C. difficile* colitis** Neonates: weight <1,200 g: 7.5 mg/kg 48 hr PO or IV; postnatal age ≤7 days weight 1,200-2,000 g: 7.5 mg/kg/24 hr q 24 hr PO or IV; weight 2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; postnatal age <7 days weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; weight >2,000 g: 30 mg/kg/24 hr divided q 12 hr PO or IV Children: 30 mg/kg/24 hr divided q 6-8 hr PO or IV Adults: 30 mg/kg/24 hr divided q 6 hr PO or IV (max dose: 4 g/24 hr)	*Cautions:* Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. Administer IV slow over 30-60 min. Adjust dose with hepatic impairment *Drug interactions:* Carbamazepine, rifampin, phenobarbital may enhance metabolism; may increase levels of warfarin, phenytoin, lithium

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Mezlocillin sodium Mezlin Infection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia*, and *Bacteroides;* limited antipseudomonal activity** Neonates: Postnatal age ≤7 days: 150 mg/kg/24 hr divided q 12 hr IV; >7 days: 225 mg/kg divided q 8 hr IV Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis 300-450 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.8 mEq sodium. Interferes with platelet aggregation with high doses; increases noted in liver function test results. Renally eliminated. Inactivated by β-lactamase enzyme *Drug interaction:* Probenecid
Mupirocin Bactroban Ointment	**Topical antibiotic active against *Staphylococcus* and *Streptococcus*** Topical application: Nasal (eliminate nasal carriage) and to the skin 2-4 times per day	*Caution:* Minimal systemic absorption as drug metabolized within the skin.
Nafcillin sodium Nafcil, Unipen Injection Capsule: 250 mg Tablet: 500 mg	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 75 mg/kg/q 8 hr; weight >2,000 g: 100 mg/kg divided q 6-8 hr IV (meningitis: 200 mg/kg/24 hr divided q 6 hr IV) Children: 100-200 mg/kg/24 hr divided q 4-6 hr IV Adults: 4-12 g/24 hr divided q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), phlebitis; painful given intramuscularly; oral absorption highly variable and erratic (not recommended) *Adverse effect:* Neutropenia
Nalidixic acid NegGram Tablet: 250, 500, 1,000 mg Suspension: 250 mg/5 mL	**First-generation quinolone effective for short-term treatment of lower urinary tract infections caused by *E. coli, Enterobacter, Klebsiella*, and *Proteus*** Children: 50-55 mg/kg/24 hr divided q 6 hr PO; suppressive therapy 25-33 mg/kg/24 hr divided q 6-8 hr PO Adults: 1 g q 6 hr PO; suppressive therapy: 500 mg q 6 hr PO	*Cautions:* Vertigo, dizziness, rash. Not for use in systemic infections *Drug interactions:* Liquid antacids
Neomycin sulfate Mycifradin Tablet: 500 mg Topical cream, ointment Solution: 125 mg/5 mL	**Aminoglycoside antibiotic used for topical application or orally before surgery to decrease gastrointestinal flora (nonabsorbable) and hyperammonemia** Infants: 50 mg/kg/24 hr divided q 6 hr PO Children: 50-100 mg/kg/24 hr divided q 6-8 hr PO Adults: 500-2,000 mg/dose q 6-8 hr PO	*Cautions:* In patients with renal dysfunction because small amount absorbed may accumulate *Adverse events:* Primarily related to topical application, abdominal cramps, diarrhea, rash Aminoglycoside ototoxicity and nephrotoxicity if absorbed
Nitrofurantoin Furadantin, Furan, Macrodantin Capsule: 50, 100 mg Extended-release capsule: 100 mg Macrocrystal: 50, 100 mg Suspension: 25 mg/5 mL	**Effective in the treatment of lower urinary tract infections caused by Gram-positive and Gram-negative pathogens** Children: 5-7 mg/kg/24 hr divided q 6 hr PO (max dose: 400 mg/24 hr); suppressive therapy 1-2.5 mg/kg/24 hr divided q 12-24 hr PO (max dose: 100 mg/24 hr) Adults: 50-100 mg/24 hr divided q 6 hr PO	*Cautions:* Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use with moderate to severe renal dysfunction *Drug interactions:* Liquid antacids
Ofloxacin Ocuflox 0.3% ophthalmic solution: 1, 5, 10 mL Floxin 0.3% otic solution: 5, 10 mL	**Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution) and otitis externa or chronic suppurative otitis media (otic solution) caused by susceptible Gram-positive, Gram-negative, anaerobic bacteria, or *C. trachomatis*** *Child >1-12 yr:* Conjunctivitis: 1-2 drops in affected eye(s) q 2-4 hr for 2 days, then 1-2 drops qid for 5 days Corneal ulcers: 1-2 drops q 30 min while awake and at 4 hr intervals at night for 2 days, then 1-2 drops hourly for 5 days while awake, then 1-2 drops q 6 hr for 2 days Otitis externa (otic solution): 5 drops into affected ear bid for 10 days Chronic suppurative otitis media: treat for 14 days *Child >12 yr and adults:* Ophthalmic solution doses same as for younger children. Otitis externa (otic solution): Use 10 drops bid for 10 or 14 days as for younger children	*Adverse events:* Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Oxacillin sodium Prostaphlin Injection Capsule: 250, 500 mg Suspension: 250 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV; weight >2,000 g: 75 mg/kg/24 hr IV divided q 8 hr IV; postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV divided q 12 hr IV; weight 1,200-2,000 g: 75 mg/kg/24 hr divided q 8 hr IV; weight >2,000 g: 100 mg/kg/24 hr IV divided q 6 hr IV Infants: 100-200 mg/kg/24 hr divided q 4-6 hr IV Children: PO 50-100 mg/kg/24 hr divided q 4-6 hr IV Adults: 2-12 g/24 hr divided q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia) Moderate oral bioavailability (35-65%) Primarily renally eliminated *Drug interaction:* Probenecid *Adverse effect:* Neutropenia
Penicillin G Injection Tablets	**Penicillin active against most Gram-positive cocci; *S. pneumoniae* (resistance is increasing), group A *Streptococcus*, and some Gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50,000 units/kg/24 hr divided q 12 hr IV or IM (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV or IM); weight >2,000 g: 75,000 units/kg/24 hr divided q 8 hr IV or IM (meningitis: 150,000 units/kg/24 hr divided q 8 hr IV or IM); postnatal age >7 days weight ≤1,200 g: 50,000 units/kg/24 hr divided q 12 hr IV (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV); weight 1,200-2,000 g: 75,000 units/kg/24 hr q 8 hr IV (meningitis: 225,000 units/kg/24 hr divided q 8 hr IV); weight >2,000 g: 100,000 units/kg/24 hr divided q 6 hr IV (meningitis: 200,000 units/kg/24 hr divided q 6 hr IV) Children: 100,000-250,000 units/kg/24 hr divided q 4-6 hr IV or IM (max dose: 400,000 units/kg/24 hr) Adults: 2-24 million units/24 hr divided q 4-6 hr IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, benzathine Bicillin Injection	**Long-acting repository form of penicillin effective in the treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk), e.g., group A *Streptococcus* pharyngitis, rheumatic fever prophylaxis** Neonates weight >1,200 g: 50,000 units/kg IM once Children: 300,000-1.2 million units/kg q 3-4 wk IM (max dose: 1.2-2.4 million units/dose) Adults: 1.2 million units IM q 3-4 wk	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, procaine Crysticillin Injection	**Repository form of penicillin providing low penicillin concentrations for 12 hr** Neonates weight >1,200 g: 50,000 units/kg/24 hr IM Children: 25,000-50,000 units/kg/24 hr IM for 10 days (max dose: 4.8 million units/dose) Gonorrhea: 100,000 units/kg (max dose: 4.8 million units/24 hr) IM once with probenecid 25 mg/kg (max dose: 1 g) Adults: 0.6-4.8 million units q 12-24 hr IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia) allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin V Pen VK, V-Cillin K Tablet: 125, 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Preferred oral dosing form of penicillin, active against most Gram-positive cocci; *S. pneumoniae* (resistance is increasing), other streptococci, and some Gram-negative bacteria (e.g., N. *gonorrhoeae, N. meningitidis*)** Children: 25-50 mg/kg/24 hr divided q 4-8 hr PO Adults: 125-500 mg q 6-8 hr PO (max dose: 3 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with renal disease. Substantial pathogen resistance. Primarily renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid
Piperacillin Pipracil Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa*, and *Bacteroides*** Neonates: Postnatal age ≤7 days 150 mg/kg/24 hr divided q 8-12 hr IV; >7 days; 200 mg/kg divided q 6-8 hr IV Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 350-500 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr (max dose: 24 g/24 hr) IV	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation/serum sickness-like reaction with high doses; increases in liver function tests. Renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Piperacillin-tazobactam Zosyn Injection	**Extended-spectrum penicillin (piperacillin) combined with a β-lactamase inhibitor (tazobactam) active against *S. aureus, H. influenzae, E. coli, Enterobacter, Serratia, Acinetobacter, P. aeruginosa,* and *Bacteroides*** Children: 300-400 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 3.375 g q 6-8 hr IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium Interferes with platelet aggregation, serum sickness–like reaction with high doses, increases in liver function test results. Renally eliminated *Drug interaction:* Probenecid
Quinupristin/dalfopristin Synercid IV injection: powder for reconstitution, 10 mL contains 150 mg quinupristin, 350 mg dalfopristin	**Streptogramin antibiotic (quinupristin) active against vancomycin-resistant *E. faecium* (VRE) and methicillin-resistant *S. aureus* (MRSA). Not active against *E. faecalis*** Children and adults: VRE: 7.5 mg/kg q 8 hr IV for VRE; skin infections: 7.5 mg/kg q 12 hr IV	*Adverse events:* Pain, edema, or phlebitis at injection site, nausea, diarrhea *Drug interactions*: Synercid is a potent inhibitor of CYP 3A4
Sulfadiazine Tablet: 500 mg	**Sulfonamide antibiotic primarily indicated for the treatment of lower urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella*** Toxoplasmosis: Neonates: 100 mg/kg/24 hr divided q 12 hr PO with pyrimethamine 1 mg/kg/24 hr PO (with folinic acid) Children: 120-200 mg/kg/24 hr divided q 6 hr PO with pyrimethamine 2 mg/kg/24 hr divided q 12 hr PO ≥3 days then 1 mg/kg/24 hr (max dose: 25 mg/24 hr) with folinic acid Rheumatic fever prophylaxis: weight ≤30 kg: 500 mg/24 hr q 24 hr PO; weight >30 kg: 1 g/24 hr q 24 hr PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~10 hr *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Sulfamethoxazole Gantanol Tablet: 500 mg Suspension: 500 mg/5 mL	**Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections due to susceptible bacteria** Children: 50-60 mg/kg/24 hr divided q 12 hr PO Adults: 1 g/dose q 12 hr PO (max dose: 3 g/24 hr)	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life 12 hr. Initial dose often a loading dose (doubled) *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Sulfisoxazole Gantrisin Tablet: 500 mg Suspension: 500 mg/5 mL Ophthalmic solution, ointment	**Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections caused by susceptible bacteria** Children: 120-150 mg/kg/24 hr divided q 4-6 hr PO (max dose: 6 g/24 hr) Adults: 4-8 g/24 hr divided q 4-6 hr PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~7-12 hr. Initial dose often a loading dose (doubled) *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Ticarcillin Ticar Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*** Neonates: Postnatal age ≤7 days weight <2,000 g: 150 mg/kg/24 hr divided q 8-12 hr IV; >7 days weight <2,000 g: 225 mg/kg/24 hr divided q 8 hr IV; >7 days weight <1,200 g: 150 mg/kg/24 hr divided q 12 hr IV; weight 1,200-2,000 g: 225 mg/kg/24 hr divided q 8 hr IV; weight >2,000 g: 300 mg/kg/24 hr divided q 6-8 hr IV Children: 200-400 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 400-600 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr IV (max dose: 24 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 5-6 mEq sodium. Interferes with platelet aggregation; increases in liver function tests. Renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid
Ticarcillin-clavulanate Timentin Injection	**Extended-spectrum penicillin (ticarcillin) combined with a β-lactamase inhibitor (clavulanate) active against *S. aureus, H. influenzae, Enterobacter, E. coli, Serratia, P. aeruginosa, Acinetobacter,* and *Bacteroides*** Children: 280-400 mg/kg/24 hr q 4-8 hr IV or IM Adults: 3.1 g q 4-8 hr IV or IM (max dose: 18-24 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 5-6 mEq sodium. Interferes with platelet aggregation; increases in liver function tests. Renally eliminated *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Tigecycline Tygacil Injection	**Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and anaerobes** Children: unknown Adults: 100 mg loading dose followed by 50 mg q 12 hr IV	*Cautions:* Pregnancy; children <8 yr of age; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance) *Drug interaction:* Warfarin; mycophenolate mofetil
Tobramycin Nebcin, Tobrex Injection Ophthalmic solution, ointment	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *E. coli, Klebsiella, Enterobacter, Serratia, Proteus,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 2.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 12 hr IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 8 hr IV or IM Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV. Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM	*Cautions: S. pneumoniae,* other *Streptococcus,* and anaerobes are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 6-12 mg/L; trough <2 mg/L
Trimethoprim Proloprim, Trimpex Tablet: 100, 200 mg	**Folic acid antagonist effective in the prophylaxis and treatment of *E. coli, Klebsiella, P. mirabilis,* and *Enterobacter* urinary tract infections; *P. carinii* pneumonia** Children: For urinary tract infection: 4-6 mg/kg/24 hr divided q 12 hr PO Children >12 yr and adults: 100-200 mg q 12 hr PO. *P. carinii* pneumonia (with dapsone): 15-20 mg/kg/24 hr divided q 6 hr for 21 days PO	*Cautions:* Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash *Drug interactions:* Possible interactions with phenytoin, cyclosporine, rifampin, warfarin
Vancomycin Vancocin, Lyphocin Injection Capsule: 125 mg, 250 mg Suspension	**Glycopeptide antibiotic active against most Gram-positive pathogens including staphylococci (including MRSA and coagulase-negative staphylococci), *S. pneumoniae* including penicillin-resistant strains, *Enterococcus* (resistance is increasing), and *C. difficile*–associated colitis** Neonates: Postnatal age ≤7 days, weight <1,200 g: 15 mg/kg/24 hr divided q 24 hr IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 12-18 hr IV; weight >2,000 g: 30 mg/kg/24 hr divided q 12 hr IV; postnatal age >7 days, weight <1,200 g: 15 mg/kg/24 hr divided q 24 hr IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8-12 hr IV; weight >2,000 g: 45 mg/kg/24 hr divided q 8 hr IV Children: 45-60 mg/kg/24 hr divided q 8-12 hr IV; *C. difficile*–associated colitis; 40-50 mg/kg/24 hr divided q 6-8 hr PO.40-50 mg/kg/24 hr divided q 6-8 hr PO	*Cautions:* Ototoxicity and nephrotoxicity particularly when co-administered with other ototoxic and nephrotoxic drugs Infuse IV over 45-60 min. Flushing (red man syndrome) associated with rapid IV infusions, fever, chills, phlebitis (central line is preferred). Renally eliminated *Target serum concentrations:* Peak (1 hr after 1 hr infusion) 30-40 mg/L; trough 5-10 mg/L

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-4 Adverse Reactions to Penicillins*

TYPE OF REACTION	FREQUENCY (%)	OCCURS MOST FREQUENTLY WITH*
ALLERGIC		
Immunoglobulin E antibody	0.004-0.4	Penicillin G
• Anaphylaxis		
• Early urticaria (<72 hr)		
Cytotoxic antibody	Rare	Penicillin G
• Hemolytic anemia		
Antigen–antibody complex disease	Rare	Penicillin G
• Serum sickness		
Delayed hypersensitivity	4-8	Ampicillin
• Contact dermatitis		
IDIOPATHIC	4-8	Ampicillin
Skin rash		
Fever		
Late-onset urticaria		
GASTROINTESTINAL	2-5	
Diarrhea	2-5	Ampicillin
Enterocolitis	<1	Ampicillin
HEMATOLOGIC		
Hemolytic anemia	Rare	Penicillin G
Neutropenia	1-4	Penicillin G, nafcillin, oxacillin, piperacillin
Platelet dysfunction	3	Ticarcillin
HEPATIC		
Elevated serum aspartate transaminase level	1-4	Flucloxacillin, nafcillin, oxacillin
ELECTROLYTE DISTURBANCE		
Sodium overload	Variable	Ticarcillin
Hypokalemia	Variable	Ticarcillin
Hyperkalemia—acute	Rare	Penicillin G
NEUROLOGIC		
Seizures	Rare	Penicillin G
Bizarre sensations		Procaine penicillin
RENAL		
Interstitial nephritis	<1%	Any penicillin

*All the reactions can occur with any of the penicillins.

Table 180-6 Potential Adverse Effects of Cephalosporins

TYPE	SPECIFIC	FREQUENCY
Hypersensitivity	Rash	1-3%
	Urticaria	<1%
	Serum sickness	<1%
	Anaphylaxis	0.01%
Gastrointestinal	Diarrhea	1-19%
	Nausea, vomiting	1-6%
	Transient transaminase elevation	1-7%
	Biliary sludge	20-46%*
Hematologic	Eosinophilia	1-10%
	Neutropenia	<1%
	Thrombocytopenia	<1-3%
	Hypoprothrombinemia	<1%
	Impaired platelet aggregation	<1%
	Hemolytic anemia	<1%
Renal	Interstitial nephritis	<1%
Central nervous system	Seizures	<1%
	Encephalopathy	<1%
False-positive laboratory	Coombs positive	3%
	Glucosuria	Rare
	Serum creatinine	Rare
Other	Drug fever	Rare
	Disulfiram-like reaction*	Rare
	Superinfection	Rare
	Phlebitis	Rare
	Calcium-antibiotic precipitation (ceftriaxone)	Unknown; is associated with embolic events

*Cephalosporins with thiomethyl tetrazole ring (MTT) side chain.

Table 180-5 Classification of Parenteral and Oral Cephalosporins

CEPHALOSPORINS	FIRST GENERATION	SECOND GENERATION	CEPHAMYCINS	THIRD GENERATION	FOURTH GENERATION	FIFTH GENERATION
Parenteral	Cefazolin (Ancef, Kefzol) Cephalothin (Keflin, Seffin) Cephapirin (Cefadyl) Cephradine (Velosef)	Cefamandole (Mandol) Cefonicid (Monocid) Cefuroxime (Kefurox, Zinacef)	Cefmetazole (Zefazone) Cefotetan (Cefotan) Cefoxitin (Mefoxin)	Cefoperazone (Cefobid) Cefotaxime (Claforan) Ceftazidime (Fortaz) Ceftizoxime (Cefizox) Ceftriaxone (Rocephin)	Cefepime (Maxipime) Cefpirome (Cefrom) Ceftolozane (combined with tazobactam; CXA-101)	Ceftaroline (Teflaro) Ceftobiprole (Zeftera)
Oral	Cefadroxil (Duricef, Ultracef) Cephalexin (Keflex, Biocef, Keftab) Cephradine (Velosef)	Cefaclor (Ceclor) Cefprozil (Cefzil) Cefuroxime-axetil (Ceftin) Loracarbef (Lorabid)		Cefdinir (Omnicef) Cefditoren (Spectracef) Cefixime (Suprax) Cefpodoxime (Vantin) Ceftibuten (Cedax)		

Adapted from Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Elsevier, Table 22-1.*

Table 181-1 Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus* Infections

SUSCEPTIBILITY	ANTIMICROBIAL AGENTS	COMMENTS
I. INITIAL EMPIRIC THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)		
Drugs of choice:	Vancomycin (15 mg/kg Q6-H + nafcillin or oxacillin)	For life-threatening infections (i.e., septicemia, endocarditis, CNS infection); linezolid could be substituted if the patient has received several recent courses of vancomycin
	Vancomycin (15 mg/kg Q8H)	For non–life-threatening infection without signs of severe sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and infection in the community are substantial
	Clindamycin	For non–life-threatening infection without signs of severe sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is low
II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT *S. AUREUS*		
Drugs of choice:	Nafcillin or oxacillin[†]	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
Alternatives (depending on susceptibility results):	Cefazolin	
	Clindamycin	
	Vancomycin	Only for penicillin- and cephalosporin-allergic patients
	Ampicillin + sulbactam	
III. MRSA (OXACILLIN MIC, 4 µG/ML OR GREATER)		
A. Healthcare-Associated (Multidrug-Resistant)		
Drugs of choice:	Vancomycin + gentamicin[†]	
Alternatives: susceptibility testing results available before alternative drugs are used	Trimethoprim-sulfamethoxazole	
	Linezolid[‡]	
	Quinupristin-dalfopristin[‡]	
	Fluoroquinolones	Not recommended for people younger than 18 yr of age or as monotherapy
B. Community (Not Multidrug-Resistant)		
Drugs of choice:	Vancomycin + gentamicin[†]	For life-threatening infections
	Clindamycin (if strain susceptible)	For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections
	Trimethoprim-sulfamethoxazole	For skin or soft tissue infections
Alternatives:	Vancomycin	
IV. VANCOMYCIN INTERMEDIATELY SUSCEPTIBLE OR *S. AUREUS*[†] (MIC, 4 TO 16 µG/ML)[‡]		
Drugs of choice:	Optimal therapy is not known	Dependent on in vitro susceptibility test results
	Linezolid[‡]	
	Daptomycin[§]	
	Quinupristin-dalfopristin[‡]	
	Tigecycline[‡]	
Alternatives:	Vancomycin + linezolid ± gentamicin	
	Vancomycin + trimethoprim-sulfamethoxazole[†]	

[†]One of the adjunctive agents, gentamicin or rifampin, should be added to the therapeutic regimen for life-threatening infections such as endocarditis or CNS infection or infections with a vancomycin-intermediate *S. aureus* strain. Consultation with an infectious diseases specialist should be considered to determine which agent to use and duration of use.

[‡]Linezolid, quinupristin-dalfopristin, and tigecycline are agents with activity in vitro and efficacy in adults with multidrug-resistant, Gram-positive organisms, including *S. aureus*. Because experience with these agents in children is limited, consultation with an infectious diseases specialist should be considered before use.

[§]Daptomycin is active in vitro against multidrug-resistant, Gram-positive organisms, including *S. aureus*, but has not been evaluated in children. Daptomycin is approved by the US FDA only for the treatment of complicated skin and skin structure infections and for *S. aureus* bloodstream infections. Daptomycin is ineffective for treatment of pneumonia and is not indicated for patients 18 yr of age and older.

CNS, central nervous system; MRSA, methicillin-resistant *S. aureus*; MIC, minimum inhibitory concentration.

From Pickering LK, editor: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Table 182-5 Medical Conditions or Other Indications for Administration of PCV13,* and Indications for PPSV23† Administration, and Revaccination for Children Age 6–18 Years‡

RISK GROUP	UNDERLYING MEDICAL CONDITION	PCV13 RECOMMENDED	PPSV23 RECOMMENDED	REVACCINATION 5 YR AFTER 1ST DOSE
Immunocompetent persons	Chronic heart disease§		✓	
	Chronic lung disease‖		✓	
	Diabetes mellitus		✓	
	Cerebrospinal fluid leaks	✓	✓	
	Cochlear implants	✓	✓	
	Alcoholism		✓	
	Chronic liver disease		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓

Table 182-3 Recommended Routine Vaccination Schedule for 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Among Infants and Children Who Have Not Received Previous Doses of 7-Valent Vaccine (PCV7) or PCV13, by Age at First Dose—Advisory Committee on Immunization Practices (ACIP), United States, 2010

AGE AT 1ST DOSE (MO)	PRIMARY PCV13 SERIES*	PCV13 BOOSTER DOSE†
2-6	3 doses	1 dose at age 12-15 mo
7-11	2 doses	1 dose at age 12-15 mo
12-23	2 doses	—
24-59 (healthy children)	1 dose	—
24-71 (children with certain chronic diseases or immunocompromising conditions)	2 doses	—

*Minimum interval between doses is 8 wk except for children vaccinated at age <12 mo for whom minimum interval between doses is 4 wk. Minimum age for administration of 1st dose is 6 wk.

†Given at least 8 wk after the previous dose.

From Centers for Disease Control and Prevention (CDC): Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010, MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 2.*

Table 182-4 Recommended Transition Schedule from 7-Valent Pneumococcal Conjugate Vaccine (PCV7) to 13-Valent Vaccine (PCV13) Vaccination Among Infants and Children, According to Number of Previous PCV7 Doses Received—Advisory Committee on Immunization Practices (ACIP), United States, 2010

INFANT SERIES			BOOSTER DOSE	SUPPLEMENTAL PCV13 DOSE
2 mo	4 mo	6 mo	≥12 mo*	14-59 mo†
PCV7	PCV13	PCV13	PCV13	—
PCV7	PCV7	PCV13	PCV13	—
PCV7	PCV7	PCV7	PCV13	—
PCV7	PCV7	PCV7	PCV7	PCV13

*No additional PCV13 doses are indicated for children age 12-23 mo who have received 2 or 3 doses of PCV before age 12 mo and at least 1 dose of PCV13 at age ≥12 mo.

†For children with underlying medical conditions (see Table 182-1), a single supplemental PCV13 dose is recommended through age 71 mo.

From Centers for Disease Control and Prevention (CDC): Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010, MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 3.*

Table 183-1 Definition of Streptococcal Toxic Shock Syndrome

CLINICAL CRITERIA
Hypotension plus 2 or more of the following:
- Renal impairment
- Coagulopathy
- Hepatic involvement
- Adult respiratory distress syndrome
- Generalized erythematous macular rash
- Soft-tissue necrosis

DEFINITE CASE
Clinical criteria plus group A streptococcus from a normally sterile site

PROBABLE CASE
Clinical criteria plus group A streptococcus from a nonsterile site

Table 181-2 Diagnostic Criteria of Staphylococcal Toxic Shock Syndrome

MAJOR CRITERIA (ALL REQUIRED)
Acute fever; temperature >38.8°C (101.8°F)
Hypotension (orthostatic, shock; blood pressure below age-appropriate norms)
Rash (erythroderma with convalescent desquamation)

MINOR CRITERIA (ANY 3 OR MORE)
Mucous membrane inflammation (vaginal, oropharyngeal or conjunctival hyperemia, strawberry tongue)
Vomiting, diarrhea
Liver abnormalities (bilirubin or transaminase greater than twice upper limit of normal)
Renal abnormalities (urea nitrogen or creatinine greater than twice upper limit of normal, or greater than 5 white blood cells per high-power field)
Muscle abnormalities (myalgia or creatinine phosphokinase greater than twice upper limit of normal)
Central nervous system abnormalities (alteration in consciousness without focal neurologic signs)
Thrombocytopenia (100,000/mm^3 or less)

EXCLUSIONARY CRITERIA
Absence of another explanation
Negative blood cultures (except occasionally for *Staphylococcus aureus*)

Data from Pickering LK, editor: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Table 183-2 Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)[1-5]

MAJOR MANIFESTATIONS	MINOR MANIFESTATIONS	SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION
Carditis Polyarthritis Erythema marginatum Subcutaneous nodules Chorea	**Clinical features:** Arthralgia Fever **Laboratory features:** Elevated acute phase reactants: Erythrocyte sedimentation rate C-reactive protein	Positive throat culture or rapid streptococcal antigen test Elevated or increasing streptococcal antibody titer
	Prolonged P-R interval	

From Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 2015 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association (in press).

1. *Initial attack:* 2 major manifestations, or 1 major and 2 minor manifestations, plus evidence of recent GAS infection. *Recurrent attack:* 2 major, or 1 major and 2 minor, or 3 minor manifestations (the latter only in the Moderate/High-Risk population), plus evidence of recent GAS infection (see text).
2. Low-Risk population is defined as ARF incidence <2 per 100,000 school-age children per year, or all-age RHD prevalence of <1 per 1000 population. Moderate/High-Risk population is defined as ARF incidence >2 per 100,000 school-age children per year, or all-age RHD prevalence of >1 per 1000 population.
3. Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis). See Table 183-3.
4. Arthritis (major) refers only to polyarthritis in Low-Risk populations, but also to monoarthritis or polyarthralgia in Moderate/High-Risk populations.
5. Minor criteria for Moderate/High-Risk populations only include monoarthralgia (polyarthralgia for Low-Risk populations), fever of >38° C (>38.5° C in Low-Risk populations), ESR >30 mm/hr (>60 mm/hr in Low-Risk populations).

Table 183-5 Chemoprophylaxis for Recurrences of Acute Rheumatic Fever (Secondary Prophylaxis)

DRUG	DOSE	ROUTE
Penicillin G benzathine	600,000 IU for children weighing ≤60 lb 1.2 million IU for children weighing >60 lb, every 4 wk*	Intramuscular
or		
Penicillin V	250 mg, twice a day	Oral
or		
Sulfadiazine or sulfisoxazole	0.5 g, once a day for patients weighing ≤60 lb 1.0 g, once a day for patients weighing >60 lb	Oral
FOR PEOPLE WHO ARE ALLERGIC TO PENICILLIN AND SULFONAMIDE DRUGS		
Macrolide or azalide	Variable	Oral

*In high-risk situations, administration every 3 wk is recommended.

Table 183-6 Duration of Prophylaxis for People Who Have Had Acute Rheumatic Fever: Recommendations of the American Heart Association

CATEGORY	DURATION
Rheumatic fever without carditis	5 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis but without residual heart disease (no valvular disease*)	10 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 yr or until 40 yr of age, whichever is longer; sometimes lifelong prophylaxis

*Clinical or echocardiographic evidence.

Table 183-3 Echocardiographic Findings in Rheumatic Valvulitis

PATHOLOGIC MITRAL REGURGITATION (ALL 4 MET)	PATHOLOGIC AORTIC REGURGITATION (ALL 4 MET)
1. Seen in at least 2 views 2. Jet length ≥2 cm in at least 1 view 3. Peak velocity >3 meters/second 4. Pan-systolic jet in at least 1 envelope	1. Seen in at least 2 views 2. Jet length ≥1 cm in at least 1 view 3. Peak velocity >3 meters/second 4. Pan-diastolic jet in at least 1 envelope

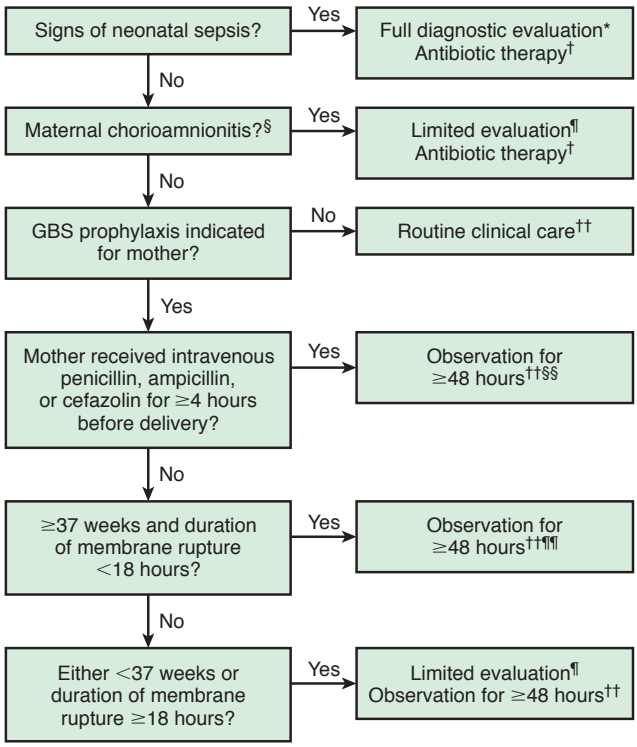
Table 183-4 Differential Diagnosis of Acute Rheumatic Fever

ARTHRITIS	CARDITIS	CHOREA
Juvenile idiopathic arthritis	Viral myocarditis	Huntington chorea
Reactive arthritis (e.g., *Shigella, Salmonella, Yersinia*)	Viral pericarditis	Wilson disease
Serum sickness	Infective endocarditis	Systemic lupus erythematosus
Sickle cell disease	Kawasaki disease	Cerebral palsy
Malignancy	Congenital heart disease	Tic disorder
Systemic lupus erythematosus	Mitral valve prolapse	Hyperactivity
Lyme disease (*Borrelia burgdorferi*)	Innocent murmurs	
Pyogenic arthritis		
Poststreptococcal reactive arthritis		

Table 184-1 Characteristics of Early- and Late-Onset Group B Streptococcus Disease

	EARLY-ONSET DISEASE	LATE-ONSET DISEASE
Age at onset	0-6 days	7-90 days
Increased risk after obstetric complications	Yes	No
Common clinical manifestations	Sepsis, pneumonia, meningitis	Bacteremia, meningitis, other focal infections
Common serotypes	Ia, Ib, II, III, V	III predominates
Case fatality rate	4.7%	2.8%

Adapted from Schrag SJ, Zywicki S, Farley MM, et al: Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis, N Engl J Med *342:15–20, 2000.*



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

Figure 184-2 Algorithm for secondary prevention of early-onset group B streptococcal disease among newborns.

Table 184-2 Recommended Duration of Therapy for Manifestations of Group B Streptococcus Disease

TREATMENT	DURATION
Bacteremia without a focus	10 days
Meningitis	2-3 wk
Ventriculitis	At least 4 wk
Septic arthritis or osteomyelitis	3-4 wk

Table 188-1 Types of *Listeria monocytogenes* Infections

Listeriosis in pregnancy
Neonatal listeriosis:
  Early onset
  Late onset
Foodborne outbreaks/febrile gastroenteritis
Listeriosis in normal children and adults (rare)
Focal listeria infections (e.g., meningitis, endocarditis, pneumonia, liver abscess, osteomyelitis, septic arthritis)
Listeriosis in immunocompromised persons:
  Lymphohematogenous malignancies
  Collagen vascular diseases
  Diabetes mellitus
  HIV infection
  Transplantation
  Renal failure with peritoneal dialysis
Listeriosis in the elderly

Table 188-2 Characteristic Features of Early- and Late-Onset Neonatal Listeriosis

EARLY ONSET (<5 DAYS)	LATE ONSET (≥5 DAYS)
Positive result of maternal *Listeria* culture	Negative results of maternal *Listeria* culture
Obstetric complications	Uncomplicated pregnancy
Premature delivery	Term delivery
Low birthweight	Normal birthweight
Neonatal sepsis	Neonatal meningitis
Mean age at onset 1.5 days	Mean age at onset 14.2 days
Mortality rate >30%	Mortality rate <10% Nosocomial outbreaks

Table 188-3 Prevention of Food-Borne Listeriosis

General recommendations to prevent an infection with *Listeria:*	FDA recommendations for washing and handling food.
	• Rinse raw produce, such as fruits and vegetables, thoroughly under running tap water before eating, cutting, or cooking. Even if the produce will be peeled, it should still be washed first.
	• Scrub firm produce, such as melons and cucumbers, with a clean produce brush.
	• Dry the produce with a clean cloth or paper towel.
	• Separate uncooked meats and poultry from vegetables, cooked foods, and ready-to-eat foods.
	Keep your kitchen and environment cleaner and safer.
	• Wash hands, knives, countertops, and cutting boards after handling and preparing uncooked foods.
	• Be aware that *Listeria monocytogenes* can grow in foods in the refrigerator. Use an appliance thermometer, such as a refrigerator thermometer, to check the temperature inside your refrigerator. The refrigerator should be 4.5°C (40°F) or lower and the freezer –17.8°C (0°F) or lower.
	• Clean up all spills in your refrigerator right away–especially juices from hot dog and lunch meat packages, raw meat, and raw poultry.
	• Clean the inside walls and shelves of your refrigerator with hot water and liquid soap, then rinse.
	Cook meat and poultry thoroughly.
	• Thoroughly cook raw food from animal sources, such as beef, pork, or poultry to a safe internal temperature. For a list of recommended temperatures for meat and poultry, visit the safe minimum cooking temperatures chart at http://www.FoodSafety.gov.
	Store foods safely.
	• Use precooked or ready-to-eat food as soon as you can. Do not store the product in the refrigerator beyond the use-by date; follow USDA refrigerator storage time guidelines:
	  • Hot dogs–store opened package no longer than 1 wk and unopened package no longer than 2 wk in the refrigerator.
	  • Luncheon and deli meat–store factory-sealed, unopened package no longer than 2 wk. Store-opened packages and meat sliced at a local deli no longer than 3-5 days in the refrigerator.
	• Divide leftovers into shallow containers to promote rapid, even cooling. Cover with airtight lids or enclose in plastic wrap or aluminum foil. Use leftovers within 3-4 days.
	Choose safer foods.
	• Do not drink raw (unpasteurized) milk, and do not eat foods that have unpasteurized milk in them.

Continued

Table 188-3 Prevention of Food-Borne Listeriosis—cont'd

Recommendations for persons at higher risk, such as pregnant women, persons with weakened immune systems, and older adults in addition to the recommendations listed above, include:	Meats • Do not eat hot dogs, luncheon meats, cold cuts, other deli meats (e.g., bologna), or fermented or dry sausages unless they are heated to an internal temperature of 73.9°C (165°F) or until steaming hot just before serving. • Avoid getting fluid from hot dog and lunch meat packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli meats. • Pay attention to labels. Do not eat refrigerated pâté or meat spreads from a deli or meat counter or from the refrigerated section of a store. Foods that do not need refrigeration, like canned or shelf-stable pâté and meat spreads, are safe to eat. Refrigerate after opening. Cheeses • Do not eat soft cheese such as feta, queso blanco, queso fresco, brie, Camembert, blue-veined, or panela (queso panela) unless it is labeled as made with pasteurized milk. Make sure the label says, "MADE WITH PASTEURIZED MILK." Seafood • Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole, or unless it is a canned or shelf-stable product. • Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as "nova-style," "lox," "kippered," "smoked," or "jerky." • These fish are typically found in the refrigerator section or sold at seafood and deli counters of grocery stores and delicatessens. • Canned and shelf stable tuna, salmon, and other fish products are safe to eat. Follow this general FDA advice for melon safety: • Consumers and food preparers should wash their hands with warm water and soap for at least 20 sec before and after handling any whole melon, such as cantaloupe, watermelon, or honeydew. • Scrub the surface of melons, such as cantaloupes, with a clean produce brush under running water and dry them with a clean cloth or paper towel before cutting. Be sure that your scrub brush is sanitized after each use, to avoid transferring bacteria between melons. • Promptly consume cut melon or refrigerate promptly. Keep your cut melon refrigerated at, or less than 4.5°C (40°F) (0-1.1°C [32-34°F] is best), for no more than 7 days. • Discard cut melons left at room temperature for more than 4 hr.

Adapted from the Centers for Disease Control and Prevention: Listeria *(Listeriosis): prevention. Available at:* http://www.cdc.gov/listeria/prevention.html

Table 191-2 Treatment of *Neisseria meningitidis* Invasive Infections

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSING INTERVAL (hr)	MAXIMUM DAILY DOSE	NOTES
Penicillin G	IM or IV	300,000 units/kg/day	4-6	12-24 million units	Does not clear carriage and "prophylaxis" is required at the end of treatment
Ampicillin	IM or IV	200-400 mg/kg/day	6	6-12 g	Does not clear carriage and "prophylaxis" is required at the end of treatment
Cefotaxime	IM or IV	200-300 mg/kg/day	6-8	8-12 g	Recommended in the neonate
Ceftriaxone	IM or IV	100 mg/kg/day	12-24	2-4 g	Preferred treatment as only once or twice daily and may reduce skin complications
ALTERNATIVE THERAPY IN THE FACE OF LIFE-THREATENING β-LACTAM ALLERGY					
Chloramphenicol*	IV	50-100 mg/kg/day	6	2-4 g	
Ciprofloxacin†	IV	30-40 mg/kg/day	12	1-1.5 g	
Meropenem‡	IV	60-120 mg/kg/day	8	1.5-6 g	

*Monitor blood levels to avoid toxicity.
†Licensed for individuals older than age 18 yr.
‡Rate of crossreactivity in penicillin-allergic adults is 2-3%.
IM, intramuscular; IV, intravenous.

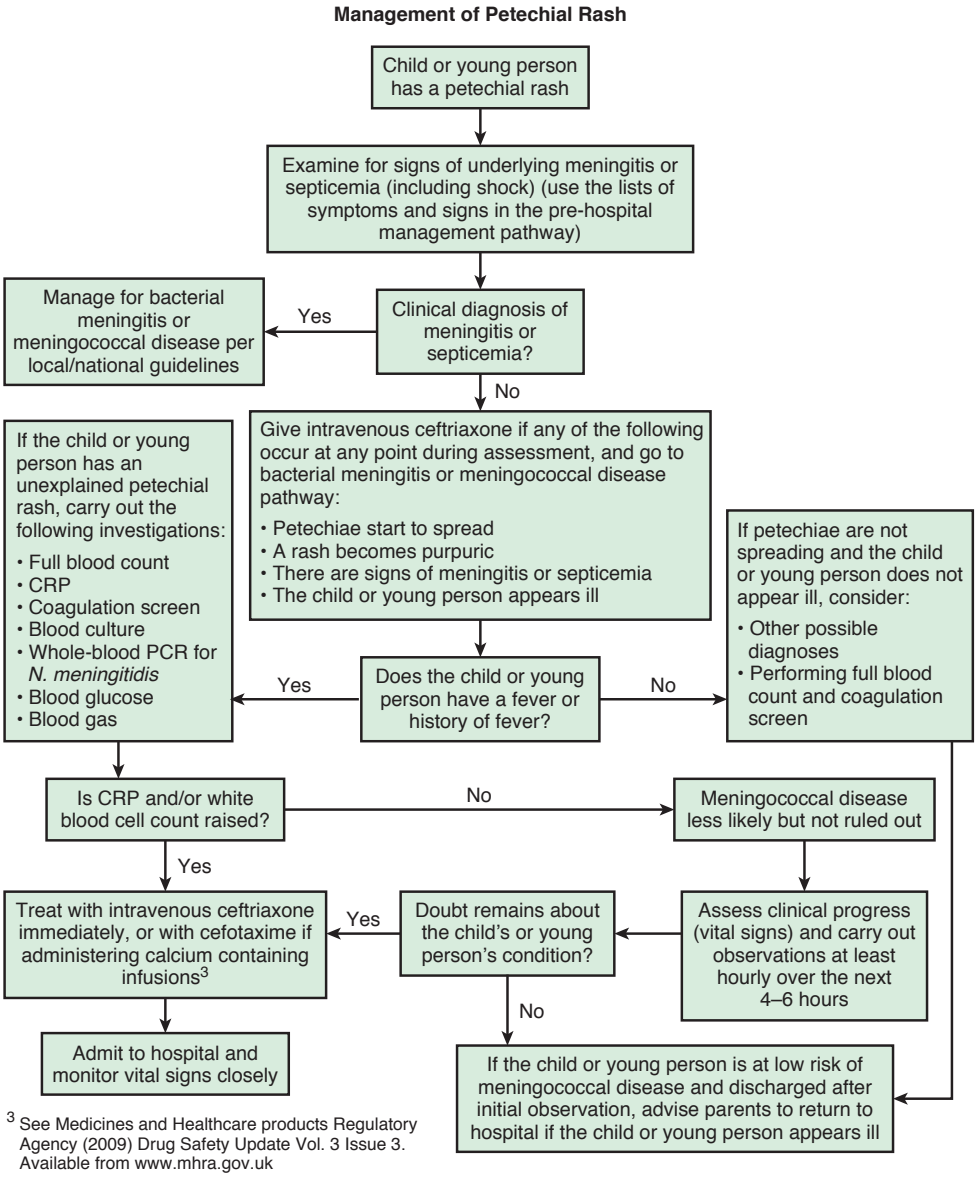


Figure 191-3 An approach to management of petechial rash. *(From National Collaborating Center for Women's and Children's Health (UK):* Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE clinical guidelines, No. 102. *London, 2010, RCOG Press.)*

Table 198-3 Treatment of *Salmonella* Gastroenteritis

ORGANISM AND INDICATION	DOSE AND DURATION OF TREATMENT
Salmonella infections in infants <3 mo of age or immunocompromised persons (in addition to appropriate treatment for underlying disorder)	Cefotaxime 100-200 mg/kg/day every 6-8 hr for 5-14 days *or* Ceftriaxone 75 mg/kg/day once daily for 7 days *or* Ampicillin 100 mg/kg/day every 6-8 hr for 7 days *or* Cefixime 15 mg/kg/day for 7-10 days

Table 191-3 Antibiotic Prophylaxis to Prevent *Neisseria meningitidis* Infection*

DRUG	DOSE	DURATION
RIFAMPIN†		
Infants <1 mo	5 mg/kg PO every 12 hr	2 days (4 doses)
Children ≥1 mo	10 mg/kg PO every 12 hr (maximum: 600 mg)	2 days (4 doses)
Adults	600 mg PO every 12 hr	2 days (4 doses)
CEFTRIAXONE		
Children <15 yr	125 mg IM	1 dose
Children ≥15 yr	250 mg IM	1 dose
CIPROFLOXACIN		
Children ≥1 mo†‡	20 mg/kg (maximum: 500 mg) PO	1 dose

*Recommended for household and kissing contacts. In the United States, chemoprophylaxis is recommended for:

- Household contact, especially children younger than 2 yr of age
- Childcare or preschool contact at any time during 7 days before onset of illness
- Direct exposure to index patient's secretions through kissing, sharing toothbrushes or eating utensils at any time during 7 days before onset of illness
- Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness
- Frequently slept in same dwelling as index patient during 7 days before onset of illness
- Passengers seated directly next to the index case during airline flights lasting more than 8 hr

†Not recommended for pregnant women.

‡Not recommended routinely for people younger than 18 yr of age; use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.

IM, intramuscular; PO, by mouth.

Table 198-5 Common Clinical Features of Typhoid Fever in Children*

FEATURE	RATE (%)
High-grade fever	95
Coated tongue	76
Anorexia	70
Vomiting	39
Hepatomegaly	37
Diarrhea	36
Toxicity	29
Abdominal pain	21
Pallor	20
Splenomegaly	17
Constipation	7
Headache	4
Jaundice	2
Obtundation	2
Ileus	1
Intestinal perforation	0.5

Table 191-4 Recommendations for Meningococcal Vaccination

GENERAL POPULATION <2 YR	2-10 YR	11-21 YR	22-55 YR
Not recommended	Not recommended	A single dose of MenACWY-D or MenACWY-CRM at age 11-12 yr or at 13-18 yr if not previously vaccinated. Age 19-21 yr: not routinely recommended but may be given as catch-up for those who have not received a dose after their 16th birthday. A booster dose 5 yr later (see text)*	Not recommended

SPECIAL POPULATIONS AT INCREASED RISK OF MENINGOCOCCAL DISEASE‡ RISK FACTOR	2-18 MONTHS	9-23 MONTHS	2-55 YR†
Persistent complement deficiencies, functional or anatomic asplenia	4 doses of Hib-MenCY-TT at 2, 4, 6, and 12-15 months	2 doses of MenACWY-D 12 wk apart§	2 doses of MenACWY 8-12 wk apart‖
At risk during a community outbreak with a vaccine serogroup	4 doses of Hib-MenCY-TT at 2, 4, 6, and 12-15 months	2 doses of MenACWY-D 12 wk apart	1 dose of MenACWY
Travel to or resident of countries where meningococcal disease is hyperendemic or epidemic¶	Should receive a quadrivalent meningococcal vaccination licensed for children aged ≥9 mo prior to travel	2 doses of MenACWY-D 12 wk apart**	1 dose of MenACWY
Have HIV, if another indication for vaccination exists	—	2 doses of MenACWY-D 12 wk apart	2 doses of MenACWY 8-12 wk apart‖
Other risk factors	—	—	1 dose MenACWY

*Otherwise healthy adolescents who received a 1st dose at age 11-12 yr should receive a booster dose of a meningococcal conjugate vaccine at 16 yr of age. For those given a 1st dose at age 13-15 yr, and who have not yet reached their 21st birthday, the booster dose should be given 5 yr after the 1st dose.

†Assuming not previously vaccinated.

‡Persons previously vaccinated at 7 yr of age or older who are at prolonged increased risk should be revaccinated 5 yr after their previous meningococcal vaccine and every 5 yr thereafter. Persons previously vaccinated at ages 2 mo-6 yr who are at prolonged increased risk should be revaccinated 3 yr after their previous meningococcal vaccination and every 5 yr thereafter.

§Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should not be immunized with MenACWY-D before age 2 yr to avoid interference with the immune response to the pneumococcal conjugate vaccine (PCV).

‖If MenACWY-D is used, it should be administered at least 4 wk after completion of all PCV doses.

¶For example, visitors to the "meningitis belt" of sub-Saharan Africa. Vaccination also is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

**If receiving the vaccine prior to travel, 2 doses may be administered as early as 8 wk apart.

Adapted from American Academy of Pediatrics Committee on Infectious Diseases: Updated recommendations on the use of meningococcal vaccines. Pediatrics *134:400–403, 2014.*

Table 197-2 Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, By Age Group

	Primary Agents		Alternate Agent*	
AGE GROUP	AZITHROMYCIN	ERYTHROMYCIN	CLARITHROMYCIN	TMP-SMZ
<1 mo	Recommended agent 10 mg/kg/day in a single dose for 5 days (only limited safety data available)	Not preferred Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants <2 mo of age (risk for kernicterus)
1-5 mo	10 mg/kg/day in a single dose for 5 days	40-50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Contraindicated at age <2 mo For infants age ≥2 mo: TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses for 14 days
Infants age ≥6 mo and children	10 mg/kg in a single dose on day 1 (maximum: 500 mg), then 5 mg/kg/day (maximum: 250 mg) on days 2-5	40-50 mg/kg/day (maximum: 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (maximum: 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses (maximum TMP: 320 mg/day) for 14 days
Adults	500 mg in a single dose on day 1 then 250 mg/day on days 2-5	2 g/day in 4 divided doses for 14 days	1 g/day in 2 divided doses for 7 days	TMP 320 mg/day, SMZ 1,600 mg/day in 2 divided doses for 14 days

*Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative agent to macrolides in patients age ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis.*

From Centers for Disease Control and Prevention (CDC): Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines, MMWR Morb Mortal Wkly Rep *54:1–16, 2005.*

Table 198-6 Extraintestinal Infectious Complications of Typhoid Fever Caused By *Salmonella enterica* Serotype Typhi

ORGAN SYSTEM INVOLVED	PREVALENCE (%)	RISK FACTORS	COMPLICATIONS
Central nervous system	3-35	Residence in endemic region, malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, and osteomyelitis of the skull	Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis
Cardiovascular system	1-5	Cardiac abnormalities—e.g., existing valvular abnormalities, rheumatic heart disease, or congenital heart defects	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary system	1-6	Residence in endemic region, past pulmonary infection, sickle cell anemia, alcohol abuse, diabetes, HIV infection	Pneumonia, empyema, bronchopleural fistula
Bone and joint	<1	Sickle cell anemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, extremes of age, and steroid use	Osteomyelitis, septic arthritis
Hepatobiliary system	1-26	Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, hemoglobinopathy	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary system	<1	Urinary tract, pelvic pathology, and systemic abnormalities	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft-tissue infections	At least 17 cases reported in the English language literature	Diabetes	Psoas abscess, gluteal abscess, cutaneous vasculitis
Hematologic	At least 5 cases reported in the English language literature		Hemophagocytosis syndrome

From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of Salmonella enterica *serotype Typhi infection,* Lancet Infect Dis *5:341–348, 2005.*

Table 198-7 Treatment of Typhoid Fever in Children

	Optimal Therapy			Alternative Effective Drugs		
SUSCEPTIBILITY	ANTIBIOTIC	DAILY DOSE (mg/kg/day)	DAYS	ANTIBIOTIC	DAILY DOSE (mg/kg/day)	DAYS
UNCOMPLICATED TYPHOID FEVER						
Fully sensitive	Chloramphenicol	50-75	14-21	Fluoroquinolone, e.g., ofloxacin or ciprofloxacin	15	5-7*
	Amoxicillin	75-100	14			
Multidrug-resistant	Fluoroquinolone	15	5-7	Azithromycin	8-10	7
	or					
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone-resistant†	Azithromycin	8-10	7	Cefixime	20	7-14
	or					
	Ceftriaxone	75	10-14			
SEVERE TYPHOID FEVER						
Fully sensitive	Fluoroquinolone, e.g., ofloxacin	15	10-14	Chloramphenicol	100	14-21
				Amoxicillin	100	
Multidrug-resistant	Fluoroquinolone	15	10-14	Ceftriaxone	60	10-14
				or		
				Cefotaxime	80	10-14
Quinolone-resistant	Ceftriaxone	60	10-14	Azithromycin	10-20	7
	Cefotaxime	80	10-14	Fluoroquinolone	20	7-14

*A 3-day course is also effective, particularly for epidemic containment.

†The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, third-generation cephalosporins, or high-dose fluoroquinolones for 10-14 days is effective.

Modified from World Health Organization: Treatment of typhoid fever. In: World Health Organization: Background document: the diagnosis, prevention and treatment of typhoid fever. Communicable disease surveillance and response: vaccines and biologicals, *Geneva, 2003, World Health Organization, pp. 19–23. Available at: http://whqlibdoc.who.int/hq/2003/WHO_V&B_03.07.pdf*

Table 200-1 Clinical Characteristics, Pathogenesis, and Diagnosis of Diarrheagenic *E. coli*

PATHOGEN	POPULATIONS AT RISK	Characteristics of Diarrhea			Main Virulence Factors		DIAGNOSIS
		WATERY	BLOODY	DURATION	ADHERENCE FACTORS	TOXINS	
ETEC	>1 yr old and travelers	+++	—	Acute	Colonization factor antigens (CFs or CFAs); ECP	Heat-labile enterotoxin (LT) Heat-stable enterotoxin (ST)	Detection of enterotoxins (LT and ST) by enzyme immunoassays or PCR (*lt, st*)
EIEC	>1 yr old	+	++	Acute	Invasion plasmid antigen (IpaABCD)		Detection of invasion plasmid antigen of *Shigella* (*ipaH*) by PCR
EPEC	<2 yr old	+ + +	+	Acute, prolonged or persistent	A/E lesion, intimin/Tir, EspABD, Bfp	EspF, Map, EAST1, SPATEs (*EspC*)	Detection of intimin gene (*eae*) ± bundle-forming pili (*bfp*A) by PCR, and absence of *Shiga* toxins; HEp-2 cells adherence assay (LA, LLA)
STEC (EHEC/ VTEC)	6 mo-10 yr and the elderly	+	+++	Acute	A/E lesion, intimin/Tir, EspABD	*Shiga* toxins (Stx1, Stx2, and variants of Stx2)	Detection of *Shiga* toxins by enzyme immunoassays or PCR (*Stx*1, *Stx2*); stool culture on MacConkey-sorbitol media to detect *E. coli* O157. Simultaneous culture for O157 and nonculture assays to detect *Shiga* toxins
EAEC	<2 yr old, HIV-infected patients, and travelers	+++	+	Acute, prolonged, or persistent	Aggregative adherence fimbriae (AAF)	SPATEs (Pic, Pet), ShET1, EAST1	Detection of *AggR*, AA plasmid, and other virulence genes: *aap*, *aatA*, *astA*, *set1A* by PCR; HEp-2 cells adherence assay (AA)
DAEC	>1 yr old and travelers	++	—	Acute	Afa/Dr, AIDA-I	SPATEs (Sat)	Detection of Dr adhesins (daaC or daaD) and Dr-associated genes by PCR; HEp-2 cells adherence assay (DA)

—, Not present; +, present; ++, common; +++, very common; A/E lesion, attaching and effacing lesion; AA, aggregative adherence; Bfp, bundle-forming pili; DA, diffuse adherence; DAEC, diffusely adherent *E. coli;* EAEC, enteroaggregative *E. coli;* EAST1, enteroaggregative heat stable toxin; ECP, *E. coli* common pilus; EHEC, enterohemorrhagic *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli;* EspABD, *E. coli* secreted proteins A, B, and D; ETEC, enterotoxigenic *E. coli;* LA, localized adherence; LLA, localized-like adherence; PCR, polymerase chain reaction; ShET1, *Shigella* enterotoxin 1; SPATEs, serine protease autotransporter of Enterobacteriaceae; STEC, *Shiga* toxin–producing *E. coli;* Tir, translocated intimin receptor; VTEC, verotoxin-producing *E. coli.*

Table 210-1 Diagnoses Considered in Subsequently Laboratory-Confirmed Cases of Infant Botulism

ADMISSION DIAGNOSIS	SUBSEQUENTLY CONSIDERED DIAGNOSES
Suspected sepsis, meningitis	Guillain-Barré syndrome
Pneumonia	Myasthenia gravis
Dehydration	Disorders of amino acid metabolism
Viral syndrome	Hypothyroidism
Hypotonia of unknown etiology	Drug ingestion Organophosphate poisoning
Constipation	Brainstem encephalitis
Failure to thrive	Heavy metal poisoning (Pb, Mg, As)
Spinal muscular atrophy type 1 (Werdnig-Hoffmann disease)	Poliomyelitis Viral polyneuritis Hirschsprung disease Metabolic encephalopathy Medium chain acetyl–coenzyme A dehydrogenase deficiency

Table 210-2 Diagnoses Considered in Foodborne and Wound Botulism

Acute gastroenteritis
Myasthenia gravis
Guillain-Barré syndrome
Organophosphate poisoning
Meningitis
Encephalitis
Psychiatric illness
Cerebrovascular accident
Poliomyelitis
Hypothyroidism
Aminoglycoside-associated paralysis
Tick paralysis
Hypocalcemia
Hypermagnesemia
Carbon monoxide poisoning
Hyperemesis gravidarum
Laryngeal trauma
Diabetic complications
Inflammatory myopathy
Overexertion

Table 205-1 *Pseudomonas aeruginosa* Infections

INFECTION	COMMON CLINICAL CHARACTERISTICS
Endocarditis	Native right-sided (tricuspid) valve disease with intravenous drug abuse
Pneumonia	Compromised local (lung) or systemic host defense mechanisms; nosocomial (respiratory), bacteremic (malignancy), or abnormal mucociliary clearance (cystic fibrosis) may be pathogenetic; cystic fibrosis is associated with mucoid *P. aeruginosa* organisms producing capsular slime
Central nervous system infection	Meningitis, brain abscess; contiguous spread (mastoiditis, dermal sinus tracts, sinusitis); bacteremia or direct inoculation (trauma, surgery)
External otitis	Swimmer's ear; humid warm climates, swimming pool contamination
Malignant otitis externa	Invasive, indolent, febrile toxic, destructive necrotizing lesion in young infants, immunosuppressed neutropenic patients, or diabetic patients; associated with 7th nerve palsy and mastoiditis
Chronic mastoiditis	Ear drainage, swelling, erythema; perforated tympanic membrane
Keratitis	Corneal ulceration; contact lens keratitis
Endophthalmitis	Penetrating trauma, surgery, penetrating corneal ulceration; fulminant progression
Osteomyelitis/septic arthritis	Puncture wounds of foot and osteochondritis; intravenous drug abuse; fibrocartilaginous joints, sternum, vertebrae, pelvis; open fracture osteomyelitis; indolent pyelonephritis and vertebral osteomyelitis
Urinary tract infection	Iatrogenic, nosocomial; recurrent urinary tract infections in children, instrumented patients, and those with obstruction or stones
Intestinal tract infection	Immunocompromised, neutropenia, typhlitis, rectal abscess, ulceration, rarely diarrhea; peritonitis in peritoneal dialysis
Ecthyma gangrenosum	Metastatic dissemination; hemorrhage, necrosis, erythema, eschar, discrete lesions with bacterial invasion of blood vessels; also subcutaneous nodules, cellulitis, pustules, deep abscesses
Primary and secondary skin infections	Local infection; burns, trauma, decubitus ulcers, toe web infection, green nail (paronychia); whirlpool dermatitis; diffuse, pruritic, folliculitis, vesiculopustular or maculopapular, erythematous lesions

Table 207-1 Recommended Therapy for the Treatment of Brucellosis

AGE AND CONDITION	ANTIMICROBIAL AGENT	DOSE	ROUTE	DURATION
≥8 yr	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	6 wk
	+			
	Rifampin	15-20 mg/kg/day; maximum: 600-900 mg/day	PO	6 wk
	Alternative:			
	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	6 wk
	+			
	Streptomycin	15-30 mg/kg/day; maximum: 1 g/day	IM	2-3 wk
	or			
	Gentamicin	3-5 mg/kg/day	IM/IV	1-2 wk
<8 yr	Trimethoprim-sulfamethoxazole (TMP-SMZ)	TMP (10 mg/kg/day; maximum: 480 mg/day) and SMZ (50 mg/kg/day; maximum: 2.4 g/day)	PO	4-8 wk
	+			
	Rifampin	15-20 mg/kg/day	PO	6 wk
Meningitis, osteomyelitis, endocarditis	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	4-6 mo
	+			
	Gentamicin	3-5 mg/kg/day	IV	1-2 wk
	±			
	Rifampin	15-20 mg/kg/day; maximum: 600-900 mg/day	PO	4-6 mo

Table 211-1 Tetanus Prophylaxis in Routine Wound Management

	Clean, Minor Wounds		All Other Wounds*	
HISTORY OF ABSORBED TETANUS TOXOID	TDAP OR TD[†]	TIG[‡]	TDAP OR TD[†]	TIG[‡]
Uncertain or <3 doses	Yes	No	Yes	Yes
3 or more doses	No[§]	No	No[‖]	No

*Such as, but not limited to, wounds contaminated with dirt, feces, and saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, and frostbite.

[†]For children younger than 7 yr of age, DTaP is preferred to tetanus toxoid alone if <3 doses of DTaP have been previously given. If pertussis vaccine is contraindicated, DT is given. For persons 7 yr of age or older, Td (or Tdap for adolescents 11-18 yr of age) is preferred to tetanus toxoid alone. Tdap is preferred to Td for adolescents 11-18 yr of age who have never received Tdap. Td is preferred to tetanus toxoid for adolescents who received Tdap previously or when Tdap is not available.

[‡]TIG should be administered for tetanus-prone wounds in HIV-infected patients regardless of the history of tetanus immunizations.

[§]Yes, if 10 yr or longer since the last tetanus toxoid–containing vaccine dose.

[‖]Yes, if 5 yr or longer since the last tetanus toxoid–containing vaccine dose. (More frequent boosters are not needed and can accentuate adverse events.)

DT, diphtheria and tetanus toxoid vaccine; DTaP, combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; Td, tetanus toxoid and reduced diphtheria toxoid vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; TIG, tetanus immune globulin.

Table 213-1 Infections Associated with Anaerobic Bacteria

SITE AND INFECTION	MAJOR RISK FACTORS	ANAEROBIC BACTERIA*
CENTRAL NERVOUS SYSTEM		
Cerebral abscess	Cyanotic heart disease Cystic fibrosis Penetrating trauma	Polymicrobial
Epidural and subdural empyemas, meningitis	Direct extension from contiguous sinusitis, otitis media, mastoiditis, or anatomic defect involving the dura	*Bacteroides fragilis*† *Fusobacterium* *Peptostreptococcus* *Veillonella*
UPPER RESPIRATORY TRACT		
Dental abscess	Poor periodontal hygiene	*Peptostreptococcus*
Ludwig angina (cellulitis of sublingual-submandibular space)	Drugs producing gingival hypertrophy	*Fusobacterium*
Necrotizing gingivitis (Vincent stomatitis)		*Prevotella melaninogenica*
Chronic otitis-mastoiditis-sinusitis	Tympanic perforation Tympanostomy tubes	
Peritonsillar abscess	Streptococcal pharyngitis	
Retropharyngeal abscess	Penetrating injury	
Lemierre syndrome	Preexisting viral or bacterial pharyngitis	*Fusobacterium*
LOWER RESPIRATORY TRACT		
Aspiration pneumonia	Periodontal disease	Polymicrobial
Necrotizing pneumonitis	Bronchial obstruction	*P. melaninogenica*
Lung abscess	Altered gag or consciousness Aspirated foreign body Sequestered lobe Vascular anomaly	*Bacteroides intermedius* *Fusobacterium* *Peptostreptococcus, Eubacterium* *B. fragilis, Veillonella*
Septic pulmonary emboli		*Fusobacterium*
INTRAABDOMINAL		
Abscess	Appendicitis	Polymicrobial
Secondary peritonitis	Penetrating trauma (especially of the colon)	*Bacteroides* spp. *Clostridium* *Peptostreptococcus* *Eubacterium* *Fusobacterium*
FEMALE GENITAL TRACT		
Bartholin abscess	Vaginosis	*B. fragilis*
Tuboovarian abscess	Intrauterine device	*Bacteroides bivius*
Endometritis		*Peptostreptococcus*
Pelvic thrombophlebitis		*Clostridium*
Salpingitis		*Mobiluncus*
Chorioamnionitis		*Actinomyces*
Septic abortion		*Clostridium*
SKIN AND SOFT TISSUE		
Cellulitis	Decubitus ulcers	Varies with site and contamination with oral or enteric flora
Perirectal cellulitis	Abdominal wounds	*Clostridium perfringens* (myonecrosis)
Myonecrosis (gas gangrene)	Pilonidal sinus	*Bacteroides* *Clostridia*
Necrotizing fasciitis and synergistic gangrene	Trauma Human and animal bites Immunosuppressed or neutropenic patients Varicella	*Fusobacterium* *Clostridium tertium* *Clostridium septicum* Anaerobic streptococci
BLOOD		
Bacteremia	Intraabdominal infection, abscesses, myonecrosis, necrotizing fasciitis	*B. fragilis* *Clostridium* *Peptostreptococcus* *Fusobacterium*

*Infections may also be from or may involve aerobic bacteria as the sole agent or as part of a mixed infection; brain abscess may contain microaerophilic streptococci; intraabdominal infections may contain Gram-negative enteric organisms and enterococci; and salpingitis may contain *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

†*Bacteroides fragilis* is usually isolated from infections below the diaphragm except for brain abscesses.

Table 210-3 Complications of Infant Botulism

Acute respiratory distress syndrome
Aspiration
Clostridium difficile enterocolitis
Hypotension
Inappropriate antidiuretic hormone secretion
Long bone fractures
Misplaced or plugged endotracheal tube
Nosocomial anemia
Otitis media
Pneumonia
Pneumothorax
Recurrent atelectasis
Seizures secondary to hyponatremia
Sepsis
Subglottic stenosis
Tracheal granuloma
Tracheitis
Transfusion reaction
Urinary tract infection

Table 214-2 Isoniazid Drug–Drug Interactions

DRUG USED WITH ISONIAZID	EFFECTS
Acetaminophen, alcohol, rifampin	Increased hepatotoxicity of isoniazid or listed drugs
Aluminum salts (antacids)	Decreased absorption of isoniazid
Carbamazepine, phenytoin, theophylline, diazepam, warfarin	Increased level, effect, or toxicity of listed drugs due to decreased metabolism
Itraconazole, ketoconazole, oral hypoglycemic agents	Decreased level or effect of listed drugs due to increased metabolism
Cycloserine, ethionamide	Increased central nervous system adverse effects of cycloserine and ethionamide
Prednisolone	Increased isoniazid metabolism

Table 214-1 Recommended Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents

INFECTION OR DISEASE CATEGORY	REGIMEN	REMARKS
LATENT TUBERCULOSIS INFECTION*		
Isoniazid susceptible	9 mo of isoniazid, once a day	If daily therapy is not possible, DOT twice a week can be used for 9 mo
Isoniazid resistant	6 mo of rifampin, once a day	If daily therapy is not possible, DOT twice a week can be used for 6 mo
Isoniazid-rifampin resistant‡	Consult a tuberculosis specialist	
PULMONARY AND EXTRAPULMONARY INFECTION		
Except meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily, followed by 4 mo of isoniazid and rifampin† by DOT§ for drug-susceptible *Mycobacterium tuberculosis* 9-12 mo of isoniazid and rifampin for drug-susceptible *Mycobacterium bovis*	If possible drug resistance is a concern (see text), another drug (ethambutol or an aminoglycoside) is added to the initial 3 drug therapy until drug susceptibilities are determined; DOT is highly desirable If hilar adenopathy only, a 6-mo course of isoniazid and rifampin is sufficient Drugs can be given 2 or 3×/wk under DOT in the initial phase if nonadherence is likely
Meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside or ethambutol or ethionamide, once a day, followed by 7-10 mo of isoniazid and rifampin, once a day or twice a week (9-12 mo total) for drug-susceptible *M. tuberculosis* ≥12 mo of therapy without pyrazinamide for drug-susceptible *M. bovis*	A 4th drug, such as an aminoglycoside, is given with initial therapy until drug susceptibility is known For patients who might have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin

*Positive TST or IGRA result, no disease.
†Duration of therapy is longer for human immunodeficiency virus (HIV)-infected people, and additional drugs may be indicated.
‡Medications should be administered daily for the 1st 2 wk to 2 mo of treatment and then can be administered 2-3×/wk by DOT.
§If initial chest radiograph shows cavitary lesions and sputum after 2 mo of therapy remains positive, duration of therapy is extended to 9 mo.
DOT, directly observed therapy; IGRA, interferon-γ release assay; TST, tuberculin skin test.
From American Academy of Pediatrics: Tuberculosis. In Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors: Red book 2012: report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Table 214-3 Treatment of Nontuberculous Mycobacteria Infections in Children

ORGANISM	DISEASE	TREATMENT
SLOWLY GROWING SPECIES		
Mycobacterium avium complex (MAC); *Mycobacterium haemophilum; Mycobacterium lentiflavum*	Lymphadenitis	Complete excision of lymph nodes; if excision is incomplete or disease recurs, clarithromycin or azithromycin plus ethambutol or rifampin (or rifabutin)
	Pulmonary infection	Clarithromycin or azithromycin plus ethambutol with rifampin or rifabutin (pulmonary resection in some patients who fail to respond to drug therapy). For severe disease, an initial course of amikacin or streptomycin often is included. Clinical data in adults support that 3×/wk therapy is as effective as daily therapy, with less toxicity. For patients with advanced disease, drugs should be given daily
	Disseminated	See text
Mycobacterium kansasii	Pulmonary infection	Rifampin plus ethambutol with isoniazid
	Osteomyelitis	Surgical debridement and prolonged antimicrobial therapy using rifampin plus ethambutol with isoniazid
Mycobacterium marinum	Cutaneous infection	Trimethoprim-sulfamethoxazole, clarithromycin, or doxycycline for mild disease; ethambutol with clarithromycin or rifampicin for extensive disease; extensive lesions might require surgical debridement.
Mycobacterium ulcerans	Cutaneous and bone infections	Daily intramuscular streptomycin and oral rifampin × 8 wk; excision of tissue
RAPIDLY GROWING SPECIES		
Mycobacterium fortuitum group	Cutaneous infection	Initial therapy for serious disease is amikacin plus cefoxitin or imipenem IV, followed by clarithromycin, doxycycline,* or trimethoprim-sulfamethoxazole or ciprofloxacin, orally, on the basis of in vitro susceptibility testing; might require surgical excision
	Catheter infection	Catheter removal and amikacin plus cefoxitin or imipenem, IV; clarithromycin, trimethoprim-sulfamethoxazole, or ciprofloxacin, orally, on the basis of in vitro susceptibility testing
Mycobacterium abscessus	Otitis media	Clarithromycin plus initial course of amikacin plus cefoxitin or imipenem; might require surgical debridement. Base regimen on in vitro susceptibility testing (50% are amikacin resistant)
	Pulmonary infection (in cystic fibrosis)	Serious disease, clarithromycin, amikacin, and cefoxitin on the basis of susceptibility testing; might require surgical resection
Mycobacterium chelonae	Catheter infection	Catheter removal and tobramycin (initially) plus clarithromycin
	Disseminated cutaneous infection	Tobramycin and ciprofloxacin or linezolid (initially) plus clarithromycin

*Doxycycline should not be given to children younger than 8 yr of age unless the benefits of therapy are greater than the risks of dental staining. Only 50% of isolates of *Mycobacterium marinum* are susceptible to doxycycline.

From American Thoracic Society/Infectious Disease Society of America Statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367-416, 2007.

Table 215-1 Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Countries with Low Incidence

RISK FACTORS FOR TUBERCULOSIS INFECTION
Children exposed to high-risk adults
Foreign-born persons from high-prevalence countries
Homeless persons
Persons who inject drugs
Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes
Healthcare workers caring for high-risk patients (if infection control is not adequate)
RISK FACTORS FOR PROGRESSION OF LATENT TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE
Infants and children ≤4 yr of age, especially those <2 yr of age
Adolescents and young adults
Persons coinfected with HIV
Persons with skin test conversion in the past 1-2 yr
Persons who are immunocompromised, especially in cases of malignancy and solid organ transplantation, immunosuppressive medical treatments including anti–tumor necrosis factor therapies, diabetes mellitus, chronic renal failure, silicosis, and malnutrition
RISK FACTORS FOR DRUG-RESISTANT TUBERCULOSIS
Personal or contact history of treatment for tuberculosis
Contacts of patients with drug-resistant tuberculosis
Birth or residence in a country with a high rate of drug resistance
Poor response to standard therapy
Positive sputum smears (acid-fast bacilli) or culture ≥2 mo after initiating appropriate therapy

Table 215-3 Definitions of Positive Tuberculin Skin Test Results in Infants, Children, and Adolescents*

INDURATION ≥5 MM

Children in close contact with known or suspected contagious people with tuberculosis disease

Children suspected to have tuberculosis disease:

- Findings on chest radiograph consistent with active or previously tuberculosis disease
- Clinical evidence of tuberculosis disease†

Children receiving immunosuppressive therapy‡ or with immunosuppressive conditions, including HIV infection

INDURATION ≥10 MM

Children at increased risk of disseminated tuberculosis disease:

- Children younger than 4 yr of age
- Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 215-2)

Children with increased exposure to tuberculosis disease:

- Children born in high-prevalence regions of the world
- Children often exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers
- Children who travel to high-prevalence regions of the world

INDURATION ≥15 MM

Children ≥4 yr of age without any risk factors

*These definitions apply regardless of previous bacille Calmette-Guérin (BCG) immunization; erythema at TST site does not indicate a positive test result. Tests should be read at 48-72 hr after placement.

†Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (e.g., meningitis).

‡Including immunosuppressive doses of corticosteroids or tumor necrosis factor-α antagonists.

HIV, human immunodeficiency virus; TST, tuberculin skin test.

Table 215-4 Recommendations for Use of the Tuberculin Skin Test and an Interferon-γ Release Assay in Children

TST preferred, IGRA acceptable

- Children <5 yr of age*

IGRA preferred, TST acceptable

- Children >5 yr of age who have received the BCG vaccine
- Children >5 yr of age who are unlikely to return for TST reading

TST and IGRA should be considered when:

- The initial and repeat IGRA are indeterminate
- The initial test (TST or IGRA) is negative and:
  - Clinical suspicion for tuberculosis disease is moderate to high†
  - Risk of progression and poor outcome is high†
- The initial TST is positive and:
  - >5 yr of age and history of BCG vaccination
  - Additional evidence needed to increase compliance
  - Nontuberculous mycobacterial disease is suspected

*Positive result of either test is considered significant in these groups.

†IGRAs should not be used in children younger than 2 yr of age unless tuberculosis disease is suspected. In children 2-4 yr of age, there are limited data about the usefulness of IGRAs in determining tuberculosis infection, but IGRA testing can be performed if tuberculosis disease is suspected.

IGRA indicates interferon-γ release assay; TST, tuberculin skin test.

Table 215-2 Tuberculin Skin Test Recommendations for Infants, Children, and Adolescents*

CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED†:

- Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)
- Children with radiographic or clinical findings suggesting tuberculosis disease
- Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries from the former Soviet Union), including international adoptees
- Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries‡
- Children who should have annual TST or IGRA:
  - Children infected with HIV

CHILDREN AT INCREASED RISK FOR PROGRESSION OF LTBI TO TUBERCULOSIS DISEASE

Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies deserve special consideration. Without recent exposure, these children are not at increased risk of acquiring tuberculosis infection. Underlying immunodeficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST should be considered. **An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged steroid administration, use of tumor necrosis factor-α antagonists, or immunosuppressive therapy in any child requiring these treatments.**

*Bacille Calmette-Guérin immunization is not a contraindication to a TST.

†Beginning as early as 3 mo of age.

‡If the child is well and has no history of exposure, the TST or IGRA should be delayed up to 10 wk after return.

HIV, human immunodeficiency virus; IGRA indicates interferon-γ release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 740.*

Table 215-6 Less-Commonly Used Drugs for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents*

DRUGS	DOSAGE, FORMS	DAILY DOSAGE, mg/kg	MAXIMUM DOSE	ADVERSE REACTIONS
Amikacin†	Vials: 500 mg, 1 g	15-30 (IV or IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Capreomycin†	Vials: 1 g	15-30 (IM administration)	1 g	Auditory and vestibular toxicity and nephrotoxic effects
Cycloserine	Capsules: 250 mg	10-20, given in 2 divided doses	1 g	Psychosis, personality changes, seizures, rash
Ethionamide	Tablets: 250 mg	15-20, given in 2-3 divided doses	1 g	Gastrointestinal tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism
Kanamycin	Vials: 75 mg/2 mL 500 mg/2 mL 1 g/3 mL	15-30 (IM or IV administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Levofloxacin‡	Tablets: 250 mg 500 mg 750 mg Vials: 25 mg/mL	Adults: 750-1000 mg (once daily) Children: 15 mg/kg daily	1 g	Theoretic effect on growing cartilage, gastrointestinal tract disturbances, rash, headache, restlessness, confusion
Ofloxacin	Tablets: 200 mg 300 mg 400 mg Vials: 20 mg/mL 40 mg/mL	Adults and adolescents: 800 mg Children 15-20 mg/kg daily	800 mg	Arthropathy, arthritis
Moxifloxacin	Tablets: 400 mg IV solution: 400 mg/250 mL in 0.8% saline	Adults and adolescents: 400 mg Children: 7.5-10 mg/kg daily	400 mg	Arthropathy, arthritis
Paraaminosalicylic acid (PAS)	Packets: 3 g	200-300 (2-4 times a day)	10 g	Gastrointestinal tract disturbances, hypersensitivity, hepatotoxic effects
Streptomycin†	Vials: 1 g 4 g	20-40 (IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects, rash

*These drugs should be used in consultation with a specialist in tuberculosis.
†Dose adjustment in renal insufficiency.
‡Levofloxacin currently is not approved for use in children younger than 18 yr of age; its use in younger children necessitates assessment of the potential risks and benefits.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 748.*

Table 215-5 Commonly Used Drugs for the Treatment of Tuberculosis in Infants, Children, and Adolescents

DRUG	DOSAGE FORMS	DAILY DOSAGE, mg/kg	TWICE A WEEK DOSAGE, mg/kg PER DOSE	MAXIMUM DOSE	ADVERSE REACTIONS
Ethambutol	Tablets: 100 mg 400 mg	20	50	2.5 g	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Isoniazid*	Scored tablets: 100 mg 300 mg Syrup: 10 mg/mL	10-15†	20-30	Daily, 300 mg Twice a week, 900 mg	Mild hepatic enzyme elevation, hepatitis,† peripheral neuritis, hypersensitivity
Pyrazinamide*	Scored tablets: 500 mg	30-40	50	2 g	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset
Rifampin*	Capsules: 150 mg 300 mg Syrup formulated from capsules	10-20	10-20	600 mg	Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be ineffective

*Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (i.e., person weighing >50 kg) daily doses of each drug. Rifater, in the United States, is a capsule containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Isoniazid and rifampin also are available for parenteral administration.
†When isoniazid in a dosage exceeding 10 mg/kg per day is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 746.*

Table 216-1 NHDP Recommended Multidrug Therapy Regimens for Hansen Disease in the United States

TYPE OF LEPROSY	ANTIMICROBIAL THERAPY	ADULT DOSING (GIVEN ORALLY)	PEDIATRIC DOSING* (GIVEN ORALLY)	DURATION OF THERAPY
MULTIBACILLARY LEPROSY (LL, BL, BB)				
	Dapsone *and*	100 mg/day	1 mg/kg/day	24 months
	Rifampin *and*	600 mg/day	10-20 mg/kg/day	24 months
	Clofazimine	50 mg/day	1 mg/kg/day†	24 months
PAUCIBACILLARY LEPROSY (TT, BT)				
	Dapsone *and*	100 mg/day	1-2 mg/kg/day	12 months
	Rifampin	600 mg/day	10-20 mg/kg/day	12 months

NHDP multidrug therapy therapy is daily and of longer duration than World Health Organization recommended regimen.
*Daily pediatric mg/kg dose should not exceed adult daily maximum.
†Clofazimine is only available through NHDP Investigational New Drug (IND) program; minimum formulation is 50 mg and capsules should not be cut. Alternative dosing includes: clofazimine 2 mg/kg every other day *or* clarithromycin 7.5 mg/kg/day.
BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; NHDP, National Hansen's Disease Program; TT, tuberculoid.

Table 216-2 World Health Organization Recommended Multidrug Therapy Regimens for Hansen Disease

TYPE OF LEPROSY		Antimicrobial Therapy		DURATION OF THERAPY
		MONTHLY (SUPERVISED)	DAILY (SELF-ADMINISTERED)	
Multibacillary (LL, BL, BB)	Adult	Rifampicin 600 mg *and* clofazimine 300 mg	Dapsone 100 mg *and* clofazimine 50 mg	12-24 months
	Pediatric*	Rifampicin 450 mg *and* clofazimine 150 mg	Dapsone 50 mg *and* clofazimine 50 mg *every other day*	
Paucibacillary (TT, BT)	Adult	Rifampicin 600 mg	Dapsone 100 mg	6-12 months
	Pediatric*	Rifampicin 450 mg	Dapsone 50 mg	6 months
Paucibacillary (single lesion)†		Rifampicin 600 mg *and* ofloxacin 400 mg *and* minocycline 100 mg		One time, single dose

*In children younger than 10 yr of age, dosages of multidrug therapy should be in mg/kg, not to exceed the adult daily maximum: rifampicin 10 mg/kg once monthly, dapsone 2 mg/kg/day, clofazimine 1 mg/kg on alternate days.
†Paucibacillary single-lesion, one-time single-dose therapy may be less effective than the 6 mo paucibacillary multidrug therapy regimen.
BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.

Table 217-1 Diseases Caused by Nontuberculous Mycobacterial Species

CLINICAL DISEASE	COMMON SPECIES	LESS-COMMON SPECIES
Cutaneous infection	*Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium abscessus, Mycobacterium marinum*	*Mycobacterium ulcerans**
Lymphadenitis	MAC	*Mycobacterium kansasii, Mycobacterium haemophilum, Mycobacterium malmoense*†
Otologic infection	*M. abscessus*, MAC	*M. fortuitum*
Pulmonary infection	MAC, *M. kansasii, M. abscessus*	*Mycobacterium xenopi, Mycobacterium malmoense,*† *Mycobacterium szulgai, M. fortuitum, Mycobacterium simiae*
Catheter-associated infection	*M. chelonae, M. fortuitum*	*M. abscessus*
Skeletal infection	MAC, *M. kansasii, M. fortuitum*	*M. chelonae, M. marinum, M. abscessus, M. ulcerans**
Disseminated	MAC	*M. kansasii, Mycobacterium genavense, M. haemophilum, M. chelonae*

*Endemic in West Africa and Australia, minor foci in East Asia and Latin America.
†Found primarily in Northern Europe.
MAC, *Mycobacterium avium* complex.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 761.*

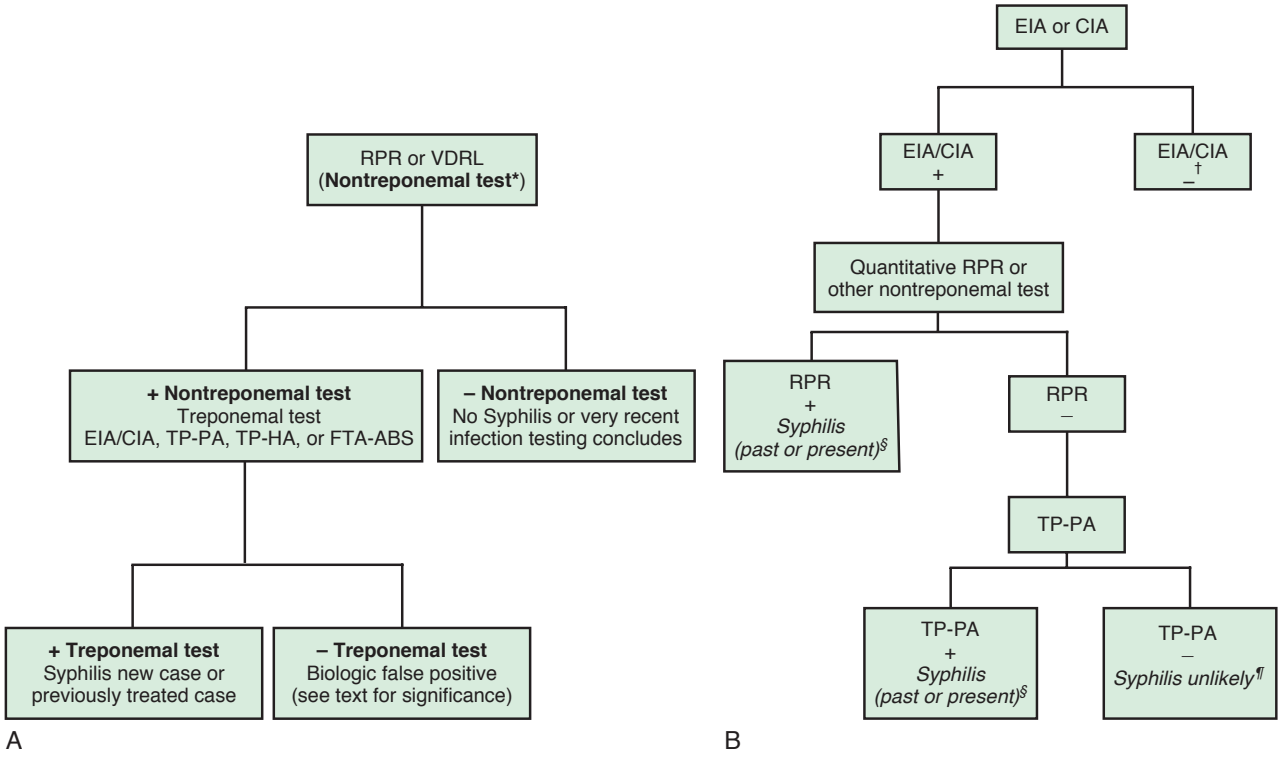


Figure 218-9 **A,** Traditional laboratory testing algorithm for syphilis. **B,** CDC-recommended algorithm for reverse sequence syphilis screening (treponemal test screening followed by nontreponemal test confirmation). Despite these recommendations for reverse sequence screening, the CDC continues to recommend the traditional algorithm with reactive nontreponemal tests confirmed by treponemal testing. *EIA/CIA*, enzyme immunoassay/chemiluminescence immunoassay; *FTA-ABS*, fluorescent treponemal antibody absorption; *RPR*, rapid plasma reagin; *TP-HA*, *Treponema pallidum* hemagglutination; *TP-PA*, Treponema pallidum particle agglutination; *VDRL*, Venereal Disease Research Laboratory. *If nontreponemal test is positive qualitatively, a titer is then quantitated. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. §Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC's 2010 STD Treatment Guidelines (available at http://www.cdc.gov/std/treatment/2010). ¶If at risk for syphilis, repeat RPR in several weeks. (***A*** *based on data from Workowski KA, Berman S; Centers for Diseases Control and Prevention [CDC]: Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 59[RR-12]:1-110, 26-29, 2010;* ***B*** *from Centers for Disease Control and Prevention [CDC]: Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep 60(5):133-137, 2011.)*

Table 234-1 Dosing of Antifungal Agents in Infants* and Number of Infants Younger Than 1 Yr of Age Studied with Reported Pharmacokinetic Parameters

DRUG	INFANTS STUDIED	SUGGESTED DOSE
Amphotericin B deoxycholate	27	1 mg/kg/day
Amphotericin B lipid complex	28	5 mg/kg/day
Liposomal amphotericin B	17	5 mg/kg/day
Amphotericin B colloidal dispersion	0	5 mg/kg/day
Fluconazole†	65	12 mg/kg/day
Micafungin‡	120	10 mg/kg/day
Caspofungin§	22	50 mg/m^2/day
Anidulafungin‡	15	1.5 mg/kg/day

*Voriconazole dosing has not been investigated in the nursery.
†A loading dose of 25 mg/kg of fluconazole is necessary to achieve therapeutic serum concentrations in the early days of therapy.
‡Micafungin has been studied in infants <120 days of life at this dosage.
§Caspofungin and anidulafungin should generally be avoided because dosing sufficient to penetrate brain tissue has not been studied.

Table 234-2 Dosing of Antifungal Agents in Children Older Than 1 Year of Age for Treatment of Invasive Disease

DRUG	SUGGESTED DOSAGE
Amphotericin B deoxycholate	1 mg/kg/day
Amphotericin B lipid complex	5 mg/kg/day
Liposomal amphotericin B	5 mg/kg/day
Amphotericin B colloidal dispersion	5 mg/kg/day
Fluconazole†	12 mg/kg/day
Voriconazole	8 mg/kg every 12 hr
Micafungin*	2-4 mg/kg/day
Caspofungin	50 mg/m^2/day
Anidulafungin	1.5 mg/kg/day

*Use adult dosages in children older than 8 yr of age.
†Loading doses should be used for fluconazole (25 mg/kg), voriconazole (9 mg/kg q 12 × 24 hr), caspofungin (70 mg/m^2), and anidulafungin (3 mg/kg).

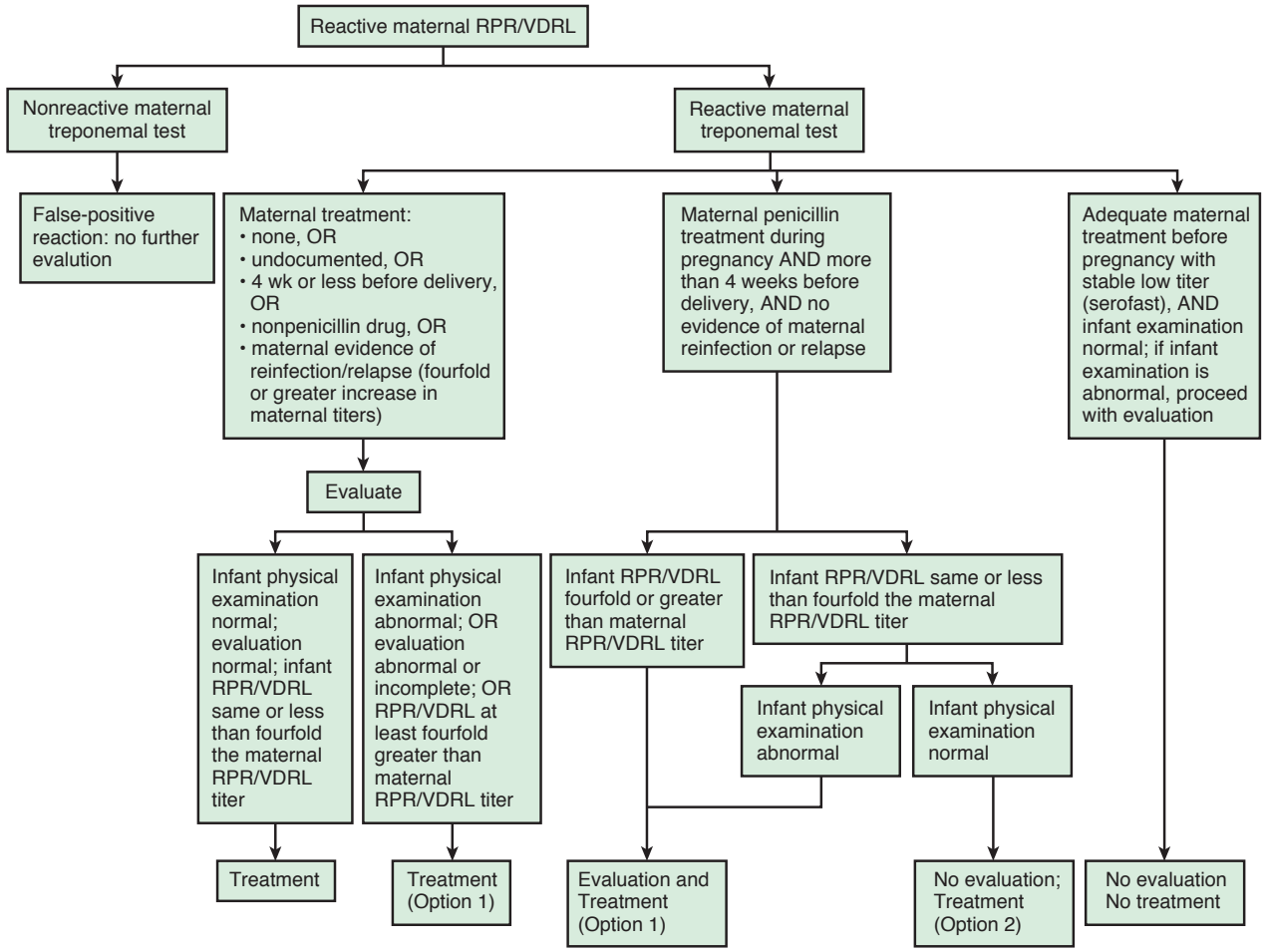


Figure 218-11 Algorithm for evaluating and treating infants born to mothers with reactive serologic tests for syphilis. *(From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics,* Fig. 3-7, *p. 695.)*

Table 233-1 Suggested Dosing of Antifungal Agents in Children and Neonates

DRUG	FORMULATIONS	SUGGESTED PEDIATRIC DOSAGE	COMMENTS
Amphotericin B deoxycholate	IV	1 mg/kg/day	Generally less toxicity in children than adults; do not start with smaller test doses
Lipid amphotericin B formulations	IV	5 mg/kg/day	Generally all lipid formulations are dosed the same; there is no clear indication of one formulation over another for clinical efficacy
Fluconazole	IV, PO	12 mg/kg/day	Loading dose (25 mg/kg) is suggested based on pharmacokinetic simulations, but insufficiently studied
Itraconazole	IV, PO	2.5 mg/kg/dose bid	Divide dosage twice daily in children; follow trough levels
Voriconazole	IV, PO	8 mg/kg/dose bid IV maintenance; 9 mg/kg/dose bid oral maintenance	Linear pharmacokinetics in children requires higher dosing than in adults; 9 mg/kg/dose bid IV loading, followed by maintenance dosing; follow trough levels
Posaconazole	PO	12-24 mg/kg/day divided tid	Dosage unclear in children at present In adults, max dosage is 800 mg/day, and optimally divide this into 2 or 3 doses; follow trough levels
Micafungin	IV	2-10 mg/kg/day	Highest dosages in neonates (10 mg/kg/day), and lower dosages in children; older than 8 yr of age, use adult dosage
Anidulafungin	IV	1.5 mg/kg/day	Loading dose of 3 mg/kg/day
Caspofungin	IV	50 mg/m^2/day	Load with 70 mg/m^2/day, then 50/mg/m^2/day as maintenance dosage

Table 218-2 Clues That Suggest a Diagnosis of Congenital Syphilis*

EPIDEMIOLOGIC BACKGROUND	CLINICAL FINDINGS
Untreated early syphilis in the mother	Osteochondritis, periostitis
Untreated latent syphilis in the mother	Snuffles, hemorrhagic rhinitis
An untreated mother who has contact with a known syphilitic during pregnancy	Condylomata lata
	Bullous lesions, palmar or plantar rash
Mother treated for syphilis during pregnancy with a drug other than penicillin	Mucous patches
	Hepatomegaly, splenomegaly
Mother treated for syphilis during pregnancy without follow-up to demonstrate 4-fold change in titer	Jaundice
	Nonimmune hydrops fetalis
Mother coinfected with HIV	Generalized lymphadenopathy
	Central nervous system signs; elevated cell count or protein in cerebrospinal fluid
	Hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia
	Pneumonitis
	Nephrotic syndrome
	Placental villitis or vasculitis (unexplained enlarged placenta)
	Intrauterine growth restriction

*Arranged in decreasing order of confidence of diagnosis.
Modified from Remington JS, Klein JO, Wilson CB, et al, editors: Infectious diseases of the fetus and newborn infant, *ed 6. Philadelphia, 2006, WB Saunders, p. 556.*

Table 218-3 Recommended Management of Neonates (≤1 Month of Age) Born to Mothers with Serologic Tests for Syphilis

CLINICAL STATUS	EVALUATION (IN ADDITION TO PHYSICAL EXAMINATION AND QUANTITATIVE NONTREPONEMAL TESTING)	ANTIMICROBIAL THERAPY*
Proven or highly probable disease†	CSF analysis for VDRL, cell count, and protein CBC and platelet count Other tests as clinically indicated (e.g., long-bone radiography, liver function tests, ophthalmologic examination)	Aqueous crystalline penicillin G, 100,000-150,000 units/kg/day, administered as 50,000 units/kg/dose IV q12hr during the 1st 7 days of life and 18 hr thereafter for a total of 10 days *or* Penicillin G procaine, 50,000 units/kg/day IM in a single dose × 10 days
NORMAL PHYSICAL EXAMINATION AND SERUM QUANTITATIVE NONTREPONEMAL TITER ≤4 TIMES THE MATERNAL TITER:		
(a) (i) Mother was not treated or inadequately treated or has no documented treatment; (ii) mother was treated with erythromycin or other nonpenicillin regimen; (iii) mother received treatment ≤4 wk before delivery; (iv) maternal evidence of reinfection or relapse (<4-fold decrease in titers)	CSF analysis for VDRL, cell count, and protein§ CBC and platelet count§ Long-bone radiography§	Aqueous crystalline penicillin G IV × 10 days§ *or* Penicillin G procaine‡ 50,000 units/kg IM in a single dose × 10 days§ *or* Penicillin G benzathine‡ 50,000 units/kg IM in a single dose§
(b) (i) Adequate maternal therapy given >4 wk before delivery; (ii) mother has no evidence of reinfection or relapse	None	Clinical, serologic follow-up, and penicillin G benzathine 50,000 units/kg IM in a single dose‖
(c) Adequate therapy before pregnancy and mother's nontreponemal serologic titer remained low and stable during pregnancy and at delivery	None	None¶

*If more than 1 day of therapy is missed, the entire course should be restarted.
†Abnormal physical examination, serum quantitative nontreponemal titer that is 4-fold greater than the mother's titer, or positive result of darkfield or fluorescent antibody test of body fluid(s).
‡Penicillin G benzathine and penicillin G procaine are approved for IM administration only.
§A complete evaluation (CSF analysis, bone radiography, CBC) is not necessary if 10 days of parenteral therapy is administered, but it may be useful to support a diagnosis of congenital syphilis. If a single dose of penicillin G benzathine is used, then the infant must be evaluated fully, results of the full evaluation must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed or if the CSF analysis is uninterpretable, the 10-day course of penicillin is required.
‖Some experts would not treat the infant but would provide close serologic follow-up.
¶Some experts would treat with penicillin G benzathine, 50,000 units/kg, as a single IM injection, if follow-up is uncertain.
CBC, complete blood cell count; CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.
From American Academy of Pediatrics: Red book: 2009 report of the Committee on Infectious Diseases, *28/e. Elk Grove Village, IL, 2009, American Academy of*

Table 218-4 Recommended Treatment for Syphilis in Patients Older Than 1 Month of Age

STATUS	CHILDREN	ADULTS
Congenital syphilis	Aqueous crystalline penicillin G 200,000-300,000 units/kg/day IV administered as 50,000 units/kg q4-6hr × 10 days*	
Primary, secondary, and early latent syphilis†	Penicillin G benzathine,‡ 50,000 units/kg, IM, up to the adult dose of 2.4 million units in a single dose	Penicillin G benzathine,‡ 2.4 million units IM in a single dose *or* *If allergic to penicillin and not pregnant,* doxycycline 100 mg PO bid × 14 days *or* Tetracycline 500 mg PO qid × 14 days
Late latent syphilis§ or syphilis of unknown duration	Penicillin G benzathine,‡ 50,000 units/kg IM up to the adult dose of 2.4 million units, administered as 3 single doses at 1 wk intervals (total 150,000 units/kg, up to the adult dose of 7.2 million units)	Penicillin G benzathine‡ 7.2 million units total administered as 3 doses of 2.4 million units IM, each at 1 wk intervals *or* *If allergic to penicillin and not pregnant,* doxycycline 100 mg PO bid × 4 wk *or* Tetracycline 500 mg PO qid × 4 wk
Tertiary syphilis		Penicillin G benzathine‡ 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1 wk intervals *If allergic to penicillin and not pregnant, same as for late latent syphilis*
Neurosyphilis‖	Aqueous crystalline penicillin G 200,000-300,000 units/kg/day q4-6hr × 10-14 days in doses not to exceed the adult dose	Aqueous crystalline penicillin G 18-24 million units/day administered as 3-4 million units IV q4hr × 10-14 days¶ *or* Penicillin G procaine,‡ 2.4 million units IM once daily *plus* probenecid 500 mg PO qid, both × 10-14 days¶

*If the patient has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL result is negative, some experts would treat with up to 3 weekly doses of penicillin G benzathine 50,000 units/kg IM. Some experts also suggest giving these patients a single dose of penicillin G benzathine 50,000 units/kg IM after the 10-day course of IV aqueous penicillin.
†Early latent syphilis is defined as being acquired within the preceding year.
‡Penicillin G benzathine and penicillin G procaine are approved for IM administration only.
§Late latent syphilis is defined as syphilis beyond 1 year's duration.
‖Patients who are allergic to penicillin should be desensitized.
¶Some experts administer penicillin G benzathine 2.4 million units IM, once per week for up to 3 wk after completion of these neurosyphilis treatment regimens.
CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 698, Table 3.72.*

Table 222-2 Recommended Treatment of Lyme Disease

DRUG	PEDIATRIC DOSING
Amoxicillin	50 mg/kg/day in 3 divided doses (max: 1,500 mg/day)
Doxycycline	4 mg/kg/day in 2 divided doses (max: 200 mg/day) (see text regarding doxycycline use in children)
Cefuroxime axetil	30 mg/kg/day in 2 divided doses (max: 1,000 mg/day)
Ceftriaxone (IV)*†	50-75 mg/kg/day once daily (max: 2,000 mg/day)
RECOMMENDED THERAPY BASED ON CLINICAL MANIFESTATION	
Erythema migrans	Oral regimen, 14-21 days
Meningitis	Ceftriaxone, 10-28 days
Cranial nerve palsy	Oral regimen, 14-21 days (see text regarding possible need for lumbar puncture)
Cardiac disease	Oral regimen or ceftriaxone, 14-21 days (see text for specifics)
Arthritis‡	Oral regimen, 28 days
Late neurologic disease	Ceftriaxone, 14-28 days

*Cefotaxime and penicillin G are alternative parenteral agents.
†Doses of 100 mg/kg/day should be used for meningitis.
‡Persistent arthritis can be treated with a second oral regimen or ceftriaxone.
From Wormser GP, Dattwyler RJ, Shapiro ED, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America, Clin Infect Dis *43:1089–1134, 2006.*

Table 222-1 Clinical Stages of Lyme Disease

DISEASE STAGE	TIMING AFTER TICK BITE	TYPICAL CLINICAL MANIFESTATIONS
Early localized	3-30 days	Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue)
Early disseminated	3-12 wk	Erythema migrans (single or multiple), worse constitutional symptoms, cranial neuritis, meningitis, carditis, ocular disease
Late	>2 mo	Arthritis

Table 245-1 Currently Licensed Antiviral Drugs*

ANTIVIRAL	TRADE NAME	MECHANISM OF ACTION
Acyclovir	Zovirax	Inhibits viral DNA polymerase
Adefovir	Hepsera	Nucleotide reverse transcriptase inhibitor
Amantadine	Symmetrel	Blocks M2 protein ion channel
Cidofovir	Vistide	Inhibits viral DNA polymerase
Famciclovir	Famvir	Inhibits viral DNA polymerase
Fomivirsen	Vitravene	Phosphorothioate oligonucleotide inhibits viral replication via antisense mechanism
Foscarnet	Foscavir	Inhibits viral DNA polymerase and reverse transcriptase at pyrophosphate-binding site
Ganciclovir	Cytovene	Inhibits viral DNA polymerase
Idoxuridine	Herplex	Inhibits viral DNA polymerase
Interferon-α	Intro-A (interferon-α2b) Roferon-A (interferon-α2a) Infergen (interferon alfacon-1)	Produces multiple effector proteins that exert antiviral effects; also directly interacts with immune system components
Interferon-α2b plus ribavirin	Rebetron	Not established
Lamivudine	Epivir	Inhibits viral DNA polymerase and reverse transcriptase
Oseltamivir	Tamiflu	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
Pegylated interferon	PEG-Intron (α2b), Pegasys (α2a)	Same as interferon
Penciclovir	Denavir	Inhibits viral DNA polymerase
Ribavirin	Virazole, Rebetol, Copegus	Interference with viral messenger RNA
Rimantadine	Flumadine	Blocks M2 protein ion channel
Trifluridine	Viroptic	Inhibits viral DNA polymerase
Valacyclovir	Valtrex	Same as acyclovir
Valganciclovir	Valcyte	Same as ganciclovir
Vidarabine	ara-A	Inhibits viral DNA polymerase (and to lesser extent, cellular DNA polymerase)
Zanamivir	Relenza	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
FDA-APPROVED COMBINATION THERAPIES		
Interferon-α2b + ribavirin	Rebetron (Intron-A plus Rebetol)	
Interferon-α2a + ribavirin	Roferon-A + ribavirin	
Pegylated interferon-α2b + ribavirin	PEG-Intron + Rebetol	
Pegylated interferon-α2a + ribavirin	Pegasys + Copegus	

*See Chapter 276 for antiretroviral drugs.

Table 246-2 Recommendations for Measles Immunization

CATEGORY	RECOMMENDATIONS
Unimmunized, no history of measles (12-15 mo of age)	A 2 dose schedule (with MMR) is recommended The 1st dose is recommended at 12-15 mo of age; the 2nd is recommended at 4-6 yr of age
Children 6-11 mo of age in epidemic situations or prior to international travel	Immunize with MMR vaccine, but this dose is not considered valid, and 2 valid doses administered on or after the 1st birthday are required, The 1st valid dose should be administered at 12-15 mo of age. The 2nd valid dose is recommended at least 28 days later and is given at 4 through 6 yr of age
Students in kindergarten or elementary, middle, and high school who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the 2nd dose
Students in college and other post–high school institutions who have received 1 dose of measles vaccine at ≥12 mo of age	Administer the 2nd dose
History of immunization before the 1st birthday	Do not consider valid and immunize (2 doses)
History of receipt of inactivated measles vaccine or unknown type of vaccine, 1963-1967	Do not consider valid and immunize (2 doses)
Further attenuated or unknown vaccine given with Ig	Do not consider valid and immunize (2 doses)
Allergy to eggs	Immunize; no reactions likely
Neomycin allergy, nonanaphylactic	Immunize; no reactions likely
Severe hypersensitivity (anaphylaxis) to neomycin or gelatin	Avoid immunization
Tuberculosis	Immunize; if patient has untreated tuberculosis disease, start antituberculosis therapy before immunizing
Measles exposure	Immunize and/or give Ig, depending on circumstances
HIV-infected	Immunize (2 doses) unless severely immunocompromised, and give Ig if exposed to measles
Personal or family history of seizures	Immunize; advise parents of slightly increased risk of seizures
Ig or blood recipient	Immunize at the appropriate interval (see Table 246-3)

Ig, immunoglobulin; MMR, measles-mumps-rubella vaccine.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 494.*

Table 245-2 Antiviral Therapies for Non-HIV Clinical Conditions

VIRUS	CLINICAL SYNDROME	ANTIVIRAL AGENT OF CHOICE	ALTERNATIVE ANTIVIRAL AGENTS
Influenza A	Treatment	Oseltamivir (>1 yr old)	Rimantadine Amantadine
	Prophylaxis	Oseltamivir (>1 yr old)	Amantadine Rimantadine Zanamivir (>7 yr old)
Influenza B	Treatment	Oseltamivir	Zanamivir (>7 yr old)
Respiratory syncytial virus	Bronchiolitis or pneumonia in high-risk host	Ribavirin aerosol	
Cytomegalovirus (CMV)	Congenital CMV infection	Ganciclovir (IV)	Valganciclovir (if oral therapy appropriate; long-term oral valganciclovir investigational but may improve developmental and hearing outcomes)
	Retinitis in AIDS patients	Valganciclovir	Ganciclovir Cidofovir Foscarnet Ganciclovir ocular insert
	Pneumonitis, colitis; esophagitis in immunocompromised patients	Ganciclovir (IV)	Foscarnet Cidofovir Valganciclovir
Herpes simplex virus (HSV)	Neonatal herpes	Acyclovir (IV)	
	Suppressive therapy following neonatal herpes with central nervous system involvement	Acyclovir (PO)	
	HSV encephalitis	Acyclovir (IV)	
	HSV gingivostomatitis	Acyclovir (PO)	Acyclovir (IV)
	First episode genital infection	Acyclovir (PO)	Valacyclovir Famciclovir Acyclovir (IV) (severe disease)
	Recurrent genital herpes	Acyclovir (PO)	Valacyclovir Famciclovir
	Suppression of genital herpes	Acyclovir (PO)	Valacyclovir Famciclovir
	Cutaneous HSV (whitlow, herpes gladiatorum)	Acyclovir (PO)	Penciclovir (topical)
	Eczema herpeticum	Acyclovir (PO)	Acyclovir (IV) (severe disease)
	Mucocutaneous infection in immunocompromised host (mild)	Acyclovir (IV)	Acyclovir (PO) (if outpatient therapy acceptable)
	Mucocutaneous infection in immunocompromised host (moderate to severe)	Acyclovir (IV)	
	Prophylaxis in bone marrow transplant recipients	Acyclovir (IV)	Valacyclovir Famciclovir
	Acyclovir-resistant HSV	Foscarnet	Cidofovir
	Keratitis or keratoconjunctivitis	Trifluridine	Vidarabine
Varicella-zoster virus	Chickenpox, healthy child	Supportive care	Acyclovir (PO)
	Chickenpox, immunocompromised child	Acyclovir (IV)	
	Zoster (not ophthalmic branch of trigeminal nerve), healthy child	Supportive care	Acyclovir (PO)
	Zoster (ophthalmic branch of trigeminal nerve), healthy child	Acyclovir (IV)	
	Zoster, immunocompromised child	Acyclovir (IV)	Valacyclovir

Modified from Kimberlin DW: Antiviral therapies in children: Has their time arrived? Pediatr Clin North Am *52:837–867, 2005.*

Table 246-3 Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*

INDICATION FOR IMMUNOGLOBULIN	Dose ROUTE	UNITS (U) OR MILLILITERS (mL)	mg IgG/kg	INTERVAL (mo)†
Tetanus (as tetanus Ig)	IM	250 U	10	3
Hepatitis A prophylaxis (as Ig):				
Contact prophylaxis	IM	0.02 mL/kg	3.3	3
International travel	IM	0.06 mL/kg	10	3
Hepatitis B prophylaxis (as hepatitis B Ig)	IM	0.06 mL/kg	10	3
Rabies prophylaxis (as rabies Ig)	IM	20 IU/kg	22	4
Varicella prophylaxis (as VariZIG)	IM	125 U/10 kg (maximum 625 U)	20-40	5
Measles prophylaxis (as Ig):				
Standard	IM	0.25 mL/kg	40	5
Immunocompromised host	IM	0.50 mL/kg	80	6
Respiratory syncytial virus prophylaxis (palivizumab monoclonal antibody)‡	IM	—	15 mg/kg (monoclonal)	None
Cytomegalovirus immune globulin	IV	3 mL/kg	150	6
Blood transfusion:				
Washed RBCs	IV	10 mL/kg	Negligible	0
RBCs, adenine-saline added	IV	10 mL/kg	10	3
Packed RBCs	IV	10 mL/kg	20-60	5
Whole blood	IV	10 mL/kg	80-100	6
Plasma or platelet products	IV	10 mL/kg	160	7

Continued

Table 246-3 Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*—cont'd

INDICATION FOR IMMUNOGLOBULIN	Dose ROUTE	UNITS (U) OR MILLILITERS (mL)	mg IgG/kg	INTERVAL (mo)†
Replacement (or therapy) of immune deficiencies (as IVIG)	IV	—	300-400	8
ITP (as IVIG)	IV	—	400	8
ITP	IV	—	1,000	10
ITP or Kawasaki disease	IV	—	1,600-2,000	11

*Immunization in the form of measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), or monovalent measles vaccine.

†These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of Ig or measles vaccine may be indicated after exposure to measles (see text).

‡Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.

Ig, immunoglobulin; IgG, immunoglobulin G; ITP, immune (formerly termed "idiopathic") thrombocytopenic purpura; IVIG, intravenous Ig; RBCs, red blood cells.

Table 247-2 Clinical Manifestations of Congenital Rubella Syndrome in 376 Children Following Maternal Rubella*

MANIFESTATION	RATE (%)
Deafness	67
Ocular	71
Cataracts	29
Retinopathy	39
Heart disease†	48
Patent ductus arteriosus	78
Right pulmonary artery stenosis	70
Left pulmonary artery stenosis	56
Valvular pulmonic stenosis	40
Low birthweight	60
Psychomotor retardation	45
Neonatal purpura	23
Death	35

*Other findings: hepatitis, linear streaking of bone, hazy cornea, congenital glaucoma, delayed growth.

†Findings in 87 patients with congenital rubella syndrome and heart disease who underwent cardiac angiography.

Table 249-1 Differential Diagnosis of Acute Flaccid Paralysis

SITE, CONDITION, FACTOR, OR AGENT	CLINICAL FINDINGS	ONSET OF PARALYSIS	PROGRESSION OF PARALYSIS	SENSORY SIGNS AND SYMPTOMS	REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES	RESIDUAL PARALYSIS	PLEOCYTOSIS
ANTERIOR HORN CELLS OF SPINAL CORD							
Poliomyelitis (wild and vaccine-associated paralytic poliomyelitis)	Paralysis	Incubation period 7-14 days (range: 4-35 days)	24-48 hr to onset of full paralysis; proximal → distal, asymmetric	No	Yes	Yes	Aseptic meningitis (moderate polymorphonuclear leukocytes at 2-3 days)
Nonpolio enteroviruses	Hand-foot-and-mouth disease, aseptic meningitis, acute hemorrhagic conjunctivitis, possibly idiopathic epidemic flaccid paralysis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	As in poliomyelitis
West Nile virus	Meningitis encephalitis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	Yes
OTHER NEUROTROPIC VIRUSES							
Rabies virus		Month–year	Acute, symmetric, ascending	Yes	Yes	No	±
Varicella-zoster virus	Exanthematous vesicular eruptions	Incubation period 10-21 days	Acute, symmetric, ascending	Yes	±	±	Yes
Japanese encephalitis virus		Incubation period 5-15 days	Acute, proximal, asymmetric	±	±	±	Yes
GUILLAIN-BARRÉ SYNDROME							
Acute inflammatory polyradiculoneuropathy	Preceding infection, bilateral facial weakness	Hours to 10 days	Acute, symmetric, ascending (days to 4 wk)	Yes	Yes	±	No
Acute motor axonal neuropathy	Fulminant, widespread paralysis, bilateral facial weakness, tongue involvement	Hours to 10 days	1-6 days	No	Yes	±	No

ACUTE TRAUMATIC SCIATIC NEURITIS							
Intramuscular gluteal injection	Acute, asymmetric	Hours to 4 days	Complete, affected limb	Yes	Yes	±	No
Acute transverse myelitis	Preceding *Mycoplasma pneumoniae, Schistosoma,* other parasitic or viral infection	Acute, symmetric hypotonia of lower limbs	Hours to days	Yes	Yes, early	Yes	Yes
Epidural abscess	Headache, back pain, local spinal tenderness, meningismus	Complete		Yes	Yes	±	Yes
Spinal cord compression; trauma		Complete	Hours to days	Yes	Yes	±	±
NEUROPATHIES							
Exotoxin of *Corynebacterium diphtheriae*	In severe cases, palatal paralysis, blurred vision	Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)		Yes	Yes		±
Toxin of *Clostridium botulinum*	Abdominal pain, diplopia, loss of accommodation, mydriasis	Incubation period 18-36 hr	Rapid, descending, symmetric	±	No		No
Tick bite paralysis	Ocular symptoms	Latency period 5-10 days	Acute, symmetric, ascending	No	Yes		No
DISEASES OF THE NEUROMUSCULAR JUNCTION							
Myasthenia gravis	Weakness, fatigability, diplopia, ptosis, dysarthria		Multifocal	No	No	No	No
DISORDERS OF MUSCLE							
Polymyositis	Neoplasm, autoimmune disease	Subacute, proximal → distal	Weeks to months	No	Yes		No
Viral myositis		Pseudoparalysis	Hours to days	No	No		No
METABOLIC DISORDERS							
Hypokalemic periodic paralysis		Proximal limb, respiratory muscles	Sudden postprandial	No	Yes	±	No
INTENSIVE CARE UNIT WEAKNESS							
Critical illness polyneuropathy	Flaccid limbs and respiratory weakness	Acute, following systemic inflammatory response syndrome/sepsis	Hours to days	±	Yes	±	No

Modified from Marx A, Glass JD, Sutter RW: Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance, Epidemiol Rev *22:298–316, 2000.*

Table 258-3 Centers for Disease Control and Prevention Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis

ANTIVIRAL AGENT	USE	CHILDREN	ADULTS*
Oseltamivir (Tamiflu)	Treatment (5 days)	**If child is younger than 1 yr old**[†]: 3 mg/kg/dose twice daily[‡] **If child is 1 yr or older, dose varies by child's weight:** 15 kg or less, the dose is 30 mg **twice** a day >15-23 kg, the dose is 45 mg **twice** a day >23-40 kg, the dose is 60 mg **twice** a day >40 kg, the dose is 75 mg **twice** a day	75 mg twice daily
	Chemoprophylaxis (7 days)	If child is younger than 3 mo old, use of oseltamivir for chemoprophylaxis is not recommended unless situation is judged critical because of limited data in this age group **If child's age is 3 mo or older and younger than 1 yr old**[†]: 3 mg/kg/dose **once** daily[‡] **If child is 1 yr or older, dose varies by child's weight:** 15 kg or less, the dose is 30 mg **once** a day >15-23 kg, the dose is 45 mg **once** a day >23-40 kg, the dose is 60 mg **once** a day >40 kg, the dose is 75 mg **once** a day	75 mg once daily
Zanamivir[¶] (Relenza)	Treatment (5 days)	**For children age 7 yr and older:** 10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) **twice** daily
	Chemoprophylaxis (7 days)	**For children age 5 yr and older:** 10 mg (two 5-mg inhalations) once daily	10 mg (two 5-mg inhalations) **once** daily

Current for 2013-2014 influenza season, United States.

*Intravenous peramivir (Rapivab) was approved on December 19, 2014, for use in the treatment of acute uncomplicated influenza in people 18 years and older.

[†]Oral oseltamivir is approved by the FDA for treatment of acute uncomplicated influenza with twice-daily dosing in persons older than 14 days of age, and for prophylaxis with once-daily dosing in persons 1 yr and older. Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants younger than 14 days old, and for prophylaxis in infants 3 mo to 1 yr of age, is recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics.

[‡]This is the FDA-approved oral and CDC-recommended oseltamivir treatment dose for infants 14 days and older and less than 1 yr old, and provides oseltamivir exposure in children similar to that achieved by the approved dose of 75 mg orally twice daily for adults, as shown in 2 studies of oseltamivir pharmacokinetics. The American Academy of Pediatrics recommends an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants ages 9-11 mo for the 2013-2014 season, on the basis of data that indicated that the higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the Collaborative Antiviral Study Group (CASG) 114 study. It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5 mg/kg dose is harmful or causes more adverse events to infants in this age group.

[¶]Inhaled zanamivir is approved for treatment of acute uncomplicated influenza with twice-daily dosing in persons age 7 yr and older, and for prophylaxis with once-daily dosing in persons age 5 yr and older.

Adapted from Centers for Disease Control and Prevention (CDC): Influenza antiviral medications: summary for clinicians. *Available at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. For current details, consult annually updated recommendations at http://www.cdc.gov/flu*

Table 255-1 Findings in Infants with Symptomatic Congenital Cytomegalovirus Infection Identified Through Newborn Screening Program*

	PERCENTAGE (%) OF INFANTS
CLINICAL FINDINGS	
Prematurity (<37 wk)	24
Jaundice (direct bilirubin >2 mg/dL)	42
Petechiae	54
Hepatosplenomegaly	19
Purpura	3
Microcephaly	35
Small gestational age	28
1 Clinical finding	41
2 Clinical findings	59
LABORATORY FINDINGS	
Elevated alanine aminotransferase (>80 IU/mL)	71
Thrombocytopenia (<100,000/μL)	43
Direct hyperbilirubinemia (>2 mg/dL)	54
Head CT abnormalities	42

*Findings in 70 infants with symptomatic congenital CMV infection identified during the newborn screening program for infants with congenital CMV infection performed at the University of Alabama Hospitals over an approximate 20 yr interval.

Table 250-2 Differential Diagnosis of Enterovirus Infections

CLINICAL MANIFESTATION	BACTERIAL PATHOGENS	VIRAL PATHOGENS
Nonspecific febrile illness	*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis*	Influenza viruses, human herpesviruses 6 and 7, human parechoviruses
Exanthems/enanthems	Group A streptococcus, *Staphylococcus aureus, N. meningitidis*	Herpes simplex virus, adenoviruses, varicella-zoster virus, Epstein-Barr virus, measles virus, rubella virus, human herpesviruses 6 and 7, human parechoviruses
Respiratory illness/conjunctivitis	*S. pneumoniae, H. influenzae* (nontypeable and type b), *N. meningitidis, Mycoplasma pneumoniae, Chlamydia pneumoniae*	Adenoviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, human metapneumovirus, coronaviruses
Myocarditis/pericarditis	*S. aureus, H. influenzae* type b, *M. pneumoniae*	Adenoviruses, influenza virus, parvovirus, cytomegalovirus
Meningitis/encephalitis	*S. pneumoniae, H. influenzae* type b, *N. meningitidis, Mycobacterium tuberculosis, Borrelia burgdorferi, M. pneumoniae, Bartonella henselae, Listeria monocytogenes*	Herpes simplex virus, West Nile virus, influenza viruses, adenoviruses, Epstein-Barr virus, mumps virus, lymphocytic choriomeningitis virus, arboviruses, human parechoviruses
Neonatal infections	Group B streptococcus, Gram-negative enteric bacilli, *L. monocytogenes, Enterococcus*	Herpes simplex virus, adenoviruses, cytomegalovirus, rubella virus, human parechoviruses

Table 274-1 Rabies Postexposure Prophylaxis Guide

ANIMAL TYPE	EVALUATION AND DISPOSITION OF ANIMAL	POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS
Dogs, cats, and ferrets	Healthy and available for 10 days of observation Rabid or suspected of being rabid† Unknown (escaped)	Prophylaxis only if animal shows signs of rabies* Immediate immunization and RIG Consult public health officials for advice
Bats, skunks, raccoons, foxes, and most other carnivores; woodchucks	Regarded as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests†	Immediate immunization and RIG
Livestock, rodents, and lagomorphs (rabbits, hares, and pikas)	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice and other rodents, rabbits, hares, and pikas almost never require antirabies treatment

*During the 10-day observation period, at the first sign of rabies in the biting dog, cat, or ferret, treatment of the exposed person with RIG (human) and vaccine should be initiated. The animal should be euthanized immediately and tested.

†The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Immunization is discontinued if immunofluorescent test result for the animal is negative.

RIG, rabies immunoglobulin.

From American Academy of Pediatrics: Red book 2012: report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

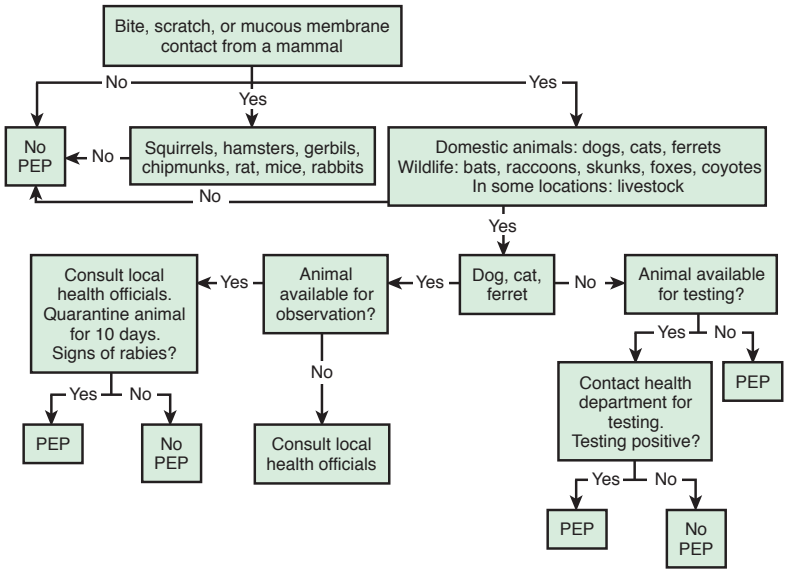


Figure 274-1 **Algorithm for evaluating a child for rabies postexposure prophylaxis.** This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.

Table 276-2 Stage 3—Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent*
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive†
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 mo duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV‡
Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 mo duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary,† disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci (previously known as *Pneumocystis carinii*) pneumonia
Pneumonia, recurrent†
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 mo
Wasting syndrome attributed to HIV‡

*Only among children aged <6 yr.

†Only among adults, adolescents, and children aged≥6 yr.

‡Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:

Table 276-3 Laboratory Diagnosis of HIV Infection

TEST	COMMENT
HIV DNA PCR	Preferred test to diagnose HIV-1 subtype B infection in infants and children younger than 18 mo of age; highly sensitive and specific by 2 wk of age and available; performed on peripheral blood mononuclear cells. False negatives can occur in non-B subtype HIV-1 infections
HIV culture	Expensive, not easily available, requires up to 4 wk to do test; not recommended
HIV RNA PCR	Preferred test to identify non-B subtype HIV-1infections. Similar sensitivity and specificity to HIV DNA PCR in infants and children younger than 18 mo of age, but DNA PCR is generally preferred because of greater clinical experience with that assay

Table 276-1 HIV Infection Stage* Based on Age-Specific $CD4^+$ T-Lymphocyte Count or $CD4^+$ T-Lymphocyte Percentage of Total Lymphocytes

	Age on Date of $CD4^+$ T-Lymphocyte Test					
	<1 Yr		1-5 Yr		≥6 Yr	
Stage	CELLS/μL	%	CELLS/μL	%	CELLS/μL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750-1,499	26-33	500-999	22-29	200-499	14-25
3	<750	<26	<500	<22	<200	<14

*Stage is based primarily on the $CD4^+$ T-lymphocyte count. The $CD4^+$ T-lymphocyte count takes precedence over the $CD4^+$ T-lymphocyte percentage, and the percentage is considered only if the count is missing.

From Centers for Disease Control and Prevention: Revised surveillance case definition for HIV infection—United States, 2014. MMWR 63(No RR-3):1-10, 2014.

Table 276-4 Summary of Antiretroviral Therapies Available in 2014

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Lactic acidosis with hepatic steatosis	
Abacavir (ABC) Ziagen, ABC Tablet: 300 mg Oral solution: 20 mg/mL Trizivir: combination of zidovudine (ZDV), lamivudine, ABC (300, 150, 300 mg) Epzicom: combination of lamivudine, ABC (300, 600 mg)	Children: ≥3 mo to 13 yr: 8 mg/kg bid (maximum dose 300 mg bid) >30 kg: 300 mg bid Children with viral load <40 copies/mm^3:16 mg/kg once daily (max 600 mg) Adolescents >16 yr and adults: 600 mg once daily Trizivir (>40 kg): 1 tablet bid Epzicom (>16 yr of age): 1 tablet bid	Common: nausea, vomiting, anorexia, fever, headache, diarrhea, rash Less common: hypersensitivity, lactic acidosis with hepatic steatosis, pancreatitis, elevated triglycerides, myocardial infarction	Can be given with food Genetic screening for HLAB*5701 is recommended prior to initiation of ABC-containing treatment. If test is positive avoid ABC. Do not restart ABC in patients who had hypersensitivity-like symptoms (e.g., flu-like symptoms)
Didanosine Videx, ddI Powder for oral solution (prepared with solution containing antacid): 10 mg/mL	2 wk to <3 mo: 50 mg/m^2 bid 3-8 mo: 100 mg/m^2 bid >8 mo: 120 mg/m^2 (maximum 200 mg per dose) bid Adolescents (>13 yr) and adults <60 kg: 250 mg once daily >60 kg: 400 mg once daily (to increase adherence) If combined with tenofovir <60 kg–200 mg once daily >60 kg–250 mg once daily	Common: diarrhea, abdominal pain, nausea, vomiting Less common: pancreatitis, peripheral neuropathy, electrolyte abnormalities, lactic acidosis with hepatic steatosis, hepatomegaly, retinal depigmentation	Food decreases bioavailability up to 50%. Take 30 min before or 2 hr after meal. Tablets dissolved in water are stable for 1 hr (4 hr in buffered solution) Drug interactions: antacids/gastric acid antagonists may increase bioavailability; possible decreased absorption of fluoroquinolones, ganciclovir, ketoconazole, itraconazole, dapsone, and some protease inhibitors. Combination with d4T enhances toxicity, also common if combined with tenofovir
Videx EC Capsule, delayed release: 125, 200, 250, 400 mg Generic: 200, 250, 400 mg	Children: not established 20-25 kg: 200 mg once daily 25-60 kg: 250 mg once daily ≥60 kg: 400 mg once daily	Same as for ddI	Same as for ddI
Emtricitabine Emtriva, FTC Capsules: 200 mg Oral solution: 10 mg/mL Truvada: combination FTC, tenofovir disoproxil fumarate (TDF) (200, 300 mg) Atripla: Combination FTC, TDF, efavirenz (EFV) (200, 300, 600 mg) Complera: combination of FTC, TDF, rilpivirine (RPV) (200, 300, 25mg) Stribild: combination of FTC, TDF, elvitegravir (EVG), cobicistat (COBI) (200, 300, 150, 150 mg)	Infants: 0-3 mo: 3 mg/kg once daily Children ≥3 mo to 17 yr: 6 mg/kg (maximum 240 mg) once daily >33 kg, adolescent and adult: 200 mg capsule or 240 mg solution once daily Truvada or Atripla or Complera or Stribild adult dose: 1 tablet once daily	Common: headache, insomnia, diarrhea, nausea, skin discoloration Less common: lactic acidosis with hepatic steatosis, neutropenia	Closely monitor patients with hepatitis B coinfection Can be given without regard to food. Oral solution should be refrigerated if temperature above 25°C (77°F)
Lamivudine Epivir, Epivir HBV, 3TC Tablet: 150 (scored), 300 mg (Epivir) 100 mg (Epivir HBV) Solution: 5 mg/mL (Epivir HBV), 10 mg/mL (Epivir) Combivir: combination of ZDV, lamivudine (300, 150 mg) Trizivir and Epzicom combination (see abacavir)	Neonates (<30 days): 2 mg/kg bid >1 mo: 4 mg/kg bid (maximum 150 mg bid) ≥30 kg: 150 mg bid or 300 mg once daily Children with VL <40 copies/mL: 8-10 mg/kg qd Combivir, Trizivir (>30 kg): 1 tablet bid Epzicom (>16 yr): 1 tablet qd	Common: headache, nausea Less common: pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, lipodystrophy	No food restrictions Combination with ZDV may prevent ZDV resistance. Patient should be screened for hepatitis B virus (HBV) and if positive watched for HBV exacerbation when lamivudine is discontinued
Stavudine Zerit, d4T Capsule: 15, 20, 30, 40 mg Solution: 1 mg/mL	Neonates (0-13 days): 0.5 mg/kg bid 14 days to 30 kg: 1 mg/kg bid >30 kg: 30 mg bid	Common: headache, nausea, hyperlipidemia, fat maldistribution Less common: peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis	No food restrictions. Should not be administered with ZDV because of virologic antagonism. Higher incidence of lactic acidosis. Increased toxicity if combined with ddI

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Tenofovir Viread, TDF Tablet: 150, 200, 250, 300 mg Powder: 40 mg per 1 gr powder Truvada: combination of FTC, TDF (200, 300 mg) Atripla: Combination of FTC, TDF, EFV (200, 300, 600 mg) Complera: combination of FTC, TDF, RPV (200, 300, 25 mg) Stribild: combination of FTC, TDF, EVG, COBI (200, 300, 150, 150 mg)	2 to <12 yr: 8 mg/kg qd >12 yr and 35 kg, adolescent >12 yr and 35 kg and adult: 300 mg once daily Truvada, Atripla, Complera, and Stribild (see FTC)	Common: nausea, vomiting, diarrhea Less common: lactic acidosis with hepatic steatosis, hepatomegaly, reduced bone density, renal toxicity	High-fat meal increases absorption; coadministration with ddI may increase ddI toxicity, decrease atazanavir (ATV) levels (therefore boosting ATV with ritonavir is required). ATV and lopinavir (LPV) increase TDF levels and potential toxicity. Screen for HBV before TDF given, as exacerbation of hepatitis may occur when TDF is discontinued
Zidovudine Retrovir, AZT, ZDV Capsule: 100 mg Tablet: 300 mg Syrup: 10 mg/mL Injection: 10 mg/mL Combivir: combination of ZDV, lamivudine (300, 150 mg) Trizivir: Combination of ZDV, lamivudine, ABC (300, 150, 300 mg)	**Prophylaxis:** 0-6 wk: Premature infants: 1.5 mg/kg IV every 12 hr *or* 2 mg/kg orally every 12 hr for 2 wk (for gestational age 30 to 35 wk) or 4 wk (for gestational age <30 wk); then increase to 3 mg/kg every 12 hr to complete 6 wk (if needed) For gestational age >35 wk: 3 mg/kg/dose IV every 12 hr *or* 4 mg/kg orally every 12 hr **Treatment:** 6 wk to 18 yr: 240 mg/m^2 every 12 hr *or* 4 kg to <9 kg: 12 mg/kg bid 9 kg to <30 kg: 9 mg/kg bid >30 kg, adolescent and adult: 200 mg tid or 300 mg bid Combivir *or* Trizivir: 1 tablet bid	Common: bone marrow suppression (e.g., macrocytic anemia, leukopenia), headache, nausea, vomiting, anorexia Less common: liver toxicity, lactic acidosis with hepatic steatosis, myopathy, fat redistribution	No food restrictions Drug interactions: should not be given with d4T or doxorubicin Rifampin may increase metabolism Cimetidine, fluconazole, valproic acid may decrease metabolism Ganciclovir, IFN-α, ribavirin increase ZDV toxicity
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Rash is mild to severe, usually within 1st 6 wk. Discontinue the drug if severe rash (with blistering, desquamation, muscle involvement, or fever)	
Efavirenz Sustiva, EFV Capsule: 50, 200 mg Tablet: 600 mg Atripla combination of EFV, FTC, TDF (600, 200, 300 mg)	Children <3 yr: consult with expert Children ≥3 yr: 10 to <15 kg: 200 mg qd 15 to <20 kg: 250 mg qd 20 to <25 kg: 300 mg qd 25 to <32.5 kg: 350 mg qd 32.5 to <40 kg: 400 mg qd ≥40 kg: 600 mg qd or 370 mg/m^2 body surface area Atripla (see FTC)	Common: skin rashes, CNS abnormalities (e.g., abnormal dreams, impaired concentration, insomnia, depression, hallucination) Less common: increased liver enzymes; potentially teratogenic	Capsules can be opened for mixing in food. Can be given without regard to food except fatty foods (because absorption is increased 50%) Drug interactions: Efavirenz induces/inhibits CYP3A4 enzymes. Increase clearance of drugs metabolized by this pathway (e.g., antihistamines, sedatives and hypnotics, cisapride, ergot derivatives, warfarin, ethinyl estradiol) and several other ARVs (i.e., protease inhibitors). Drugs that induce CYP3A4 (e.g., phenobarbital, rifampin, rifabutin) decrease efavirenz levels. Clarithromycin levels decrease with EFV and azithromycin should be considered
Etravirine (ETR), Intelence, ETR, tablet: 25, 100, 200 mg	Children <6 yr: consult with expert 16 to <20 kg: 100 mg bid 20 to <25 kg: 125 mg bid 25 to <30 kg: 150 mg bid >30 kg, adolescent and adult: 200 mg bid	Common: nausea, rash, diarrhea Less common: hypersensitivity reactions	Given only with food. Tablets can be dispensed in water Inducer of CYP3A4 enzymes and inhibitor of CYP2C9 and CYP2C19, causing multiple interactions that should be checked before initiating ETR. Should not be given in combination with TPV, Fos-APV, ATZ, or other nonnucleoside reverse transcriptase inhibitors

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Nevirapine Viramune, NVP Tablet: 200 mg Extended-release (XR) tablet: 100, 400 mg Suspension: 10 mg/mL	**Prophylaxis:** For infant of woman with no antepartum ARV treatment: 2 mg/kg birth to 48 hr 2 mg/kg 48 hr after 1st dose 2 mg/kg 96 hr after 2nd dose **Treatment:** <8 yr: 200 mg/m^2 once daily for 14 days; then same dose bid (maximum 200 mg per dose) or XR 400 mg qd >8 yr: 120-150 mg/m^2 once daily for 14 days; then bid (maximum 200 mg per dose) Adolescent and adult: 200 mg once daily for 14 days; then 200 mg bid *or* XR 400 mg qd	Common: skin rash, headache, fever, nausea, abnormal liver function tests Less common: hepatotoxicity (rarely life-threatening), hypersensitivity reactions	No food restrictions Drug interactions: induces hepatic CYP450A enzymes (including CYP3A and CYP2B6) activity and decreases protease inhibitor concentrations (e.g., IND, SQV, LPV). Should not be given with ATV. Reduces ketoconazole concentrations (fluconazole should be used as an alternative). Rifampin decreases nevirapine serum levels. Anticonvulsants and psychotropic drugs using same metabolic pathways as NVP should be monitored. Oral contraceptives may also be affected
Rilpivirine Edurant, RPV Tablet: 25 mg Complera combination of RPV, FTC, TDF (25, 200, 300 mg)	Pediatrics: consult with expert Adolescent (>18 yr) and adult: 25 mg	Headache, insomnia, rash, depression, mood changes	Given with food only Should not be used if viral load >100,000 copies/mm^3 or drugs that induce CYP3A or with proton pump inhibitors
PROTEASE INHIBITORS		Class adverse effects: hyperglycemia, hyperlipidemia (except atazanavir), lipodystrophy, increased transaminases, increased bleeding disorders in hemophiliacs. Can induce metabolism of ethinyl estradiol; use alternate contraception (other than estrogen-containing oral contraceptives). All undergo hepatic metabolism, mostly by CYP3A4, with many drug interactions	
Atazanavir Reyataz, ATV Capsules: 100, 150, 200, 300 mg	<6 yr: consult with expert 6-18 yr: 15 to <20 kg: 150 mg + 100 RTV qd 20 to 40 kg: 200 mg + 100 RTV qd >40 kg, adolescent and adult: 300 mg + 100 RTV qd *or* 400 mg if unboosted with food If given with EFV (600 mg) or TDF (300 mg): 400 mg + 100 RTV qd	Common: elevation of indirect bilirubin; headache, arthralgia, depression, insomnia, nausea, vomiting, diarrhea, paresthesias Less common: prolongation of PR interval on electrocardiogram (ECG); rash, rarely Stevens-Johnson syndrome, diabetes mellitus, nephrolithiasis	Administer with food to increase absorption. Review drug interactions before initiating because ATV inhibits CYP3A4, CYP1A2,CYP2C9, and UGT1A1 enzymes. Use with caution with cardiac conduction disease or liver impairment. Combination with EFV should not be used in treatment-experienced patients because it decreases ATV levels. TDF, antacids, H_2-receptor antagonists, and proton-pump inhibitors decreases ATV concentrations. Patients taking buffered ddI should take it at least 2 hr before ATV
Darunavir Prezista, DRV Tablets: 75, 150, 400, 600, 800 mg Suspension: 100 mg/mL	<3 yr: consult with expert 3 to <18 yr: 10 to <15 kg: 20 mg/kg DRV + 3 mg/kg RTV 15 to <30 kg: 375 mg DRV + 50 mg RTV bid 30 to <40 kg: 450 DRV mg + 100 mg RTV bid >40 kg, adolescent and adult: 600 mg DRV + 100 mg RTV bid *or* Adolescent (>12 yr and 40 kg) and adult: 800 mg DRV + 100 mg RTV qd with food If any DRV resistance is found: 600 mg DRV = 100 mg RTV bid	Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, headache Less common: skin rashes (including Stevens-Johnson syndrome), lipid and liver enzyme elevations, hyperglycemia, fat maldistribution	DRV should not be given without food. Contraindicated for concurrent therapy with cisapride, ergot alkaloids, benzodiazepines, pimozide, or any major CYP3A4 substrates. Use with caution in patients taking strong CYP3A4 inhibitors, or moderate/strong CYP3A4 inducers. Adjust dose with concurrent rifamycin therapy. Contains sulfa moiety: potential for cross-sensitivity with sulfonamide class

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Fosamprenavir Lexiva, FPV Tablets: 700 mg Suspension: 50 mg/mL	6 mo to 18 yr: <11 kg: 45 mg/kg FPV + 7 mg/kg RTV bid 11 to <15 kg: 30 mg/kg + 3 mg/kg RTV bid 15 to <20 kg: 23 mg/kg + 3 mg/kg RTV bid >20 kg: 18 mg/kg (max 700 mg) + 3 mg/kg (max: 100 mg) RTV bid Adolescent >18 yr and adult: FPV 700 mg + RTV 100 mg bid *or* FPV 1,400 mg + RTV 200 mg qd For protease inhibitor (PI)-experienced, the once daily dose is not recommended	Common: nausea, vomiting, perioral paresthesias, headache, rash, lipid abnormalities Less common: Stevens-Johnson syndrome, fat redistribution, neutropenia, elevated creatine kinase, hyperglycemia, diabetes mellitus, elevated liver enzymes, angioedema, nephrolithiasis	Should be given with food. FPV is an inhibitor of the CYP450 system and an inducer, inhibitor, and substrate of CYP3A4, which can cause multiple drug interactions. Use with caution in sulfa-allergic individuals
Indinavir Crixivan, IDV Capsule: 100, 200, 400 mg	Infants: not approved Children: 500 mg/m^2 every 8 hr (max dose: 800 mg per dose) *or* 400 mg/m^2 + RTV 100 mg/m^2 bid Adolescent and adult: 800 mg IDV + 100 *or* 200 mg RTV bid	Common: nausea, abdominal pain, hyperbilirubinemia, headache, dizziness, lipid abnormalities, nephrolithiasis, metallic taste Less common: fat redistribution, hyperglycemia, diabetes mellitus, hepatitis, acute hemolytic anemia	Administer on empty stomach if given without RTV. Reduce dose (600 mg IDV every 8 hr) with mild to moderate liver dysfunction. Adequate hydration (at least 48 oz fluid/day in adults) necessary to minimize risk of nephrolithiasis. IDV is cytochrome P450 3A4 inhibitor and substrate, which can cause multiple drug interactions: rifampin reduces levels; ketoconazole, ritonavir, and other protease inhibitors increase IDV levels. Do not coadminister with EFV, astemizole cisapride, terfenadine
Lopinavir/Ritonavir Kaletra, LPV/r Tablets: 100/25 mg, 200/50 mg Solution: 80/20 mg per/mL (contains 42% alcohol)	14 days to 18 yr: 300 mg/m^2 LPV +75 mg/m^2 RTV bid Adolescent (>18 yr) and adult: 400 mg LPV +100 mg RTV bid *or* 800 mg LPV +200 mg RTV qd If taken with NVP, EFV, FPV, or NFV: LPV 600 mg + RTV 150 mg bid	Common: diarrhea, headache, nausea and vomiting, lipid elevation Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation	No food restrictions. High-fat meal and flavoring of solution to increase palpability are recommended if oral solution is used. Interacts with drugs using CYP3A4, which can cause multiple drug interactions
Nelfinavir Viracept, NFV Tablet: 250, 625 mg	<2 yr: not recommended Children 2-13 yr: 45-55 mg/kg bid Adolescents and adults: 1,250 mg bid	Common: diarrhea asthenia, abdominal pain, skin rashes, lipid abnormalities Less common: exacerbation of liver disease, fat redistribution, hyperglycemia, diabetes mellitus, elevation of liver enzymes	Administer with a meal to optimize absorption; avoid acidic food or drink (e.g., orange juice). Tablet can be crushed or dissolved in water to administer as a solution Drug interactions: Nelfinavir inhibits CYP3A4 activity, which may cause multiple drug interactions. Rifampin, phenobarbital, and carbamazepine reduce levels. Ketoconazole, ritonavir, indinavir, and other protease inhibitors increase levels. Do not coadminister astemizole, cisapride, terfenadine. RTV boosting has no effect. Because of very high variation in plasma levels, TDM should be used for dose adjustment

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Ritonavir Norvir, RTV Capsule: 100 mg Tablet: 100 mg Solution: 80 mg/mL (contains 43% alcohol)	Only use is to enhance other PIs; dose varies (see information for specific PI)	Common: nausea, headache, vomiting, abdominal pain, diarrhea, taste aversion, lipid abnormalities, perioral paresthesias Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, allergic reactions	Administration with food enhances bioavailability and reduces gastrointestinal symptoms. RTV solution should not be refrigerated RTV is potent inhibitor of CYP3A4 and CYP2D6 and inducer of CYP3A4 and CYP1A2 that leads to many drug interactions (e.g., protease inhibitors, antiarrhythmics, antidepressants, cisapride). Use cautiously with inhaled steroids
Saquinavir Invirase, SQV Hard gel: 200 mg Film-coated tablets: 500 mg	Infants and children <2 yr: not established SQV must be boosted with RTV >2 yr: 5 to <15 kg: 50 mg/kg + 3 mg/kg RTV bid 15-40 kg: 50 mg/kg + 2.5 mg/kg RTV bid >40: 50 mg/kg + 100 RTV bid Adolescent and adult: SQV 1,000 mg + 100 mg RTV bid	Common: diarrhea, abdominal pain, headache, nausea, skin rashes, lipid abnormalities Less common: exacerbation of chronic liver disease, diabetes mellitus, pancreatitis, elevated liver transaminases, fat maldistribution, increase in both QT and PR in ECG	Administration with a high-fat meal to enhance bioavailability. Use only in combination with ritonavir boosting dose. SQV is metabolized by CYP3A4, which may cause many drug interactions): rifampin, phenobarbital, and carbamazepine decrease serum levels. Saquinavir may decrease metabolism of calcium channel antagonists, azoles (e.g., ketoconazole), macrolides
Tipranavir Aptivus, TPV Capsule: 250 mg Solution 100 mg/mL (contains 116 IU vitamin E/mL)	<2 yr: not established. 2-18 yr: 375 mg/m^2 TPV + 150 mg/m^2 RTV (maximum 500 mg TPV + 200 mg RTV) bid *or* 14 mg TPV + 6 mg RTV per kg (maximum-same) bid Adolescent (>18 yr) and adult: 500 mg TPV +200 mg RTV bid	Common: diarrhea, nausea, vomiting, fatigue, headache, skin rashes, elevated liver enzymes, lipid abnormalities Less common: fat redistribution, hepatitis, hyperglycemia, diabetes mellitus, intracranial hemorrhage	No food restrictions. Better tolerated with meal. TPV must be boosted with RTV. Can inhibit human platelet aggregation: use with caution in patients at risk for increased bleeding (trauma, surgery, etc.) or in patients receiving concurrent medications that may increase the risk of bleeding. TPV is metabolized by CYP3A4, which may cause many drug interactions. Contraindicated in patients with hepatic insufficiency or receiving concurrent therapy with amiodarone, cisapride, ergot alkaloids, benzodiazepines, pimozide. TPV contains sulfonamide moiety and caution should be taken in patients with sulfonamide allergy
FUSION INHIBITORS Enfuvirtide Fuzeon, ENF Injection: lyophilized powder of 108 mg reconstituted in 1.1 mL of sterile water delivers 90 mg/mL	<6 yr: not established Children >6 yr to 16 yr: 2 mg/kg SQ (maximum 90 mg) bid Adolescent and adult: 90 mg SQ bid	Common: Local injection site reactions in 98% (e.g., erythema, induration nodules, cysts, ecchymoses) Less common: increased incidence of bacterial pneumonia, hypersensitivity, fever, nausea, vomiting, chills, elevated liver enzymes, hypotension, immune-mediated reactions (e.g., glomerulonephritis, Guillain-Barré syndrome, respiratory distress)	Must be given subcutaneously. Severity of reactions increased if given intramuscularly. Apply ice after injection and massage the area to reduce local reactions. Injection sites should be rotated

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
ENTRY INHIBITORS			
Maraviroc Selzentry, MVC Tablets: 150, 300 mg	Not approved for children or adolescents <16 yr Adolescents >16 yr and adults: 150 mg bid if given with potent CYP3A inhibitor (e.g., protease inhibitor except TPV) 300 mg bid if given with not potent CYP3A4 inhibitors (e.g., NRTI, TPV, NVP, ENF, RAL) 600 mg bid if given with potent CYP3A4 inducer (e.g., EFV, ETR, rifampin, phenobarbital)	Common: fever, upper respiratory infection–like symptoms, rash, abdominal pain, musculoskeletal symptoms, dizziness Less common: cardiovascular abnormalities, cholestatic jaundice, rhabdomyolysis, myositis, osteonecrosis	No food restrictions. MVC is a CYP3A4 and P-glycoprotein (Pgp) substrate, which may cause many drug interactions Tropism assay to exclude the presence of CXCR4 HIV is required before using MVC. Caution should be used when given to patients with hepatic impairment or cardiac disease or receiving CYP3A4 or Pgp modulating drugs
INTEGRASE INHIBITORS			
Dalutegravir Tivicay, DTG Tablet: 50 mg	Children <12 yr: consult with expert >12 yr and 40 kg, adolescents, and adults: 50 mg qd If taken with EFV, FPV, TPV, or rifampin: 50 mg bid	Insomnia Headache	No food restrictions UGT1A1 and CYP450 (CYP) 3A substrate Should be taken 2 hr before or 6 hr after taking laxatives, sucralfate, iron or calcium supplements, or buffered medications
Elvitegravir EVG Only as Stribild combination of EVG, FTC, TDF, cobicistat (COBI) (150, 200, 300, 150 mg)	Children and adolescents (<18 yr): not established Adolescent (>18 yr) and adult: 1 tablet qd	Common: nausea, diarrhea Less common: increased serum creatinine, urea, and phosphate, decreased bone density; lactic acidosis, hepatomegaly with stenosis	Administer with food EVG is metabolized by CYP3A4 and modestly induces CYP2D6 that can cause multiple drug interactions. Cautiously use with nephrotoxic drugs. Stribild should not be used with ritonavir
Raltegravir Isentress, RAL Film-coated tablet: 400 mg Chewable tablet: 25, 100 mg Solution: 20 mg/ml	Oral solution: 3 to <4 kg: 20 mg bid 4 to <6 kg: 30 mg bid 6 to <8 kg: 40 mg bid 8 to <11 kg: 60 mg bid 11 to <14 kg: 80 mg bid 14 to <20 kg: 100 mg bid Chewable tablet: 10 to <14 kg: 75 mg bid 14 to <20 kg: 100 mg bid 20 to <28 kg: 150 mg bid 28 to <40 kg: 200 mg bid Adolescent (>12 yr) and adult: 400 mg bid	Common: nausea, headache, dizziness, diarrhea, fatigue Less common: abdominal pain, vomiting, itching, creatine phosphokinase elevation, myopathy, rhabdomyolysis, depression, hypersensitivity	No food restrictions Film-coated tablet and chewable tablet are not interchangeable RAL is metabolized by UGT1A1 glucuronidation, and inducers of this system (e.g., rifampin, TPV) will reduce RGV levels, whereas inhibitors (e.g., ATV) will increase it

Antiretroviral drugs often have significant drug–drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any new medication.

Vaccine	Birth	1 mo	2 mo	4 mo	6 mo	12 mo	15 mo	18 mo	24 mo	4-6 yr	11-12 yr	14-16 yr
Hepatitis B	Hep B	Hep B			Hep B							
Measles, Mumps, Rubella*						MMR†	MMR†					
Influenza					Influenza‡							
Pneumococcal Conjugate and Hemophilus b			PCV Hib	PCV Hib	PCV Hib	PCV Hib					Pneumococcal§	
Diphtheria, Tetanus, Pertussis			DTap	DTap	DTap		DTap					
Polio (inactivated)			Polio	Polio	Polio							
Varicella						Varicella						
Hepatitis A						Hep A¶						
Rotavirus*			RV¶	RV	RV							

See text.
†Contraindicated in children with AIDS or $CD4^+$ <15%. Give 2 doses 1-3 mo apart.
‡Revaccination is recommended every year. Attenuated vaccine can be used >2 yr of age only if $CD4^+$ >15%.
§Revaccination with pneumococcal polysaccharide vaccine (PPV) every 5 yr.
¶Two doses at least 6 mo apart.
*First dose 6 through 14 wk of age and final dose no later than 8 mo 0 days of age. If using Rotarix, only 2 doses (2 and 4 mo) are needed.

Figure 276-4 Routine childhood immunization schedule for HIV-infected children.

Table 276-6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*

		Preventive Regimen	
PATHOGEN	**INDICATION**	**FIRST CHOICE**	**ALTERNATIVE**
STRONGLY RECOMMENDED AS STANDARD OF CARE			
Pneumocystis pneumonia†	HIV-infected or HIV-indeterminate infants aged 1-12 mo; HIV-infected children aged 1-5 yr with CD4 count of <500 cells/μL or CD4 percentage of <15%; HIV-infected children aged 6-12 yr with CD4 count of <200 cells/μL or CD4 percentage of <15%	**TMP-SMX**, 150/750 mg/m^2 body surface area per day (max: 320/1600 mg) orally qd or bid 3 times weekly on consecutive days *or* qd or bid orally 3 times weekly on alternate days	**Dapsone**: age ≥1 mo: 2 mg/kg (max: 100 mg) orally qd; *or* 4 mg/kg (max: 200 mg) orally once a week **Atovaquone**: age 1-3 mo and >24 mo: 30 mg/kg orally qd; age 4-24 mo: 45 mg/kg orally qd **Aerosolized pentamidine**: age ≥5 yr: 300 mg once a month by Respirgard II (Marquest, Englewood, CO) nebulizer **Doxycycline** age >8 yr: 2.2 mg/kg qd
Malaria	Living or traveling to area in which malaria is endemic	Same for HIV-infected and HIV-uninfected children. Refer to http://www.cdc.gov/malaria/ for the most recent recommendations. **Mefloquine**, 5 mg/kg orally 1 time weekly (max: 250 mg) **Atovaquone/proguanil** (Malarone) qd 11-20 kg: 62.5 mg/25 mg (1 pediatric tablet) 21-30 kg: 2 pediatric tablets 31-40 kg: 3 pediatric tablets >40 kg: 1 adult tablet (250 mg/100 mg)	**Doxycycline**, 100 mg orally qd for children >8 yr **Chloroquine,** 5 mg/kg base (equal 7.5 mg/kg chloroquine phosphate) orally up to 300 mg weekly (only for regions where the parasite is sensitive)
Mycobacterium tuberculosis			
Isoniazid-sensitive	TST reaction ≥5 mm *or* Prior positive TST result without treatment *or* Close contact with any person who has contagious TB. TB disease must be excluded before start of treatment	**Isoniazid,** 10-15 mg/kg body weight (max: 300 mg) qd for 9 mo *or* 20-30 mg/kg body weight (max: 900 mg) orally 2 times weekly for 9 mo	**Rifampin,** 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo
Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB	**Rifampin,** 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo	Uncertain
Multidrug-resistant (isoniazid and rifampin)	Same as previous pathogen; increased probability of exposure to multidrug-resistant TB	Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from source patient	
Mycobacterium avium complex‡	For children age ≥6 yr with CD4 count of <50 cells/μL; age 2-5 yr with CD4 count of <75 cells/μL; age 1-2 yr with CD4 count of <500 cells/μL; age <1 yr with CD4 count of <750 cells/μL	**Clarithromycin,** 7.5 mg/kg (max: 500 mg) orally bid *or* **Azithromycin,** 20 mg/kg (max: 1,200 mg) orally once a week	**Azithromycin,** 5 mg/kg body weight (max: 250 mg) orally qd *or* Children age ≥6 yr *or* **Rifabutin**, 300 mg orally qd
Varicella-zoster virus§	Exposure to varicella or shingles with no history of varicella *or* Zoster or seronegative status for VZV *or* Lack of evidence for age-appropriate vaccination	Varicella-zoster immunoglobulin (VariZIG), 125 IU per 10 kg (max: 625 IU) IM, administered within 96 hr after exposure‖	If VariZIG is not available and <96 hr from exposures, **acyclovir** 20 mg/kg (max: 800 mg) 4 times a day for 5-7 days *or* IVIG, 400 mg/kg, administered once
Vaccine-preventable pathogens	Standard recommendations for HIV-exposed and HIV-infected children	Routine vaccinations (see Fig. 276-3)	

Table 276-6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States—cont'd

	Preventive Regimen		
PATHOGEN	**INDICATION**	**FIRST CHOICE**	**ALTERNATIVE**
USUALLY RECOMMENDED			
Toxoplasma gondii[¶]	Seropositive IgG to *Toxoplasma* and severe immunosuppression: age <6 yr with CD4 <15%; age ≥6 yr with CD4 <100 cells/μL	TMP-SMZ, 150/750 mg/m^2 orally bid *or* Same dosage qd 3 times weekly on consecutive days *or* bid 3 times weekly on alternate days	**Dapsone,** age ≥1 mo: 2 mg/kg or 15 mg/m^2 (max: 25 mg) orally qd *plus* **Pyrimethamine,** 1 mg/kg (max: 25 mg) orally qd *plus* **Leucovorin,** 5 mg orally twice a week *or* **Atovaquone,** age 1-3 mo and >24 mo, 30 mg/kg orally qd; children age 4-24 mo, 45 mg/kg orally qd with or without **pyrimethamine,** 1 mg/kg (or 15 mg/m^2) (max: 25 mg) qd *plus* **Leucovorin,** 5 mg orally twice a week (3 days apart)
Invasive bacterial infections	Hypogammaglobulinemia (i.e., IgG <400 mg/dL)	IVIG 400 mg/kg body weight every 2-4 wk	
Cytomegalovirus	CMV antibody positivity and severe immunosuppression (CD4 <50 cells/μL)	**Valganciclovir,** 900 mg orally qd with food for older children who can receive adult dosing	

*Information in these guidelines might not represent FDA approval or FDA-approved labeling for products or indications. Specifically, the terms "safe" and "effective" might not be synonymous with the FDA-defined legal standards for product approval.

[†]Daily trimethoprim-sulfamethoxazole (TMP-SMZ) reduces the frequency of certain bacterial infections. Compared with weekly dapsone, daily dapsone is associated with lower incidence of PCP but higher hematologic toxicity and mortality. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need TMP-SMZ. TMP-SMZ, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine) protect against toxoplasmosis; however, data have not been prospectively collected.

[‡]Substantial drug interactions can occur between rifamycins (i.e., rifampin and rifabutin) and protease inhibitors and nonnucleoside reverse transcriptase inhibitors. A specialist should be consulted.

[§]Children routinely being administered intravenous immunoglobulin (IVIG) should receive VariZIG if the last dose of IVIG was administered more than 21 days before exposure.

[‖]As of 2007, VariZIG can be obtained only under a treatment Investigational New Drug protocol (1-800-843-7477, FFF Enterprises, Temecula, CA).

[¶]Protection against toxoplasmosis is provided by the preferred anti-*Pneumocystis* regimens and possibly by atovaquone.

CMV, cytomegalovirus; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus IgG, immunoglobulin G; IM, intramuscularly; IVIG, intravenous immunoglobulin; PCP, *Pneumocystis* pneumonia; TMP-SMZ, trimethoprim-sulfamethoxazole; TB, tuberculosis; TST, tuberculin skin test;; VZV, varicella-zoster virus.

From Centers for Disease Control and Prevention (CDC): Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children, MMWR Recomm Rep *58(RR-11):127–128, 2009, Table 1.*

Table 276-5 Recommendations for PCP Prophylaxis and CD4 Monitoring for HIV-Exposed Infants and HIV-Infected Children, by Age and HIV Infection Status

AGE/HIV INFECTION STATUS	PCP PROPHYLAXIS	CD4 MONITORING
Birth to 4-6 wk, HIV exposed	No prophylaxis	None
HIV infection reasonably excluded*	No prophylaxis	None
<1 yr, HIV-infected or indeterminate	Prophylaxis regardless of CD4 count or percentage	According to local practice for initiation or follow-up of cART
1-5 yr, HIV infected	Prophylaxis if: CD4 <500 cells/μL or <15%[†]	According to local practice for initiation or follow-up of cART
>6 yr, HIV infected	Prophylaxis if: CD4 <200 cells/μL or <15%[†‡]	According to local practice for initiation or follow-up of cART

The National Perinatal HIV Hotline (1-888-448-8765) provides consultation on all aspects of perinatal HIV care.

*See text.

[†]More frequent monitoring (e.g., monthly) is recommended for children whose CD4 counts or percentages are approaching the threshold at which prophylaxis is recommended.

[‡]Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PCP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PCP should receive PCP prophylaxis until their CD4 count is >20% (for >6 yr of age) or >25% (for 2-5 yr of age) on continuous cART.

cART, combined antiretroviral therapy; PCP, *Pneumocystis carinii* (also called *P. jirovecii*) pneumonia.

Table 279-1 Drugs for Parasitic Infections

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of AIDS, physicians anywhere may see infections caused by previously unfamiliar parasites. The table below lists first-choice and alternative drugs for most parasitic infections.

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Acanthamoeba keratitis			
Drug of choice:	See footnote 1		
Amebiasis *(Entamoeba histolytica)*			
Asymptomatic			
Drug of choice:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day (max 2 g) in 3 doses PO × 20 days
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Alternative:	Diloxanide furoate[2]	500 mg tid PO × 10 days	20 mg/kg/day PO in 3 doses × 10 days
Mild to moderate intestinal disease[3]			
Drug of choice[4]:	Metronidazole	500-750 mg tid PO × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[5]	2 g PO once daily × 3 days	50 mg/kg/day PO (max 2 g) in 1 dose × 3 days
Either followed by:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Severe intestinal and extraintestinal disease[3]			
Drug of choice:	Metronidazole	750 mg PO tid × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[5]	2 g PO once daily × 5 days	50 mg/kg/day PO (max 2 g) × 5 days
Either followed by:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Amebic meningoencephalitis, primary and granulomatous			
Naegleria			
Drug of choice:	Amphotericin B[6,7]	1.5 mg/kg/day IV in 2 doses × 3 days, then 1.5 mg/kg/day IV × 6 days	1.5 mg/kg/day IV in 2 doses × 3 days, then 1 mg/kg/d IV × 6 days
or		1 mg/kg IV once/day plus 0.5 mg/day intraventricularly (max of 1.5 mg/kg by both routes)	1 mg/kg IV once/daily plus 0.5 mg/d intraventricularly (max of 1.5 mg/kg by both routes)
or			
	Rifampin Fluconazole Azithromycin	10 mg/kg IV once/daily (max 600 mg/d) 12 mg/kg IV once/daily 500 mg IV once/daily	10 mg/kg IV once/daily (max 600 mg/d) 12 mg/kg IV once/daily 20 mg/kg IV once/daily (max 500 mg/d)
Acanthamoeba			
Drug of choice:	See footnote 8		

[1]For treatment of keratitis caused by *Acanthamoeba*, concurrent topical use of 0.1% propamidine isethionate (Brolene) plus neomycin-polymyxin B-gramicidin ophthalmic solution has been successful (Hargrave SL, et al: *Ophthalmology* 106:952, 1999). In some European countries, propamidine is not available and hexamidine (Desmodine) has been used (Seal DV: *Eye* 17:893, 2003). In addition, 0.02% topical polyhexamethylene biguanide (PHMB) and/or chlorhexidine has been used successfully in a large number of patients (Tabin G, et al: *Cornea* 20:757, 2001; Wysenbeek YS, et al: *Cornea* 19:464, 2000). PHMB is available from Leiter's Park Avenue Pharmacy, San Jose, CA (800-292-6773; www.leiterrx.com). The combination of chlorhexidine, natamycin (pimaricin), and debridement also has been successful (Kitagawa K, et al: *Jpn J Ophthalmol* 47:616, 2003).

[2]The drug is not available commercially, but as a service can be compounded by Panorama Compounding Pharmacy, 6744 Balboa Blvd, Van Nuys, CA 91406 (800-247-9767) or Medical Center Pharmacy, New Haven, CT (203-688-6816).

[3]Treatment should be followed by a course of iodoquinol or paromomycin in the dosage used to treat asymptomatic amebiasis.

[4]Nitazoxanide is FDA approved as a pediatric oral suspension for treatment of *Cryptosporidium* in immunocompetent children younger than 12 yr old and for *Giardia* (*Med Lett* 2003;45:29). It may also be effective for mild to moderate amebiasis (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003). Nitazoxanide is available in 500 mg tablets and an oral suspension; it should be taken with food.

[5]A nitroimidazole similar to metronidazole, tinidazole was recently approved by the FDA and appears to be as effective and better tolerated than metronidazole. It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist may crush the tablets and mix them with cherry syrup (Humco, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use. Ornidazole, a similar drug, is also used outside the United States.

[6]*Naegleria* infection has been treated successfully with intravenous and intrathecal use of both amphotericin B and miconazole plus rifampin and with amphotericin B, rifampin, and ornidazole (Seidel J, et al: *N Engl J Med* 306:346, 1982; Jain R, et al: *Neurol India* 50:470, 2002). Other reports of successful therapy are less-well documented.

[7]An approved drug, but considered investigational for this condition by the FDA.

[8]Strains of *Acanthamoeba* isolated from fatal granulomatous amebic encephalitis are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and (less so) to amphotericin B. Chronic *Acanthamoeba* meningitis has been successfully treated in 2 children with a combination of oral trimethoprim-sulfamethoxazole, rifampin, and ketoconazole (Singhal T, et al: *Pediatr Infect Dis J* 20:623, 2001), and in an AIDS patient with fluconazole, sulfadiazine, and pyrimethamine combined with surgical resection of the CNS lesion (Seijo Martinez M, et al: *J Clin Microbiol* 38:3892, 2000). Disseminated cutaneous infection in an immunocompromised patient has been treated successfully with IV pentamidine isethionate, topical chlorhexidine, and 2% ketoconazole cream, followed by oral itraconazole (Slater CA, et al: *N Engl J Med* 331:85, 1994).

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Balamuthia mandrillaris			
Drug of choice:	See footnote 9		
Sappinia diploidea			
Drug of choice:	See footnote 10		
Ancylostoma caninum (eosinophilic enterocolitis)			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days
or	Pyrantel pamoate[7]	11 mg/kg PO (max 1 g) × 3 days	11 mg/kg PO (max 1 g) × 3 days
or	Endoscopic removal		
Ancylostoma duodenale, see Hookworm			
Angiostrongyliasis *(Angiostrongylus cantonensis, Angiostrongylus costaricensis)*			
Drug of choice:	See footnote 11		
Anisakiasis (*Anisakis* spp.)			
Treatment of choice[12]:	Surgical or endoscopic removal		
Ascariasis (*Ascaris lumbricoides*, roundworm)			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days or 500 mg PO once	100 mg PO bid × 3 days or 500 mg PO once
or	Ivermectin[7]	150-200 µg/kg PO once	150-200 µg/kg PO once
Babesiosis *(Babesia microti)*			
Drugs of choice[13]:	Atovaquone[7] **plus** azithromycin[7]	750 mg PO bid × 7-10 days 600 mg PO daily × 7-10 days	20 mg/kg PO bid × 7-10 days 10 mg/kg PO on day 1 (max 500 mg/dose), then 5 mg/kg/d (max 250 mg/dose) PO days 2-10
or	Clindamycin[7] **plus** quinine[7]	300-600 mg IV qid or 600 mg tid PO × 7-10 days 650 mg tid PO × 7-10 days	20-40 mg/kg/day IV or PO in 3 or 4 doses × 7-10 days (max 600 mg/dose) 24 mg/kg/day PO in 3 doses × 7-10 days
Balamuthia mandrillaris, see Amebic meningoencephalitis, primary			
Balantidiasis *(Balantidium coli)*			
Drug of choice:	Tetracycline[7,14]	500 mg PO qid × 10 days	40 mg/kg/day PO (max 2 g) in 4 doses × 10 days
Alternatives:	Metronidazole[7] Iodoquinol[7]	750 mg PO tid × 5 days 650 mg PO tid × 20 days	35-50 mg/kg/day PO in 3 doses × 5 days 40 mg/kg/day PO in 3 doses × 20 days

[9]A free-living leptomyxid ameba that causes subacute to fatal granulomatous CNS disease. Several cases of *Balamuthia* encephalitis have been successfully treated with flucytosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin (phenothiazines were also used) combined with surgical resection of the CNS lesion (Deetz TR, et al: *Clin Infect Dis* 37:1304, 2003; Jung S, et al: *Arch Pathol Lab Med* 128:466, 2004). Miltefosine is another option currently being evaluated but it is not approved for any indication in the United States at this time. Case reports and in vitro data suggest it may have some antiamebic activity (AC Aichelburg et al., *Emerg Infect Dis* 2008; 14:1743; DY Martinez et al., *Clin Infect Dis* 2010; 51:e7; FL Schuster et al., *J Eukaryot Microbiol* 2006; 53:121). Miltefosine (Impavido) is manufactured in 10 or 50 mg capsules by Paladin (Canada) and is available in the United States from the CDC for treatment of infections with free-living amebas.

[10]A free-living ameba not previously known to be pathogenic to humans. It has been successfully treated with azithromycin, IV pentamidine, itraconazole, and flucytosine combined with surgical resection of the CNS lesion (Gelman BB, et al: *J Neuropathol Exp Neurol* 62:990, 2003).

[11]Most patients have a self-limited course and recover completely. Analgesics, corticosteroids, and careful removal of CSF at frequent intervals can relieve symptoms from increased intracranial pressure (Lo Re V III, Gluckman SJ: *Am J Med* 114:217, 2003). No anthelmintic drug is proven to be effective, and some patients have worsened with therapy (Slom TJ, et al: *N Engl J Med* 346:668, 2002). Mebendazole or albendazole and a corticosteroid appeared to shorten the course of infection (K Sawanyawisuth and K Sawanyawisuth, *Trans R Soc Trop Med Hyg* 2008; 102:990; V Chotmongkol et al. *Am J Trop Med Hyg* 2009;81:443).

[12](Repiso Ortega A, et al: *Gastroenterol Hepatol* 26:341, 2003.) Successful treatment of a patient with *Anisakiasis* with albendazole has been reported (Moore DA, et al *Lancet* 360:54, 2002).

[13]Exchange transfusion has been used in severely ill patients and those with high (>10%) parasitemia (Hatcher JC, et al *Clin Infect Dis* 32:1117, 2001). In patients who were not severely ill, combination therapy with atovaquone and azithromycin was as effective as clindamycin and quinine and may have been better tolerated (Krause PJ, et al: *N Engl J Med* 343:1454, 2000). Highly immunosuppressed patients should be treated for a minimum of 6 wk and at least 2 wk past the last positive smear (PJ Krause et al., *Clin Infect Dis* 2008; 46:370). High doses of azithromycin (600-1,000 mg) have been used in combination with atovaquone for the treatment of immunocompromised patients (LM Weiss et al., *N Engl J Med* 2001; 344:773). Resistance to atovaquone plus azithromycin has been reported in immunocompromised patients treated with a single subcurative course of this regimen (GP Wormser et al., *Clin Infect Dis* 2010; 50:381).

[14]Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Baylisascariasis *(Baylisascaris procyonis)*			
Drug of choice:	See footnote 15		
Blastocystis hominis infection			
Drug of choice:	See footnote 16		
Capillariasis *(Capillaria philippinensis)*			
Drug of choice:	Mebendazole[7]	200 mg PO bid × 20 days	200 mg PO bid × 20 days
Alternatives:	Albendazole[7]	400 mg PO daily × 10 days	400 mg PO daily × 10 days
Chagas disease, see Trypanosomiasis			
Clonorchis sinensis, see Fluke infection			
Cryptosporidiosis *(Cryptosporidium)*			
Immunocompetent			
Drug of choice:	Nitazoxanide[4]	500 mg PO bid × 3 days[7]	1-3 yr: 100 mg PO bid × 3 days
			4-11 yr: 200 mg PO bid × 3 days
HIV infected			
Drug of choice:	See footnote 17		
Cutaneous larva migrans (creeping eruption, dog and cat hookworm)			
Drug of choice[18]:	Albendazole[7]	400 mg PO daily × 3 days	400 mg PO daily × 3 days
or	Ivermectin[7]	200 μg/kg PO daily × 1-2 days	200 μg/kg PO daily × 1-2 days
Alternative:	Thiabendazole	Topically	Topically
Cyclosporiasis *(Cyclospora cayetanensis)*			
Drug of choice[19]:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 7-10 days	TMP 5 mg/kg, SMX 25 mg/kg bid PO × 7-10 days
Alternative:	Ciprofloxacin	500 mg PO bid × 7 days	-
Cysticercosis, see Tapeworm infection			
Drug of choice:			
Cystoisosporiasis *(Cystoisospora belli, formerly known as Isospora)*			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 10 days	TMP 5 mg/kg, SMX 25 mg/kg PO bid × 10 days
Dientamoeba fragilis infection[20]			
	Paromomycin[7]	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
or	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO (max 2 g) in 3 doses × 20 days
or	Metronidazole	500-750 mg tid × 10 days	20-40 mg/kg/day in 3 doses × 10 days
Diphyllobothrium latum, see Tapeworm infection			

[15]No drugs have been consistently demonstrated to be effective. The combination of albendazole 37 mg/kg/d PO and high-dose steroids has been used successfully (JM Peters et al., *Pediatrics* 2012; 129:e806; S Haider, *Emerg Infect Dis* 2012; 18:347). Albendazole 25 mg/kg/d PO × 20 d started as soon as possible (up to 3 d after possible infection) might prevent clinical disease and is recommended for children with known exposure, such as in the setting of ingestion of raccoon stool or contaminated soil (WJ Murray and KR Kazacos, *Clin Infect Dis* 2004; 39:1484). Mebendazole, levamisole, or ivermectin could be tried if albendazole is not available. Ocular baylisascariasis has been treated successfully using laser photocoagulation therapy to destroy the intraretinal larvae.

[16]Clinical significance of these organisms is controversial; metronidazole 750 mg tid × 10 days, iodoquinol 650 mg tid × 20 days or trimethoprim-sulfamethoxazole 1 DS tab bid × 7 days have been reported to be effective (Stenzel DJ, Borenam PFL: *Clin Microbiol Rev* 9:563, 1996; Ok UZ, et al: *Am J Gastroenterol* 94:3245, 1999). Metronidazole resistance may be common (Haresh K, et al: *Trop Med Int Health* 4:274, 1999). Nitazoxanide has been effective in children (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003).

[17]Nitazoxanide has not consistently been shown to be superior to placebo in HIV-infected patients (Amadi B, et al: *Lancet* 360;1375, 2002). For HIV-infected patients, potent antiretroviral therapy (ART) is the mainstay of treatment. Nitazoxanide (treatment duration of 5-21 days), paromomycin, or a combination of paromomycin and azithromycin may be tried to decrease diarrhea and recalcitrant malabsorption of antimicrobial drugs, which can occur with chronic cryptosporidiosis (B Pantenburg et al., *Expert Rev Anti Infect Ther* 2009; 7:385).

[18]Albanese G, et al: *Int J Dermatol* 40:67, 2001.

[19]HIV-infected patients may need higher dosage and long-term maintenance (Kansouzidou A, et al: *J Trav Med* 11:61, 2004).

[20]Norberg A, et al: *Clin Microbiol Infect* 9:65, 2003.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Dracunculus medinensis (guinea worm) infection			
Drug of choice:	See footnote 21		
Echinococcus, see Tapeworm Infection			
Entamoeba histolytica, see Amebiasis			
Enterobius vermicularis (pinworm) infection			
Drug of choice[22]:	Albendazole[7]	400 mg PO once; repeat in 2 wk	400 mg PO once; repeat in 2 wk
or	Mebendazole	100 mg PO once; repeat in 2 wk	100 mg PO once; repeat in 2 wk
or	Pyrantel pamoate	11 mg/kg base PO once (max 1 g); repeat in 2 wk	11 mg/kg base PO once (max 1 g); repeat in 2 wk
Fasciola hepatica, see Fluke infection			
Filariasis[23]			
Wuchereria bancrofti, Brugia malayi, Brugia timori			
Drug of choice[24]:	Diethylcarbamazine	6 mg/kg PO in 3 doses × 14 days[25]	6 mg/kg PO in 3 doses × 14 days[25]
Loa loa			
Drug of choice[26]:	Diethylcarbamazine	9 mg/kg PO in 3 doses × 14 days[25]	9 mg/kg PO in 3 doses × 14 days[25]
Mansonella ozzardi			
Drug of choice:	See footnote 27		
Mansonella perstans			
Drug of choice:	Doxycycline[7,14]	100 mg bid PO × 7 days	4 mg/kg/day in 2 doses PO × 7 days
Mansonella streptocerca[28]			
Drug of choice:	Diethylcarbamazine Ivermectin[7]	6 mg/kg/day PO × 14 days 150 µg/kg PO once	6 mg/kg/day PO × 14 days 150 µg/kg PO once
Tropical pulmonary eosinophilia (TPE)[29]			
Drug of choice:	Diethylcarbamazine	6 mg/kg/day in 3 doses × 12-21 days	6 mg/kg/day in 3 doses × 12-21 days
Onchocerca volvulus (river blindness)			
Drug of choice:	Invermectin[30]	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic
Fluke, hermaphroditic, infection			

[21]Treatment of choice is slow extraction of worm combined with wound care (*MMWR Morbid Mortal Wkly Rep* 2011; 60:1450). 10 days' treatment with metronidazole 250 mg tid in adults and 25 mg/kg/day in 3 doses in children is not curative, but decreases inflammation and facilitates removal of the worm. Mebendazole 400-800 mg/day × 6 days has been reported to kill the worm directly.

[22]Since all family members are usually infected, treatment of the entire household is recommended.

[23]Antihistamines or corticosteroids may be required to decrease allergic reactions due to disintegration of microfilariae from treatment of filarial infections, especially those caused by *Loa loa*. Endosymbiotic *Wolbachia* bacteria may have a role in filarial development and host response, and may represent a new target for therapy. Treatment with doxycycline 100 or 200 mg/day × 4-6 wk in lymphatic filariasis and onchocerciasis has resulted in substantial loss of *Wolbachia* with subsequent block of microfilariae production and absence of microfilaria when followed for 24 mo after treatment (Hoerauf A, et al: *Med Microbiol Immunol* 192:211, 2003; Hoerauf A, et al: *BMJ* 326:207, 2003).

[24]Most symptoms caused by adult worm. Single-dose combination of albendazole (400 mg) with either ivermectin (200 µg/kg) or diethylcarbamazine (6 mg/kg) is effective for reduction or suppression of *Wuchereria bancrofti* microfilaria but does not kill the adult forms (Addiss D, et al: *Cochrane Database Syst Rev* 2004;CD003753).

[25]For patients with microfilaria in the blood, *Medical Letter* consultants would start with a lower dosage and scale up: day 1, 50 mg; day 2, 50 mg tid; day 3, 100 mg tid; day 4-14, 6 mg/kg in 3 doses (for *Loa loa* day 4-14, 9 mg/kg in 3 doses). Multidose regimens have been shown to provide more rapid reduction in microfilaria than single-dose diethylcarbamazine, but microfilaria levels are similar 6-12 mo after treatment (Andrade LD, et al: *Trans R Soc Trop Med Hyg* 89:319, 1995; Simonsen PE, et al: *Am J Trop Med Hyg* 53:267, 1995). A single dose of 6 mg/kg is used in endemic areas for mass treatment (Figueredo-Silva J, et al: *Trans R Soc Trop Med Hyg* 90:192, 1996; Noroes J, et al: *Trans R Soc Trop Med Hyg* 91:78, 1997).

[26]In heavy infections with *Loa loa*, rapid killing of microfilariae can provoke an encephalopathy. Apheresis has been reported to be effective in lowering microfilarial counts in patients heavily infected with *Loa loa* (Ottesen ES: *Infect Dis Clin North Am* 7:619, 1993). Albendazole or ivermectin have also been used to reduce microfilaremia; albendazole is preferred because of its slower onset of action and lower risk for encephalopathy (Klion AD, et al: *J Infect Dis* 168:202, 1993; Kombila M, et al: *Am J Trop Med Hyg* 58:458, 1998). Albendazole may be useful for treatment of loiasis when diethylcarbamazine is ineffective or cannot be used, but repeated courses may be necessary (Klion AD, et al: *Clin Infect Dis* 29:680, 1999). Diethylcarbamazine, 300 mg once/wk, has been recommended for prevention of loiasis (Nutman TB, et al: *N Engl J Med* 319:752, 1988).

[27]Diethylcarbamazine has no effect. Ivermectin 200 µg/kg once has been effective.

[28]Diethylcarbamazine is potentially curative because of activity against both adult worms and microfilariae. Ivermectin is only active against microfilariae. (The Medical Letter: *Drugs for parasitic infections*, ed 2, 2010).

[29]Relapse occurs and can be treated with diethylcarbamazine.

[30]Annual treatment with ivermectin, 150 µg/kg, can prevent blindness from ocular onchocerciasis (Mabey D, et al: *Ophthalmology* 103:1001, 1996). Diethylcarbamazine should not be used for treatment of this disease.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Clonorchis sinensis (Chinese liver fluke)			
Drug of choice:	Praziquantel	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
or	Albendazole[7]	10 mg/kg PO × 7 days	10 mg/kg PO × 7 days
Fasciola hepatica (sheep liver fluke)			
Drug of choice[31]:	Triclabendazole	10 mg/kg PO once or twice[32]	10 mg/kg PO once or twice[32]
Alternative:	Bithionol	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
or	Nitazoxanide	500 mg PO bid × 7 days	1-3 yr: 100 mg PO bid 4-11 yr: 200 mg PO bid
Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai (intestinal flukes)			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
Metorchis conjunctus (North American liver fluke)[33]			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
Nanophyetus salmincola			
Drug of choice:	Praziquantel[7]	60 mg/kg/day PO in 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day
Opisthorchis viverrini (Southeast Asian liver fluke)			
Drug of choice:	Praziquantel	75 mg/kg/day PO in 3 doses × 2 days	75 mg/kg/day PO in 3 doses × 2 days
or	Albendazole	10 mg/kg/day PO × 7 days	10 mg/kg/day PO × 7 days
Paragonimus westermani (lung fluke)			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 2 days	75 mg/kg/day PO in 3 doses × 2 days
or[34]	Bithionol	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
or	Triclabendazole	10 mg/kg PO once or twice	10 mg/kg PO once or twice
Giardiasis *(Giardia duodenalis)*			
Drugs of choice:	Metronidazole[7] Nitazoxanide[4] Tinidazole[5]	250 mg PO tid × 5 days 500 mg PO bid × 3 days 2 g PO once	15 mg/kg/day PO in 3 doses × 5 days 1-3 yr: 100 mg PO every 12 hr × 3 days 4-11 yr: 200 mg PO every 12 hr × 3 days 50 mg/kg PO once (max 2 g)
Alternatives[35]:	Paromomycin[7,36] Furazolidone Quinacrine[2]	25-35 mg/kg/day PO in 3 doses × 7 days 100 mg PO qid × 7-10 days 100 mg PO tid × 5 days	25-35 mg/kg/day PO in 3 doses × 7 days 6 mg/kg/day PO in 4 doses × 7-10 days 2 mg/kg tid PO × 5 days (max 300 mg/day)
Gnathostomiasis *(Gnathostoma spinigerum)*			
Treatment of choice[37]:	Albendazole[7]	400 mg PO bid × 21 days	400 mg PO bid × 21 days
or	Ivermectin[7]	200 µg/kg/day PO × 2 days	200 µg/kg/day PO × 2 days
±	Surgical removal		
Gongylonemiasis (*Gongylonema* sp.)[38]			
Treatment of choice:	Surgical removal		
or	Albendazole[7]	10 mg/kg/day PO × 3 days	10 mg/kg/day PO × 3 days

[31]Unlike infections with other flukes, *Fasciola hepatica* infections may not respond to praziquantel. Triclabendazole (Egaten, Novartis) may be safe and effective but data are limited (Graham CS, et al: *Clin Infect Dis* 33:1, 2001). It is available from Victoria Pharmacy, Zurich, Switzerland (www.pharmaworld.com; 41-1-211-24-32) and should be given with food for better absorption. A single study has found that nitazoxanide has limited efficacy for treating fascioliasis in adults and children (Favennec L, et al: *Aliment Pharmacol Ther* 17:265, 2003).

[32]Richter J, et al: *Curr Treat Options Infect Dis* 2002;4:313.

[33]MacLean JD, et al: *Lancet* 347:154, 1996.

[34]Triclabendazole may be effective in a dosage of 5 mg/kg once/day × 3 days or 10 mg/kg bid + 1 day (Calvopiña M, et al: *Trans R Soc Trop Med Hyg* 92:566, 1998). See footnote 31 for availability.

[35]Albendazole 400 mg daily × 5 days alone or in combination with metronidazole may also be effective (Hall A, Nahar Q: *Trans R Soc Trop Med Hyg* 87:84, 1993; Dutta AK, et al: *Indian J Pediatr* 61:689, 1994; Cacopardo B, et al: *Clin Ter* 146:761, 1995). Combination treatment with standard doses of metronidazole and quinacrine given for 3 wk has been effective for a small number of refractory infections (Nash TE, et al: *Clin Infect Dis* 33:22, 2001). In 1 study, nitazoxanide was used successfully in high doses to treat a case of *Giardia* resistant to metronidazole and albendazole (Abboud P, et al: *Clin Infect Dis* 32:1792, 2001).

[36]Not absorbed; may be useful for treatment of giardiasis in pregnancy.

[37]de Gorgolas M, et al: *J Travel Med* 10:358, 2003. All patients should be treated with a medication regardless of whether surgery is attempted.

[38]Eberhard ML, Busillo C: *Am J Trop Med Hyg* 61:51, 1999; Wilson ME, et al: *Clin Infect Dis* 32:1378, 2001.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Hookworm infection *(Ancylostoma duodenale, Necator americanus)*			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days or 500 mg once	100 mg PO bid × 3 days or 500 mg once
or	Pyrantel pamoate[7]	11 mg/kg (max 1 g) PO × 3 days	11 mg/kg (max 1 g) PO × 3 days
Hydatid cyst, see Tapeworm infection			
Hymenolepis nana, see Tapeworm infection			
***Leishmania* infection**			
Visceral[39, 40]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 28 days[41]	20 mg Sb/kg/day IV or IM × 28 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]
or	Amphotericin B[7]	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk
or	Liposomal amphotericin B[42]	3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21[43]	3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21[43]
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Alternative[44]:	Pentamidine[7]	4 mg/kg IV or IM daily or every 2 days for 15-30 doses	4 mg/kg IV or IM daily or every 2 days for 15-30 doses
Cutaneous[45]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 20 days[41]	20 mg Sb/kg/day IV or IM × 20 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 20 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 20 days[41]
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Alternatives[46]:	Pentamidine[7]	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses[47]	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses[47]
or	Paromomycin[7,48]	Topically 2×/day × 10-20 days	Topically 2×/day × 10-20 days

[39]Consultation with physicians experienced in management of this disease is recommended. To maximize effectiveness and minimize toxicity, the choice of drug, dosage and duration of therapy should be individualized based on the region of disease acquisition, likely infecting species, number, significance and location of lesions, and host factors such as immune status (HW Murray, Lancet 2005; 366:1561). Some of the listed drugs and regimens are effective only against certain *Leishmania* species/strains and only in certain areas of the world (S Sundar and J Chakravarty, Expert Opin Pharmacother 2013; 14:53).

[40]Visceral infection is most commonly caused by the Old World species *Leishmania donovani* (kala-azar) and *Leishmania infantum* and the New World species. *Leishmania chagasi*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[41]May be repeated or continued; a longer duration may be needed for some patients (Herwaldt BL: *Lancet* 354:1191, 1999).

[42]Three lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *Leishmania infantum,* the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis (Meyerhoff A, *Clin Infect Dis* 1999;28:42). Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) have also been used with good results but are considered investigational for this condition by the FDA.

[43]The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day (days 1-5) and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration. (Russo R, Nigro LC, Minniti S, et al: Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B [AmBisome], *J Infect* 32:133-137, 1996).

[44]For treatment of kala-azar in adults in India, oral miltefosine 100 mg/day (–205 mg/kg/day) for 3-4 wk was 97% effective after 6 mo (Jha TK, et al: *N Engl J Med* 341:1795, 1999; Sangraula H, et al: *J Assoc Physicians India* 51:686, 2003). Gastrointestinal adverse effects are common, and the drug is contraindicated in pregnancy. The dose of miltefosine in an open-label trial in children in India was 2.5 mg/kg/day × 28 days (Bhattacharya SK, et al: *Clin Infect Dis* 38:217, 2004). Miltefosine (Impavido) is available from the manufacturer (Zentaris, Frankfurt, Germany at Impavido@zentaris.de).

[45]Cutaneous infection is most commonly caused by the Old World species *Leishmania major* and *Leishmania tropica* and the New World species *Leishmania mexicana, Leishmania (Viannia) braziliensis* and others. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[46]In a placebo-controlled trial in patients 12 yr old and older, oral miltefosine was effective for the treatment of cutaneous leishmaniasis caused by *Leishmania (Viannia) panamensis* in Colombia but not *L. (V.) braziliensis* in Guatemala at a dosage of about 2.5 mg/kg/day for 28 days. "Motion sickness," nausea, headache and increased creatinine were the most frequent adverse effects (Soto J, et al: *Clin Infect Dis* 38:1266, 2004). See footnote 44 regarding miltefosine availability. For treatment of *L. major* cutaneous lesions, a study in Saudi Arabia found that oral fluconazole, 200 mg once/day × 6 wk, appeared to speed healing (Alrajhi AA, et al: *N Engl J Med* 346:891, 2002).

[47]At this dosage pentamidine has been effective against leishmaniasis in Colombia where the likely organism was *L. (V.) panamensis* (Soto-Mancipe J, et al: *Clin Infect Dis* 16:417, 1993; Soto J, et al: *Am J Trop Med Hyg* 50:107, 1994); its effect against other species is not well established.

[48]Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread. A formulation of 15% paromomycin/12% methylbenzethonium chloride (Leshcutan) in soft white paraffin for topical use has been reported to be partially effective in some patients against cutaneous leishmaniasis due to *L. major* in Israel and against *L. mexicana* and *L. (V.) braziliensis* in Guatemala, where mucosal spread is very rare (Arana BA, et al: *Am J Trop Med Hyg* 65:466, 2001). The methylbenzethonium is irritating to the skin; lesions may worsen before they improve.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Mucosal[49]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 28 days[41]	20 mg Sb/kg/day IV or IM × 28 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]
or	Amphotericin B[7]	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Lice infestation *(Pediculus humanus, Pediculus capitis, Phthirus pubis)*[50]			
Drugs of choice:	0.5% Malathion[51]	Topically	Topically
or	1% Permethrin[52]	Topically	Topically
or	Pyrethrins with piperonyl butoxide[52]	Topically	Topically
or	0.5% Ivermectin lotion	Topically, once	Topically, once
or	0.9% Spinosad susp	Topically, 2 × at least 7 days apart	Topically, 2 × at least 7 days apart
or	Ivermectin[7,53]	200 µg/kg PO × 3 doses, on days 1, 2, and 10	200 µg/kg PO × 3 doses, on days 1, 2, and 10
Loa loa, see Filariasis			
Malaria, treatment of *(Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax,* and *Plasmodium malariae)*			
P. falciparum[54] acquired in areas of **chloroquine resistance**			
Oral[55]			
Drugs of choice:	Atovaquone/proguanil[56]	2 adult tabs PO bid[58] or 4 adult tabs PO once daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO once/day × 3 days 9-10 kg: 3 pediatric tabs PO once/day × 3 days 11-20 kg: 1 adult tab PO once/day × 3 days 21-30 kg: 2 adult tabs PO once/day × 3 days 31-40 kg: 3 adult tabs PO once/day × 3 days >40 kg: 4 adult tabs PO once/day × 3 days
or	Quinine sulfate	650 mg PO every 8 hr × 3-7 days[57]	30 mg/kg/day PO in 3 doses × 3-7 days[57]
	plus doxycycline[7,14]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,14]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,59]	20 mg/kg/day PO in 3 doses × 7 days[60]	20 mg/kg/day PO in 3 doses × 7 days

[49]Mucosal infection is most commonly due to the New World species *L. (V.) braziliensis, L. (V.) panamensis,* or *L. (V.) guyanensis.* Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[50]For infestation of eyelashes with *Phthirus pubis* lice, use petrolatum; TMP-SMX has also been used (Meinking TL: *Curr Probl Dermatol* 24:157, 1996). For pubic lice, treat with 5% permethrin or ivermectin as for scabies. TMP-SMX has also been effective together with permethrin for head lice (Hipolito RB, et al: *Pediatrics* 107:E30, 2001).

[51]Yoon KS, et al: *Arch Dermatol* 139:994, 2003.

[52]A second application is recommended 1 wk later to kill hatching progeny. Some lice are resistant to pyrethrins and permethrin (Meinking et al: *Arch Dermatol* 2002;138:220).

[53]Ivermectin is effective against adult lice but has no effect on nits (Jones KN, JC English III: *Clin Infect Dis* 36:1355, 2003).

[54]Chloroquine-resistant *P. falciparum* occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Haiti, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia, and Iran). For treatment of multidrug-resistant. *P. falciparum* in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, artesunate plus mefloquine, or artemether plus mefloquine may be used (Luxemburger JC, et al: *Trans R Soc Trop Med Hyg* 88:213, 1994; Karbwang J, et al: *Trans R Soc Trop Med Hyg* 89:296, 1995).

[55]Uncomplicated or mild malaria may be treated with oral drugs.

[56]Atovaquone/proguanil is available as a fixed-dose combination tablet: adult tablets (Malarone; atovaquone 250 mg/proguanil 100 mg) and pediatric tablets (Malarone Pediatric; atovaquone 62.5 mg/proguanil 25 mg). To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown and use is generally not recommended. In a few small studies outcomes were normal in women treated with the combination in the 2nd and 3rd trimester (B Paternak et al., *Arch Intern Med* 2011; 171:259; AK Boggild et al., *Am J Trop Med Hyg* 2007; 76:208). The drug should not be given to patients with severe renal impairment (creatinine clearance <30 mL/min). There have been isolated case reports of resistance in *P. falciparum* in Africa, but *Medical Letter* consultants do not believe there is a high risk for acquisition of Malarone-resistant disease (E Schwartz et al., *Clin Infect Dis* 2003; 37:450; A Farnert et al., *BMJ* 2003; 326:628; S Kuhn et al., *Am J Trop Med Hyg* 2005; 72:407; CT Happi et al., *Malar J* 2006; 5:82).

[57]In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7 days.

[58]Although approved for once daily dosing, *Medical Letter* consultants usually divide the dose in 2 to decrease nausea and vomiting.

[59]For use in pregnancy.

[60]Lell B, Kremsner PG: *Antimicrob Agents Chemother* 46:2315, 2002.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Coartem (Artemether-lumefantrine)	1 tablet = 20 mg artemether and 120 mg lumefantrine A 3 day treatment schedule with a total of six oral doses is recommended for both adult and pediatric patients based on weight. These six doses should be administered over 3 days (4 tabs/dose at 0, 8, 24, 36, 48, and 60 hr)	5 to <15 kg: 1 tablet PO per dose 15 to <25 kg: 2 tablets PO per dose 25 to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets PO per dose
Alternative:	Mefloquine[61,62]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
P. vivax[63] acquired in areas of **chloroquine resistance**			
Oral[55]			
Drug of choice:	Quinine sulfate **plus** doxycycline[7,14] **plus** primaquine[64]	650 mg PO every 8 hr × 3-7 days[57] 100 mg PO bid × 7 days 30 mg base PO daily × 14 days	30 mg/kg/day PO in 3 doses × 3-7 days[57] 4 mg/kg/day PO in 2 doses × 7 days 0.5 mg/kg/day PO × 14 days
or	Mefloquine[61]	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
Alternatives:	Chloroquine **plus** primaquine[64]	25 mg base/kg PO in 3 doses over 48 hr 30 mg base PO daily × 14 days	25 mg base/kg PO in 3 doses over 48 hr 0.5 mg/kg/day PO × 14 days
All *Plasmodium* except **chloroquine-resistant *P. falciparum***[54] and **chloroquine-resistant *P. vivax***[63] **(areas without chloroquine resistance)**			
Oral[55]			
Drug of choice:	Chloroquine phosphate[65]	1 g (600 mg base), then 500 mg (300 mg base) 6 hr later PO, then 500 mg (300 mg base) at 24 and 48 hr	10 mg base/kg (max 600 mg base), then 5 mg base/kg 6 hr later PO, then 5 mg base/kg at 24 and 48 hr
All *Plasmodium*			
Parenteral (severe infection; chloroquine-sensitive and resistant)			
Drugs of choice[66]:	Quinidine gluconate[67]	10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started	10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started
or	Quinine dihydrochloride[67]	20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started	20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started

[61]At this dosage, adverse effects including nausea, vomiting, diarrhea, dizziness, disturbed sense of balance, toxic psychosis, and seizures can occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option because of increased risk for stillbirth (Nosten F, et al: *Clin Infect Dis* 28:808, 1999). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric illness. Mefloquine can be given to patients taking β blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine, quinidine, or halofantrine, and caution is required in using quinine, quinidine, or halofantrine to treat patients with malaria who have taken mefloquine for prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[62]*P. falciparum* with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[63]*P. vivax* with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia, and Peru.

[64]Primaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is most common in African, Asian, and Mediterranean peoples. Patients should be screened for G6PD deficiency before treatment. Primaquine should not be used during pregnancy.

[65]If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.

[66]Exchange transfusion has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema, or renal complications (Miller KD, et al: *N Engl J Med* 321:65, 1989).

[67]Continuous ECG, blood pressure, and glucose monitoring are recommended, especially in pregnant women and young children. For problems with quinidine availability, call the manufacturer (Eli Lilly, 800-545-5979) or the CDC Malaria Hotline (770-488-7788). Quinidine may have greater antimalarial activity than quinine. The loading dose should be decreased or omitted in those patients who have received quinine or mefloquine. If more than 48 hr of parenteral treatment is required, the quinine or quinidine dose should be reduced by 30-50%.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Alternative:	Artesunate[68] Plus a second oral drug	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr
Prevention of relapses: *P. vivax* and *P. ovale* only			
Drug of choice:	Primaquine phosphate[64]	30 mg base/day PO × 14 days	0.6 mg base/kg/day PO × 14 days
Malaria, prevention of[69]			
Chloroquine-sensitive areas[54]			
Drug of choice	Chloroquine phosphate[70,71]	500 mg (300 mg base), PO once/wk[72]	5 mg/kg base once/wk, up to adult dose of 300 mg base[72]
Chloroquine-resistant areas[54]			
Drug of choice:	Atovaquone/proguanil[56,71]	1 adult tab PO q day[73]	11-20 kg: 1 pediatric tab PO/day[56,73] 21-30 kg: 2 pediatric tabs PO/day[56,73] 31-40 kg: 3 pediatric tabs PO/day[56,73] >40 kg: 1 adult tab PO/day[56,73]
or	Mefloquine[61,71,74]	250 mg PO once/wk[72]	<9 kg: 5 mg/kg salt once/wk[72] 9-19 kg: ¼ tab once/wk[72] 19-30 kg: ½ tab once/wk[72] 31-45 kg: ¾ tab once/wk[72] >45 kg: 1 tab once/wk[72]
or	Doxycycline[7,71]	100 mg PO daily[75]	2 mg/kg/day, up to 100 mg/day[75]
Alternatives:	Primaquine[7]	30 mg base PO daily[76]	0.6 mg/kg base daily
Malaria, self-presumptive treatment[77]			
Drug of choice:	Atovaquone/proguanil[7,56,78]	4 adult tabs PO daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO once/day × 3 days 9-10 kg: 3 pediatric tabs PO once/day × 3 days 11-20 kg: 1 adult tab PO once/day × 3 days 21-30 kg: 2 adult tabs PO once/day × 3 days 31-40 kg: 3 adult tabs PO once/day × 3 days >40 kg: 4 adult tabs PO once/day × 3 days

[68]Oral artesunate is not available in the United States; the IV formulation is available through the CDC Malaria branch under an investigational new drug (IND) for patients with severe disease who do not have timely access or cannot tolerate, or fail to respond to IV quinidine (*Med Lett Drugs Ther* 2008; 50:37). To avoid development of resistance, adults treated with artesunate must also receive oral treatment doses of either atovaquone/proguanil, doxycycline, clindamycin, or mefloquine; children should take either atovaquone/proguanil, clindamycin, or mefloquine (F Nosten et al., *Lancet* 2000; 356:297; M van Vugt, *Clin Infect Dis* 2002; 35:1498; F Smithuis et al., *Trans R Soc Trop Med Hyg* 2004; 98:182). If artesunate is given IV, oral medication should be started when the patient is able to tolerate it (SEAQUAMAT group, *Lancet* 2005; 366:717; PE Duffy and CH Sibley, *Lancet* 2005;366:1908). Reduced susceptibility to artesunate characterized by slow parasitic clearance has been reported in Cambodia (WO Rogers et al., *Malar J* 2009; 8:10; AM Dundorp et al., *N Engl J Med* 2009; 361:455).

[69]No drug regimen guarantees protection against malaria. If fever develops within a year (particularly within the first 2 mo) after travel to malarious areas, travelers should be advised to seek medical attention. Insect repellents, insecticide-impregnated bed nets, and proper clothing are important adjuncts for malaria prophylaxis (*Med Lett* 45:41, 2003). Malaria in pregnancy is particularly serious for both mother and fetus; therefore, prophylaxis is indicated if exposure cannot be avoided.

[70]In pregnancy, chloroquine prophylaxis has been used extensively and safely.

[71]For prevention of attack after departure from areas where *P. vivax* and *P. ovale* are endemic, which includes almost all areas where malaria is found (except Haiti), some experts prescribe in addition primaquine phosphate 30 mg base/day or, for children, 0.6 mg base/kg/day during the last 2 wk of prophylaxis. Others prefer to avoid the toxicity of primaquine and rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 64.

[72]Beginning 1-2 wk before travel and continuing weekly for the duration of stay and for 4 wk after leaving malarious zone. Most adverse events occur within 3 doses. Some *Medical Letter* consultants favor starting mefloquine 3 wk prior to travel and monitoring the patient for adverse events; this allows time to change to an alternative regimen if mefloquine is not tolerated. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz of water. For pediatric doses less than ½ tablet, it is advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There are no data for use in children weighing <5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.

[73]Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving. In 1 study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (Overbosch D, et al: *Clin Infect Dis* 33:1015, 2001).

[74]Mefloquine has not been approved for use during pregnancy. However, it has been reported to be safe for prophylactic use during the 2nd or 3rd trimester of pregnancy and possibly during early pregnancy as well. Mefloquine is not recommended for patients with cardiac conduction abnormalities, and patients with a history of depression, seizures, psychosis, or psychiatric disorders should avoid mefloquine prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders; in these areas, atovaquone/proguanil or doxycycline should be used for prophylaxis.

[75]Beginning 1-2 days before travel and continuing for the duration of stay and for 4 wk after leaving. Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old. Doxycycline can cause gastrointestinal disturbances, vaginal moniliasis, and photosensitivity reactions.

[76]Studies have shown that daily primaquine beginning 1 day before departure and continued until 3-7 days after leaving the malaria area provides effective prophylaxis against chloroquine-resistant *P. falciparum* (Baird JK, et al: *Clin Infect Dis* 37:1659, 2003). Some studies have shown less efficacy against *P. vivax*. Nausea and abdominal pain can be diminished by taking with food.

[77]A traveler can be given a course of atovaquone/proguanil, mefloquine, or quinine plus doxycycline for presumptive self-treatment of febrile illness. The drug given for self-treatment should be different from that used for prophylaxis. This approach should be used only in very rare circumstances when a traveler cannot promptly get to medical care.

[78]Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving malarious zone. In 1 study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (D Overbosch et al., *Clin Infect Dis* 2001; 33:1015). The protective efficacy of Malarone against *P. vivax* is variable ranging from 84% in Indonesian New Guinea (J Ling et al., *Clin Infect Dis* 2002; 35:825) to 100% in Colombia (J Soto et al., *Am J Trop Med Hyg* 2006; 75:430). Some *Medical Letter* consultants prefer alternate drugs if traveling to areas where *P. vivax* predominates.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Quinine sulfate plus doxycycline[7,14]	650 mg PO every 8 hr × 3-7 days[57] 100 mg bid PO × 7 days	30 mg/kg/day PO in 3 doses × 3-7 days[57] 4 mg/kg/day in 2 PO doses × 7 days
or	Mefloquine[61]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg followed 12 hr later by 10 mg/kg
Microsporidiosis			
Ocular *(Encephalitozoon hellem, Encephalitozoon cuniculi, Vittaforma corneae [Nosema corneum])*			
Drug of choice:	Albendazole[7] **plus** fumagillin[79]	400 mg PO bid	
Intestinal *(Enterocytozoon bieneusi, Encephalitozoon [Septata] intestinalis)*			
E. bieneusi[80]			
Drug of choice:	Fumagillin	60 mg/day PO × 14 days in 3 divided doses	
E. intestinalis			
Drug of choice	Albendazole[7]	400 mg PO bid × 21 days	
Disseminated *(E. hellem, E. cuniculi, E. intestinalis, Pleistophora* sp., *Trachipleistophora* sp., and *Brachiola vesicularum)*			
Drug of choice[81]:	Albendazole[7]	400 mg PO bid	
Mites, see Scabies			
Moniliformis moniliformis infection			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg PO once, repeat twice, 2 wk apart	11 mg/kg PO once, repeat twice, 2 wk apart
***Naegleria* species,** see Amebic meningoencephalitis, primary			
Necator americanus, see Hookworm infection			
Oesophagostomum bifurcum			
Drug of choice:	See footnote 82		
Onchocerca volvulus, see Filariasis			
Opisthorchis viverrini, see Fluke infection			
Paragonimus westermani, see Fluke infection			
Pediculus capitis, Pediculus humanus, Phthirus pubis, see Lice			
Pinworm, see *Enterobius*			
Pneumocystis jiroveci (formerly *Pneumocystis carinii*) pneumonia (PCP)[83]			
Moderate to severe disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses × 21 days	TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses × 21 days
Alternatives:	Pentamidine *or*	3-4 mg IV daily × 21 days	3-4 mg IV daily × 21 days
	Primaquine **plus** clindamycin[7]	30 mg base PO daily × 21 days 600-900 mg IV tid or qid × 21 days, or 300-450 mg PO tid or qid × 21 days (change to PO after clinical improvement)	0.3 mg/kg base PO (max 30 mg) daily × 21 days 15-25 mg/kg IV tid or qid × 21 days, or 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days (change to PO after clinical improvement)

[79]Ocular lesions caused by *E. hellem* in HIV-infected patients have responded to fumagillin eyedrops prepared from Fumidil-B (bicyclohexyl ammonium fumagillin) used to control a microsporidial disease of honey bees (Diesenhouse MC: *Am J Ophthalmol* 115:293, 1993), available from Leiter's Park Avenue Pharmacy (see footnote 1). For lesions caused by *V. corneae,* topical therapy is generally not effective and keratoplasty may be required (Davis RM, et al: *Ophthalmology* 97:953, 1990).

[80]Oral fumagillin (Sanofi Recherche, Gentilly, France) has been effective in treating *E. bieneusi* (Molina J-M, et al: *N Engl J Med* 346:1963, 2002), but has been associated with thrombocytopenia. HAART may lead to microbiologic and clinical response in HIV-infected patients with microsporidial diarrhea (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004). Octreotide (Sandostatin) has provided symptomatic relief in some patients with large-volume diarrhea.

[81]Molina J-M, et al: *J Infect Dis* 171:245, 1995. There is no established treatment for *Pleistophora.* For disseminated disease caused by *Trachipleistophora* or *Brachiola,* itraconazole 400 mg PO once/day plus albendazole may also be tried (Coyle CM, et al: *N Engl J Med* 351:42, 2004).

[82]Albendazole or pyrantel pamoate may be effective (Ziem JB, et al: *Ann Trop Med Parasitol* 98:385, 2004).

[83]*Pneumocystis* has been reclassified as a fungus. In severe disease with room air P_{O_2} ≤70 mm Hg or A-aO_2 gradient ≥35 mm Hg, prednisone should also be used (Gagnon S, et al: *N Engl J Med* 323:1444, 1990; Caumes E, et al: *Clin Infect Dis* 18:319, 1994).

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Mild to moderate disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	2 DS tablets (160 mg/800 mg each) PO tid × 21 days	TMP 15-20 mg/kg/day SMX 75-100 mg/kg/day PO in 3 or 4 doses × 21 days
Alternative:	Dapsone **plus** trimethoprim *or* primaquine **plus** clindamycin *or* atovaquone	100 mg PO daily × 21 days 15 mg/kg/day PO in 3 doses 30 mg base PO daily × 21 days 300-450 mg PO tid or qid × 21 days 750 mg PO bid × 21 days	2 mg/kg/day (max 100 mg) PO × 21 days 15 mg/kg/day PO in 3 doses 0.3 mg/kg base PO daily (max 30 mg) × 21 days 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days 1-3 mo: 30 mg/kg/day PO in 2 doses × 21 days 4-24 mo: 45 mg/kg/day PO in 2 doses × 21 days >24 mo: 30 mg/kg/day PO in 2 doses × 21 days
Primary and secondary prophylaxis[84]			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	1 tab (single or double strength) PO daily or 1 DS tab PO 3 doses/wk	TMP 150 mg/m^2, SMX 750 mg/m^2 PO in 2 doses on 3 consecutive days per wk
Alternatives[85]:	Dapsone[7]	50 mg PO bid, or 100 mg PO daily	2 mg/kg/day (max 100 mg) PO or 4 mg/kg (max 200 mg) PO each wk
or	Dapsone[7] **plus** pyrimethamine[86]	50 mg PO daily or 200 mg PO each wk 50 mg PO or 75 mg PO each wk	
or	Pentamidine aerosol	300 mg inhaled monthly via *Respirgard II* nebulizer	≥5 yr: 300 mg inhaled monthly via *Respirgard II* nebulizer
or	Atovaquone[7]	1,500 mg/d PO in 1 or 2 doses	1-3 mo: 30 mg/kg/day PO 4-24 mo: 45 mg/kg/day PO >24 mo: 30 mg/kg/day PO
Roundworm, see Ascariasis			
Sappinia diploidea, see Amebic meningoencephalitis, primary			
Scabies *(Sarcoptes scabiei)*			
Drug of choice:	5% Permethrin	Topically, 2× at least 7 days apart[87]	Topically, 2× at least 7 days apart[87]
Alternatives[88]:	Ivermectin[7,89] 10% Crotamiton	200 µg/kg PO 2× at least 7 days apart [87] Topically overnight on days 1, 2, 3, 8	200 µg/kg PO 2× at least 7 days apart [87] Topically overnight on days 1, 2, 3, 8
Schistosomiasis *(Bilharziasis)*			
Schistosoma haematobium			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Schistosoma intercalatum			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Schistosoma japonicum			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day

[84]Primary/secondary prophylaxis in patients with HIV can be discontinued after CD4 count increases to >200 × 10^6/L for longer than 3 mo.

[85]An alternative trimethoprim-sulfamethoxazole regimen is 1 DS tab 3×/wk. Weekly therapy with sulfadoxine 500 mg/pyrimethamine 25 mg/leucovorin 25 mg was effective *Pneumocystis carinii* pneumonia (PCP) prophylaxis in liver transplant patients (Torre-Cisneros J, et al: *Clin Infect Dis* 29:771, 1999).

[86]Plus leucovorin 25 mg with each dose of pyrimethamine.

[87]In some cases, treatment may need to be repeated in 10-14 days. BJ Currie and JS McCarthy, *N Engl J Med* 2010; 362:717. A second ivermectin dose taken 2 wk later increased the cure rate to 95%, which is equivalent to that of 5% permethrin (V Usha et al., *J Am Acad Dermatol* 2000; 42:236). Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (P del Giudice, *Curr Opin Infect Dis* 2004; 15:123).

[88]Lindane (γ-benzene hexachloride; Kwell) should be reserved as a second-line agent. The FDA has recommended it should not be used for immunocompromised patients, young children, the elderly, and patients who weigh <50 kg.

[89]Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P: *Curr Opin Infect Dis* 15:123, 2004). The safety of oral ivermectin in pregnancy and young children has not been established.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Schistosoma mansoni			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Alternative:	Oxamniquine[90]	15 mg/kg PO once[91]	20 mg/kg/day PO in 2 doses × 1 day[91]
Schistosoma mekongi			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day
Sleeping sickness, see Trypanosomiasis			
Strongyloidiasis *(Strongyloides stercoralis)*			
Drug of choice[92]:	Ivermectin	200 µg/kg/day PO × 2 days	200 µg/kg/day PO × 2 days
Alternative:	Albendazole[7, 93]	400 mg PO bid × 7 days	400 mg bid PO × 7 days
Tapeworm infection			
Adult (intestinal stage)			
Diphyllobothrium latum (fish), *Taenia saginata* (beef), *Taenia solium* (pork), *Dipylidium caninum* (dog)			
Drug of choice:	Praziquantel[7]	5-10 mg/kg PO once	5-10 mg/kg PO once
Alternative:	Niclosamide	2 g PO once	50 mg/kg PO once
Hymenolepis nana (dwarf tapeworm)			
Drug of choice:	Praziquantel[7]	25 mg/kg PO once	25 mg/kg PO once
Alternative:	Niclosamide	2 g PO daily × 7 days	11-34 kg: 1 g PO on day 1 then 500 mg/day PO × 6 days[94] >34 kg: 1.5 g PO on day 1 then 1 g/d PO × 6 days[94]
Larval (tissue stage)			
Echinococcus granulosus (hydatid cyst)			
Drug of choice[95]:	Albendazole	400 mg PO bid × 1-6 mo	15 mg/kg/day PO (max 800 mg) × 1-6 mo
Echinococcus multilocularis			
Treatment of choice:	See footnote 96		
Taenia solium (cysticercosis)			
Treatment of choice		See footnote 97	
Alternative:	Albendazole	400 mg bid PO × 8-30 days; can be repeated as necessary	15 mg/kg/day PO (max 800 mg) in 2 doses × 8-30 days; can be repeated as necessary
or	Praziquantel[7]	50 mg/kg/day PO in 3 doses × 15 days	50 mg/kg/day PO × 15 day
Toxocariasis, see Visceral larva migrans			

[90]Oxamniquine has been effective in some areas in which praziquantel is less effective (Stelma FF, et al: *J Infect Dis* 176:304, 1997). Oxamniquine is contraindicated in pregnancy.

[91]In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/day × 2 days. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (Shekhar KC: *Drugs* 42:379, 1991).

[92]In immunocompromised patients or disseminated disease, it may be necessary to prolong or repeat therapy, or to use other agents. Veterinary parenteral and enema formulations of ivermectin have been used in severely ill patients unable to take oral medications (Chiodini PL, et al: *Lancet* 355:43, 2000; Orem J, et al: *Clin Infect Dis* 37:152, 2003; Tarr PE: *Am J Trop Med Hyg* 68:453, 2003).

[93]Albendazole must be taken with food; a fatty meal increases oral bioavailability.

[94]Niclosamide must be thoroughly chewed or crushed and swallowed with a small amount of water. Nitazoxanide may be an alternative (JJ Ortiz et al., *Trans R Soc Trop Med Hyg* 2002; 96:193; JC Chero et al., *Trans R Soc Trop Med Hyg* 2007; 101:203; E Diaz et al., *Am J Trop Med Hyg* 2003; 68:384).

[95]Patients may benefit from surgical resection or percutaneous drainage of cysts. Praziquantel is useful preoperatively or in case of spillage of cyst contents during surgery. Percutaneous aspiration-injection-reaspiration (PAIR) with ultrasound guidance plus albendazole therapy has been effective for management of hepatic hydatid cyst disease (Smego RA Jr, et al: *Clin Infect Dis* 37:1073, 2003).

[96]Surgical excision is the only reliable means of cure. Reports have suggested that in nonresectable cases use of albendazole or mebendazole can stabilize and sometimes cure infection (Craig P: *Curr Opin Infect Dis* 16:437, 2003).

[97]Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with antiseizure medication. Treatment of parenchymal cysticerci with albendazole or praziquantel is controversial (Maguire JM: *N Engl J Med* 350:215, 2004). Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids (6 mg dexamethasone or 40-60 mg prednisone daily) and an antiseizure medication (Garcia HH, et al: *N Engl J Med* 350:249, 2004). Patients with subarachnoid cysts or giant cysts in the fissures should be treated for at least 30 days (Proaño JV, et al: *N Engl J Med* 345:879, 2001). Surgical intervention or CSF diversion is indicated for obstructive hydrocephalus; prednisone 40 mg/day may be given with surgery. Arachnoiditis, vasculitis, or cerebral edema is treated with prednisone 60 mg/day or dexamethasone 4-6 mg/day together with albendazole or praziquantel (White Jr AC: *Annu Rev Med* 51:187, 2000). Any cysticercocidal drug may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are used. An ophthalmic exam should always precede treatment to rule out intraocular cysts.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Toxoplasmosis *(Toxoplasma gondii)*[98]			
Drugs of choice[99,100]:	Pyrimethamine[101]	200 mg PO × 1, then 50-75 mg/day × 3-6 wk	2 mg/kg/d × 3 days, then 1 mg/kg/day (max 25 mg/day) × 4 wk[102]
	plus		
	Sulfadiazine	1-1.5 g PO qid × 3-6 wk	100-200 mg/kg/day × 3-4 wk
	or		
	plus		
	Clindamycin	1.8-2.4 g/day IV or PO in 3 or 4 doses	5-7.5 mg/kg/day IV or PO in 3 or 4 doses (max 600 mg/dose)
	or		
	plus		
	Atovaquone	1,500 mg PO bid	1,500 mg PO bid
Alternative:	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses	TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses
Trichinellosis *(Trichinella spiralis)*			
Drugs of choice:	Steroids for severe symptoms	Prednisone 30-60 mg PO daily × 10-15 days	
	plus		
	Albendazole[7]	400 mg PO bid × 8-14 days	400 mg PO bid × 8-14 days
Alternative:	Mebendazole[7]	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days
Trichomoniasis *(Trichomonas vaginalis)*			
Drug of choice[103]:	Metronidazole	2 g PO once or 500 mg PO bid × 7 days	15 mg/kg/day PO in 3 doses × 7 days
or	Tinidazole[5]	2 g PO once	50 mg/kg PO once (max 2 g)
Trichostrongylus infection			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg base PO once (max 1 g)	11 mg/kg PO once (max 1 g)
Alternative:	Mebendazole[7]	100 mg PO bid × 3 days	100 mg PO bid × 3 days
or	Albendazole[7]	400 mg PO once	400 mg PO once
Trichuriasis (*Trichuris trichiura,* whipworm)			
Drug of choice:	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days
Alternative:	Albendazole[7]	400 mg PO × 3 days	400 mg PO × 3 days
	Ivermectin[7]	200 μg/kg PO × 3 days	200 μg/kg PO × 3 days
Trypanosomiasis[104]			
Trypanosoma cruzi (American trypanosomiasis, Chagas disease)			
Drug of choice:	Benznidazole	5-7 mg/kg/day PO in 2 divided doses × 60 days	≤12 yr: 10 mg/kg/day PO in 2 or 3 doses × 60 days
or	Nifurtimox[105]	8-10 mg/kg/day PO in 3-4 doses × 90 days	1-10 yr: 15-20 mg/kg/day PO in 4 doses × 90 days 11-16 yr: 12.5-15 mg/kg/day in 4 doses × 90 days

[98]In ocular toxoplasmosis with macular involvement, corticosteroids are recommended in addition to antiparasitic therapy for an antiinflammatory effect.

[99]To treat CNS toxoplasmosis in HIV-infected patients, some clinicians have used pyrimethamine 50-100 mg/day (after a loading dose of 200 mg) with sulfadiazine and, when sulfonamide sensitivity developed, have given clindamycin 1.8-2.4 g/day in divided doses instead of the sulfonamide. Atovaquone plus pyrimethamine appears to be an effective alternative in sulfa-intolerant patients (Chirgwin K, et al: *Clin Infect Dis* 34:1243, 2002). Treatment is followed by chronic suppression with lower-dosage regimens of the same drugs. For primary prophylaxis in HIV patients with $<100 \times 10^6$/L CD4 cells, either trimethoprim-sulfamethoxazole, pyrimethamine with dapsone, or atovaquone with or without pyrimethamine can be used. Primary or secondary prophylaxis may be discontinued when the CD4 count increases to $>200 \times 10^6$/L for more than 3 mo (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004).

[100]Women who develop toxoplasmosis during the 1st trimester of pregnancy can be treated with spiramycin (3-4 g/day). After the 1st trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started (Montoya JG, Liesenfeld O: *Lancet* 363:1965, 2004). Pyrimethamine is a potential teratogen and should be used only after the 1st trimester.

[101]Plus leucovorin 10-25 mg with each dose of pyrimethamine.

[102]Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for about 1 yr (Remington JS, Klein JO, editors: *Infectious disease of the fetus and newborn infant,* ed 5, Philadelphia, 2001, WB Saunders, p. 290).

[103]Sexual partners should be treated simultaneously. Metronidazole-resistant strains have been reported and can be treated with higher doses of metronidazole (2-4 g/day × 7-14 days) or with tinidazole (Hager WD: *Sex Transm Dis* 31:343, 2004).

[104]Barrett MP, et al: *Lancet* 362:1469, 2003.

[105]The addition of γ-interferon to nifurtimox for 20 days in experimental animals and in a limited number of patients appears to shorten the acute phase of Chagas disease (McCabe RE, et al: *J Infect Dis* 163:912, 1991).

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Trypanosoma brucei gambiense (West African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice[106]:	Pentamidine isethionate[7]	4 mg/kg/day IM × 7 days	4 mg/kg/day IM or IV × 7 days
Alternative:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21	2 mg/kg (test dose) IV, then 20 mg/kg IV on days 1, 3, 5, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol[107]	2.2 mg/kg/day IV × 10 days	2.2 mg/kg/day IV × 10 days
or	Eflornithine[108]	400 mg/kg/day IV in 4 doses × 14 d	400 mg/kg/day in 4 doses × 14 days
Trypanosoma brucei rhodesiense (East African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21	2 mg/kg (test dose), then 20 mg/kg IV on days 1, 3, 5, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol[107]	2.2 mg/kg/day × 10 days	2.2 mg/kg/day × 10 days
Visceral larva migrans[109] (Toxocariasis)			
Drugs of choice:	Albendazole[7] Mebendazole[7]	400 mg PO bid × 5 days 100-200 mg PO bid × 5 days	400 mg PO bid × 5 days 100-200 mg PO bid × 5 days
Whipworm, see Trichuriasis			
Wuchereria bancrofti, see Filariasis			

[106]For treatment of *T. b. gambiense,* pentamidine and suramin have equal efficacy but pentamidine is better tolerated.

[107]In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy (Pepin J, et al: *Trans R Soc Trop Med Hyg* 89:92, 1995). Up to 20% of patients with *T. b. gambiense* fail to respond to melarsoprol (Barrett MP: *Lancet* 353:1113, 1999).

[108]Eflornithine is highly effective in *T. b. gambiense* but not against *T. b. rhodesiense* infections. It is available in limited supply only from the WHO and the CDC. Eflornithine dose may be reduced to 400 mg/kg IV in 2 doses for 7 d when used in conjunction with nifurtimox at a dose of 15 mg/kg/d PO in 3 doses × 10 d.

[109]Optimum duration of therapy is not known; some *Medical Letter* consultants would treat for 20 days. For severe symptoms or eye involvement, corticosteroids can be used in addition.

CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; DS, double strength; ECG, electrocardiography; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HAART, highly active antiretroviral therapy; SMX, sulfamethoxazole; TMP, trimethoprim; WHO, World Health Organization.

From: Drugs for parasitic infection. Med Lett *11(Suppl):e1-e23, 2013. Available at http://www.medicalletter.org.*

Table 281-1 Drug Treatment for Amebiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
INVASIVE DISEASE		
Metronidazole	Colitis or liver abscess: 750 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days
or		
Tinidazole	Colitis: 2 g once daily for 3 days Liver abscess: 2 g once daily for 3-5 days	Colitis: 50 mg/kg/day once daily for 3 days Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days
or		
Diloxanide furoate†	500 mg tid for 10 days	20 mg/kg/day in 3 divided doses for 7 days
or		
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in 3 divided doses for 20 days
ASYMPTOMATIC INTESTINAL COLONIZATION		
Paromomycin (preferred)	As for invasive disease	As for invasive disease
or		
Diloxanide furoate†		
or		
Iodoquinol		

*All pediatric dosages are up to a maximum of the adult dose.

†Not available in the United States.

Table 282-2 Drug Treatment for Giardiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
RECOMMENDED		
Tinidazole	2 g once	>3 yr: 50 mg/kg once
Nitazoxanide	500 mg bid for 3 days	1-3 yr: 100 mg (5 mL) bid for 3 days 4-11 yr: 200 mg (10 mL) bid for 3 days >12 yr: 500 mg bid for 3 days
Metronidazole	250 mg tid for 5-7 days	15 mg/kg/day in 3 divided doses for 5-7 days
ALTERNATIVE		
Albendazole	400 mg once a day for 5 days	>6 yr: 400 mg once a day for 5 days
Paromomycin	25-35 mg/kg/day in 3 divided doses for 5-10 days	Not recommended
Quinacrine†	100 mg tid for 5-7 days	6 mg/kg/day in 3 divided doses for 5 days

*All pediatric dosages are up to a maximum of the adult dose.
†Not commercially available. Can be compounded by Medical Center Pharmacy in New Haven, CT (203-688-6816) or Panorama Compounding Pharmacy in Van Nuys, CA (800-247-9767).

Table 282-1 Clinical Signs and Symptoms of Giardiasis

SYMPTOM	FREQUENCY (%)
Diarrhea	64-100
Malaise, weakness	72-97
Abdominal distention	42-97
Flatulence	35-97
Abdominal cramps	44-81
Nausea	14-79
Foul-smelling, greasy stools	15-79
Anorexia	41-73
Weight loss	53-73
Vomiting	14-35
Fever	0-28
Constipation	0-27

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)

(CDC Malaria Hotline: [770] 488-7788 or [855] 856-4713 toll-free Monday-Friday 9 AM to 5 PM EST; [770] 488-7100 after hours, weekends, and holidays)

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Uncomplicated malaria/ *P. falciparum* *or* Species not identified If "species not identified" is subsequently diagnosed as *P. vivax* or *P. ovale:* see *P. vivax* and *P. ovale* (below) regarding treatment with primaquine	Chloroquine-resistant or unknown resistance[2] (All malarious regions except those specified as chloroquine-sensitive listed in the box below)	A. **Atovaquone-proguanil (Malarone)[3]** **Adult tab = 250 mg atovaquone/100 mg proguanil** 4 adult tabs PO qd × 3 days	A. **Atovaquone-proguanil (Malarone)[3]** **Adult tab = 250 mg atovaquone/100 mg proguanil** **Pediatric (ped) tab = 62.5 mg atovaquone/25 mg proguanil** 5-8 kg: 2 ped tabs PO qd × 3 days 9-10 kg: 3 ped tabs PO qd × 3 days 11-20 kg: 1adult tab PO qd × 3 days 21-30 kg: 2 adult tabs PO qd × 3 days 31-40 kg: 3 adult tabs PO qd × 3 days > 40 kg: 4 adult tabs PO qd × 3 days
		B. **Artemether-lumefantrine (Coartem)[3]** **1 tablet = 20 mg artemether and 120 mg lumefantrine** A 3 day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hr later, then 1 dose PO bid for the following 2 days 5-<15 kg: 1 tablet per dose 15-<25 kg: 2 tablets per dose 25-<35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose	
		C. **Quinine sulfate plus 1 of the following: doxycycline, tetracycline, or clindamycin** **Quinine sulfate:** 542 mg base (=650 mg salt)[4] PO tid × 3 or 7 days[5] **Doxycycline:** 100 mg PO bid × 7 days **Tetracycline:** 250 mg PO qid × 7 days **Clindamycin:** 20 mg base/kg/day PO divided tid × 7 days	C. **Quinine sulfate[4] plus 1 of the following: doxycycline[6], tetracycline,[6] or clindamycin** **Quinine sulfate:** 8.3 mg base/kg (=10 mg salt/kg) PO tid × 3 or 7 days[5] **Doxycycline:** 2.2 mg/kg PO every 12 hr × 7 days **Tetracycline:** 25 mg/kg/day PO divided qid × 7 days **Clindamycin:** 20 mg base/kg/day PO divided tid × 7 days
		D. **Mefloquine (Lariam and generics)[7]** 684 mg base (=750 mg salt) PO as initial dose, followed by 456 mg base (=500 mg salt) PO given 6-12 hr after initial dose Total dose = 1,250 mg salt	D. **Mefloquine (Lariam and generics)[7]** 13.7 mg base/kg (=15 mg salt/kg) PO as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) PO given 6-12 hr after initial dose. Total dose = 25 mg salt/kg
Uncomplicated malaria/ *P. falciparum* *or* Species not identified	Chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	**Chloroquine phosphate (Aralen and generics)[8]** 600 mg base (=1,000 mg salt) PO immediately, followed by 300 mg base (=500 mg salt) PO at 6, 24, and 48 hr Total dose: 1,500 mg base (=2,500 mg salt) ***or*** **Hydroxychloroquine (Plaquenil and generics)** 620 mg base (=800 mg salt) PO immediately, followed by 310 mg base (=400 mg salt) PO at 6, 24, and 48 hr Total dose: 1,550 mg base (=2,000 mg salt)	**Chloroquine phosphate (Aralen and generics)[8]** 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg ***or*** **Hydroxychloroquine (Plaquenil and generics)** 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg

[1]If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use 1 of the other options instead.

[2]NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum.* Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

[3]Take with food or whole milk. If patient vomits within 30 min of taking a dose, then patient should repeat the dose.

[4]U.S. manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult because of unavailability of noncapsule forms of quinine.

[5]For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

[6]Doxycycline and tetracycline are not indicated for use in children younger than 8 yr old. For children younger than 8 yr old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children younger than 8 yr old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

[7]Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia as a consequence of drug resistance.

[8]When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.

Continued

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)—cont'd

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Uncomplicated malaria/*P. malariae* or *P. knowlesi*	All regions	**Chloroquine phosphate:**[8] treatment as above *or* **Hydroxychloroquine:** treatment as above	**Chloroquine phosphate:**[8] treatment as above *or* **Hydroxychloroquine:** treatment as above
Uncomplicated malaria/*P. vivax* or *P. ovale*	All regions Note: for suspected chloroquine-resistant *P. vivax*, see row below	**Chloroquine phosphate**[8] **plus primaquine phosphate**[9] **Chloroquine phosphate:** treatment as above **Primaquine phosphate:** 30 mg base PO qd × 14 days *or* **Hydroxychloroquine plus primaquine phosphate**[9] **Hydroxychloroquine:** treatment as above **Primaquine phosphate:** 30 mg base PO qd × 14 days	**Chloroquine phosphate**[8] **plus primaquine phosphate**[9] **Chloroquine phosphate:** treatment as above **Primaquine:** 0.5 mg base/kg PO qd × 14 days *or* **Hydroxychloroquine plus primaquine phosphate**[9] **Hydroxychloroquine:** treatment as above **Primaquine phosphate:** 0.5 mg base/kg PO qd × 14 days
Uncomplicated malaria/*P. vivax*	**Chloroquine-resistant**[10] (Papua New Guinea and Indonesia)	A. **Quinine sulfate plus either doxycycline or tetracycline plus primaquine phosphate**[9] **Quinine sulfate:** treatment as above **Doxycycline or tetracycline:** Treatment as above **Primaquine phosphate:** treatment as above B. **Atovaquone-proguanil plus primaquine phosphate**[9] **Atovaquone-proguanil:** treatment as above **Primaquine phosphate:** treatment as above C. **Mefloquine plus primaquine phosphate**[9] **Mefloquine:** treatment as above **Primaquine phosphate:** treatment as above	A. **Quinine sulfate plus either doxycycline**[6] **or tetracycline**[6] **plus primaquine phosphate**[9] **Quinine sulfate:** treatment as above **Doxycycline or tetracycline:** treatment as above **Primaquine phosphate:** treatment as above B. **Atovaquone-proguanil plus primaquine phosphate**[9] **Atovaquone-proguanil:** treatment as above **Primaquine phosphate:** treatment as above C. **Mefloquine plus primaquine phosphate**[9] **Mefloquine:** treatment as above **Primaquine phosphate:** treatment as above
Uncomplicated malaria: alternatives for pregnant women[11-13]	**Chloroquine-sensitive** (See uncomplicated malaria sections above for chloroquine-sensitive species by region)	**Chloroquine phosphate:** treatment as above *or* **Hydroxychloroquine:** treatment as above	Not applicable
	Chloroquine-resistant (See sections above for regions with chloroquine-resistant *P. falciparum* and *P. vivax*)	**Quinine sulfate plus clindamycin** **Quinine sulfate:** treatment as above **Clindamycin:** treatment as above *or* **Mefloquine:** treatment as above	Not applicable

[9]Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally 1 time per week for 8 wk; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

[10]NOTE: There are 3 options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rates as a result of chloroquine-resistant *P. vivax* are well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* are also documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

[11]For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

[12]Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the 1st trimester because of a lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

[13]For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)—cont'd

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Severe malaria[14-16]	All regions	Quinidine gluconate[14] plus 1 of the following: doxycycline, tetracycline, or clindamycin **Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hr, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hr. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hr, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hr every 8 hr, starting 8 hr after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; =3 days in Africa or South America **Doxycycline:** treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hr and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days **Tetracycline:** treatment as above **Clindamycin:** treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days *Investigational new drug (contact CDC for information):* Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), doxycycline (clindamycin in pregnant women), or mefloquine	Quinidine gluconate[14] plus one of the following: doxycycline[4], tetracycline[4], or clindamycin **Quinidine gluconate:** same mg/kg dosing and recommendations as for adults **Doxycycline:** treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hr and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children >45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days **Tetracycline:** treatment as above **Clindamycin:** treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. *Investigational new drug (contact CDC for information):* Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), clindamycin, or mefloquine

[14]Persons with a positive blood smear *or* history of recent possible exposure and no other recognized pathology who have 1 or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum*.

[15]Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hr or if they have received mefloquine within the preceding 12 hr. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.

[16]Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

From the Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf

Table 288-3 Treatment of Uncomplicated Malaria

	REGIMENS
All *Plasmodium falciparum* malaria	Artemether-lumefantrine 1.5 mg/kg-9 mg/kg twice daily for 3 days with food or milk Artesunate 4 mg/kg daily for 3 days and mefloquine 25 mg base per kg (8 mg/kg/daily for 3 days*)† Dihydroartemisinin-piperaquine 2.5 mg/kg-20 mg/kg daily for 3 days
Sensitive *P. falciparum* malaria	Artesunate 4 mg/kg daily for 3 days and a single dose of sulfadoxine-pyrimethamine 25 mg/kg-1.25 mg/kg Artesunate 4 mg/kg and amodiaquine* 10 mg base per kg daily for 3 days
Chloroquine-sensitive *Plasmodium vivax*‡, *Plasmodium malariae*‡, *Plasmodium ovale*‡, *Plasmodium knowlesi*‡	Chloroquine 10 mg base per kg immediately, followed by 10 mg/kg at 24 hr and 5 mg/kg at 48 hr

*World Health Organization prequalified fixed dose formulations are preferable to loose tablets. A taste masked dispersible pediatric tablet formulation of artemether-lumefantrine is available.

†High failure rates with artesunate-mefloquine have been reported on the Thailand–Myanmar border.

‡Any of the artemisinin combination treatments can be given except for artesunate-sulfadoxine-pyrimethamine where *P. vivax* is resistant. Patients with *P. vivax* or *P. ovale* infections should also be given a 14 day course of primaquine to eradicate hypnozoites (radical cure). However, severe glucose-6-phosphate dehydrogenase deficiency is a contraindication because a 14 day course of primaquine can cause severe hemolytic anemia in this group.

From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria. Lancet *383:723–732, 2014.*

Table 288-4 Treatment of Severe Malaria in Adults and Children

- Artesunate 2·4 mg/kg by intravenous or intramuscular* injection, followed by 2.4 mg/kg at 12 hr and 24 hr; continue injection once daily if necessary†
- Artemether 3.2 mg/kg by immediate intramuscular* injection, followed by 1.6 mg/kg daily
- Quinine dihydrochloride 20 mg salt per kg infused during 4 hr, followed by maintenance of 10 mg salt per kg infused during 2-8 hr every 8 hr (can also be given by intramuscular injection* when diluted to 60-100 mg/mL)

Artesunate is the treatment of choice. Artemether should only be used if artesunate is unavailable. Quinine dihydrochloride should be given only when artesunate and artemether are unavailable.

*Intramuscular injections should be given to the anterior thigh.

†Young children with severe malaria have lower exposure to artesunate and its main biologically active metabolite dihydroartemisinin than do older children and adults. Revised dose regimens to ensure similar drug exposures have been suggested.

Table 290-1 Signs and Symptoms Occurring Before Diagnosis or During the Course of Untreated Acute Congenital Toxoplasmosis in 152 Infants (A) and in 101 of These Same Children After They Had Been Followed 4 Yr or More (B)

	Frequency of Occurrence in Patients with	
SIGNS AND SYMPTOMS	"Neurologic" Disease*	"Generalized" Disease†
A. INFANTS	108 PATIENTS (%)	44 PATIENTS (%)
Chorioretinitis	102 (94)	29 (66)
Abnormal cerebrospinal fluid	59 (55)	37 (84)
Anemia	55 (51)	34 (77)
Convulsions	54 (50)	8 (18)
Intracranial calcification	54 (50)	2 (4)
Jaundice	31 (29)	35 (80)
Hydrocephalus	30 (28)	0 (0)
Fever	27 (25)	34 (77)
Splenomegaly	23 (21)	40 (90)
Lymphadenopathy	18 (17)	30 (68)
Hepatomegaly	18 (17)	34 (77)
Vomiting	17 (16)	21 (48)
Microcephalus	14 (13)	0 (0)
Diarrhea	7 (6)	11 (25)
Cataracts	5 (5)	0 (0)
Eosinophilia	6 (4)	8 (18)
Abnormal bleeding	3 (3)	8 (18)
Hypothermia	2 (2)	9 (20)
Glaucoma	2 (2)	0 (0)
Optic atrophy	2 (2)	0 (0)
Microphthalmia	2 (2)	0 (0)
Rash	1 (1)	11 (25)
Pneumonitis	0 (0)	18 (41)
B. CHILDREN ≥4 YR OF AGE	70 PATIENTS (%)	31 PATIENTS (%)
Mental retardation	62 (89)	25 (81)
Convulsions	58 (83)	24 (77)
Spasticity and palsies	53 (76)	18 (58)
Severely impaired vision	48 (69)	13 (42)
Hydrocephalus or microcephalus	31 (44)	2 (6)
Deafness	12 (17)	3 (10)
Normal	6 (9)	5 (16)

*Patients with otherwise undiagnosed central nervous system disease in the 1st yr of life.

†Patients with otherwise undiagnosed nonneurologic diseases during the 1st 2 mo of life.

Adapted from Eichenwald H: A study of congenital toxoplasmosis. In Slim JC, editor: Human toxoplasmosis, *Copenhagen, 1960, Munksgaard, pp. 41–49. Study performed in 1947. The most severely involved institutionalized patients were n*

Table 288-5 Chemoprophylaxis of Malaria for Children

AREA	DRUG	DOSAGE (ORAL)	ADVANTAGES	DISADVANTAGES	BEST USE
Chloroquine-resistant area	Mefloquine*†	<10 kg: 4.6 mg base (5 mg salt)/kg/wk 10-19 kg: ¼ tab/wk 20-30 kg: ½ tab/wk 31-45 kg: ¾ tab/wk >45 kg: 1 tab/wk (228 mg base)	Once weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria endemic area for 4 wk or more Children unlikely to take daily medication
	Doxycycline‡	2 mg/kg daily (max 100 mg)	Inexpensive	Cannot give to children <8 yr Daily dosing Must take with food or causes stomach upset Photosensitivity	Children going to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone/proguanil§ (Malarone)	Pediatric tabs: 62.5 mg atovaquone/25 mg proguanil Adult tabs: 250 mg proguanil/100 mg proguanil 5-8 kg: pediatric tab once daily (off-label) 9-10 kg: pediatric tab once daily (off-label) 11-20 kg: 1 pediatric tab once daily 21-30 kg: 2 pediatric tabs once daily 31-40 kg: 3 pediatric tabs once daily >40 kg: 1 adult tab once daily	Pediatric formulation Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria endemic area for <4 wk
Chloroquine-susceptible area	Chloroquine phosphate	5 mg base/kg/wk (max: 300 mg base)	Once weekly dosing Inexpensive Generally well tolerated	Bitter taste No pediatric formulation	Best medication for children traveling to areas with *Plasmodium falciparum* or *Plasmodium vivax* that is chloroquine susceptible
	Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas				

*Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.

†Mefloquine resistance exists in western Cambodia and along the Thailand–Cambodia and Thailand–Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.

‡Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children younger than 8 yr of age or in pregnant women.

§Atovaquone/proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children weighing <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

The Digestive System

Table 306-2 Causes of Oropharyngeal Dysphagia

NEUROMUSCULAR DISORDERS
Cerebral palsy
Brain tumors
Cerebrovascular accidents
Polio and postpolio syndromes
Multiple sclerosis
Myositis
Dermatomyositis
Myasthenia gravis
Muscular dystrophies
Acquired or inherited dystonia syndrome
Dysautonomia
METABOLIC AND AUTOIMMUNE DISORDERS
Hyperthyroidism
Systemic lupus erythematosus
Sarcoidosis
Amyloidosis
INFECTIOUS DISEASE
Meningitis
Botulism
Diphtheria
Lyme disease
Neurosyphilis
Viral infection: polio, Coxsackievirus, herpes, cytomegalovirus
STRUCTURAL LESIONS
Inflammatory: abscess, pharyngitis
Congenital web
Cricopharyngeal bar
Dental problems
Bullous skin lesions
Plummer-Vinson syndrome
Zenker diverticulum
Extrinsic compression: osteophytes, lymph nodes, thyroid swelling
OTHER
Corrosive injury
Side effects of medications
After surgery
After radiation therapy

Table 306-3 Causes of Esophageal Dysphagia

NEUROMUSCULAR DISORDERS
GERD
Achalasia cardia
Diffuse esophageal spasm
Scleroderma
MECHANICAL
Intrinsic Lesions
Foreign bodies including pills
Esophagitis: GERD, eosinophilic esophagitis
Stricture: corrosive injury, pill induced, peptic
Esophageal webs
Esophageal rings
Esophageal diverticula
Neoplasm
Extrinsic Lesions
Vascular compression
Mediastinal lesion
Cervical osteochondritis
Vertebral abnormalities

Table 306-1 Some Nondigestive Tract Causes of Gastrointestinal Symptoms in Children

ANOREXIA
Systemic disease: inflammatory, neoplastic
Cardiorespiratory compromise
Iatrogenic: drug therapy, unpalatable therapeutic diets
Depression
Anorexia nervosa
VOMITING
Inborn errors of metabolism
Medications: erythromycin, chemotherapy, nonsteroidal anti-inflammatory drugs
Increased intracranial pressure
Brain tumor
Infection of the urinary tract
Labyrinthitis
Adrenal insufficiency
Pregnancy
Psychogenic
Abdominal migraine
Toxins
Renal disease
DIARRHEA
Infection: otitis media, urinary
Uremia
Medications: antibiotics, cisapride
Tumors: neuroblastoma
Pericarditis
Adrenal insufficiency
CONSTIPATION
Hypothyroidism
Spina bifida
Developmental delay
Dehydration: diabetes insipidus, renal tubular lesions
Medications: narcotics
Lead poisoning
Infant botulism
ABDOMINAL PAIN
Pyelonephritis, hydronephrosis, renal colic
Pneumonia (lower lobe)
Pelvic inflammatory disease
Porphyria
Angioedema
Endocarditis
Abdominal migraine
Familial Mediterranean fever
Sexual or physical abuse
Systemic lupus erythematosus
School phobia
Sickle cell crisis
Vertebral disk inflammation
Psoas abscess
Pelvic osteomyelitis or myositis
Medications
ABDOMINAL DISTENTION OR MASS
Ascites: nephrotic syndrome, neoplasm, heart failure
Discrete mass: Wilms tumor, hydronephrosis, neuroblastoma, mesenteric cyst, hepatoblastoma, lymphoma
Pregnancy
JAUNDICE
Hemolytic disease
Urinary tract infection
Sepsis
Hypothyroidism
Panhypopituitarism

Table 306-4 Differential Diagnosis of Emesis During Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Gastroenteritis	Gastroenteritis	Gastroenteritis
Gastroesophageal reflux	Systemic infection	GERD
Overfeeding	Gastritis	Systemic infection
Anatomic obstruction*	Toxic ingestion	Toxic ingestion
Systemic infection†	Pertussis syndrome	Gastritis
Pertussis syndrome	Medication	Sinusitis
Otitis media	Reflux (GERD)	Inflammatory bowel disease
	Sinusitis	Appendicitis
	Otitis media	Migraine
	Anatomic obstruction*	Pregnancy
	Eosinophilic esophagitis	Medications
		Ipecac abuse, bulimia
		Concussion
RARE		
Adrenogenital syndrome	Reye syndrome	Reye syndrome
Inborn errors of metabolism	Hepatitis	Hepatitis
Brain tumor (increased intracranial pressure)	Peptic ulcer	Peptic ulcer
Subdural hemorrhage	Pancreatitis	Pancreatitis
Food poisoning	Brain tumor	Brain tumor
Rumination	Increased intracranial pressure	Increased intracranial pressure
Renal tubular acidosis	Middle ear disease	Concussion
Ureteropelvic junction obstruction	Chemotherapy	Middle ear disease
Pseudoobstruction	Achalasia	Chemotherapy
	Cyclic vomiting (migraine)	Cyclic vomiting (migraine)
	Esophageal stricture	Biliary colic
	Duodenal hematoma	Renal colic
	Inborn error of metabolism	Diabetic ketoacidosis
	Pseudoobstruction	Pseudoobstruction
		Intestinal tumor
		Achalasia

*Includes malrotation, pyloric stenosis, intussusception, Hirschsprung disease.
†Meningitis, sepsis.
GERD, gastroesophageal reflux disease, inguinal hernia.

Table 306-5 Causes of Gastrointestinal Obstruction

ESOPHAGUS	Ileal atresia
Congenital	Meconium ileus
Esophageal atresia	Meckel diverticulum with volvulus or intussusception
Vascular rings	Inguinal hernia
Schatzki ring	Internal hernia
Tracheobronchial remnant	Intestinal duplication
Acquired	Pseudoobstruction
Esophageal stricture	***Acquired***
Foreign body	Postsurgical adhesions
Achalasia	Crohn disease
Chagas disease	Intussusception
Collagen vascular disease	Distal ileal obstruction syndrome (cystic fibrosis)
	Duodenal hematoma
STOMACH	Superior mesenteric artery syndrome
Congenital	
Antral webs	COLON
Pyloric stenosis	***Congenital***
Acquired	Meconium plug
Bezoar, foreign body	Hirschsprung disease
Pyloric stricture (ulcer)	Colonic atresia, stenosis
Chronic granulomatous disease of childhood	Imperforate anus
Eosinophilic gastroenteritis	Rectal stenosis
Crohn disease	Pseudoobstruction
Epidermolysis bullosa	Volvulus
	Colonic duplication
SMALL INTESTINE	***Acquired***
Congenital	Ulcerative colitis (toxic megacolon)
Duodenal atresia	Chagas disease
Annular pancreas	Crohn disease
Malrotation/volvulus	Fibrosing colonopathy (cystic fibrosis)
Malrotation/Ladd bands	

Table 306-8 Pharmacologic Therapies for Vomiting Episodes

THERAPEUTIC DRUG CLASS	DRUG	DOSAGE
REFLUX		
Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg PO or IV qid
GASTROPARESIS		
Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg PO or IV qid
Motilin agonist	Erythromycin	3-5 mg/kg PO or IV tid-qid
INTESTINAL PSEUDOOBSTRUCTION		
Stimulation of intestinal migratory myoelectric complexes	Octreotide (Sandostatin)	1 µg/kg SC bid-tid
CHEMOTHERAPY		
Dopamine antagonist	Metoclopramide	0.5-1.0 mg/kg IV qid, with antihistamine prophylaxis of extrapyramidal side effects
Serotoninergic 5-HT_3 antagonist	Ondansetron (Zofran)	0.15-0.3 mg/kg IV or PO tid
Phenothiazines (extrapyramidal, hematologic side effects)	Prochlorperazine (Compazine)	≈0.3 mg/kg PO bid-tid
	Chlorpromazine (Thorazine)	>6 mo of age: 0.5 mg/kg PO or IV tid-qid
Steroids	Dexamethasone (Decadron)	0.1 mg/kg PO tid
Cannabinoids	Tetrahydrocannabinol (Nabilone)	0.05-0.1 mg/kg PO bid-tid
POSTOPERATIVE		
	Ondansetron, phenothiazines	See under chemotherapy
MOTION SICKNESS, VESTIBULAR DISORDERS		
Antihistamine	Dimenhydrinate (Dramamine)	1 mg/kg PO tid-qid
Anticholinergic	Scopolamine (Transderm Scop)	Adults: 1 patch/3 days
ADRENAL CRISIS		
Steroids	Cortisol	2 mg/kg IV bolus followed by 0.2-0.4 mg/kg/hr IV (±1 mg/kg IM)
CYCLIC VOMITING SYNDROME		
Supportive		
Analgesic	Meperidine (Demerol)	1-2 mg/kg IV or IM q 4-6 hr
Anxiolytic, sedative	Lorazepam (Ativan)	0.05-0.1 mg/kg IV q 6 hr
Antihistamine, sedative	Diphenhydramine (Benadryl)	1.25 mg/kg IV q 6 hr
Abortive		
Serotoninergic 5-HT_3 antagonist	Ondansetron	See above
	Granisetron (Kytril)	10 µg/kg IV q 4-6 hr
Nonsteroidal antiinflammatory agent (GI ulceration side effect)	Ketorolac (Toradol)	0.5-1.0 mg/kg IV q 6-8 hr
Serotoninergic 5-HT_{1D} agonist	Sumatriptan (Imitrex)	>40 kg: 20 mg intranasally or 25 mg PO, 1 time only
PROPHYLACTIC*		
Antimigraine, β-adrenergic blocker	Propranolol (Inderal)	0.5-2.0 mg/kg PO bid
Antimigraine, antihistamine	Cyproheptadine (Periactin)	0.25-0.5 mg/kg/day PO ÷ bid-tid
Antimigraine, tricyclic antidepressant	Amitriptyline (Elavil)	0.33-0.5 mg/kg PO tid, and titrate to maximum of 3.0 mg/kg/day as needed Obtain baseline ECG at start of therapy, and consider monitoring drug levels
Antimigraine antiepileptic	Phenobarbital (Luminal)	2-3 mg/kg qhs
	Erythromycin (see above)	
Low-estrogen oral contraceptives	Consider for catamenial CVS episodes	

*If >1 CVS bout/mo or symptoms are extremely disabling; taken daily.
CVS, cyclic vomiting syndrome; ECG, electrocardiogram; GI, gastrointestinal.
From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p 317.*

Table 306-7 Complications of Vomiting

COMPLICATION	PATHOPHYSIOLOGY	HISTORY, PHYSICAL EXAMINATION, AND LABORATORY STUDIES
Metabolic	Fluid loss in emesis HCl loss in emesis Na, K loss in emesis Alkalosis → • Na into cells	Dehydration Alkalosis; hypochloremia Hyponatremia; hypokalemia
Nutritional	Emesis of calories and nutrients Anorexia for calories and nutrients	Malnutrition; "failure to thrive"
Mallory-Weiss tear	Retching → tear at lesser curve of gastroesophageal junction	Forceful emesis → hematemesis
Esophagitis	Chronic vomiting → esophageal acid exposure	Heartburn; Hemoccult + stool
Aspiration	Aspiration of vomitus, especially in context of obtundation	Pneumonia; neurologic dysfunction
Shock	Severe fluid loss in emesis or in accompanying diarrhea	Dehydration (accompanying diarrhea can explain acidosis?)
	Severe blood loss in hematemesis	Blood volume depletion
Pneumomediastinum, pneumothorax	Increased intrathoracic pressure	Chest x-ray
Petechiae, retinal hemorrhages	Increased intrathoracic pressure	Normal platelet count

Table 306-9 Supportive and Nonpharmacologic Therapies for Vomiting Episodes

DISEASE	THERAPY
All	Treat cause • Obstruction: operate • Allergy: change diet (±steroids) • Metabolic error: Rx defect • Acid peptic disease: H2RAs, PPIs, etc.
COMPLICATIONS	
Dehydration	IV fluids, electrolytes
Hematemesis	Transfuse, correct coagulopathy
Esophagitis	H_2RAs, PPIs
Malnutrition	NG or NJ drip feeding useful for many chronic conditions
Meconium ileus	Gastrografin enema
DIOS	Gastrografin enema; balanced colonic lavage solution (e.g., GoLYTELY)
Intussusception	Barium enema; air reduction enema
Hematemesis	Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocautery for selected upper GI tract lesions
Sigmoid volvulus	Colonoscopic decompression
Reflux	Positioning; dietary measures (infants: rice cereal, 1 tbs/oz of formula)
Psychogenic components	Psychotherapy; tricyclic antidepressants; anxiolytics (e.g., diazepam: 0.1 mg/kg PO tid-qid)

DIOS, distal intestinal obstruction syndrome; GI, gastrointestinal; H_2RA, H_2-receptor antagonist; NG, nasogastric; NJ, nasojejunal; PPIs, proton pump inhibitors; tbs, tablespoon.
From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p 319.*

Table 306-10 Mechanisms of Diarrhea

PRIMARY MECHANISM	DEFECT	STOOL EXAMINATION	EXAMPLES	COMMENT
Secretory	Decreased absorption, increased secretion, electrolyte transport	Watery, normal osmolality with ion gap < 100 mOsm/kg	Cholera, toxigenic *Escherichia coli*; carcinoid, VIP, neuroblastoma, congenital chloride diarrhea, *Clostridium difficile*, cryptosporidiosis (AIDS)	Persists during fasting; bile salt malabsorption can also increase intestinal water secretion; no stool leukocytes
Osmotic	Maldigestion, transport defects ingestion of unabsorbable substances	Watery, acidic, and reducing substances; increased osmolality with ion gap > 100 mOsm/kg	Lactase deficiency, glucose-galactose malabsorption, lactulose, laxative abuse	Stops with fasting; increased breath hydrogen with carbohydrate malabsorption; no stool leukocytes
Increased motility	Decreased transit time	Loose to normal-appearing stool, stimulated by gastrocolic reflex	Irritable bowel syndrome, thyrotoxicosis, postvagotomy dumping syndrome	Infection can also contribute to increased motility
Decreased motility	Defect in neuromuscular unit(s) stasis (bacterial overgrowth)	Loose to normal-appearing stool	Pseudoobstruction, blind loop	Possible bacterial overgrowth
Decreased surface area (osmotic, motility)	Decreased functional capacity	Watery	Short bowel syndrome, celiac disease, rotavirus enteritis	Might require elemental diet plus parenteral alimentation
Mucosal invasion	Inflammation, decreased colonic reabsorption, increased motility	Blood and increased WBCs in stool	*Salmonella, Shigella* infection; amebiasis; *Yersinia, Campylobacter* infection	Dysentery evident in blood, mucus, and WBCs

VIP, vasoactive intestinal peptide; WBC, white blood cell.
From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p 274.*

$$\text{Ion gap} = \text{Stool osmolality} - [(\text{Stool Na} + \text{stool K}) 2]$$

Table 306-6 Criteria for Cyclical Vomiting Syndrome

All of the criteria must be met for the consensus definition of cyclical vomiting syndrome:
- At least 5 attacks in any interval, or a minimum of 3 episodes during a 6-mo period
- Recurrent episodes of intense vomiting and nausea lasting 1 hr to 10 days and occurring at least 1 wk apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during episodes occurs ≥4 times/hr for ≥1 hr
- Return to baseline health between episodes
- Not attributed to another disorder

Li, B UK, Lefevre F, Chelimsky GG, et al: North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome, J Pediatr Gastroenterol Nutr *47:379–393, 2008.*

Table 306-11 Differential Diagnosis of Diarrhea

INFANT	CHILD	ADOLESCENT
ACUTE		
Common		
Gastroenteritis (viral > bacterial > protozoal)	Gastroenteritis (viral > bacterial > protozoal)	Gastroenteritis (viral > bacterial > protozoal)
Systemic infection	Food poisoning	Food poisoning
Antibiotic associated	Systemic infection	Antibiotic associated
Overfeeding	Antibiotic associated	
Rare		
Primary disaccharidase deficiency	Toxic ingestion	Hyperthyroidism
Hirschsprung toxic colitis	Hemolytic uremic syndrome	Appendicitis
Adrenogenital syndrome	Intussusception	
Neonatal opiate withdrawal		
CHRONIC		
Common		
Postinfectious secondary lactase deficiency	Postinfectious secondary lactase deficiency	Irritable bowel syndrome
Cow's milk or soy protein intolerance (allergy)	Irritable bowel syndrome	Inflammatory bowel disease
Chronic nonspecific diarrhea of infancy	Celiac disease	Lactose intolerance
Excessive fruit juice (sorbitol) ingestion	Cystic fibrosis	Giardiasis
Celiac disease	Lactose intolerance	Laxative abuse (anorexia nervosa)
Cystic fibrosis	Excessive fruit juice (sorbitol) ingestion	Constipation with encopresis
AIDS enteropathy	Giardiasis	
	Inflammatory bowel disease	
	AIDS enteropathy	
Rare		
Primary immune defects	Primary and acquired immune defects	Secretory tumor
Autoimmune enteropathy	Secretory tumors	Primary bowel tumor
IPEX and IPEX-like syndromes	Pseudoobstruction	Parasitic infections and venereal diseases
Glucose-galactose malabsorption	Sucrase-isomaltase deficiency	Appendiceal abscess
Microvillus inclusion disease (microvillus atrophy)	Eosinophilic gastroenteritis	Addison disease
Congenital transport defects (chloride, sodium)	Secretory tumors	
Primary bile acid malabsorption		
Factitious syndrome by proxy		
Hirschsprung disease		
Shwachman syndrome		
Secretory tumors		
Acrodermatitis enteropathica		
Lymphangiectasia		
Abetalipoproteinemia		
Eosinophilic gastroenteritis		
Short bowel syndrome		

Table 306-14 Distinguishing Features of Acute Gastrointestinal Tract Pain in Children

DISEASE	ONSET	LOCATION	REFERRAL	QUALITY	COMMENTS
Pancreatitis	Acute	Epigastric, left upper quadrant	Back	Constant, sharp, boring	Nausea, emesis, tenderness
Intestinal obstruction	Acute or gradual	Periumbilical-lower abdomen	Back	Alternating cramping (colic) and painless periods	Distention, obstipation, emesis, increased bowel sounds
Appendicitis	Acute	Periumbilical, then localized to lower right quadrant; generalized with peritonitis	Back or pelvis if retrocecal	Sharp, steady	Anorexia, nausea, emesis, local tenderness, fever with peritonitis
Intussusception	Acute	Periumbilical-lower abdomen	None	Cramping, with painless periods	Hematochezia, knees in pulled-up position
Urolithiasis	Acute, sudden	Back (unilateral)	Groin	Sharp, intermittent, cramping	Hematuria
Urinary tract infection	Acute	Back	Bladder	Dull to sharp	Fever, costovertebral angle tenderness, dysuria, urinary frequency

Table 306-12 Causes of Constipation

NONORGANIC (FUNCTIONAL)—RETENTIVE
ANATOMIC
Anal stenosis, atresia with fistula
Imperforate anus
Anteriorly displaced anus
Intestinal stricture (postnecrotizing enterocolitis)
Anal stricture
ABNORMAL MUSCULATURE
Prune-belly syndrome
Gastroschisis
Down syndrome
Muscular dystrophy
INTESTINAL NERVE OR MUSCLE ABNORMALITIES
Hirschsprung disease
Pseudoobstruction (visceral myopathy or neuropathy)
Intestinal neuronal dysplasia
Spinal cord defects
Tethered cord
Spinal cord trauma
Spina bifida
DRUGS
Anticholinergics
Narcotics
Methylphenidate
Phenytoin
Antidepressants
Chemotherapeutic agents (vincristine)
Pancreatic enzymes (fibrosing colonopathy)
Lead
Vitamin D intoxication
METABOLIC DISORDERS
Hypokalemia
Hypercalcemia
Hypothyroidism
Diabetes mellitus, diabetes insipidus
INTESTINAL DISORDERS
Celiac disease
Cow's milk protein intolerance
Cystic fibrosis (meconium ileus equivalent)
Inflammatory bowel disease (stricture)
Tumor
Connective tissue disorders
Systemic lupus erythematosus
Scleroderma
PSYCHIATRIC DIAGNOSIS
Anorexia nervosa

Table 306-15 Differential Diagnosis of Gastrointestinal Bleeding in Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Bacterial enteritis	Bacterial enteritis	Bacterial enteritis
Milk protein allergy intolerance	Anal fissure	Inflammatory bowel disease
Intussusception	Colonic polyps	Peptic ulcer/gastritis
Swallowed maternal blood	Intussusception	Prolapse (traumatic) gastropathy secondary to emesis
Anal fissure	Peptic ulcer/gastritis	Mallory-Weiss syndrome
Lymphonodular hyperplasia	Swallowed epistaxis	Colonic polyps
	Prolapse (traumatic) gastropathy secondary to emesis	Anal fissure
	Mallory-Weiss syndrome	
RARE		
Volvulus	Esophageal varices	Hemorrhoids
Necrotizing enterocolitis	Esophagitis	Esophageal varices
Meckel diverticulum	Meckel diverticulum	Esophagitis
Stress ulcer, gastritis	Lymphonodular hyperplasia	Pill ulcer
Coagulation disorder (hemorrhagic disease of newborn)	Henoch-Schönlein purpura	Telangiectasia-angiodysplasia
Esophagitis	Foreign body	Graft-vs-host disease
	Hemangioma, arteriovenous malformation	Duplication cyst
	Sexual abuse	
	Hemolytic-uremic syndrome	
	Inflammatory bowel disease	
	Coagulopathy	
	Duplication cyst	

Table 306-13 Chronic Abdominal Pain in Children

DISORDER	CHARACTERISTICS	KEY EVALUATIONS
NONORGANIC		
Functional abdominal pain	Nonspecific pain, often periumbilical	Hx and PE; tests as indicated
Irritable bowel syndrome	Intermittent cramps, diarrhea, and constipation	Hx and PE
Nonulcer dyspepsia	Peptic ulcer–like symptoms without abnormalities on evaluation of the upper GI tract	Hx; esophagogastroduodenoscopy
GASTROINTESTINAL TRACT		
Chronic constipation	Hx of stool retention, evidence of constipation on examination	Hx and PE; plain x-ray of abdomen
Lactose intolerance	Symptoms may be associated with lactose ingestion; bloating, gas, cramps, and diarrhea	Trial of lactose-free diet; lactose breath hydrogen test
Parasite infection (especially *Giardia*)	Bloating, gas, cramps, and diarrhea	Stool evaluation for O&P; specific immunoassays for *Giardia*
Excess fructose or sorbitol ingestion	Nonspecific abdominal pain, bloating, gas, and diarrhea	Large intake of apples, fruit juice, or candy or chewing gum sweetened with sorbitol
Crohn disease	See Chapter 336	
Peptic ulcer	Burning or gnawing epigastric pain; worse on awakening or before meals; relieved with antacids	Esophagogastroduodenoscopy, upper GI contrast x-rays, or MRI enteroscopy
Esophagitis	Epigastric pain with substernal burning	Esophagogastroduodenoscopy
Meckel diverticulum	Periumbilical or lower abdominal pain; may have blood in stool (usually painless)	Meckel scan or enteroclysis
Recurrent intussusception	Paroxysmal severe cramping abdominal pain; blood may be present in stool with episode	Identify intussusception during episode or lead point in intestine between episodes with contrast studies of GI tract
Internal, inguinal, or abdominal wall hernia	Dull abdomen or abdominal wall pain	PE, CT of abdominal wall
Chronic appendicitis or appendiceal mucocele	Recurrent RLQ pain; often incorrectly diagnosed, may be rare cause of abdominal pain	Barium enema, CT
GALLBLADDER AND PANCREAS		
Cholelithiasis	RUQ pain, might worsen with meals	Ultrasound of gallbladder
Choledochal cyst	RUQ pain, mass ± elevated bilirubin	Ultrasound or CT of RUQ
Recurrent pancreatitis	Persistent boring pain, might radiate to back, vomiting	Serum amylase and lipase ± serum trypsinogen; ultrasound, CT, or MRI-ERCP of pancreas
GENITOURINARY TRACT		
Urinary tract infection	Dull suprapubic pain, flank pain	Urinalysis and urine culture; renal scan
Hydronephrosis	Unilateral abdominal or flank pain	Ultrasound of kidneys
Urolithiasis	Progressive, severe pain; flank to inguinal region to testicle	Urinalysis, ultrasound, IVP, CT
Other genitourinary disorders	Suprapubic or lower abdominal pain; genitourinary symptoms	Ultrasound of kidneys and pelvis; gynecologic evaluation
MISCELLANEOUS CAUSES		
Abdominal migraine	See text; nausea, family Hx migraine	Hx
Abdominal epilepsy	Might have seizure prodrome	EEG (can require > 1 study, including sleep-deprived EEG)
Gilbert syndrome	Mild abdominal pain (causal or coincidental?); slightly elevated unconjugated bilirubin	Serum bilirubin
Familial Mediterranean fever	Paroxysmal episodes of fever, severe abdominal pain, and tenderness with other evidence of polyserositis	Hx and PE during an episode, DNA diagnosis
Sickle cell crisis	Anemia	Hematologic evaluation
Lead poisoning	Vague abdominal pain ± constipation	Serum lead level
Henoch-Schönlein purpura	Recurrent, severe crampy abdominal pain, occult blood in stool, characteristic rash, arthritis	Hx, PE, urinalysis
Angioneurotic edema	Swelling of face or airway, crampy pain	Hx, PE, upper GI contrast x-rays, serum C1 esterase inhibitor
Acute intermittent porphyria	Severe pain precipitated by drugs, fasting, or infections	Spot urine for porphyrins

EEG, electroencephalogram; GI, gastrointestinal; Hx, history; IVP, intravenous pyelography; O&P, ova and parasites; PE, physical exam; RLQ, right lower quadrant; RUQ, right upper quadrant.

Table 323-2 Symptoms and Signs That May Be Associated with Gastroesophageal Reflux

Symptoms
Recurrent regurgitation with or without vomiting
Weight loss or poor weight gain
Irritability in infants
Ruminative behavior
Heartburn or chest pain
Hematemesis
Dysphagia, odynophagia
Wheezing
Stridor
Cough
Hoarseness
Signs
Esophagitis
Esophageal stricture
Barrett esophagus
Laryngeal/pharyngeal inflammation
Recurrent pneumonia
Anemia
Dental erosion
Feeding refusal
Dystonic neck posturing (Sandifer syndrome)
Apnea spells
Apparent life-threatening events

From Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 4, Philadelphia, 2011, WB Saunders, Table 22-1, p. 235.*

Table 315-1 Differential Diagnosis of Oral Ulceration

CONDITION	COMMENT
COMMON	
Aphthous (canker sore)	Painful, circumscribed lesions; recurrences
Traumatic	Accidents, chronic cheek biter, or after dental local anesthesia
Hand, foot, mouth disease	Painful; lesions on tongue, anterior oral cavity, hands, and feet
Herpangina	Painful; lesions confined to soft palate and oropharynx
Herpetic gingivostomatitis	Vesicles on mucocutaneous borders; painful, febrile
Recurrent herpes labialis	Vesicles on lips; painful
Chemical burns	Alkali, acid, aspirin; painful
Heat burns	Hot food, electrical
UNCOMMON	
Neutrophil defects	Agranulocytosis, leukemia, cyclic neutropenia; painful
Systemic lupus erythematosus	Recurrent, may be painless
Behçet syndrome	Resembles aphthous lesions; associated with genital ulcers, uveitis
Necrotizing ulcerative gingivostomatitis	Vincent stomatitis; painful
Syphilis	Chancre or gumma; painless
Oral Crohn disease	Aphthous-like; painful
Histoplasmosis	Lingual
Pemphigus	May be isolated to the oral cavity
Stevens-Johnson syndrome	May be isolated or appear initially in the oral cavity

Table 308-1 Dental Problems Associated with Selected Medical Conditions

MEDICAL CONDITION	COMMON ASSOCIATED DENTAL OR ORAL FINDINGS
Cleft lip and palate	Missing teeth, extra (supernumerary) teeth, shifting of arch segments, feeding difficulties, speech problems
Kidney failure	Mottled enamel (permanent teeth), facial dysmorphology
Cystic fibrosis	Stained teeth with extensive medication, mottled enamel
Immunosuppression	Oral candidiasis with potential for systemic candidiasis, cyclosporine-induced gingival hyperplasia
Low birthweight	Palatal groove, narrow arch with prolonged oral intubation; enamel defects of primary teeth
Heart defects with susceptibility to bacterial endocarditis	Bacteremia from dental procedures or trauma
Neutrophil chemotactic deficiency	Juvenile periodontitis (loss of supporting bone around teeth)
Juvenile diabetes (uncontrolled)	Juvenile periodontitis
Neuromotor dysfunction	Oral trauma from falling; malocclusion (open bite); gingivitis from lack of hygiene
Prolonged illness (generalized) during tooth formation	Enamel hypoplasia of crown portions forming during illness
Seizures	Gingival enlargement if phenytoin is used
Maternal infections	Syphilis: abnormally shaped teeth
Vitamin D–dependent rickets	Enamel hypoplasia

Table 327-1 Ingestible Caustic Materials Around the House

CATEGORY	MOST DAMAGING AGENTS	OTHER AGENTS
Alkaline drain cleaners, milking machine pipe cleaners	Sodium or potassium hydroxide	Ammonia Sodium hypochlorite Aluminum particles
Acidic drain openers	Hydrochloric acid Sulfuric acid	
Toilet cleaners	Hydrochloric acid Sulfuric acid Phosphoric acid Other acids	Ammonium chloride Sodium hypochlorite
Oven and grill cleaners	Sodium hydroxide Perborate (borax)	
Denture cleaners	Persulfate (sulfur) Hypochlorite (bleach)	
Dishwasher detergent • Liquid • Powdered • Packaged	Sodium hydroxide Sodium hypochlorite Sodium carbonate	
Bleach	Sodium hypochlorite	Ammonia salt
Swimming pool chemicals	Acids, alkalis, chlorine	
Battery acid (liquid)	Sulfuric acid	
Disk batteries	Electric current	Zinc or other metal salts
Rust remover	Hydrofluoric, phosphoric, oxalic, and other acids	
Household delimers	Phosphoric acid Hydroxyacetic acid Hydrochloric acid	
Barbeque cleaners	Sodium and potassium hydroxide	
Glyphosate surfactant (RoundUp) acid	Glyphosate herbicide	Surfactants
Hair relaxer	Sodium hydroxide	
Weed killer	Dichlorophenoxyacetate, ammonium phosphate, propionic acid	

Source: National Library of Medicine: Health and safety information on household products *(website).* http://householdproducts.nlm.nih.gov/
From Wylie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 4, Philadelphia, 2011, WB Saunders, Table 19-1, p. 198.*

Table 327-2 Classification of Caustic Injury

GRADE	VISIBLE APPEARANCE	CLINICAL SIGNIFICANCE
Grade 0	History of ingestion, but no visible damage or symptoms	Able to take fluids immediately
Grade 1	Edema, loss of normal vascular pattern, hyperemia, no transmucosal injury	Temporary dysphagia, able to swallow within 0-2 days, no long-term sequelae
Grade 2a	Transmucosal injury with friability, hemorrhage, blistering, exudate, scattered superficial ulceration	Scarring, no circumferential damage (no stenosis), no long-term sequelae
Grade 2b	Grade 2a plus discrete ulceration and/or circumferential ulceration	Small risk of perforation, scarring that may result in later stenosis
Grade 3a	Scattered deep ulceration with necrosis of the tissue	Risk of perforation, high risk of later stenosis
Grade 3b	Extensive necrotic tissue	High risk of perforation and death, high risk of stenosis

From Wylie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 4, Philadelphia, 2011, WB Saunders, Table 19-2, p. 199.*

Table 332-2 Chronic Constipation: Rome III Criteria

INFANTS AND TODDLERS

Must include 1 mo of **at least 2** of the following in infants up to 4 yr of age:

- ≤2 Defecations per week
- ≥1 Episode of incontinence after the acquisition of toilet training skills
- History of excessive stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of a large-diameter stool that might obstruct the toilet

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.

CHILDREN WITH A DEVELOPMENTAL AGE OF 4-18 YR

Must include **2 or more** of the following in a child with a developmental age of at least 4 yr with insufficient criteria for diagnosis of irritable bowel syndrome*:

- ≤2 Defecations per week
- ≥1 Episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of a large-diameter stool that might obstruct the toilet

*Criteria fulfilled at least once per week for at least 2 mo before diagnosis.

From Hyman P, Milla P. Benninga M, et al: Childhood functional gastrointestinal disorders: neonate/toddler, Gastroenterology *130:1519–1526, 2006; and Rasquin A, DiLorenzo C, Forbes D, et al: Childhood functional gastrointestinal disorders: child/adolescent,* Gastroenterology *130:1527–1537, 2006.*

Table 332-1 Findings in Pseudoobstruction

GI SEGMENT	FINDINGS*
Esophageal motility	Abnormalities in approximately half of CIPO, although in some series up to 85% demonstrate abnormalities Decreased LES pressure Failure of LES relaxation Esophageal body: low-amplitude waves, poor propagation, tertiary waves, retrograde peristalsis, occasionally aperistalsis
Gastric emptying	May be delayed
EGG	Tachygastria or bradygastria may be seen
ADM	Postprandial antral hypomotility is seen and correlates with delayed gastric emptying Myopathic subtype: low-amplitude contractions, <10-20 mm Hg Neuropathic subtype: contractions are uncoordinated, disorganized Absence of fed response Fasting MMC is absent, or MMC is abnormally propagated
Colonic	Absence of gastrocolic reflex because there is no increased motility in response to a meal
ARM	Normal rectoanal inhibitory reflex

*Findings can vary according to the segment(s) of the GI tract that are involved.

ADM, Antroduodenal manometry; ARM, anorectal manometry; CIPO, chronic intestinal pseudoobstruction; EGG, electrogastrography; GI, gastrointestinal; LES, lower esophageal sphincter; MMC, migrating motor complex.

From Steffen R: Gastrointestinal motility. In Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, WB Saunders, p. 66.*

Table 332-3 Suggested Medications and Dosages for Disimpaction

MEDICATION	AGE	DOSAGE
RAPID RECTAL DISIMPACTION		
Glycerin suppositories	Infants and toddlers	
Phosphate enema	<1 yr	60 mL
	>1 yr	6 mL/kg bodyweight, up to 135 mL twice
Milk of molasses enema	Older children	(1:1 milk:molasses) 200-600 mL
SLOW ORAL DISIMPACTION IN OLDER CHILDREN		
Over 2-3 Days		
Polyethylene glycol with electrolytes		25 mL/kg bodyweight/hr, up to 1000 mL/hr until clear fluid comes from the anus
Over 5-7 Days		
Polyethylene without electrolytes		1.5 g/kg bodyweight/day for 3 days
Milk of magnesia		2 mL/kg bodyweight twice/day for 7 days
Mineral oil		3 mL/kg bodyweight twice/day for 7 days
Lactulose or sorbitol		2 mL/kg bodyweight twice/day for 7 days

From Loening-Baucke V: Functional constipation with encopresis. In Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, WB Saunders, p 183.*

Table 332-4 Suggested Medications and Dosages for Maintenance Therapy of Constipation

MEDICATION	AGE	DOSE
FOR LONG-TERM TREATMENT (YEARS)		
Milk of magnesia	>1 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Mineral oil	>12 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Lactulose or sorbitol	>1 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Polyethylene glycol 3350 (MiraLAX)	>1 mo	0.7 g/kg bodyweight/day, divided into 1-2 doses
FOR SHORT-TERM TREATMENT (MONTHS)		
Senna (Senokot) syrup, tablets	1-5 yr	5 mL (1 tablet) with breakfast, max 15 mL daily
	5-15 yr	2 tablets with breakfast, maximum 3 tablets daily
Glycerin enemas	>10 yr	20-30 mL/day (½ glycerin and ½ normal saline)
Bisacodyl suppositories	>10 yr	10 mg daily

Table 332-5 Distinguishing Features of Hirschsprung Disease and Functional Constipation

VARIABLE	FUNCTIONAL	HIRSCHSPRUNG DISEASE
HISTORY		
Onset of constipation	After 2 yr of age	At birth
Encopresis	Common	Very rare
Failure to thrive	Uncommon	Possible
Enterocolitis	None	Possible
Forced bowel training	Usual	None
EXAMINATION		
Abdominal distention	Uncommon	Common
Poor weight gain	Rare	Common
Rectum	Filled with stool	Empty
Rectal examination	Stool in rectum	Explosive passage of stool
Malnutrition	None	Possible
INVESTIGATIONS		
Anorectal manometry	Relaxation of internal anal sphincter	Failure of internal anal sphincter relaxation
Rectal biopsy	Normal	No ganglion cells, increased acetylcholinesterase staining
Barium enema	Massive amounts of stool, no transition zone	Transition zone, delayed evacuation (>24 hr)

From Imseis E, Gariepy C: Hirschsprung disease. In Walker WA, Goulet OJ, Kleinman RE et al, editors: Pediatric gastrointestinal disease, *ed 4, Hamilton, Ontario, 2004, BC Decker, p. 1035.*

Table 335-2 Recommended Eradication Therapies for *Helicobacter pylori*—Associated Disease in Children

MEDICATIONS	DOSE	DURATION OF TREATMENT
Amoxicillin	50 mg/kg/day in 2 divided doses	14 days
Clarithromycin	15 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo
or		
Amoxicillin	50 mg/kg/day in 2 divided doses	14 days
Metronidazole	20 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo
or		
Clarithromycin	15 mg/kg/day in 2 divided doses	14 days
Metronidazole	20 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo

Adapted from Gold BD, Colletti RB, Abbott M, et al: Medical position statement: The North American Society for Pediatric Gastroenterology and Nutrition. Helicobacter pylori *infection in children: recommendations for diagnosis and treatment,* J Pediatr Gastroenterol Nutr *31:490–497, 2000.*

Table 335-3 Antisecretory Therapy with Pediatric Dosages

MEDICATION	PEDIATRIC DOSE	HOW SUPPLIED
H_2 RECEPTOR ANTAGONISTS		
Cimetidine	20-40 mg/kg/day Divided 2-4 × a day	Syrup: 300 mg/mL Tablets: 200, 300, 400, 800 mg
Ranitidine	4-10 mg/kg/day Divided 2 or 3 × a day	Syrup: 75 mg/5 mL Tablets: 75, 150, 300 mg
Famotidine	1-2 mg/kg/day Divided twice a day	Syrup: 40 mg/5 mL Tablets: 20, 40 mg
Nizatidine	5-10 mg/kg/day divided twice a day Older than 12 yr: 150 mg twice a day	Solution: 15 mg/ml Capsule 150, 300 Tablet: 75 mg
PROTON PUMP INHIBITORS		
Omeprazole	1.0-3.3 mg/kg/day weigh <20 kg: 10 mg/day weigh >20 kg: 20 mg/day Approved for use in those older than 2 yr	Capsules: 10, 20, 40 mg
Lansoprazole	0.8-4 mg/kg/day weigh <30 kg: 15 mg/day weigh >30 kg: 30 mg/day Approved for use in those older than 1 yr	Capsules: 15, 30 mg Powder packet: 15, 30 mg SoluTab: 15, 30 mg
Rabeprazole	1-11 yr(weigh <15 kg): 5 mg/day 1-11 yr (weigh >15 kg): 10 mg/day >12 yr: 20 mg tablet	Delayed release capsule: 5, 10 mg Delayed release tablet: 20 mg
Pantoprazole	1-5 yr:0.3-1.2 mg/kg/day (limited data) >5 yr of age: weigh >15 kg to <40 kg: 20 mg/day weigh >40 kg: 40 mg/day	Tablet: 20, 40 mg Powder pack: 40 mg
CYTOPROTECTIVE AGENTS		
Sucralfate	40-80 mg/kg/day	Suspension: 1,000 mg/5 mL Tablet: 1,000 mg

Table 336-3 Montreal Classification of Extent and Severity of Ulcerative Colitis

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): 4 or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): 4 stools per day, minimum signs of systemic symptoms
- S3 (severe): 6 or more bloody stools per day, pulse rate of ≥90 beats per min, temperature ≥37.5°C (99.5°F), hemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/hr

E, extent; S, severity.
From Ordàs I, Eckmann L, Talamini M, et al: Ulcerative colitis, Lancet *380:1606–1616, 2012 (Panel 2, p. 1610).*

Table 335-1 Etiologic Classification of Peptic Ulcers

Positive for *Helicobacter pylori* infection
Drug (NSAID)-induced
H. pylori and NSAID-positive
H. pylori and NSAID-negative*
Acid hypersecretory state (Zollinger-Ellison syndrome)
Anastomosis ulcer after subtotal gastric resection
Tumors (cancer, lymphoma)
Rare specific causes
Crohn disease of the stomach or duodenum
Eosinophilic gastroduodenitis
Systemic mastocytosis
Radiation damage
Viral infections (cytomegalovirus or herpes simplex infection, particularly in immunocompromised patients)
Colonization of stomach with *Helicobacter heilmannii*
Severe systemic disease
Cameron ulcer (gastric ulcer where a hiatal hernia passes through the diaphragmatic hiatus)
True idiopathic ulcer

*Requires search for other specific causes.

Table 336-6 Pediatric Ulcerative Colitis Activity Index

ITEM	POINTS
(1) *Abdominal pain*	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) *Rectal bleeding*	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) *Stool consistency of most stools*	
Formed	0
Partially formed	5
Completely unformed	10
(4) *Number of stools per 24 h*	
0-2	0
3-5	5
6-8	10
>8	15
(5) *Nocturnal stools (any episode causing wakening)*	
No	0
Yes	10
(6) *Activity level*	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of Index (0-85)	

Table 336-1 Comparison of Crohn Disease and Ulcerative Colitis

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Rectal bleeding	Sometimes	Common
Diarrhea, mucus, pus	Variable	Common
Abdominal pain	Common	Variable
Abdominal mass	Common	Not present
Growth failure	Common	Variable
Perianal disease	Common	Rare
Rectal involvement	Occasional	Universal
Pyoderma gangrenosum	Rare	Present
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Thrombosis	Less common	Present
Colonic disease	50-75%	100%
Ileal disease	Common	None except backwash ileitis
Stomach–esophageal disease	More common	Chronic gastritis can be seen
Strictures	Common	Rare
Fissures	Common	Rare
Fistulas	Common	Rare
Toxic megacolon	None	Present
Sclerosing cholangitis	Less common	Present
Risk for cancer	Increased	Greatly increased
Discontinuous (skip) lesions	Common	Not present
Transmural involvement	Common	Unusual
Crypt abscesses	Less common	Common
Granulomas	Common	None
Linear ulcerations	Uncommon	Common
Perinuclear antineutrophil cytoplasmic antibody–positive	<20%	70%

Table 336-2 Extraintestinal Complications of Inflammatory Bowel Disease

MUSCULOSKELETAL
Peripheral arthritis
Granulomatous monoarthritis
Granulomatous synovitis
Rheumatoid arthritis
Sacroiliitis
Ankylosing spondylitis
Digital clubbing and hypertrophic osteoarthropathy
Periosteitis
Osteoporosis, osteomalacia
Rhabdomyolysis
Pelvic osteomyelitis
Recurrent multifocal osteomyelitis
Relapsing polychondritis

SKIN AND MUCOUS MEMBRANES
Oral lesions
Cheilitis
Aphthous stomatitis, glossitis
Granulomatous oral Crohn disease
Inflammatory hyperplasia fissures and cobblestone mucosa
Peristomatitis vegetans

DERMATOLOGIC
Erythema nodosum
Pyoderma gangrenosum
Sweet syndrome
Metastatic Crohn disease
Psoriasis
Epidermolysis bullosa acquisita
Perianal skin tags
Polyarteritis nodosa

OCULAR
Conjunctivitis
Uveitis, iritis
Episcleritis
Scleritis
Retrobulbar neuritis
Chorioretinitis with retinal detachment
Crohn keratopathy
Posterior segment abnormalities
Retinal vascular disease

BRONCHOPULMONARY
Chronic bronchitis with bronchiectasis
Chronic bronchitis with neutrophilic infiltrates
Fibrosing alveolitis
Pulmonary vasculitis
Small airway disease and bronchiolitis obliterans
Eosinophilic lung disease
Granulomatous lung disease
Tracheal obstruction

CARDIAC
Pleuropericarditis
Cardiomyopathy
Endocarditis
Myocarditis

MALNUTRITION
Decreased intake of food
- Inflammatory bowel disease
- Dietary restriction

Malabsorption
- Inflammatory bowel disease
- Bowel resection
- Bile salt depletion
- Bacterial overgrowth

Intestinal losses
- Electrolytes
- Minerals
- Nutrients

Increased caloric needs
- Inflammation
- Fever

HEMATOLOGIC
Anemia: iron deficiency (blood loss)
Vitamin B_{12} (ileal disease or resection, bacterial overgrowth, folate deficiency)
Anemia of chronic inflammation
Anaphylactoid purpura (Crohn disease)
Hyposplenism
Autoimmune hemolytic anemia
Coagulation abnormalities
Increased activation of coagulation factors
Activated fibrinolysis
Anticardiolipin antibody
Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions

RENAL AND GENITOURINARY
Metabolic
- Urinary crystal formation (nephrolithiasis, uric acid, oxylate)

Hypokalemic nephropathy
Inflammation
- Retroperitoneal abscess
- Fibrosis with ureteral obstruction
- Fistula formation

Glomerulitis
Membrane nephritis
Renal amyloidosis, nephrotic syndrome

PANCREATITIS
Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition)
Ampullary Crohn disease
Granulomatous pancreatitis
Decreased pancreatic exocrine function
Sclerosing cholangitis with pancreatitis

HEPATOBILIARY
Primary sclerosing cholangitis
Small duct primary sclerosing cholangitis (pericholangitis)
Carcinoma of the bile ducts
Fatty infiltration of the liver
Cholelithiasis
Autoimmune hepatitis

ENDOCRINE AND METABOLIC
Growth failure, delayed sexual maturation
Thyroiditis
Osteoporosis, osteomalacia

NEUROLOGIC
Peripheral neuropathy
Meningitis
Vestibular dysfunction
Pseudotumor cerebri
Cerebral vasculitis
Migraine

Modified from Kugathasan S: Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, WB Saunders, p. 285.*

Table 336-4 Infectious Agents Mimicking Inflammatory Bowel Disease

AGENT	MANIFESTATIONS	DIAGNOSIS	COMMENTS
BACTERIAL			
Campylobacter jejuni	Acute diarrhea, fever, fecal blood, and leukocytes	Culture	Common in adolescents, may relapse
Yersinia enterocolitica	Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood, and leukocytes Extraintestinal manifestations, mimics Crohn disease	Culture	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
Clostridium difficile	Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay	May be nosocomial Toxic megacolon possible
Escherichia coli O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing	Hemolytic uremic syndrome
Salmonella	Watery → bloody diarrhea, foodborne, fecal leukocytes, fever, pain, cramps	Culture	Usually acute
Shigella	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture	Dysentery symptoms
Edwardsiella tarda	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
Aeromonas hydrophila	Cramps, diarrhea, fecal blood	Culture	May be chronic Contaminated drinking water
Plesiomonas shigelloides	Diarrhea, cramps	Culture	Shellfish source
Tuberculosis	Rarely bovine, now *Mycobacterium tuberculosis* Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy	Can mimic Crohn disease
PARASITES			
Entamoeba histolytica	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
Giardia lamblia	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	"Owl"-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
AIDS-ASSOCIATED ENTEROPATHY			
Cryptosporidium	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease
Isospora belli	As in *Cryptosporidium*		Tropical location
Cytomegalovirus	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

Table 338-10 Common Micronutrient Deficiencies in Inflammatory Bowel Disease

MICRONUTRIENT	CROHN DISEASE AND/OR ULCERATIVE COLITIS	MALABSORPTION	INTESTINAL LOSSES	INADEQUATE INTAKE
Iron	CD and UC	+ (CD)	+++	++
Vitamins A, D, E, K	CD > UC	++ (CD)		+++
Vitamin B_{12}	CD	+++		+
Vitamin B_1, B_2, B_6	CD > UC			++
Vitamin C, glutathione (antioxidants)	CD and UC		++	++
Folate	CD and UC	++		+
Calcium, magnesium, selenium, zinc	CD and UC	++	+++	+
Polyunsaturated fatty acids	CD	++		++

Table 336-5 Chronic Inflammatory-Like Intestinal Disorders Including Monogenetic Diseases

INFECTION (see Table 336-4)
AIDS-Associated
Toxin
Immune–Inflammatory
Severe combined immunodeficiency diseases
Agammaglobulinemia
Chronic granulomatous disease
Wiskott-Aldrich syndrome
Common variable immunodeficiency diseases
Acquired immunodeficiency states
Dietary protein enterocolitis
Autoimmune polyendocrine syndrome type 1
Behçet disease
Lymphoid nodular hyperplasia
Eosinophilic gastroenteritis
Omenn syndrome
Graft-versus-host disease
IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndromes
Interleukin-10 signaling defects
Autoimmune enteropathy*
Microscopic colitis
Hyperimmunoglobulin M syndrome
Hyperimmunoglobulin E syndromes
Mevalonate kinase deficiency
Familial Mediterranean fever
Phospholipase $C\gamma_2$ defects
Familial hemophagocytic lymphohistiocytosis type 5
X-linked lymphoproliferative syndromes types 1, 2
Congenital neutropenias
Leukocyte adhesion deficiency 1
VASCULAR–ISCHEMIC DISORDERS
Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)
Henoch-Schönlein purpura
Hemolytic uremic syndrome
Granulomatosis with angiitis
OTHER
Glycogen storage disease type 1b
Dystrophic epidermolysis bullosa
X-linked ectodermal dysplasia and immunodeficiency
Dyskeratosis congenita
ADAM-17 deficiency
Prestenotic colitis
Diversion colitis
Radiation colitis
Neonatal necrotizing enterocolitis
Typhlitis
Sarcoidosis
Hirschsprung colitis
Intestinal lymphoma
Laxative abuse
Endometriosis
Hermansky-Pudlak syndrome
Trichohepatoenteric syndrome
PTEN hamartoma syndrome

*May be the same as IPEX

Table 338-3 Diarrheal Diseases Appearing in the Neonatal Period

CONDITION	CLINICAL FEATURES
Microvillus inclusion disease	Secretory watery diarrhea
Tufting enteropathy	Secretory watery diarrhea
Congenital glucose-galactose malabsorption	Acidic diarrhea
Congenital lactase deficiency	Acidic diarrhea
Congenital chloride diarrhea	Hydramnion, secretory watery diarrhea Metabolic alkalosis
Congenital defective jejunal Na^+-H^+ exchange	Hydramnion, secretory watery diarrhea
Congenital bile acid malabsorption	Steatorrhea
Congenital enterokinase deficiency	Failure to thrive, edema
Congenital trypsinogen deficiency	Failure to thrive, edema
Congenital lipase and/or colipase deficiency	Failure to thrive, oily stool
Enteric anendocrinosis (NEUROG 3 mutation)	Hyperchloremic acidosis, failure to thrive
Immunodeficiency and autoinflammatory diseases (see Table 336-5)	Failure to thrive, opportunistic infections, eczema

Table 336-7 Differential Diagnosis of Presenting Symptoms of Crohn Disease

PRIMARY PRESENTING SYMPTOM	DIAGNOSTIC CONSIDERATIONS
Right lower quadrant abdominal pain, with or without mass	Appendicitis, infection (e.g., *Campylobacter, Yersinia* spp.), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst
Chronic periumbilical or epigastric abdominal pain	Irritable bowel syndrome, constipation, lactose intolerance, peptic disease
Rectal bleeding, no diarrhea	Fissure, polyp, Meckel diverticulum, rectal ulcer syndrome
Bloody diarrhea	Infection, hemolytic-uremic syndrome, Henoch-Schönlein purpura, ischemic bowel, radiation colitis
Watery diarrhea	Irritable bowel syndrome, lactose intolerance, giardiasis, *Cryptosporidium* infection, sorbitol, laxatives
Perirectal disease	Fissure, hemorrhoid (rare), streptococcal infection, condyloma (rare)
Growth delay	Endocrinopathy
Anorexia, weight loss	Anorexia nervosa
Arthritis	Collagen vascular disease, infection
Liver abnormalities	Chronic hepatitis

Table 338-1 Malabsorption Disorders and Chronic Diarrhea Associated with Generalized Mucosal Defect

- Mucosal disorders
  - Gluten-sensitive enteropathy (celiac disease)
  - Cow's milk and other protein-sensitive enteropathies
  - Eosinophilic enteropathy
- Protein-losing enteropathy
  - Lymphangiectasia (congenital and acquired)
  - Disorders causing bowel mucosal inflammation, Crohn disease
- Congenital bowel mucosal defects
  - Microvillous inclusion disease
  - Tufting enteropathy
  - Carbohydrate-deficient glycoprotein syndrome
  - Enterocyte heparan sulfate deficiency
  - Enteric anendocrinosis (NEUROG 3 mutation)
  - Tricho-hepatic-enteric syndrome
- Immunodeficiency disorders
  - Congenital immunodeficiency disorders
    - Selective immunoglobulin A deficiency (can be associated with celiac disease)
    - Severe combined immunodeficiency
    - Agammaglobulinemia
    - X-linked hypogammaglobulinemia
    - Wiskott-Aldrich syndrome
    - Common variable immunodeficiency disease
    - Chronic granulomatous disease
  - Acquired immune deficiency
    - HIV infection
    - Immunosuppressive therapy and post–bone marrow transplantation
- Autoimmune enteropathy
  - IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked inheritance)
  - IPEX-like syndromes
  - Autoimmune polyglandular syndrome type 1
- Miscellaneous
  - Immunoproliferative small intestinal disease
  - Short bowel syndrome
  - Blind loop syndrome
  - Radiation enteritis
  - Protein–calorie malnutrition
  - Crohn disease
  - Pseudoobstruction

Table 338-7 Other Causes of Flat Mucosa

- Autoimmune enteropathy
- Tropical sprue
- Giardiasis
- HIV enteropathy
- Bacterial overgrowth
- Crohn disease
- Eosinophilic gastroenteritis
- Cow's milk enteropathy
- Soy protein enteropathy
- Primary immunodeficiency
- Graft-versus-host disease
- Chemotherapy and radiation
- Protein energy malnutrition
- Tuberculosis
- Lymphoma
- Nongluten food intolerances

Table 338-2 Classification of Malabsorption Disorders and Chronic Diarrhea Based on the Predominant Nutrient Malabsorbed

CARBOHYDRATE MALABSORPTION
- Lactose malabsorption
- Congenital lactase deficiency
- Hypolactasia (adult type)
- Secondary lactase deficiency
- Congenital sucrase-isomaltase deficiency
- Glucose galactose malabsorption

FAT MALABSORPTION
- Abetalipoproteinemia
- Lymphangiectasia
- Homozygous hypobetalipoproteinemia
- Chylomicron retention disease (Anderson disease)
- Cystic fibrosis
- Shwachman-Diamond syndrome
- Johanson-Blizzard syndrome
- Pearson syndrome
- Secondary exocrine pancreatic insufficiency
- Isolated enzyme deficiency
- Enterokinase deficiency
- Trypsinogen deficiency
- Lipase/colipase deficiency
- Chronic pancreatitis
- Protein–calorie malnutrition
- Decreased pancreozymin/cholecystokinin secretion
- Disrupted enterohepatic circulation of bile salts
- Cholestatic liver disease
- Bile acid synthetic defects
- Bile acid malabsorption (terminal ileal disease)

PROTEIN/AMINO ACID MALABSORPTION
- Lysinuric protein intolerance (defect in dibasic amino acid transport)
- Hartnup disease (defect in free neutral amino acids)
- Blue diaper syndrome (isolated tryptophan malabsorption)
- Oasthouse urine disease (defect in methionine absorption)
- Lowe syndrome (lysine and arginine malabsorption)
- Enterokinase deficiency

MINERAL AND VITAMIN MALABSORPTION
- Congenital chloride diarrhea
- Congenital sodium absorption defect
- Acrodermatitis enteropathica (zinc malabsorption)
- Menkes disease (copper malabsorption)
- Vitamin D–dependent rickets
- Folate malabsorption
  - Congenital
  - Secondary to mucosal damage (celiac disease)
- Vitamin B_{12} malabsorption
  - Autoimmune pernicious anemia
  - Decreased gastric acid (H_2 blockers or proton pump inhibitors)
  - Terminal ileal disease (e.g., Crohn disease) or resection
  - Inborn errors of vitamin B_{12} transport and metabolism
- Primary hypomagnesemia

DRUG INDUCED
- Sulfasalazine: folic acid malabsorption
- Cholestyramine: calcium and fat malabsorption
- Anticonvulsant drugs such as phenytoin (causing vitamin D deficiency and folic acid and calcium malabsorption)
- Gastric acid suppression: vitamin B_{12}
- Methotrexate: mucosal injury

Table 338-4 Some Clinical Manifestations of Celiac Disease in Children and Adolescents

SYSTEM	MANIFESTATION	(POSSIBLE) CAUSE
Gastrointestinal	Diarrhea Distended abdomen Vomiting Anorexia Weight loss Failure to thrive Rectal prolapse Aphthous stomatitis Intussusception	Atrophy of the small bowel mucosa Malabsorption
Hematologic	Anemia	Iron malabsorption
Skeletal	Rickets Osteoporosis Enamel hypoplasia of the teeth	Calcium/vitamin D malabsorption
Muscular	Atrophy	Malnutrition
Neurologic	Peripheral neuropathy Epilepsy Irritability Cerebral calcifications Cerebellar ataxia	Thiamine/vitamin B_{12} deficiency
Endocrinologic	Short stature Pubertas tarda Secondary hyperparathyroidism	Malnutrition Calcium/vitamin D malabsorption
Dermatologic	Dermatitis herpetiformis Alopecia areata Erythema nodosum	Autoimmunity
Respiratory	Idiopathic pulmonary hemosiderosis	

Table 338-8 Causes of Protein-Losing Enteropathy

Mucosal inflammation
Infection
Cytomegalovirus
Bacterial overgrowth
Invasive bacterial infection
Clostridium difficile
Helicobacter pylori
Giardiasis
Measles
Strongyloides stercoralis
Gastric inflammation
Menetrier disease
Eosinophilic gastroenteropathy
Intestinal inflammation
Celiac disease
Crohn disease
Eosinophilic gastroenteropathy
Tropical sprue
Radiation enteritis
Primary intestinal lymphangiectasia
Secondary intestinal lymphangiectasia
Constrictive pericarditis
Congestive heart failure
Post-Fontan procedure
Malrotation
Lymphoma
Noonan syndrome
Sarcoidosis
Radiation therapy
Arsenic poisoning
Colonic inflammation
Inflammatory bowel diseases
Necrotizing enterocolitis
Congenital disorders of glycosylation
Enterocyte heparin sulfate deficiency

Table 338-5 Risk Groups for Celiac Disease Case-Finding

First-degree relatives
Dermatitis herpetiformis
Unexplained iron-deficiency anemia
Autoimmune thyroiditis
Type 1 diabetes
Unexplained infertility
Recurrent abortion
Dental enamel hypoplasia
Cryptic hypertransaminasemia
Autoimmune liver disease
Short stature
Delayed puberty
Down, Williams, and Turner syndromes
Irritable bowel syndrome
Unexplained osteoporosis
Sjögren syndrome
Epilepsy (poorly controlled) with occipital calcifications
Selective immunoglobulin A deficiency
Autoimmune endocrinopathies
Addison disease
Aphthous stomatitis
Ataxia
Alopecia
Polyneuropathy
Irritable bowel syndrome

Modified from Di Sabatino A, Corazza GR: Coeliac disease, Lancet *373:1480–1490, 2009.*

Table 338-6 Clinical Spectrum of Celiac Disease

SYMPTOMATIC
Frank malabsorption symptoms: chronic diarrhea, failure to thrive, weight loss
Extraintestinal manifestations: anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis

SILENT
No apparent symptoms in spite of histologic evidence of villous atrophy
In most cases identified by serologic screening in at-risk groups (see Table 330-1)

LATENT
Subjects who have a normal histology, but at some other time, before or after, have shown a gluten-dependent enteropathy

POTENTIAL
Subjects with positive celiac disease serology but without evidence of altered jejunal histology
It might or might not be symptomatic

Table 338-9	Causes of Short Bowel Syndrome
CONGENITAL	
Congenital short bowel syndrome	
Multiple atresias	
Gastroschisis	
BOWEL RESECTION	
Necrotizing enterocolitis	
Volvulus with or without malrotation	
Long segment Hirschsprung disease	
Meconium peritonitis	
Crohn disease	
Trauma	

Table 339-1	Causes of Intestinal Failure in Children Requiring Transplantation
SHORT BOWEL	
• Congenital disorders	
• Volvulus	
• Gastroschisis	
• Necrotizing enterocolitis	
• Intestinal atresia	
• Trauma	
INTESTINAL DYSMOTILITY	
• Intestinal pseudoobstruction	
• Intestinal aganglionosis (Hirschsprung disease)	
ENTEROCYTE DYSFUNCTION	
• Microvillus inclusion disease	
• Tufting enteropathy	
• Autoimmune disorders	
• Crohn disease	
TUMORS	
• Familial polyposis	
• Inflammatory pseudotumor	

Table 340-8	Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis
SPECIFIC INFECTIOUS PROCESSES	
Bacillary dysentery *(Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Shigella boydii;* invasive *Escherichia coli)*	
Campylobacteriosis *(Campylobacter jejuni)*	
Amebic dysentery *(Entamoeba histolytica)*	
Ciliary dysentery *(Balantidium coli)*	
Bilharzial dysentery *(Schistosoma japonicum, Schistosoma mansoni)*	
Other parasitic infections *(Trichinella spiralis)*	
Vibriosis *(Vibrio parahaemolyticus)*	
Salmonellosis *(Salmonella typhimurium)*	
Typhoid fever *(Salmonella typhi)*	
Enteric fever *(Salmonella choleraesuis, Salmonella paratyphi)*	
Yersiniosis *(Yersinia enterocolitica)*	
Spirillar dysentery (*Spirillum* spp.)	
PROCTITIS	
Gonococcal *(Neisseria gonorrhoeae)*	
Herpetic (herpes simplex virus)	
Chlamydial *(Chlamydia trachomatis)*	
Syphilitic *(Treponema pallidum)*	
OTHER SYNDROMES	
Necrotizing enterocolitis of the newborn	
Enteritis necroticans	
Pseudomembranous enterocolitis *(Clostridium difficile)*	
Typhlitis	
CHRONIC INFLAMMATORY PROCESSES	
Enteropathogenic and enteroaggregative *E. coli*	
Gastrointestinal tuberculosis	
Gastrointestinal mycosis	
Parasitic enteritis	
SYNDROMES WITHOUT KNOWN INFECTIOUS CAUSE	
Idiopathic ulcerative colitis	
Crohn disease	
Radiation enteritis	
Ischemic colitis	
Allergic enteritis	

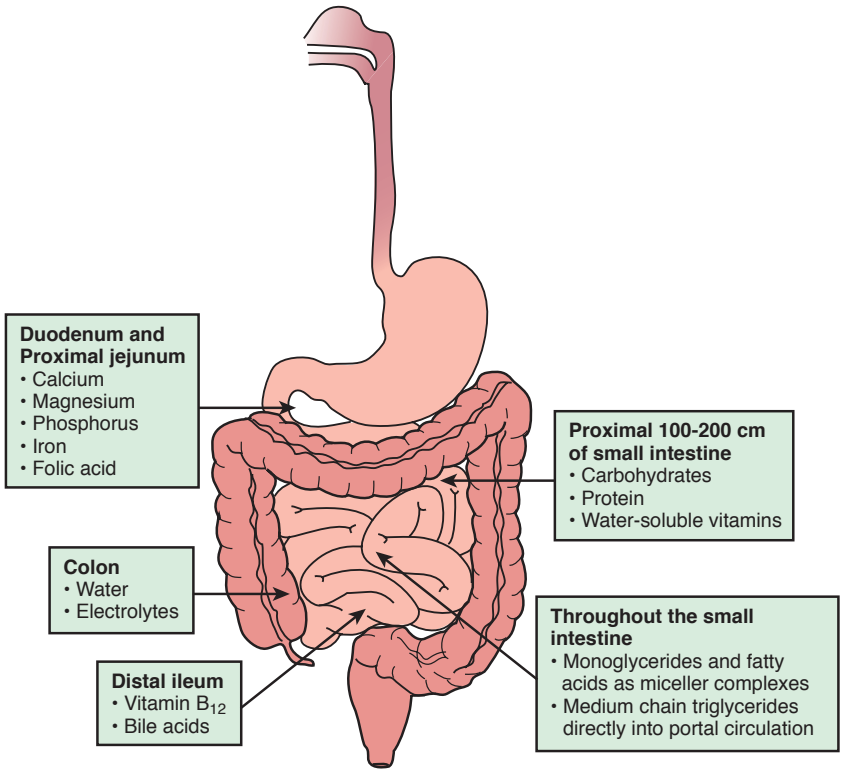


Figure 338-7 Absorption of nutrients in the small bowel varies with the region.

Table 340-9 Extraintestinal Manifestations of Enteric Infections

MANIFESTATION	ASSOCIATED ENTERIC PATHOGEN(S)	ONSET AND PROGNOSIS
Focal infections from systemic spread of bacterial pathogens, including vulvovaginitis, urinary tract infection, endocarditis, osteomyelitis, meningitis, pneumonia, hepatitis, peritonitis, chorioamnionitis, soft-tissue infection, and septic thrombophlebitis	All major pathogens can cause such direct extraintestinal infections, including *Salmonella, Shigella, Yersinia, Campylobacter, Clostridium difficile*	Onset usually during the acute infection but can occur subsequently Prognosis depends on infection site
Reactive arthritis	*Salmonella, Shigella, Yersinia, Campylobacter, Cryptosporidium, C. difficile*	Typically occurs 1-3 wk after infection Relapses after reinfection can develop in 15-50% of people, but most children recover fully within 2-6 mo after the first symptoms appear
Guillain-Barré syndrome	*Campylobacter*	Usually occurs a few weeks after the original infection Prognosis is good although 15-20% may have sequelae
Glomerulonephritis	*Shigella, Campylobacter, Yersinia*	Can be of sudden onset in acute, referring to a sudden attack of inflammation, or chronic, which comes on gradually In most cases, the kidneys heal with time
Immunoglobulin A (IgA) nephropathy	*Campylobacter*	Characterized by recurrent episodes of blood in the urine, this condition results from deposits of the protein IgA in the glomeruli. IgA nephropathy can progress for years with no noticeable symptoms Men seem more likely to develop this disorder than women
Erythema nodosum	*Yersinia, Campylobacter, Salmonella*	Although painful, is usually benign and more commonly seen in adolescents Resolves with 4-6 wk
Hemolytic uremic syndrome	*Shigella dysenteriae* 1, *Escherichia coli* O157:H7, others	Sudden onset, short-term renal failure In severe cases, renal failure requires several sessions of dialysis to take over the kidney function, but most children recover without permanent damage to their health
Hemolytic anemia	*Campylobacter, Yersinia*	Relatively rare complication and can have a chronic course

From Centers for Disease Control and Prevention: Managing acute gastroenteritis among children, MMWR Recomm Rep *53:1–33, 2004.*

Table 340-10 Symptoms Associated with Dehydration

SYMPTOM	MINIMAL OR NO DEHYDRATION (<3% LOSS OF BODY WEIGHT)	MILD TO MODERATE DEHYDRATION (3-9% LOSS OF BODY WEIGHT)	SEVERE DEHYDRATION (>9% LOSS OF BODY WEIGHT)
Mental status	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing	Normal	Normal; fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skinfold	Instant recoil	Recoil in <2 sec	Recoil in >2 sec
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output	Normal to decreased	Decreased	Minimal

Adapted from Duggan C, Santosham M, Glass RI: The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy, MMWR Recomm Rep *41(RR-16):1–20, 1992; and World Health Organization:* The treatment of diarrhoea: a manual for physicians and other senior health workers, *Geneva, 1995, World Health Organization; Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses,* MMWR *53(RR-4):1-33, 2004.*

Table 340-11 Summary of Treatment Based on Degree of Dehydration

DEGREE OF DEHYDRATION	REHYDRATION THERAPY	REPLACEMENT OF LOSSES	NUTRITION
Minimal or no dehydration	Not applicable	<10 kg body weight: 60-120 mL ORS for each diarrheal stool or vomiting episode >10 kg body weight: 120-240 mL ORS for each diarrheal stool or vomiting episode	Continue breastfeeding or resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance*
Mild to moderate dehydration	ORS, 50-100 mL/kg body weight over 3-4 hr	Same	Same
Severe dehydration	Lactated Ringer solution or normal saline in 20 mL/kg body weight IV until perfusion and mental status improve; then administer 100 mL/kg body weight ORS over 4 hr or 5% dextrose normal saline IV at twice maintenance fluid rates	Same; if unable to drink, administer through nasogastric tube or administer 5% dextrose in normal saline with 20 mEq/L potassium chloride IV	Same

*Overly restricted diets should be avoided during acute diarrheal episodes. Breastfed infants should continue to nurse ad libitum even during acute rehydration. Infants too weak to eat can be given milk or formula through a nasogastric tube. Lactose-containing formulas are usually well tolerated. If lactose malabsorption appears clinically substantial, lactose-free formulas can be used. Complex carbohydrates, fresh fruits, lean meats, yogurt, and vegetables are all recommended. Carbonated drinks or commercial juices with a high concentration of simple carbohydrates should be avoided.

ORS, oral rehydration solution.

From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR *53(RR-4):1-33, 2004.*

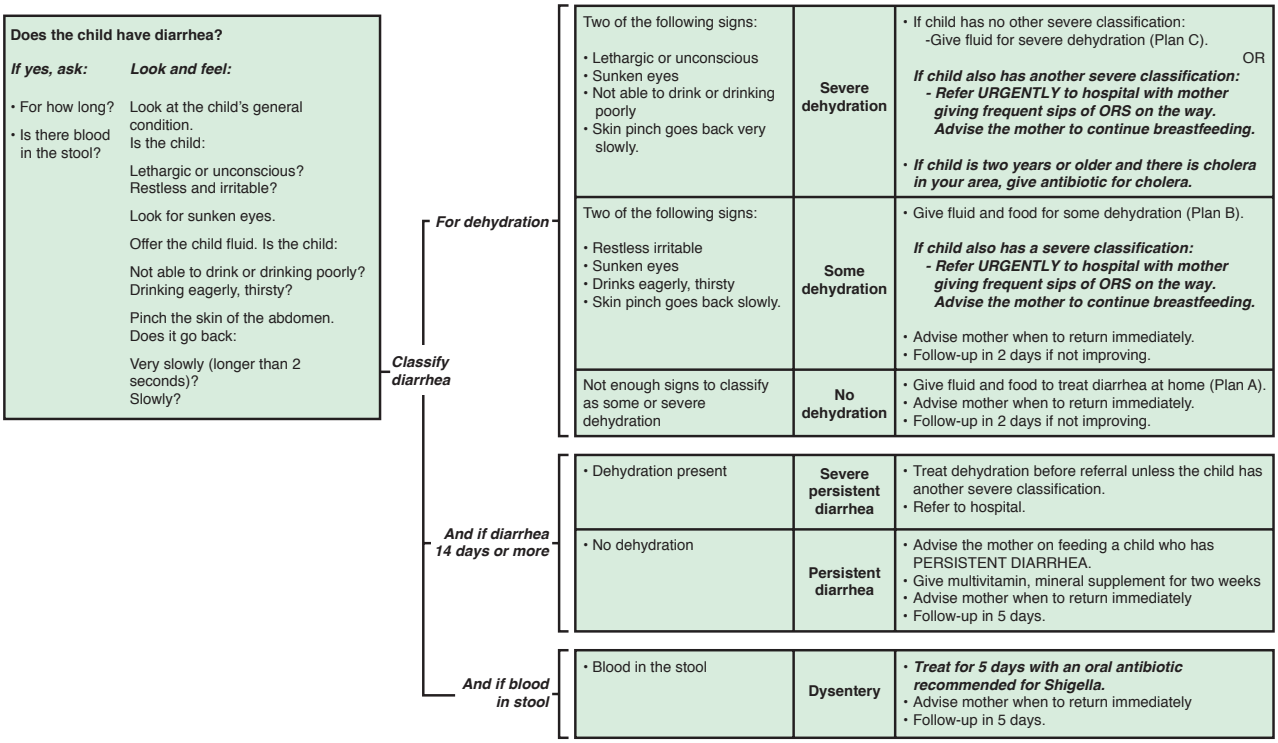


Figure 340-6 Integrated Management of Childhood Illnesses (IMCI) protocol for the recognition and management of diarrhea in developing countries. *ORS*, Oral rehydration solution.

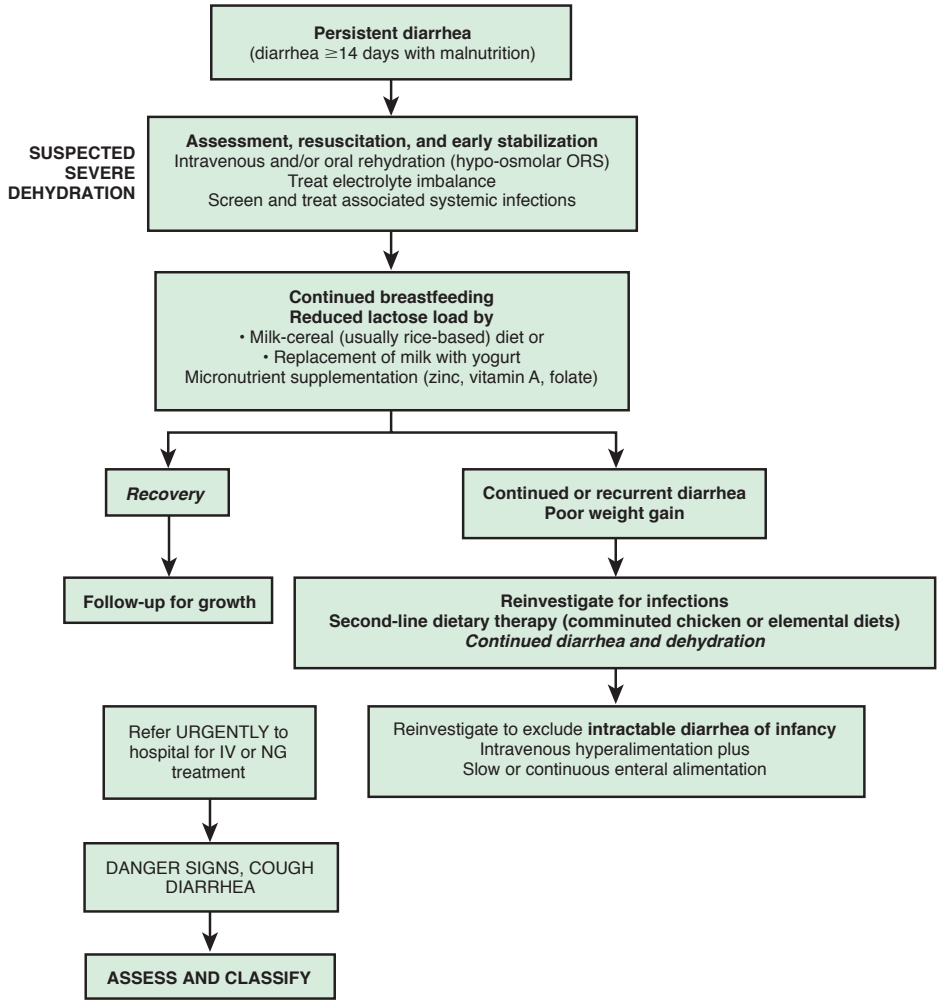


Figure 340-7 Management of persistent diarrhea. *IV*, Intravenous; *NG*, nasogastric tube; *ORS*, oral rehydration solution.

Table 340-12 Antibiotic Therapy for Infectious Diarrhea

ORGANISM	DRUG OF CHOICE	DOSAGE AND DURATION OF TREATMENT
Shigella (severe dysentery and EIEC dysentery)	Ciprofloxacin, ampicillin, ceftriaxone, azithromycin, or TMP-SMX Most strains are resistant to several antibiotics	Ceftriaxone 50-100 mg/kg/day IV or IM, qd or bid × 7 days Ciprofloxacin 20-30 mg/kg/day PO bid × 7-10 days Ampicillin PO, IV 50-100 mg/kg/day qid × 7 days
EPEC, ETEC, EIEC	TMP-SMX or ciprofloxacin	TMP 10 mg/kg/day and SMX 50 mg/kg/day bid × 5 days Ciprofloxacin PO 20-30 mg/kg/day qid for 5-10 days
Salmonella	No antibiotics for uncomplicated gastroenteritis in normal hosts caused by nontyphoidal species **Treatment** indicated in infants younger than 3 mo, and patients with malignancy, chronic GI disease, severe colitis hemoglobinopathies, or HIV infection, and other immunocompromised patients Most strains are resistant to multiple antibiotics	See treatment of *Shigella*
Aeromonas/Plesiomonas	TMP-SMX Ciprofloxacin	TMP 10 mg/kg/day and SMX 50 mg/kg/day bid for 5 days Ciprofloxacin PO 20-30 mg/kg/day divided bid × 7-10 days
Yersinia spp.	Antibiotics are not usually required for diarrhea Deferoxamine therapy should be withheld for severe infections or associated bacteremia Treat sepsis as for immunocompromised hosts, using combination therapy with parenteral doxycycline, aminoglycoside, TMP-SMX, or fluoroquinolone	
Campylobacter jejuni	Erythromycin or azithromycin	Erythromycin PO 50 mg/kg/day divided tid × 5 days Azithromycin PO 5-10 mg/kg/day qid × 5 days
Clostridium difficile	Metronidazole (first line) Discontinue initiating antibiotic Vancomycin (second line)	PO 30 mg/kg/day divided qid × 5 days; max 2 g PO 40 mg/kg/day qid × 7 days, max 125 mg
Entamoeba histolytica	Metronidazole followed by iodoquinol or paromomycin	Metronidazole PO 30-40 mg/kg/day tid × 7-10 days Iodoquinol PO 30-40 mg/kg/day tid × 20 days Paromomycin PO 25-35 mg/kg/day tid × 7 days
Giardia lamblia	Furazolidone or metronidazole or albendazole or quinacrine	Furazolidone PO 25 mg/kg/day qid × 5-7 days Metronidazole PO 30-40 mg/kg/day tid × 7 days Albendazole PO 200 mg bid × 10 days
Cryptosporidium spp.	Nitazoxanide PO treatment may not be needed in normal hosts In immunocompromised, PO immunoglobulin + aggressively treat HIV, etc.	Children 1-3 yr: 100 mg bid × 3 days Children 4-11 yr: 200 mg bid
Isospora spp.	TMP-SMX	PO TMP 5 mg/kg/day and SMX 25 mg/kg/day, bid × 7-10 days
Cyclospora spp.	TMP/SMX	PO TMP 5 mg/kg/day and SMX 25 mg/kg/day bid × 7 days
Blastocystis hominis	Metronidazole or iodoquinol	Metronidazole PO 30-40 mg/kg/day tid × 7-10 days Iodoquinol PO 40 mg/kg/day tid × 20 days

EIEC, Enteroinvasive *Escherichia coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; GI, gastrointestinal; max, maximum; SMX, sulfamethoxazole; TMP, trimethoprim.

Table 341-2 Main Etiologies of Noninfectious Chronic Diarrhea in Children Older and Younger Than 2 Yr of Age

ETIOLOGY	YOUNGER THAN 2 YR	OLDER THAN 2 YR
Abnormal digestive processes	Shwachman-Diamond syndrome, isolated pancreatic enzyme deficiency, chronic pancreatitis, Johanson-Blizzard syndrome, Pearson syndrome. Trypsinogen and enterokinase deficiency: chronic cholestasis; use of bile acids sequestrants; primary bile acid malabsorption	Cystic fibrosis, terminal ileum resection
Nutrient malabsorption	Congenital sucrase-isomaltase deficiency; congenital lactase deficiency; glucose-galactose malabsorption; fructose malabsorption; congenital short bowel	Hypoalactasia; acquired short bowel
Immune/inflammatory	Food allergy; autoimmune enteropathy; primary and secondary immunodeficiencies; IPEX syndrome	Celiac disease; eosinophilic gastroenteritis, inflammatory bowel diseases
Structural defects	Microvillus inclusion disease, tufting enteropathy, phenotypic diarrhea, heparan-sulphate deficiency, $\alpha_2\beta_1$ and $\alpha_6\beta_4$ integrin deficiency, lymphangiectasia, enteric anendocrinosis (neurogenin-3 mutation)	Rare
Defects of electrolyte and metabolite transport	Congenital chloride diarrhea, congenital sodium diarrhea, acrodermatitis enteropathica, selective folate deficiency, abetalipoproteinemia, activating guanylate cyclase mutation	Late onset chloride diarrhea
Motility disorders	Hirschsprung disease, chronic intestinal pseudoobstruction (neurogenic and myopathic)	Thyrotoxicosis
Neoplastic diseases	Neuroendocrine hormone-secreting tumors: Apudomas such as VIPoma, Zollinger- Ellison, and mastocytosis	Neuroendocrine hormone-secreting tumors: Apudomas such as VIPoma, Zollinger-Ellison, and mastocytosis
Diarrhea associated with exogenous substances	Excessive intake of carbonated fluid, foods or drinks containing sorbitol, mannitol, or xylitol; excessive intake of antacids or laxatives containing lactulose or $Mg(OH)_2$; excessive intake of methylxanthines-containing drinks (cola, tea, coffee)	Excessive intake of carbonated fluid, foods or drinks containing sorbitol, mannitol, or xylitol; excessive intake of antacids or laxatives containing lactulose or $Mg(OH)_2$; excessive intake of methylxanthines-containing drinks (cola, tea, coffee)
Chronic nonspecific diarrhea	Functional diarrhea*	Irritable bowel syndrome†

*Until 4 yr of age, according to Rome III criteria.
†Older than 5 yr of age according to Rome III criteria.
IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; VIPoma, vasoactive intestinal polypeptide tumor.

Table 341-4 Degree of Malnutrition as Estimated by Visceral Protein Concentrations in Children with Chronic Diarrhea

VISCERAL PROTEIN	HALF-LIFE	NORMAL VALUES	MILD MALNUTRITION	MODERATE MALNUTRITION	SEVERE MALNUTRITION
Albumin	20 days	30-45 g/L	3.0-2.9 g/L	2.8-2.5 g/L	<2.5 g/L
Prealbumin	2 days	0.2-04 g/L	0.2-0.18 g/L	0.17-0.1 g/L	<0.1 g/L
Retinol binding protein	12 hr	2.6-7.6 g/L	2.5-2.0 g/L	1.9 -1.5 g/L	<1 g/L
Transferrin	8 days	218-411 µg/dL	200-150 µg/dL	149-100 µg/dL	<100 µg/dL
Serum iron	11-19 hr	16-124 µg/dL	15-13 µg/dL	12-10 µg/dL	<10 µg/dL

Consider also the concentrations of the following micronutrients: calcium, zinc, magnesium, iodine, vitamin A, vitamin C, vitamin B_1.

Table 341-5 Noninvasive Tests for Intestinal Digestive–Absorptive Function and Inflammation

TEST	NORMAL VALUES	IMPLICATION
α_1-Antitripsin concentration	<0.9 mg/g	Increased intestinal permeability/protein loss
Steatocrit	<2.5% (older than 2 yr) fold increase over age-related values (younger than 2 yr)	Fat malabsorption
Fecal-reducing substances	Absent	Carbohydrate malabsorption
Elastase concentration	>200 µg/g	Pancreatic function
Chymotrypsin concentration	>7.5 units/g >375 units/24 hr	Pancreatic function
Fecal occult blood	Absent	Blood loss in the stools/inflammation
Fecal calprotectin concentration	<100 µg/g (in children to 4 yr of age) <50 µg/g (older than 4 yr)	Intestinal inflammation
Fecal leukocytes	<5/microscopic field	Colonic inflammation
Nitric oxide in rectal dialysate	<5 µM of NO_2^-/NO_3^-	Rectal inflammation
Dual sugar (cellobiose/mannitol) absorption test	Urine excretion ratio: 0.010 ± 0.018	Increased intestinal permeability
Xylose oral load	25 mg/dL	Reduced intestinal surface

Table 341-3 Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES

DISEASE	GENE		TRANSMISSION AND INCIDENCE	MECHANISM
	Name	Location		
Genes Encoding Brush-Border Enzymes				
Congenital lactase deficiency (LD)	*LCT*	2q21.3	AR, 1 in 60,000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	*SI*	3q26.1	AR, 1 in 5,000; higher incidence in Greenland, Alaska, and Canada	Osmotic
Congenital maltase-glucoamylase deficiency (MGD)	Not defined	—	Few cases described	Osmotic
Genes Encoding Membrane Carriers				
Glucose-galactose malabsorption (GGM)	*SLC5A1*	22q13.1	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	Not defined	—	Up to 40%	Osmotic
Fanconi-Bickel syndrome (FBS)	*SLC2A2*	3q26.2	AR, rare, higher frequency in consanguineous	Osmotic
Acrodermatitis enteropathica (ADE)	*SLC39A4*	8q24.3	AR, 1 in 500,000	Osmotic
Congenital chloride diarrhea (CCD, DIAR 1)	*SLC26A3*	7q31.1	AR, sporadic; frequent in some ethnicities	Osmotic
Lysinuric protein intolerance (LPI)	*SLC7A7*	14q11.2	AR, about 1 in 60,000 in Finland and Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	*SLC10A2*	13q33.1	AR	Secretory
Cystic fibrosis (CF)	*CFTR*	7q31.2	AR, 1 in 2,500	Osmotic
Genes Encoding Pancreatic Enzymes				
Enterokinase deficiency (EKD)	*PRSS7*	21q21	AR	Osmotic
Hereditary pancreatitis (HP)	*PRSS1* *SPINK1*	7q34 5q32	AR, cases with compound mutations in different genes; *SPINK1* mutations may also cause tropical pancreatitis	Osmotic
Congenital absence of pancreatic lipase (APL)	*PNLIP*	10q25.3	—	Osmotic
Genes Encoding Proteins of Lipoprotein Metabolism				
Abetalipoproteinemia (ALP)	*MTTP*	4q27	AR, about 100 cases described; higher frequency among Ashkenazi Jews	Osmotic
Hypobetalipoproteinemia (HLP)	*Apo B*	2p24.1	Autosomal codominant	Osmotic
Chylomicron retention disease (CRD)	*SAR1B*	5q31.1	AR, about 40 cases described	Osmotic
Genes Encoding Other Types of Proteins				
Congenital sodium diarrhea (CSD, DIAR 3)	*SPINT2* (only syndromic CSD)	19q13.2	AR	Osmotic
Shwachman-Diamond syndrome (SDS)	*SBDS*	7q11	AR	Osmotic
Activating GUCY2C mutation	Guanylate cyclase-C	Unknown	AD	Secretory
Genes Encoding for Other Enzymes				
Defect in triglyceride synthesis	*DGAT1*	Splice variant (chromosome 8, 145541756 A G) in the splice donor site 32 of exon 8, altering the invariant GT to GC	AR	Protein-losing enteropathy

DISEASE	OMIM NUMBER	TRANSMISSION AND INCIDENCE	MECHANISM
DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION			
Microvillous inclusion disease (MVID, DIAR 2)	251850	AR; rare; higher frequency among Navajo	Secretory
Congenital tufting enteropathy (CTE, DIAR 5)	613217	AR; 1 in 50,000-100,000; higher among Arabians	Secretory
Trichohepatoenteric syndrome (THE)	222470	AR; 1 in 400,000	Secretory
DEFECTS OF ENTEROENDOCRINE CELL DIFFERENTIATION			
Congenital malabsorptive diarrhea (CMD, DIAR 4)	610370	AR; few cases described	Osmotic
Proprotein convertase 1/3 deficiency (PCD)	600955	AR	Osmotic
DEFECTS OF MODULATION OF INTESTINAL IMMUNE RESPONSE			
Autoimmune polyglandular syndrome type 1 (APS1)	240300	AR; AD (1 family)	Secretory
Immune dysfunction, polyendocrinopathy, X-linked (IPEX)	601410	X-linked (autosomal cases described), very rare	Secretory
IPEX-like syndrome	—	Not X-linked	Secretory

AD, autosomal dominant; AR, autosomal recessive.

Table 341-6 Stepwise Diagnostic Approach to Children with Diarrhea

STEP 1	STEP 2
Intestinal Microbiology	***Evaluation of Intestinal Morphology:***
Stool cultures	Endoscopy and standard jejunal/colonic histology*
Microscopy for parasites	Morphometry
Viruses	PAS staining
H_2 breath test	Electron microscopy
Screening Test for Celiac Disease:	Imaging (upper or lower bowel series, capsule endoscopy)
Serology according to age and level of IgA (including AGA IgA/IgG, EMA IgA/IgG, tTG IgA/IgG)	**STEP 3**
Noninvasive Tests for:	***Special Investigations:***
Intestinal function (including double sugar test, xylosemia, iron absorption test)	Intestinal immunohistochemistry
Pancreatic function (amylase, lipase, fecal elastase)	Antienterocyte antibodies
Intestinal inflammation (fecal calprotectin, rectal nitric oxide)	Serum chromogranin and catecholamines
Tests for Food Allergy:	Autoantibodies
Prick/patch tests for foods	^{75}SeHCAT measurement
Abdominal Ultrasounds (Scan of Last Ileal Loop)	Brush-border enzymatic activities
	Motility and electrophysiologic studies

*The decision to perform an upper or a lower endoscopy may be supported by noninvasive tests.
AGA, antigliadin antibody; EMA, endomysial antibody; Ig, immunoglobulin; PAS, periodic acid–Schiff; ^{75}SeHCAT, ^{75}Se-homocholic acid-taurine; tTG, tissue transglutaminase.

Table 341-7 Treatment of Infectious Persistent Diarrhea

	FACTOR	INDICATIONS	DOSAGE	DURATION
Antibiotics	Trimethoprim-sulfamethoxazole	*Salmonella* spp., *Shigella*	10-50 mg/kg/day in 2 divided doses–daily os	7 days
	Azithromycin	*Shigella*	1° day: 12 mg/kg/day once–daily os 2°-5° days: 6 mg/kg/day once–daily os	5 days
	Ciprofloxacin		20-30 mg/kg/day in 2 divided doses–os or iv	7 days
	Ceftriaxone		50-100 mg/kg/day once–im or iv	7 days
	Erythromycin	*Campylobacter*	50 mg/kg/day in 2-3 divided doses–os	7 days
	Metronidazole	*Giardia, Entamoeba*	20-30 mg/kg/day in 2-3 divided doses–os	7 days Small intestinal bacterial overgrowth
Antiparasitic	Nitazoxanide Albendazole	*Amebiasis*, *Giardiasis*, *Cryptosporidiosis* and helminth infections	100 mg every 12 hr for children ages 12-47 mo 200 mg every 12 hr for children ages 4-11 yr 500 mg every 12 hr for children older than 11 yr 400 mg once	3 days
Probiotics	*Lactobacillus* GG		1-2 × 10^{11}–1 × 10^{11} CFU/day–os	For a minimum period of 7 days or until diarrhea stopped
	Saccharomyces boulardii		1 × 10^{10} germs live (500 mg)/day–os	For a minimum period of 7 days or till diarrhea stopped
Human serum immunoglobulin		Severe *Rotavirus* diarrhea	300 mg/kg single oral administration	
Antisecretory	Racecadotril	Secretory diarrhea	1.5 mg/kg every 8 hr–os	For a minimum period of 7 days or till diarrhea stopped
Adsorbents	Diosmectite		3-6 g every 12-24 hr–os	5 days

Table 342-6 Effectiveness of Treatments for Abdominal Pain in Children

THERAPY	DEFINITION OF DISORDER	EFFECTIVENESS
Cognitive behavioral (family) therapy	Recurrent abdominal pain	Beneficial
Famotidine	Recurrent abdominal pain and dyspeptic symptoms	Inconclusive
Added dietary fiber	Recurrent abdominal pain	Unlikely to be beneficial
Lactose-free diet	Recurrent abdominal pain	Unlikely to be beneficial
Peppermint oil	Irritable bowel syndrome	Likely to be beneficial
Amitriptyline	Functional gastrointestinal disorders, irritable bowel syndrome	Inconsistent results
Lactobacillus GG	Irritable bowel syndrome using Rome III criteria	Unlikely to be beneficial

The effectiveness of analgesics, antispasmodics, sedatives, and antidepressants is currently unknown.
From Berger MY, Gieteling MJ, Benninga MA: Chronic abdominal pain in children, BMJ *334:997–1002, 2007.*

Table 342-1 Recommended Clinical Definitions of Long-Standing Intermittent or Constant Abdominal Pain in Children

DISORDER	DEFINITION
Chronic abdominal pain	Long-lasting intermittent or constant abdominal pain that is functional or organic (disease based)
Functional abdominal pain	Abdominal pain without demonstrable evidence of pathologic condition, such as anatomic metabolic, infectious, inflammatory or neoplastic disorder. Functional abdominal pain can manifest with symptoms typical of functional dyspepsia, irritable bowel syndrome, abdominal migraine or functional abdominal pain syndrome
Functional dyspepsia	Functional abdominal pain or discomfort in the upper abdomen
Irritable bowel syndrome	Functional abdominal pain associated with alteration in bowel movements
Abdominal migraine	Functional abdominal pain with features of migraine (paroxysmal abdominal pain associated with anorexia, nausea, vomiting or pallor as well as maternal history of migraine headaches)
Functional abdominal pain syndrome	Functional abdominal pain without the characteristics of dyspepsia, irritable bowel syndrome, or abdominal migraine

Adapted from Di Lorenzo C, Colletti RB, Lehmann HP, et al; American Academy of Pediatrics Subcommittee on Chronic Abdominal Pain; NASPGHAN Committee on Abdominal Pain: Chronic abdominal pain in children: a clinical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, J Pediatr Gastroenterol Nutr *40(3):245–248, 2005.*

Table 342-4 Alarm Symptoms Usually Needing Further Investigations

Pain that wakes up the child from sleep
Persistent right upper or right lower quadrant pain
Significant vomiting (bilious vomiting, protracted vomiting, cyclical vomiting, or worrisome pattern to the physician)
Unexplained fever
Genitourinary tract symptoms
Dysphagia
Chronic severe diarrhea or nocturnal diarrhea
Gastrointestinal blood loss
Involuntary weight loss
Deceleration of linear growth
Delayed puberty
Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease

Table 342-5 Alarm Signs Usually Needing Further Investigations

Localized tenderness in the right *upper* quadrant
Localized tenderness in the right *lower* quadrant
Localized fullness or mass
Hepatomegaly
Splenomegaly
Jaundice
Costovertebral angle tenderness
Arthritis
Spinal tenderness
Perianal disease
Abnormal or unexplained physical findings
Hematochezia
Anemia

Table 342-2 Childhood Functional GI Disorders: Child/Adolescent (Category H)

H1. Vomiting and aerophagia
H1a. Adolescent rumination syndrome
H1b. Cyclic vomiting syndrome
H1c. Aerophagia
H2. Abdominal pain—related functional gastrointestinal disorders
H2a. Functional dyspepsia
H2b. Irritable bowel syndrome
H2c. Abdominal migraine
H2d. Childhood functional abdominal pain
H2d1. Childhood functional abdominal pain syndrome
H3. Constipation and incontinence
H3a. Functional constipation
H3b. Nonretentive fecal incontinence

Adapted from Rome Foundation: Rome III disorders and criteria. www.romecriteria.org/criteria/.

Table 342-3 Rome III Criteria for Childhood Functional Abdominal Pain H2d and Childhood Functional Abdominal Pain Syndrome H2d1

H2d. CHILDHOOD FUNCTIONAL ABDOMINAL PAIN
Diagnostic criteria* must include **all** of the following:
- Episodic or continuous abdominal pain
- Insufficient criteria for other functional gastrointestinal disorders
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

H2d1. CHILDHOOD FUNCTIONAL ABDOMINAL PAIN SYNDROME
Diagnostic criteria* must satisfy criteria for childhood functional abdominal pain and have at least 25% of the time **one or more** of the following:
- Some loss of daily function
- Additional somatic symptoms such as headache, limb pain, or difficulty sleeping

*Criteria fulfilled at least once per week for ≥2 mo prior to diagnosis.
Adapted from Rome Foundation: Rome III disorders and criteria. http://www.romecriteria.org/criteria/.

Table 342-7 Rome III Criteria for Child/Adolescent Irritable Bowel Syndrome H2b

Diagnostic criteria* must include **all** of the following:
1. Abdominal discomfort† or pain associated with 2 or more of the following at least 25% of the time:
   a. Improvement with defecation
   b. Onset associated with a change in frequency of stool
   c. Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

*Criteria fulfilled at least once per week for at least 6 mo prior to diagnosis.
†"Discomfort" means an uncomfortable sensation not described as pain.
Adapted from Rome Foundation: Rome III disorders and criteria. http://www.romecriteria.org/criteria/

Table 346-1 Predisposing Factors for Hernias

Prematurity
Urogenital
- Cryptorchidism
- Exstrophy of the bladder or cloaca
- Ambiguous genitalia
- Hypospadias/epispadius

Increased peritoneal fluid
- Ascites
- Ventriculoperitoneal shunt
- Peritoneal dialysis catheter

Increased intraabdominal pressure
- Repair of abdominal wall defects
- Severe ascites (chylous)
- Meconium peritonitis

Chronic respiratory disease
- Cystic fibrosis

Connective tissue disorders
- Ehlers-Danlos syndrome
- Hunter-Hurler syndrome
- Marfan syndrome
- Mucopolysaccharidosis

Table 350-1 Pancreatic Enzyme Replacement Therapy

Infants (up to 12 mo)	2000-4000 units lipase/120 mL breast milk or formula
12 mo-4 yr	1000 units lipase/kg/meal initially, then titrate per response
Children older than 4 yr and adults	500 units lipase/kg/meal initially, up to maximum of 2500 units lipase/kg/meal or 10,000 units lipase/kg/day or 4,000 units lipase/g fat ingested per day
PLUS: one half the standard meal dose to be given with snacks	

Table 343-1 Pediatric Appendicitis Scores

FEATURE	SCORE
Fever >38°C (100.4°F)	1
Anorexia	1
Nausea/vomiting	1
Cough/percussion/hopping tenderness	2
Right lower quadrant tenderness	2
Migration of pain	1
Leukocytosis >10,000 (10^9/L)	1
Polymorphonuclear-neutrophilia >7,500 (10^9/L)	1
Total	10

From Acheson J, Banerjee J: Management of suspected appendicitis in children, Arch Dis Child Educ Pract Ed *95:9–13, 2010.*

Table 344-1 Associated Malformations

GENITOURINARY
Vesicoureteric reflux
Renal agenesis
Renal dysplasia
Ureteral duplication
Cryptorchidism
Hypospadias
Bicornuate uterus
Vaginal septums

VERTEBRAL
Spinal dysraphism
Tethered chord
Presacral masses
Meningocele
Lipoma
Dermoid
Teratoma

CARDIOVASCULAR
Tetralogy of Fallot
Ventricular septal defect
Transposition of the great vessels
Hypoplastic left-heart syndrome

GASTROINTESTINAL
Tracheoesophageal fistula
Duodenal atresia
Malrotation
Hirschsprung disease

CENTRAL NERVOUS SYSTEM
Spina bifida
Tethered cord

Table 345-1 General Features of the Inherited Colorectal Cancer Syndromes

SYNDROME	POLYP DISTRIBUTION	AGE OF ONSET	RISK OF COLON CANCER	GENETIC LESION	CLINICAL MANIFESTATIONS	ASSOCIATED LESIONS
HAMARTOMATOUS POLYPS						
Juvenile polyposis	Large and small intestine, gastric polyps	1st decade	~10-50%	*PTEN, SMAD4, BMPR1A* Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Congenital abnormalities in 20% of the nonfamilial type, clubbing, AV malformations
Peutz-Jeghers syndrome	Small and large intestine	1st decade	Increased	*LKB1/STK11* Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Orocutaneous melanin pigment spots
Cowden syndrome	Colon	2nd decade	Not increased	*PTEN* gene	Macrocephaly, breast/thyroid/endometrial cancers, developmental delay	
Bannayan-Riley-Ruvalcaba syndrome	Colon	2nd decade	Not increased	*PTEN* gene	Macrocephaly, speckled penis, thyroid/breast cancers, hemangiomas, lipomas	
ADENOMATOUS POLYPS						
Familial adenomatous polyposis (FAP)	Large intestine, often >100	16 yr (range: 8-34 yr)	100%	5q (*APC* gene), autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Desmoids, CHRPE, upper GI polyps, osteoma, hepatoblastoma, thyroid cancer
Attenuated familial adenomatous polyposis (AFAP)	Colon (fewer in number)	>18 yr	Increased	*APC* gene	Same as FAP	Fewer associated lesions
MYH-associated polyposis	Colon	>20yr	High risk	*MYH* autosomal recessive	Same as FAP	May be confused with sporadic FAP or AFAP; few extraintestinal findings
Gardner syndrome	Large and small intestine	16 yr (range: 8-34 yr)	100%	5q (*APC* gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoid tumors, multiple osteomas, fibromas, epidermoid cysts
Hereditary nonpolyposis colon cancer, (Lynch syndrome)	Large intestine	40 yr	30%	DNA mismatch repair genes *(MMR)* Autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Other tumors (e.g., ovary, ureter, pancreas, stomach)

AV, Arteriovenous; CHRPE, congenital hypertrophy of the retinal pigment epithelium; GI, gastrointestinal.

Table 351-2 Differential Diagnosis of Hyperamylasemia

PANCREATIC PATHOLOGY
Acute or chronic pancreatitis
Complications of pancreatitis (pseudocyst, ascites, abscess)
Factitious pancreatitis

SALIVARY GLAND PATHOLOGY
Parotitis (mumps, *Staphylococcus aureus*, cytomegalovirus, HIV, Epstein-Barr virus)
Sialadenitis (calculus, radiation)
Eating disorders (anorexia nervosa, bulimia)

INTRAABDOMINAL PATHOLOGY
Biliary tract disease (cholelithiasis)
Peptic ulcer perforation
Peritonitis
Intestinal obstruction
Appendicitis

SYSTEMIC DISEASES
Metabolic acidosis (diabetes mellitus, shock)
Renal insufficiency, transplantation
Burns
Pregnancy
Drugs (morphine)
Head injury
Cardiopulmonary bypass

Table 354-2 Causes of Impaired Bile Acid Metabolism and Enterohepatic Circulation

DEFECTIVE BILE ACID SYNTHESIS OR TRANSPORT
Inborn errors of bile acid synthesis (reductase deficiency, isomerase deficiency)
Progressive familial intrahepatic cholestasis (PFIC1, PFIC2, PFIC3)
Intrahepatic cholestasis (neonatal hepatitis)
Acquired defects in bile acid synthesis secondary to severe liver disease

ABNORMALITIES OF BILE ACID DELIVERY TO THE BOWEL
Celiac disease (sluggish gallbladder contraction)
Extrahepatic bile duct obstruction (e.g., biliary atresia, gallstones)

LOSS OF ENTEROHEPATIC CIRCULATION OF BILE ACIDS
External bile fistula
Cystic fibrosis
Small bowel bacterial overgrowth syndrome (with bile acid precipitation, increased jejunal absorption, and "short-circuiting")
Drug-induced entrapment of bile acids in intestinal lumen (e.g., cholestyramine)

BILE ACID MALABSORPTION
Primary bile acid malabsorption (absent or inefficient ileal active transport)
Secondary bile acid malabsorption
Ileal disease or resection
Cystic fibrosis

DEFECTIVE UPTAKE OR ALTERED INTRACELLULAR METABOLISM
Parenchymal disease (acute hepatitis, cirrhosis)
Regurgitation from cells
Portosystemic shunting
Cholestasis

Table 351-1 Etiology of Acute and Recurrent Pancreatitis in Children

DRUGS AND TOXINS
Acetaminophen overdose
Alcohol
L-Asparaginase
Azathioprine
Carbamazepine
Cimetidine
Corticosteroids
Enalapril
Erythromycin
Estrogen
Furosemide
Glucagon-like peptide-1 agents
Isoniazid
Lisinopril
6-Mercaptopurine
Methyldopa
Metronidazole
Octreotide
Organophosphate poisoning
Pentamidine
Retrovirals: DDC (dideoxycytidine), DDI (dideoxyinosine), tenofovir
Sulfonamides: mesalamine, 5-aminosalicytates, sulfasalazine, trimethoprim-sulfamethoxazole
Sulindac
Tetracycline
Thiazides
Valproic acid
Venom (spider, scorpion, Gila monster lizard)
Vincristine
Volatile hydrocarbons

GENETIC
Cationic trypsinogen gene *(PRSS1)*
Chymotrypsin C gene *(CTRC)*
Cystic fibrosis gene *(CFTR)*
Trypsin inhibitor gene *(SPINK1)*

INFECTIOUS
Ascariasis
Coxsackie B virus
Epstein-Barr virus
Hepatitides A, B
Influenzae A, B
Leptospirosis
Malaria
Measles
Mumps
Mycoplasma
Rubella
Rubeola
Reye syndrome: varicella, influenza B
Septic shock

OBSTRUCTIVE
Ampullary disease
Ascariasis
Biliary tract malformations
Choledochal cyst
Choledochocele
Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge)
Duplication cyst
Endoscopic retrograde cholangiopancreatography (ERCP) complication
Pancreas divisum
Pancreatic ductal abnormalities
Postoperative
Sphincter of Oddi dysfunction
Tumor

SYSTEMIC DISEASE
Autoimmune pancreatitis (IgG_4-related systemic disease)
Brain tumor
Collagen vascular diseases
Crohn disease
Diabetes mellitus (ketoacidosis)
Head trauma
Hemochromatosis
Hemolytic uremic syndrome
Hyperlipidemia: types I, IV, V
Hyperparathyroidism/hypercalcemia
Kawasaki disease
Malnutrition
Organic academia
Peptic ulcer
Periarteritis nodosa
Renal failure
Systemic lupus erythematosus
Transplantation: bone marrow, heart, liver, kidney, pancreas
Vasculitis

TRAUMATIC
Blunt injury
Burns
Child abuse
Hypothermia
Surgical trauma
Total-body cast

Table 355-2 Differential Diagnosis of Unconjugated Hyperbilirubinemia

INCREASED PRODUCTION OF UNCONJUGATED BILIRUBIN FROM HEME
Hemolytic Disease (Hereditary or Acquired)
Isoimmune hemolysis (neonatal; acute or delayed transfusion reaction; autoimmune)
- Rh incompatibility
- ABO incompatibility
- Other blood group incompatibilities

Congenital spherocytosis
Hereditary elliptocytosis
Infantile pyknocytosis
Erythrocyte enzyme defects
Hemoglobinopathy
- Sickle cell anemia
- Thalassemia
- Others

Sepsis
Microangiopathy
- Hemolytic-uremic syndrome
- Hemangioma
- Mechanical trauma (heart valve)

Ineffective erythropoiesis
Drugs
Infection
Enclosed hematoma
Polycythemia
- Diabetic mother
- Fetal transfusion (recipient)
- Delayed cord clamping

DECREASED DELIVERY OF UNCONJUGATED BILIRUBIN (IN PLASMA) TO HEPATOCYTE
Right-sided congestive heart failure
Portacaval shunt

DECREASED BILIRUBIN UPTAKE ACROSS HEPATOCYTE MEMBRANE
Presumed enzyme transporter deficiency
Competitive inhibition
- Breast milk jaundice
- Lucey-Driscoll syndrome
- Drug inhibition (radiocontrast material)

Miscellaneous
- Hypothyroidism
- Hypoxia
- Acidosis

DECREASED STORAGE OF UNCONJUGATED BILIRUBIN IN CYTOSOL (DECREASED Y AND Z PROTEINS)
Competitive inhibition
Fever

DECREASED BIOTRANSFORMATION (CONJUGATION)
Neonatal jaundice (physiologic)
Inhibition (drugs)
Hereditary (Crigler-Najjar)
- Type I (complete enzyme deficiency)
- Type II (partial deficiency)

Gilbert disease
Hepatocellular dysfunction

ENTEROHEPATIC RECIRCULATION
Breast milk jaundice
Intestinal obstruction
- Ileal atresia
- Hirschsprung disease
- Cystic fibrosis
- Pyloric stenosis

Antibiotic administration

Table 355-1 Mechanisms of Hepatomegaly

INCREASE IN THE NUMBER OR SIZE OF THE CELLS INTRINSIC TO THE LIVER
Storage
Fat: malnutrition, obesity, diabetes mellitus, metabolic liver disease (diseases of fatty acid oxidation and Reye syndrome–like illnesses), lipid infusion (total parenteral nutrition), cystic fibrosis, medication related, pregnancy
Specific lipid storage diseases: Gaucher, Niemann-Pick, Wolman disease
Glycogen: glycogen storage diseases (multiple enzyme defects); total parenteral nutrition; infant of diabetic mother, Beckwith syndrome
Miscellaneous: α_1-antitrypsin deficiency, Wilson disease, hypervitaminosis A, neonatal iron storage disease
Inflammation
Hepatocyte enlargement (hepatitis)
- Viral: acute and chronic
- Bacterial: sepsis, abscess, cholangitis
- Toxic: drugs
- Autoimmune

Kupffer cell enlargement
- Sarcoidosis
- Systemic lupus erythematosus
- Macrophage activating syndrome

INFILTRATION OF CELLS
Primary Liver Tumors: Benign
Hepatocellular
- Focal nodular hyperplasia
- Nodular regenerative hyperplasia
- Hepatocellular adenoma

Mesodermal
- Infantile hemangioendothelioma
- Mesenchymal hamartoma

Cystic masses
- Choledochal cyst
- Hepatic cyst
- Hematoma
- Parasitic cyst
- Pyogenic or amebic abscess

Primary Liver Tumors: Malignant
Hepatocellular
- Hepatoblastoma
- Hepatocellular carcinoma

Mesodermal
- Angiosarcoma
- Undifferentiated embryonal sarcoma

Secondary or metastatic processes
- Lymphoma
- Leukemia
- Histiocytosis
- Neuroblastoma
- Wilms tumor

INCREASED SIZE OF VASCULAR SPACE
Intrahepatic obstruction to hepatic vein outflow
- Venoocclusive disease
- Hepatic vein thrombosis (Budd-Chiari syndrome)
- Hepatic vein web

Suprahepatic
- Congestive heart failure
- Pericardial disease
- Tamponade

Post-Fontan procedure
Constrictive pericarditis
Hematopoietic: sickle cell anemia, thalassemia

INCREASED SIZE OF BILIARY SPACE
Congenital hepatic fibrosis
Caroli disease
Extrahepatic obstruction

IDIOPATHIC
Various
- Riedel lobe
- Normal variant
- Downward displacement of diaphragm

Table 355-3 Differential Diagnosis of Neonatal and Infantile Cholestasis

INFECTIOUS
Generalized bacterial sepsis
Viral hepatitis
- Hepatitides A, B, C, D, E
- Cytomegalovirus
- Rubella virus
- Herpesviruses: herpes simplex, human herpesvirus 6 and 7
- Varicella virus
- Coxsackievirus
- Echovirus
- Reovirus type 3
- Parvovirus B19
- HIV
- Adenovirus

Others
- Toxoplasmosis
- Syphilis
- Tuberculosis
- Listeriosis
- Urinary tract infection

TOXIC
Sepsis
Parenteral nutrition related
Drug, dietary supplement, herbal related

METABOLIC
Disorders of amino acid metabolism
- Tyrosinemia

Disorders of lipid metabolism
- Wolman disease
- Niemann-Pick disease (type C)
- Gaucher disease

Cholesterol ester storage disease
Disorders of carbohydrate metabolism
- Galactosemia
- Fructosemia
- Glycogenosis IV

Disorders of bile acid biosynthesis
Other metabolic defects
- α_1-Antitrypsin deficiency
- Cystic fibrosis
- Hypopituitarism
- Hypothyroidism
- Zellweger (cerebrohepatorenal) syndrome
- Wilson disease
- Neonatal iron storage disease
- Indian childhood cirrhosis/infantile copper overload
- Congenital disorders of glycosylation
- Mitochondrial hepatopathies
- Citrin deficiency

GENETIC OR CHROMOSOMAL
Trisomies 17, 18, 21

INTRAHEPATIC CHOLESTASIS SYNDROMES
"Idiopathic" neonatal hepatitis
Alagille syndrome
Intrahepatic cholestasis (progressive familial intrahepatic cholestasis [PFIC])
- FIC-1 deficiency
- BSEP (bile salt export pump) deficiency
- MDR3 deficiency

Familial benign recurrent cholestasis associated with lymphedema (Aagenaes syndrome)
ARC (arthrogryposis, renal dysfunction, and cholestasis) syndrome
Caroli disease (cystic dilation of intrahepatic ducts)

EXTRAHEPATIC DISEASES
Biliary atresia
Sclerosing cholangitis
Bile duct stricture/stenosis
Choledochal–pancreaticoductal junction anomaly
Spontaneous perforation of the bile duct
Choledochal cyst
Mass (neoplasia, stone)
Bile/mucous plug ("inspissated bile")

MISCELLANEOUS
Shock and hypoperfusion
Associated with enteritis
Associated with intestinal obstruction
Neonatal lupus erythematosus
Myeloproliferative disease (trisomy 21)
Hemophagocytic lymphohistiocytosis (HLH)
COACH syndrome (coloboma, oligophrenia, ataxia, cerebellar vermis hypoplasia, hepatic fibrosis)
Cholangiocyte cilia defects

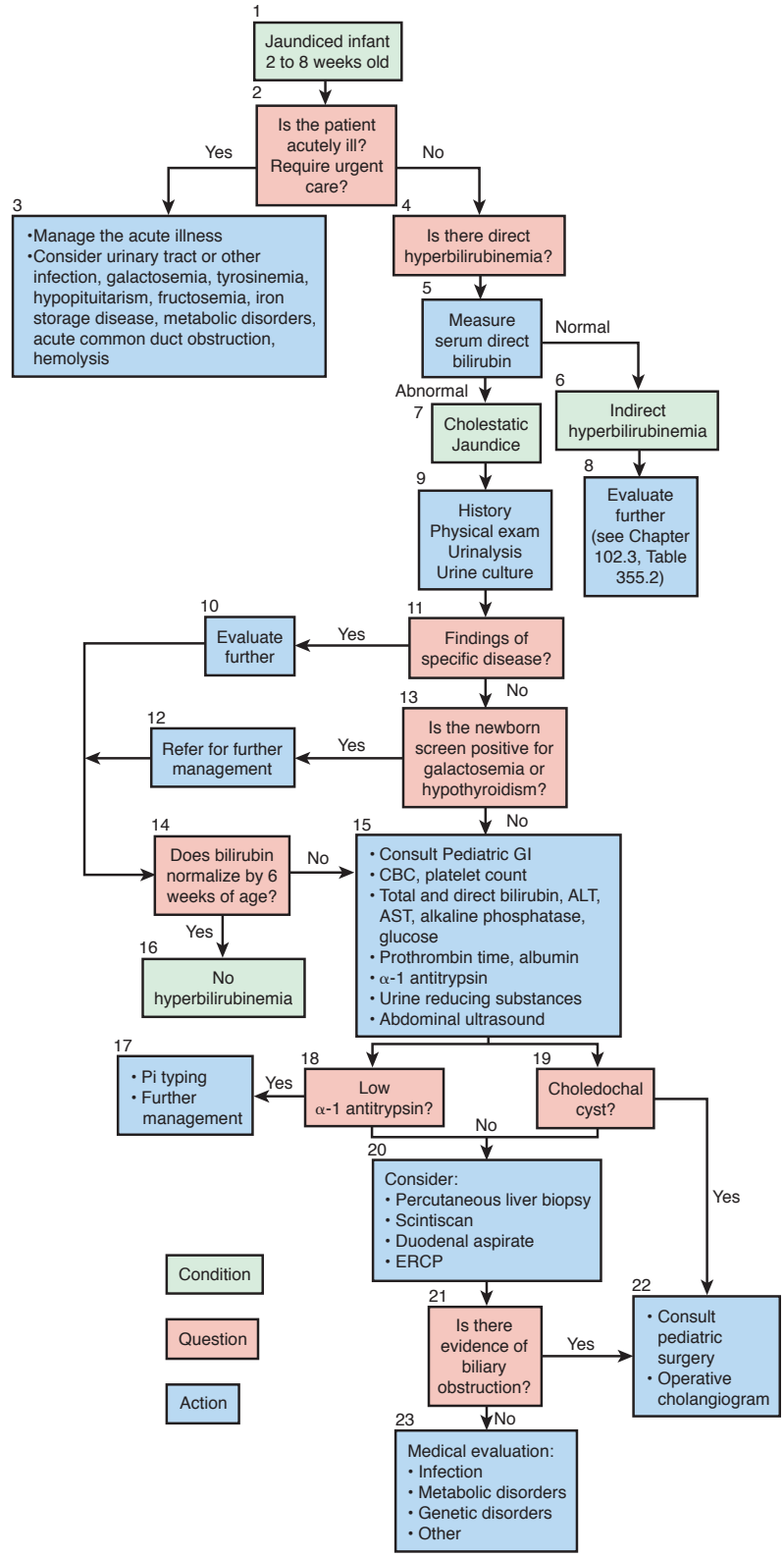


Figure 355-1 Cholestasis clinical practice guideline. Algorithm for a 2-8 wk old. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography. *(From Moyer V, Freese DK, Whitington PF, et al; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition: Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition,* J Pediatr Gastroenterol Nutr *39:115–128, 2004.)*

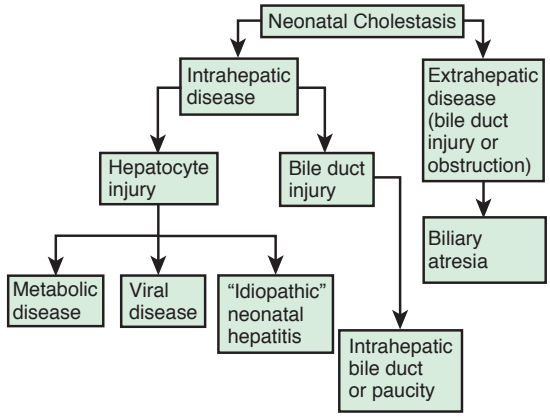


Figure 356-1 Neonatal cholestasis. Conceptual approach to the group of diseases presenting as cholestasis in the neonate. There are areas of overlap: patients with biliary atresia might have some degree of intrahepatic injury. Patients with "idiopathic" neonatal hepatitis might, in the future, be determined to have a primary metabolic or viral disease.

Table 356-1 Proposed Subtypes of Intrahepatic Cholestasis

A. Disorders of membrane transport and secretion
   1. Disorders of canalicular secretion
      a. Bile acid transport: BSEP deficiency
         i. Persistent, progressive (PFIC type 2)
         ii. Recurrent, benign (BRIC type 2)
      b. Phospholipid transport: MDR3 deficiency (PFIC type 3)
      c. Ion transport: cystic fibrosis *(CFTR)*
   2. Complex or multiorgan disorders
      a. FIC1 deficiency
         i. Persistent, progressive (PFIC type 1, Byler disease)
         ii. Recurrent, benign (BRIC type 1)
      b. Neonatal sclerosing cholangitis *(CLDN1)*
      c. Arthrogryposis-renal dysfunction-cholestasis syndrome *(VPS33B)*
B. Disorders of bile acid biosynthesis and conjugation
   1. 3-oxoΔ-4-steroid 5β-reductase deficiency
   2. 3β-hydroxy-5-C_{27}-steroid dehydrogenase/isomerase deficiency
   3. Oxysterol 7α-hydroxylase deficiency
   4. Bile acid-coenzyme A (CoA) ligase deficiency
   5. BAAT deficiency (familial hypercholanemia)
C. Disorders of embryogenesis
   1. Alagille syndrome (Jagged1 defect, syndromic bile duct paucity)
   2. Ductal plate malformation (ARPKD, ADPLD, Caroli disease)
D. Unclassified (idiopathic "neonatal hepatitis"): mechanism unknown

Note: FIC1 deficiency, BSEP deficiency, and some of the disorders of bile acid biosynthesis are characterized clinically by low levels of serum GGT despite the presence of cholestasis. In all other disorders listed, the serum GGT level is elevated.

ADPLD, autosomal dominant polycystic liver disease (cysts in liver only); ARPKD, autosomal recessive polycystic kidney disease (cysts in liver and kidney); BAAT, bile acid transporter; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane regulator; GGT, γ-glutamyl transpeptidase; PFIC, progressive familial intrahepatic cholestasis.

Table 356-2 Value of Specific Tests in the Evaluation of Patients with Suspected Neonatal Cholestasis

TEST	RATIONALE
Serum bilirubin fractionation (i.e., assessment of the serum level of conjugated bilirubin)	Indicates cholestasis
Assessment of stool color (does the baby have pigmented or acholic stools?)	Indicates bile flow into intestine
Urine and serum bile acids measurement	Confirms cholestasis; might indicate inborn error of bile acid biosynthesis
Hepatic synthetic function (albumin, coagulation profile)	Indicates severity of hepatic dysfunction
α_1-Antitrypsin phenotype	Suggests (or excludes) PiZZ
Thyroxine and TSH	Suggests (or excludes) endocrinopathy
Sweat chloride and mutation analysis	Suggests (or excludes) cystic fibrosis
Urine and serum amino acids and urine reducing substances	Suggests (or excludes) metabolic liver disease
Ultrasonography	Suggests (or excludes) choledochal cyst; might detect the triangular cord sign, suggesting biliary atresia
Hepatobiliary scintigraphy	Documents bile duct patency or obstruction
Liver biopsy	Distinguishes biliary atresia; suggests alternative diagnosis

PiZZ, protease inhibitor ZZ phenotype; TSH, thyroid-stimulating hormone

Table 356-3 Molecular Defects Causing Liver Disease

GENE	PROTEIN	FUNCTION, SUBSTRATE	DISORDER
ATP8b1	FIC1	P-type ATPase; aminophospholipid translocase that flips phosphatidylserine and phosphatidylethanolamine from the outer to the inner layer of the canalicular membrane	PFIC 1 (Byler disease), BRIC 1, GFC
ABCB11	BSEP	Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a pump transporting bile acids through the canalicular domain	PFIC 2, BRIC 2
ABCB4	MDR3	Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a phospholipid flippase in canalicular membrane	PFIC 3, ICP, cholelithiasis
AKR1D1	5β-reductase	3-oxoΔ-4-steroid 5β-reductase gene; regulates bile acid synthesis	BAS: neonatal cholestasis with giant cell hepatitis
HSD3B7	C27-3β-HSD	3β-hydroxy-5-C_{27}-steroid oxidoreductase (C27-3β-HSD) gene; regulates bile acid synthesis	BAS: chronic intrahepatic cholestasis
CYP7BI	CYP7BI	Oxysterol 7α-hydroxylase; regulates the acidic pathway of bile acid synthesis	BAS: neonatal cholestasis with giant cell hepatitis
JAG1	JAG1	Transmembrane, cell-surface proteins that interact with Notch receptors to regulate cell fate during embryogenesis	Alagille syndrome
TJP2	Tight junction protein	Belongs to the family of membrane-associated guanylate kinase homologs that are involved in the organization of epithelial and endothelial intercellular junction; regulates paracellular permeability	FHC
BAAT	BAAT	Enzyme that transfers the bile acid moiety from the acyl coenzyme A thioester to either glycine or taurine	FHC
EPHX1	Epoxide hydrolase	Microsomal epoxide hydrolase regulates the activation and detoxification of exogenous chemicals	FHC
ABCC2	MRP2	Canalicular protein with ATP-binding cassette (ABC family of proteins); regulates canalicular transport of GSH conjugates and arsenic	Dubin-Johnson syndrome
ATP7B	ATP7B	P-type ATPase; function as copper export pump	Wilson disease
CLDN1	Claudin 1	Tight junction protein	NSC
CIRH1A	Cirhin	Cell signaling?	NAICC
CFTR	CFTR	Chloride channel with ATP-binding cassette (ABC family of proteins); regulates chloride transport	Cystic fibrosis
PKHD1	Fibrocystin	Protein involved in ciliary function and tubulogenesis	ARPKD
PRKCSH	Hepatocystin	Assembles with glucosidase II α subunit in endoplasmic reticulum	ADPLD
VPS33B	Vascular Protein sorting 33	Regulates fusion of proteins to cellular membrane	ARC

ADPLD, autosomal dominant polycystic liver disease; ARC, arthrogryposis–renal dysfunction–cholestasis syndrome*; ARPKD, autosomal recessive polycystic kidney disease; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; BAAT, bile acid transporter; BAS, bile acid synthetic defect; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane conductance regulator; FHC, familial hypercholanemia; GFC, Greenland familial cholestasis; GSH, glutathione; ICP, intrahepatic cholestasis of pregnancy; NAICC, North American Indian childhood cirrhosis; NSC, neonatal sclerosing cholangitis with ichthyosis, leukocyte vacuoles, and alopecia; PFIC, progressive familial intrahepatic cholestasis*. (*Low γ-glutamyl transpeptidase [PFIC types 1 and 2, BRIC types 1 and 2, ARC].)

Table 356-4 Progressive Familial Intrahepatic Cholestasis

	PFIC 1	PFIC 2	PFIC 3
Transmission	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosome	18q21-22	2q24	7q21
Gene	*ATP8B1/F1C1*	*ABCB11/BSEP*	*ABCB4/MDR3*
Protein	FIC1	BSEP	MDR3
Location	Hepatocyte, colon, intestine, pancreas; on apical membranes	Hepatocyte canalicular membrane	Hepatocyte canalicular membrane
Function	ATP-dependent aminophospholipid flippase; unknown effects on intracellular signaling	ATP-dependent bile acid transport	ATP-dependent phosphatidylcholine translocation
Phenotype	Progressive cholestasis, diarrhea, steatorrhea, growth failure, severe pruritus	Rapidly progressive cholestatic giant cell hepatitis, growth failure, pruritus	Later-onset cholestasis, portal hypertension, minimal pruritus, intraductal and gallbladder lithiasis
Histology	Initial bland cholestatic; coarse, granular canalicular bile on EM	Neonatal giant cell hepatitis, amorphous canalicular bile on EM	Proliferation of bile ductules, periportal fibrosis, eventually biliary cirrhosis
Biochemical features	Normal serum GGT; high serum, low biliary bile acid concentrations	Normal serum GGT; high serum, low biliary bile acid concentrations	Elevated serum GGT; low to absent biliary PC; absent serum LPX; normal biliary bile acid concentrations
Treatment	Biliary diversion, ileal exclusion, liver transplantation, but post-OLT diarrhea, steatorrhea, fatty liver	Biliary diversion, liver transplantation	UDCA if residual PC secretion; liver transplantation

ATP, adenosine triphosphate; BSEP, bile salt export pump; EM, electron microscopy; GGT, γ-glutamyl transpeptidase; LPX, lipoprotein X; OLT, orthotopic liver transplantation; PC, phosphatidylcholine; PFIC, progressive familial intrahepatic cholestasis; UDCA, ursodeoxycholic acid.

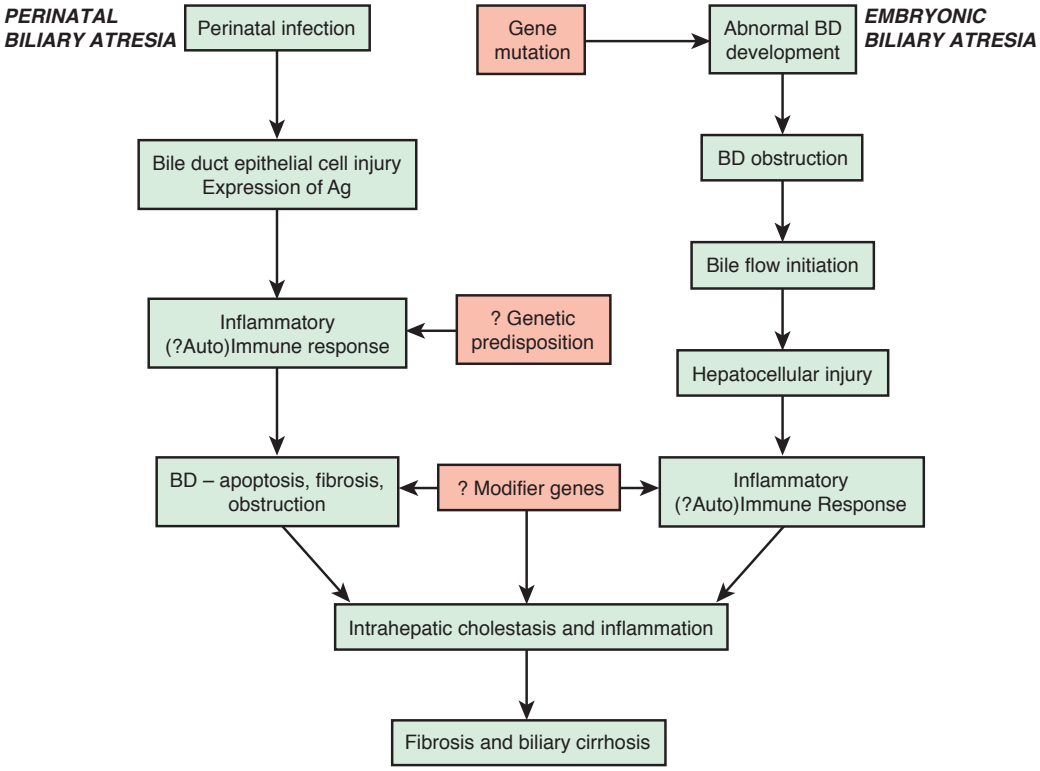


Figure 356-2 Proposed pathways for pathogenesis of 2 forms of biliary atresia (BA). *Perinatal* BA can develop when a perinatal insult, such as a cholangiotropic viral infection, triggers bile duct (BD) epithelial cell injury and exposure of self-antigens or neoantigens that elicit a subsequent immune response. The resulting inflammation induces apoptosis and necrosis of extrahepatic BD epithelium, resulting in fibro-obliteration of the lumen and obstruction of the BD. Intrahepatic bile ducts can also be targets in the ongoing TH1 immune (autoimmune?) attack and the cholestatic injury, resulting in progressive portal fibrosis and culminating in biliary cirrhosis. *Embryonic* BA may be the result of mutations in genes controlling normal bile duct formation or differentiation, which secondarily induces an inflammatory/immune response within the common bile duct and liver after the initiation of bile flow at approximately 11-13 wk of gestation. Secondary hepatocyte and intrahepatic bile duct injury ensue either as a result of cholestatic injury or as targets for the immune (autoimmune?) response that develops. The end result is intrahepatic cholestasis and portal tract fibrosis, culminating in biliary cirrhosis. Other major factors may be the role played by genetic predisposition to autoimmunity and modifier genes that determine the extent and type of cellular and immune response and the generation of fibrosis. *(From Mack CL, Sokol RJ: Unraveling the pathogenesis and etiology of biliary atresia,* Pediatr Res *57:87R–94R, 2005.)*

Table 356-5 Suggested Medical Management of Persistent Cholestasis

CLINICAL IMPAIRMENT	MANAGEMENT
Malnutrition resulting from malabsorption of dietary long-chain triglycerides	Replace with dietary formula or supplements containing medium-chain triglycerides
Fat-soluble vitamin malabsorption:	
Vitamin A deficiency (night blindness, thick skin)	Replace with 10,000-15,000 IU/day as Aquasol A
Vitamin E deficiency (neuromuscular degeneration)	Replace with 50-400 IU/day as oral α-tocopherol or TPGS
Vitamin D deficiency (metabolic bone disease)	Replace with 5,000-8,000 IU/day of D_2 or 3-5 μg/kg/day of 25-hydroxycholecalciferol
Vitamin K deficiency (hypoprothrombinemia)	Replace with 2.5-5.0 mg every other day as water-soluble derivative of menadione
Micronutrient deficiency	Calcium, phosphate, or zinc supplementation
Deficiency of water-soluble vitamins	Supplement with twice the recommended daily allowance
Retention of biliary constituents such as cholesterol (itch or xanthomas)	Administer choleretic bile acids (ursodeoxycholic acid, 15-30 mg/kg/day)
Progressive liver disease; portal hypertension (variceal bleeding, ascites, hypersplenism)	Interim management (control bleeding; salt restriction; spironolactone)
End-stage liver disease (liver failure)	Transplantation

TPGS, D-tocopherol polyethylene glycol 1,000 succinate.

Table 357-1 Inborn Errors of Metabolism That Affect the Liver

DISORDERS OF CARBOHYDRATE METABOLISM
Disorders of galactose metabolism
Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Disorders of fructose metabolism
Hereditary fructose intolerance (aldolase deficiency)
Fructose-1,6 diphosphatase deficiency
Glycogen storage diseases
Type I
Von Gierke Ia (glucose-6-phosphatase deficiency)
Type Ib (glucose-6-phosphatase transport defect)
Type III Cori/Forbes (glycogen debrancher deficiency)
Type IV Andersen (glycogen branching enzyme deficiency)
Type VI Hers (liver phosphorylase deficiency)
Congenital disorders of glycosylation (multiple subtypes)
DISORDERS OF AMINO ACID AND PROTEIN METABOLISM
Disorders of tyrosine metabolism
Hereditary tyrosinemia type I (fumarylacetoacetate deficiency)
Tyrosinemia, type II (tyrosine aminotransferase deficiency)
Inherited urea cycle enzyme defects
CPS deficiency (carbamoyl phosphate synthetase I deficiency)
OTC deficiency (ornithine transcarbamoylase deficiency)
Citrullinemia type I (argininosuccinate synthetase deficiency)
Argininosuccinic aciduria (argininosuccinate deficiency)Argininemia (arginase deficiency)
N-AGS deficiency (*N*-acetylglutamate synthetase deficiency)
Maple serum urine disease (multiple possible defects*)
DISORDERS OF LIPID METABOLISM
Wolman disease (lysosomal acid lipase deficiency)
Cholesteryl ester storage disease (lysosomal acid lipase deficiency)
Homozygous familial hypercholesterolemia (low-density lipoprotein receptor deficiency)
Gaucher disease type I (β-glucocerebrosidase deficiency)
Niemann-Pick type C (NPC 1 and 2 mutations)
DISORDERS OF BILE ACID METABOLISM
Defects in bile acid synthesis
Zellweger syndrome—cerebrohepatorenal (multiple mutations in peroxisome biogenesis genes)
DISORDERS OF METAL METABOLISM
Wilson disease (ATP7B mutations)
Hepatic copper overload
Indian childhood cirrhosis (ICC)
Neonatal iron storage disease
DISORDERS OF BILIRUBIN METABOLISM
Crigler-Najjar (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase mutations)
Type I
Type II
Gilbert disease (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase polymorphism)
Dubin-Johnson syndrome (multiple drug-resistant protein 2 mutation)
Rotor syndrome
MISCELLANEOUS
α_1-Antitrypsin deficiency
Citrullinemia type II (citrin deficiency)
Cystic fibrosis (cystic fibrosis transmembrane conductance regulator mutations)
Erythropoietic protoporphyria (ferrochelatase deficiency)
Polycystic kidney disease

*Maple syrup urine disease can be caused by mutations in branched-chain α-keto dehydrogenase, keto acid decarboxylase, lipoamide dehydrogenase, or dihydrolipoamide dehydrogenase.

Table 358-2 Causes and Differential Diagnosis of Hepatitis in Children

INFECTIOUS
Hepatotropic viruses
• HAV
• HBV
• HCV
• HDV
• HEV
• Hepatitis non–A-E viruses
Systemic infection that can include hepatitis
• Adenovirus
• Arbovirus
• Coxsackievirus
• Cytomegalovirus
• Enterovirus
• Epstein-Barr virus
• "Exotic" viruses (e.g., yellow fever)
• Herpes simplex virus
• Human immunodeficiency virus
• Paramyxovirus
• Rubella
• Varicella zoster
Other
NONVIRAL LIVER INFECTIONS
Abscess
Amebiasis
Bacterial sepsis
Brucellosis
Fitz-Hugh-Curtis syndrome
Histoplasmosis
Leptospirosis
Tuberculosis
Other
AUTOIMMUNE
Autoimmune hepatitis
Sclerosing cholangitis
Other (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis)
METABOLIC
α_1-Antitrypsin deficiency
Tyrosinemia
Wilson disease
Other
TOXIC
Iatrogenic or drug induced (e.g., acetaminophen)
Environmental (e.g., pesticides)
ANATOMIC
Choledochal cyst
Biliary atresia
Other
HEMODYNAMIC
Shock
Congestive heart failure
Budd-Chiari syndrome
Other
NONALCOHOLIC FATTY LIVER DISEASE
Idiopathic
Reye syndrome
Other

Table 357-2	Clinical Manifestations That Suggest the Possibility of Metabolic Disease
Recurrent vomiting, failure to thrive, short stature	
Dysmorphic features	
Jaundice, hepatomegaly (±splenomegaly), fulminant hepatic failure, edema/anasarca	
Hypoglycemia, organic acidemia, lactic acidemia, hyperammonemia, bleeding (coagulopathy)	
Developmental delay/psychomotor retardation, hypotonia, progressive neuromuscular deterioration, seizures, myopathy, neuropathy	
Cardiac dysfunction/failure	
Unusual odors	
Rickets	
Cataracts	

Table 358-1 Features of the Hepatotropic Viruses

VIROLOGY	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Incubation (days)	15-19	60-180	14-160	21-42	21-63
Transmission					
• Parenteral	Rare	Yes	Yes	Yes	No
• Fecal–oral	Yes	No	No	No	Yes
• Sexual	No	Yes	Yes	Yes	No
• Perinatal	No	Yes	Rare	Yes	No
Chronic infection	No	Yes	Yes	Yes	No
Fulminant disease	Rare	Yes	Rare	Yes	Yes

Table 358-3 Diagnostic Blood Tests: Serology and Viral PCR

HAV	HBV	HCV	HDV	HEV
ACUTE/ACTIVE INFECTION				
Anti-HAV IgM(+) Blood PCR positive*	Anti-HBc IgM(+) HBsAg(+) Anti-HBs(–) HBV DNA(+) (PCR)	Anti-HCV(+) HCV RNA(+) (PCR)	Anti-HDV IgM(+) Blood PCR positive HBsAg(+) Anti-HBs(–)	Anti-HEV IgM(+) Blood PCR positive
PAST INFECTION (RECOVERED)				
Anti-HAV IgG(+)	Anti-HBs(+) Anti-HBc IgG(+)	Anti-HCV(–) Blood PCR(–)	Anti-HDV IgG(+) Blood PCR (–)	Anti-HEV IgG(+) Blood PCR(–)
CHRONIC INFECTION				
N/A	Anti-HBc IgG(+) HBsAg(+) Anti-HBs(–) PCR (+)or (–)	Anti-HCV(+) Blood PCR (+)	Anti-HDV IgG(+) Blood PCR (–) HBsAg(+) Anti-HBs(–)	N/A
VACCINE RESPONSE				
Anti-HAV IgG(+)	Anti-HBs(+) Anti-HBc(–)	N/A	N/A	N/A

*Research tool.
HAV, hepatitis A virus; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; PCR, polymerase chain reaction.

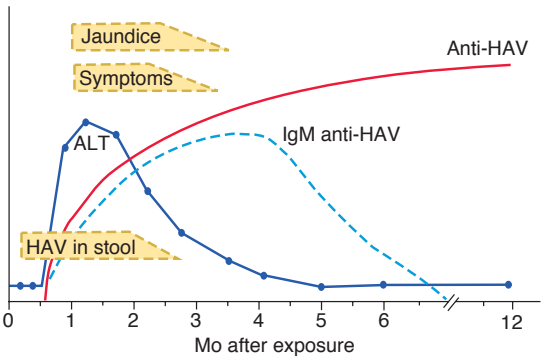


Figure 358-1 The serologic course of acute hepatitis A. *ALT*, alanine aminotransferase; *HAV*, hepatitis A virus. *(From Goldman L, Ausiello D: Cecil textbook of medicine, ed 22, Philadelphia, 2004, WB Saunders, p 913.)*

Table 358-4 Hepatitis A Virus Prophylaxis

PREEXPOSURE PROPHYLAXIS (TRAVELERS TO ENDEMIC REGIONS)		
AGE	**EXPECTED EXPOSURE DURATION**	**DOSE**
<1 year of age	<3 months 3-5 months Long term (>5months)	Ig 0.02 mL/kg Ig 0.06 mL/kg Ig 0.06 mL/kg at departure and every 5 mo thereafter
≥1 year of age	Healthy host Immunocompromised host, or one with chronic liver disease or chronic health problems	HAV vaccine HAV vaccine and Ig 0.02 mL/kg
POSTEXPOSURE PROPHYLAXIS*		
EXPOSURE	**RECOMMENDATIONS**	
≤2 wk since exposure	<1 year-old: Ig 0.02 mL/kg Immunocompromised host, or host with chronic liver disease or chronic health problems: Ig 0.02 mL/kg and HAV vaccine >1 year and healthy host: HAV vaccine, Ig remains optional Sporadic non–household or close contact exposure: prophylaxis not indicated*	
>2 wk since exposure	None	

*Decision for prophylaxis in nonhousehold contacts should be tailored to individual exposure and risk. Ig, Immunoglubulin.

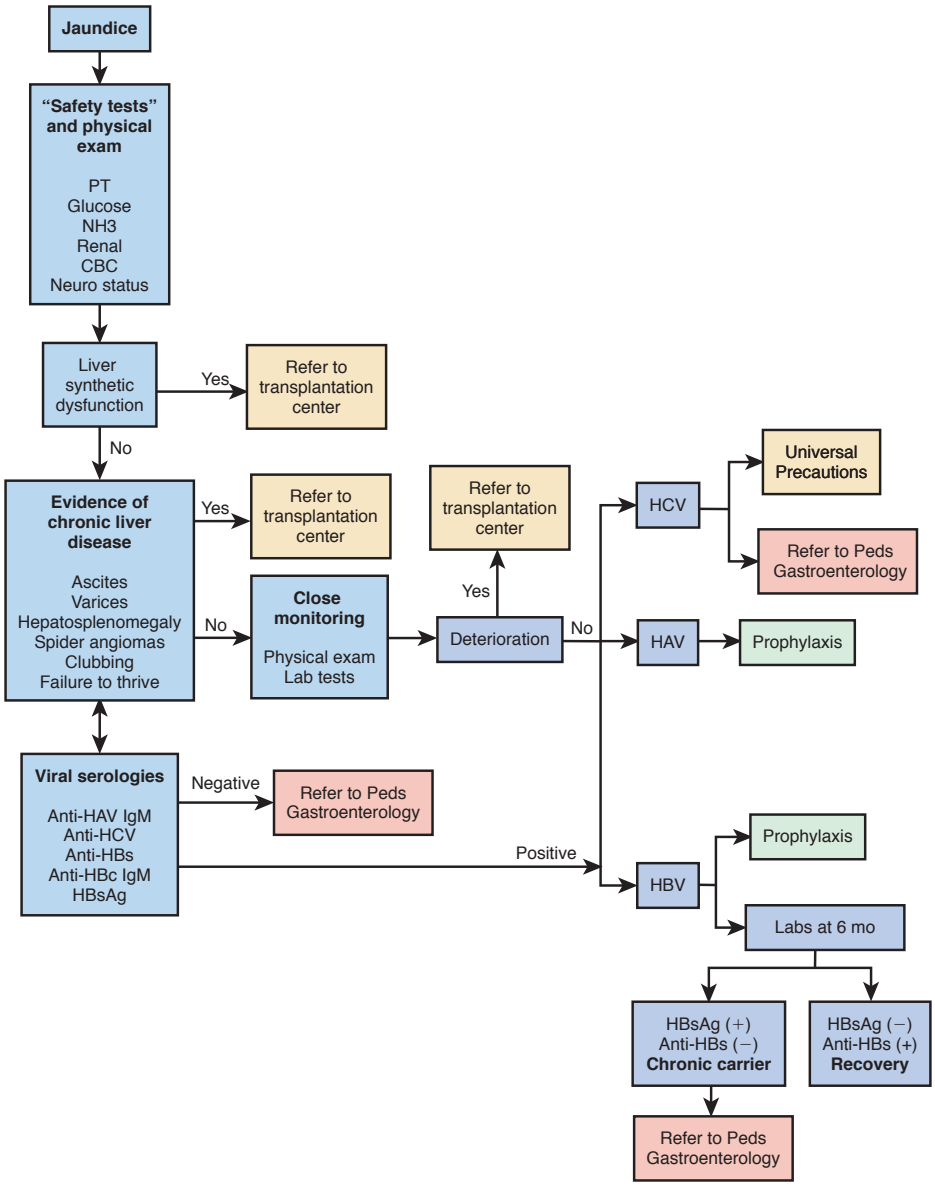


Figure 358-6 Clinical approach to viral hepatitis. *CBC*, complete blood count with differential; *HAV*, hepatitis A virus; *HBs*, hepatitis B surface; *HBsAg*, hepatitis B surface antigen; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *IgM*, immunoglobulin M; NH_3, ammonia; *PT*, prothrombin time.

Table 361-2 Genotypic Classification of Primary Mitochondrial Hepatopathies and Organ Involvement

GENE	RESPIRATORY CHAIN COMPLEX	HEPATIC HISTOLOGY	OTHER ORGANS INVOLVED	CLINICAL FEATURES
Deletion	Multiple (Pearson)	Steatosis, fibrosis	Kidney, heart, CNS, muscle	Sideroblastic anemia, variable thrombocytopenia and neutropenia, persistent diarrhea
MPV17	I, III, IV	Steatosis	CNS, muscle, gastrointestinal tract	Adult-onset multisystemic involvement: myopathy, ophthalmoplegia, severe constipation, parkinsonism
DGUOK	I, III, IV	Steatosis, fibrosis	Kidneys, CNS, muscle	Nystagmus, hypotonia, renal Fanconi syndrome, acidosis
MPV17	I, III, IV	Steatosis, fibrosis	CNS, PNS	Hypotonia
SUCLG1	I, III, IV	Steatosis	Kidneys, CNS, muscle	Myopathy, sensorineural hearing loss, respiratory failure
POLG1	I, III, IV	Steatosis, fibrosis	CNS, muscle	Liver failure preceded by neurologic symptoms, intractable seizures, ataxia, psychomotor regression
C10orf2/Twinkle	I, III, IV	Steatosis	CNS, muscle	Infantile-onset spinocerebellar ataxia, loss of skills
BCS1L	III (GRACILE)		CNS ±, muscle ±, kidneys	Fanconi-type renal tubulopathy
SCO1	IV	Steatosis, fibrosis	Muscle	
TRMU	I, III, IV	Steatosis, fibrosis		Infantile liver failure with subsequent recovery
EFG1	I, III, IV	Steatosis	CNS	Severe, rapidly progressive encephalopathy
EFTu	I, III, IV	Unknown	CNS	Severe lactic acidosis, rapidly fatal encephalopathy

CNS, central nervous system; *GRACILE*, growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death; *PNS*, peripheral nervous system.

Table 361-3 Clinical Staging of Reye Syndrome and Reye-Like Diseases

Symptoms at the time of admission:
I. Usually quiet, **lethargic** and sleepy, vomiting, laboratory evidence of liver dysfunction
II. Deep lethargy, **confusion,** delirium, combativeness, hyperventilation, hyperreflexia
III. Obtunded, **light coma** ± seizures, **decorticate** rigidity, intact pupillary light reaction
IV. Seizures, deepening coma, **decerebrate rigidity,** loss of oculocephalic reflexes, fixed pupils
V. Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, **flaccidity/decerebration** (intermittent); isoelectric electroencephalogram

Table 361-4 Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome

Metabolic disease
- Organic aciduria
- Disorders of oxidative phosphorylation
- Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)
- Defects in fatty acid oxidation metabolism
- Acyl–coenzyme A dehydrogenase deficiencies
- Systemic carnitine deficiency
- Hepatic carnitine palmitoyltransferase deficiency
- 3-OH, 3-methylglutaryl-coenzyme A lyase deficiency
- Fructosemia

Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy
Hemorrhagic shock with encephalopathy
Drug or toxin ingestion (salicylate, valproate)

Table 361-1 Classification of Primary Mitochondrial Hepatopathies

Respiratory chain (electron transport) defects (oxidative phosphorylation)
Neonatal liver failure
Complex I deficiency
Complex IV deficiency (*SCO1* mutations)
Complex III deficiency (*BCS1L* mutations)
Coenzyme Q deficiency
Multiple complex deficiencies (transfer and elongation factor mutations)
mtDNA depletion syndrome (*DUGOK*, *MPV17*, *POLG*, *SUCLG1*, *C10orf2/Twinkle* mutations)
Later-onset liver dysfunction or failure
Alpers-Huttenlocher disease (*POLG* mutations)
Pearson marrow-pancreas syndrome (mtDNA deletion)
Mitochondrial neurogastrointestinal encephalopathy (*TYMP* mutations)
Navajo neurohepatopathy (*MPV17* mutations)
Fatty acid oxidation defects
Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase
Carnitine palmitoyltransferases I and II deficiencies
Carnitine–acylcarnitine translocase deficiency
Urea cycle enzyme deficiencies
Electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase deficiencies
Phosphoenolpyruvate carboxykinase (mitochondrial) deficiency; nonketotic hyperglycemia
Citrin deficiency; neonatal intrahepatic cholestasis caused by citrin deficiency (*SLC25A13* mutations)

Table 362-1 Disorders Producing Chronic Hepatitis

Chronic viral hepatitis
- Hepatitis B
- Hepatitis C
- Hepatitis D

Autoimmune hepatitis
- Anti-actin antibody positive
- Anti–liver-kidney microsomal antibody positive
- Anti-soluble liver antigen antibody-positive
- Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein)
- Overlap syndrome with sclerosing cholangitis and autoantibodies
- Systemic lupus erythematosus
- Celiac disease

Drug-induced hepatitis
Metabolic disorders associated with chronic liver disease
- Wilson disease
- Nonalcoholic steatohepatitis
- α_1-Antitrypsin deficiency
- Tyrosinemia
- Niemann-Pick disease type 2
- Glycogen storage disease type iv
- Cystic fibrosis
- Galactosemia
- Bile acid biosynthetic abnormalities

Table 370-1 Causes of Ascites

HEPATIC
Cirrhosis
Congenital hepatic fibrosis
Portal vein obstruction
Fulminant hepatic failure
Budd-Chiari syndrome
Lysosomal storage disease
RENAL
Nephrotic syndrome
Obstructive uropathy
Perforation of urinary tract
Peritoneal dialysis
CARDIAC
Heart failure
Constrictive pericarditis
Inferior vena cava web
INFECTIOUS
Abscess
Tuberculosis
Chlamydia
Schistosomiasis
GASTROINTESTINAL
Infarcted bowel
Perforation
Protein-losing enteropathy
NEOPLASTIC
Lymphoma
Neuroblastoma
GYNECOLOGIC
Ovarian tumors
Ovarian torsion, rupture
PANCREATIC
Pancreatitis
Ruptured pancreatic duct
MISCELLANEOUS
Systemic lupus erythematosus
Autoinflammatory recurrent fever syndromes
Ventriculoperitoneal shunt
Eosinophilic ascites
Chylous ascites
Hypothyroidism

Table 363-1 Patterns of Hepatic Drug Injury

DISEASE	DRUG
Centrilobular necrosis	Acetaminophen Halothane
Microvesicular steatosis	Valproic acid
Acute hepatitis	Isoniazid
General hypersensitivity	Sulfonamides Phenytoin
Fibrosis	Methotrexate
Cholestasis	Chlorpromazine Erythromycin Estrogens
Sinusoidal obstruction syndrome (venoocclusive disease)	Irradiation plus busulfan Cyclophosphamide
Portal and hepatic vein thrombosis	Estrogens Androgens
Biliary sludge	Ceftriaxone
Hepatic adenoma or hepatocellular carcinoma	Oral contraceptives Anabolic steroids

Table 363-2 Potentially Hepatotoxic Herbal or Dietary Supplements

Celandine
Chaparral (creosote bush, greasewood, *Larrea tridentata*)
Chinese herbs
Comfrey leaves (pyrrolizidine alkaloids)
Germander extracts *(Teucrium chamaedrys)*
Kava (*Kava kava*, awa, kew)
LipoKinetix (phenylpropanolamine, sodium usinate, diiodothyronine, yohimbine, caffeine)
Ma huang *(Ephedra)*
Mushroom *(Amanita phalloides, Galerina)*
Senecio
Valerian with skullcap

Table 367-1 Causes of Portal Hypertension

EXTRAHEPATIC PORTAL HYPERTENSION
Portal vein agenesis, atresia, stenosis
Portal vein thrombosis or cavernous transformation
Splenic vein thrombosis
Increased portal flow
Arteriovenous fistula
INTRAHEPATIC PORTAL HYPERTENSION
Hepatocellular disease
Acute and chronic viral hepatitis
Cirrhosis
Congenital hepatic fibrosis
Wilson disease
α_1-Antitrypsin deficiency
Glycogen storage disease type IV
Hepatotoxicity
Methotrexate
Parenteral nutrition
Biliary tract disease
Extrahepatic biliary atresia
Cystic fibrosis
Choledochal cyst
Sclerosing cholangitis
Intrahepatic bile duct paucity
Idiopathic portal hypertension
Postsinusoidal obstruction
Budd-Chiari syndrome
Venoocclusive disease

Table 365-1 Renal Disorders Associated with Fibropolycystic Liver Diseases

FIBROPOLYCYSTIC LIVER DISEASE	ASSOCIATED RENAL DISORDER
Congenital hepatic fibrosis (CHF)	Autosomal-recessive polycystic kidney disease* Autosomal-dominant polycystic kidney disease Cystic renal dysplasia Nephronophthisis None
Caroli syndrome (CS)	Autosomal-recessive polycystic kidney disease* Autosomal-dominant polycystic kidney disease None
Caroli disease	Autosomal-recessive polycystic kidney disease
von Meyenburg complexes (isolated)	?
von Meyenburg complexes with CHF or CS	Autosomal-recessive polycystic kidney disease
von Meyenburg complexes with polycystic liver disease	Autosomal-dominant polycystic kidney disease
Polycystic liver disease	Autosomal-dominant polycystic kidney disease* ? None

*Most common associated disorders.

Table 365-2 Syndromes Associated with Congenital Hepatic Fibrosis

SYNDROME	FEATURES
Jeune syndrome	Asphyxiating thoracic dystrophy, with cystic renal tubular dysplasia and congenital hepatic fibrosis (15q13)
Joubert syndrome	Oculo-encephalo-hepato-renal *(AH11, HPHP1)*
COACH syndrome	Cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis *(MKS3, CC2D2A, RPGRIP1L)*
Meckel syndrome type 1	Cystic renal dysplasia abnormal bile duct development with fibrosis, posterior encephalocele, and polydactyly (13q13, 17a21, 8q24)
Carbohydrate-deficient glycoprotein syndrome type 1b	Phosphomannose isomerase 1 deficiency (PMI)
Ivemark syndrome type 2	Autosomal-recessive renal-hepatic-pancreatic dysplasia
Miscellaneous syndromes	Intestinal lymphangiectasia, enterocolitis cystic Short rib (Beemer-Langer) syndrome Osteochondrodysplasia

From Suchy FJ, Sokol RJ, Balistreri WF, editors: Liver disease in children, *ed 3, New York, 2007, Cambridge University Press, p. 931.*

Table 364-1 Stages of Hepatic Encephalopathy

	STAGES			
	I	II	III	IV
Symptoms	Periods of lethargy, euphoria; reversal of day–night sleeping; may be alert	Drowsiness, inappropriate behavior, agitation, wide mood swings, disorientation	Stupor but arousable, confused, incoherent speech	Coma IVa responds to noxious stimuli IVb no response
Signs	Trouble drawing figures, performing mental tasks	Asterixis, fetor hepaticus, incontinence	Asterixis, hyperreflexia, extensor reflexes, rigidity	Areflexia, no asterixis, flaccidity
Electroencephalogram	Normal	Generalized slowing, q waves	Markedly abnormal, triphasic waves	Markedly abnormal bilateral slowing, d waves, electric-cortical silence

Table 366-1 Conditions Associated with Hydrops of the Gallbladder

Kawasaki disease
Streptococcal pharyngitis
Staphylococcal infection
Leptospirosis
Ascariasis
Threadworm
Sickle cell crisis
Typhoid fever
Thalassemia
Total parenteral nutrition
Prolonged fasting
Viral hepatitis
Sepsis
Henoch-Schönlein purpura
Mesenteric adenitis
Necrotizing enterocolitis

Table 366-2 Conditions Associated with Cholelithiasis

Biliary dyskinesia
Chronic hemolytic disease (sickle cell anemia, spherocytosis, thalassemia, Gilbert disease)
Ileal resection or disease
Cystic fibrosis
Cirrhosis
Cholestasis
Crohn disease
Obesity
Insulin resistance
Prolonged parenteral nutrition
Prematurity with complicated medical or surgical course
Prolonged fasting or rapid weight reduction
Treatment of childhood cancer
Abdominal surgery
Pregnancy
Sepsis
Genetic *(ABCB4, ABCG5/G8)* progressive familial intrahepatic cholestasis
Cephalosporins

Respiratory System

Table 374-1	Lung Sound Nomenclature
TYPE	**SOUND**
DISCONTINUOUS	
Fine (high pitch, low amplitude, short duration)	Fine crackles/rales
Coarse (low pitch, high amplitude, long duration)	Coarse crackles
CONTINUOUS	
High pitch	Wheezes
Low pitch	Rhonchi

Table 374-2	Nonpulmonary Diseases Associated with Clubbing
CARDIAC	
Cyanotic congenital heart disease	
Subacute bacterial endocarditis	
Chronic congestive heart failure	
HEMATOLOGIC	
Thalassemia	
Congenital methemoglobinemia (rare)	
GASTROINTESTINAL	
Crohn disease	
Ulcerative colitis	
Celiac disease	
Chronic dysentery, sprue	
Polyposis coli	
Severe gastrointestinal hemorrhage	
Small bowel lymphoma	
Liver cirrhosis (including α_1-antitrypsin deficiency)	
OTHER	
Thyroid deficiency (thyroid acropachy)	
Chronic pyelonephritis (rare)	
Toxic (e.g., arsenic, mercury, beryllium)	
Lymphomatoid granulomatosis	
Fabry disease	
Raynaud disease, scleroderma	
Familial	
UNILATERAL CLUBBING	
Vascular disorders (e.g., subclavian arterial aneurysm, brachial arteriovenous fistula)	
Subluxation of shoulder	
Median nerve injury	
Local trauma	

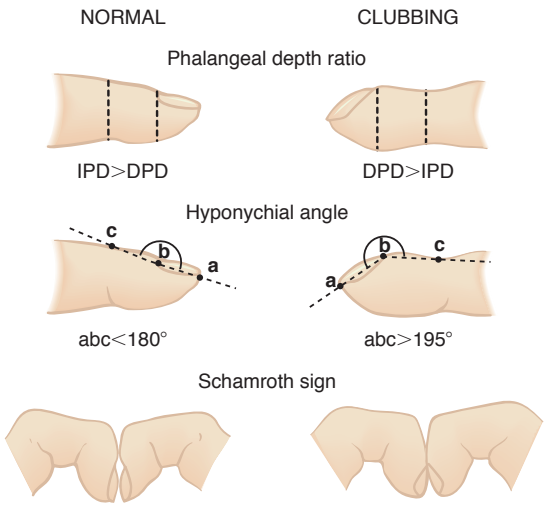


Figure 374-1 Finger clubbing can be measured in different ways. The ratio of the distal phalangeal diameter (DPD) over the interphalangeal diameter (IPD), or the phalangeal depth ratio, is <1 in normal subjects but increases to >1 with finger clubbing. The DPD/IPD can be measured with calipers or, more accurately, with finger casts. The hyponychial angle can be measured from lateral projections of the finger contour on a magnifying screen and is usually <180 degrees in normal subjects but >195 degrees in patients with finger clubbing. For bedside clinical assessment, the Schamroth sign is useful. The dorsal surfaces of the terminal phalanges of similar fingers are placed together. With clubbing, the normal diamond-shaped aperture or "window" at the bases of the nail beds disappears, and a prominent distal angle forms between the ends of the nails. In normal subjects, this angle is minimal or nonexistent. *(From Pasterkamp H: The history and physical examination. In Wilmott RW, Boat TF, Bush A, et al, editors:* Kendig and Chernick's disorders of the respiratory tract in children, *ed 8, Philadelphia, 2012, Elsevier.)*

Table 375-5	Environmental Factors Associated with Increased Risk for Sudden Infant Death Syndrome
MATERNAL AND ANTENATAL RISK FACTORS	
Elevated 2nd trimester serum α-fetoprotein	
Smoking	
Alcohol use	
Drug use (cocaine, heroin)	
Nutritional deficiency	
Inadequate prenatal care	
Low socioeconomic status	
Younger age	
Lower education	
Single marital status	
Shorter interpregnancy interval	
Intrauterine hypoxia	
Fetal growth restriction	
INFANT RISK FACTORS	
Age (peak 2-4 mo, but may be decreasing)	
Male gender	
Race and ethnicity (African-American and Native American, other minorities)	
Growth failure	
No breast-feeding	
No pacifier (dummy)	
Prematurity	
Prone and side sleep position	
Recent febrile illness (mild infections)	
Inadequate immunizations	
Smoking exposure (prenatal and postnatal)	
Soft sleeping surface, soft bedding	
Bed sharing with parent(s) or other children	
Thermal stress, overheating	
Colder season, no central heating	

Table 375-1 Differential Diagnosis of Sudden Unexpected Infant Death

CAUSE OF DEATH	PRIMARY DIAGNOSTIC CRITERIA	CONFOUNDING FACTOR(S)	FREQUENCY DISTRIBUTION (%)
EXPLAINED AT AUTOPSY			
Natural			18-20*
Infections	History, autopsy, and cultures	If minimal findings: SIDS	35-46†
Congenital anomaly	History and autopsy	If minimal findings: SIDS	14-24†
Unintentional injury	History, scene investigation, autopsy	Traumatic child abuse	15*
Traumatic child abuse	Autopsy and scene investigation	Unintentional injury	13-24*
Other natural causes	History and autopsy	If minimal findings: SIDS, or intentional suffocation	12-17*
UNEXPLAINED AT AUTOPSY			
SIDS	History, scene investigation, absence of explainable cause at autopsy	Intentional suffocation	80-82%
Intentional suffocation (filicide)	Perpetrator confession, absence of explainable cause at autopsy	SIDS	Unknown, but <5% of all SUID
Accidental suffocation or strangulation in bed (ASSB)	History and scene investigation, ideally including doll re-enactment	Assigned to ICD-10 code (SIDS) for U.S. vital statistics database Unexplained Undetermined	Varies with individual medical examiners and coroners

*As a percentage of all sudden unexpected infant deaths explained at autopsy.
†As a percentage of all natural causes of sudden unexpected infant deaths explained at autopsy.
ICD-10, International Classification of Diseases, Version 10; SIDS, sudden infant death syndrome; SUDI, sudden unexpected death in infancy.
Adapted from Hunt CE: Sudden infant death syndrome and other causes of infant mortality: diagnosis, mechanisms and risk for recurrence in siblings, Am J Respir Crit Care Med *164:346–357, 2001.*

Table 375-2 Conditions That Can Cause Apparent Life-Threatening Events or Sudden Unexpected Infant Death

CENTRAL NERVOUS SYSTEM Arteriovenous malformation Subdural hematoma Seizures Congenital central hypoventilation Neuromuscular disorders (Werdnig-Hoffmann disease) Chiari crisis Leigh syndrome	INFECTION Sepsis Meningitis Encephalitis Brain abscess Pyelonephritis Bronchiolitis (respiratory syncytial virus) Infant botulism Pertussis
CARDIAC Subendocardial fibroelastosis Aortic stenosis Anomalous coronary artery Myocarditis Cardiomyopathy Arrhythmias (prolonged Q-T syndrome, Wolff-Parkinson-White syndrome, congenital heart block)	TRAUMA Child abuse Accidental or intentional suffocation Physical trauma Factitious syndrome (formerly Munchausen syndrome) by proxy
PULMONARY Pulmonary hypertension Vocal cord paralysis Aspiration Laryngotracheal disease	POISONING (INTENTIONAL OR UNINTENTIONAL) Boric acid Carbon monoxide Salicylates Barbiturates Ipecac Cocaine Insulin Others
GASTROINTESTINAL Diarrhea and/or dehydration Gastroesophageal reflux Volvulus	
ENDOCRINE–METABOLIC Congenital adrenal hyperplasia Malignant hyperpyrexia Long- or medium-chain acyl coenzyme A deficiency Hyperammonemias (urea cycle enzyme deficiencies) Glutaric aciduria Carnitine deficiency (systemic or secondary) Glycogen storage disease type I Maple syrup urine disease Congenital lactic acidosis Biotinidase deficiency	

Table 375-3 Differential Diagnosis of Recurrent Sudden Infant Death in a Sibship

IDIOPATHIC
Recurrent sudden infant death syndrome
CENTRAL NERVOUS SYSTEM
Congenital central hypoventilation
Neuromuscular disorders
Leigh syndrome
CARDIAC
Endocardial fibroelastosis
Wolff-Parkinson-White syndrome
Prolonged Q-T syndrome or other cardiac channelopathy
Congenital heart block
PULMONARY
Pulmonary hypertension
ENDOCRINE–METABOLIC
See Table 375-2
INFECTION
Disorders of immune host defense
CHILD ABUSE
Filicide or infanticide
Factitious syndrome (formerly Munchausen syndrome) by proxy

Table 377-1 Possible Causes of Epistaxis

Epistaxis digitorum (nose picking)
Rhinitis (allergic or viral)
Chronic sinusitis
Foreign bodies
Intranasal neoplasm or polyps
Irritants (e.g., cigarette smoke)
Septal deviation
Septal perforation
Trauma including child abuse
Vascular malformation or telangiectasia (hereditary hemorrhage telangiectasia)
Hemophilia
von Willebrand disease
Platelet dysfunction
Thrombocytopenia
Hypertension
Leukemia
Liver disease (e.g., cirrhosis)
Medications (e.g., aspirin, anticoagulants, nonsteroidal antiinflammatory drugs, topical corticosteroids)
Cocaine abuse

Table 375-4 Identified Genes for Which the Distribution of Polymorphisms Differs in Sudden Infant Death Syndrome Infants Compared to Control Infants

CARDIAC CHANNELOPATHIES (11)
Potassium ion channel genes *(KCNE2, KCNH2, KCNQ1, KCNJ8)*
Sodium ion channel gene *(SCN5A)* (long QT syndrome 3, Brugada syndrome)
GPD1-L-encoded connexin43 (Brugada syndrome)
SCN3B (Brugada syndrome)
CAV3 (long QT syndrome 9)
SCN4B (long QT syndrome 10)
SNTA-1 (long QT syndrome 11)
RyR2 (catecholaminergic polymorphic ventricular tachycardia)
SEROTONIN (5-HT) (3)
5-HT transporter protein *(5-HTT)*
Intron 2 of *SLC6A4* (variable number tandem repeat [VNTR] polymorphism)
5-HT fifth Ewing variant (FEV) gene
GENES PERTINENT TO DEVELOPMENT OF AUTONOMIC NERVOUS SYSTEM (9)
Paired-like homeobox 2a *(PHOX2A)*
PHOX2B
Rearranged during transfection factor *(RET)*
Endothelin converting enzyme-1 *(ECE1)*
T-cell leukemia homeobox *(TLX3)*
Engrailed-1 *(EN1)*
Tyrosine hydroxylase *(THO1)*
Monamine oxidase A *(MAOA)*
Sodium/proton exchanger 3 *(NHE3)* (medullary respiratory control)
INFECTION AND INFLAMMATION (8)
Complement C4A
Complement C4B
Interleukin-1RN (gene encoding IL-1 receptor antagonist [ra]; proinflammatory)
Interleukin-6 (IL-6; proinflammatory)
Interleukin-8 (IL-8; proinflammatory; associated with prone sleeping position)
Interleukin-10 (IL-10)
Vascular endothelial growth factor (VEGF) (proinflammatory)
Tumor necrosis factor (TNF)-α (proinflammatory)
OTHER (3)
Mitochondrial DNA (mtDNA) polymorphisms (energy production)
Flavin-monooxygenase 3 (*FMO3*) (enzyme metabolizes nicotine; risk factor with smoking mothers)
Aquaporin-4 (T allele and CT/TT genotype associated with maternal smoking and with increased brain/body weight ratio in SIDS infants)

Table 381-1 Infectious Agents That Cause Pharyngitis

VIRUSES	BACTERIA
Adenovirus	*Streptococcus pyogenes* (Group A streptococcus)
Coronavirus	*Arcanobacterium haemolyticum*
Cytomegalovirus	*Fusobacterium necrophorum*
Epstein-Barr virus	*Corynebacterium diphtheriae*
Enteroviruses	*Neisseria gonorrhoeae*
Herpes simplex virus	Group C streptococci
Human immunodeficiency virus	Group G streptococci
Human metapneumovirus	*Francisella tularensis*
Influenza viruses	*Chlamydophila pneumoniae*
Measles virus	*Chlamydia trachomatis*
Parainfluenza viruses	*Mycoplasma pneumoniae*
Respiratory syncytial virus	
Rhinoviruses	

Table 379-1 Pathogens Associated with the Common Cold

ASSOCIATION	PATHOGEN	RELATIVE FREQUENCY*	OTHER COMMON SYMPTOMS AND SIGNS
Agents primarily associated with the common cold	Human rhinoviruses	Frequent	Wheezing/bronchiolitis
	Coronaviruses	Occasional	
Agents primarily associated with other clinical syndromes that also cause common cold symptoms	Respiratory syncytial viruses	Occasional	Bronchiolitis in children <2 yr of age
	Human metapneumovirus	Occasional	Pneumonia and bronchiolitis
	Influenza viruses	Uncommon	Influenza, pneumonia, croup
	Parainfluenza viruses	Uncommon	Croup, bronchiolitis
	Adenoviruses	Uncommon	Pharyngoconjunctival fever (palpebral conjunctivitis, watery eye discharge, pharyngeal erythema)
	Enteroviruses Coxsackievirus A Other nonpolio enteroviruses	Uncommon	Herpangina (fever and ulcerated papules on posterior oropharynx Aseptic meningitis

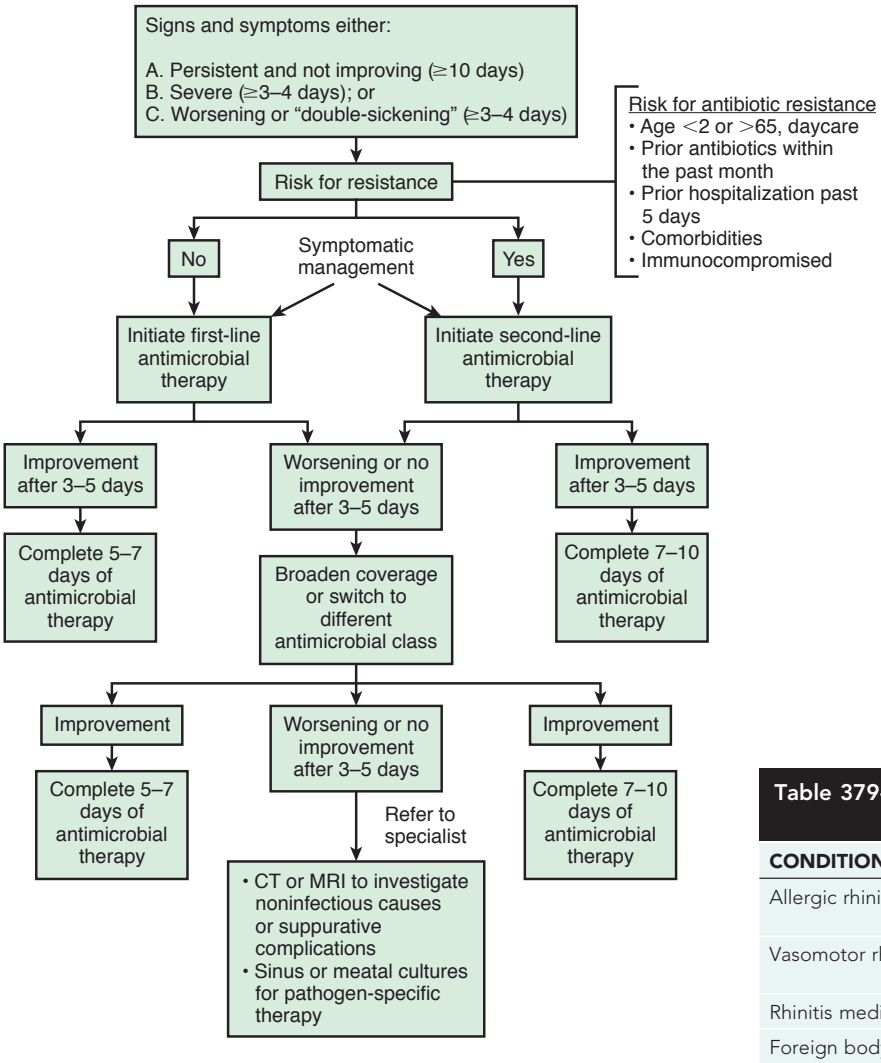


Figure 380-1 Algorithm for the management of acute bacterial rhinosinusitis. *(From Chow AW, Benninger MS, Brook I, et al: Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults.* Clin Infect Dis *54(8):e72–e112, 2012, Fig. 1.)*

Table 379-2 Conditions That Can Mimic the Common Cold

CONDITION	DIFFERENTIATING FEATURES
Allergic rhinitis	Prominent itching and sneezing, nasal eosinophils
Vasomotor rhinitis	May be triggered by irritants, weather changes, spicy foods, etc.
Rhinitis medicamentosa	History of nasal decongestant use
Foreign body	Unilateral, foul-smelling secretions Bloody nasal secretions
Sinusitis	Presence of fever, headache or facial pain, or periorbital edema or persistence of rhinorrhea or cough for longer than 14 days
Streptococcosis	Mucopurulent nasal discharge that excoriates the nares
Pertussis	Onset of persistent or severe paroxysmal cough
Congenital syphilis	Persistent rhinorrhea with onset in the 1st 3 mo of life

Table 381-3 Recommended Treatment for Acute Streptococcal Pharyngitis

MOST PATIENTS				
	WEIGHT <27 kg	**WEIGHT ≥27 kg**	**ROUTE**	**DURATION**
Amoxicillin	50 mg/kg once daily (maximum 1000 mg)		Oral	10 days
Penicillin V	250 mg bid	500 mg bid	Oral	10 days
Benzathine penicillin G	600,000 units	1.2 million units	IM	Once
Benzathine penicillin G + procaine penicillin G	900,000 units + 300,000 units	900,000 units + 300,000 units	IM	Once

PENICILLIN-ALLERGIC PATIENTS			
	ORAL DOSE	**FREQUENCY**	**DURATION**
Cephalosporins*	Varies with agent chosen		10 days
Erythromycin Ethylsuccinate	40 mg/kg/day up to 1000 mg/day	bid	10 days
Estolate	20-40 mg/kg/day up to 1000 mg/day	bid	10 days
Clarithromycin	15 mg/kg/day up to 500 mg/day	bid	10 days
Azithromycin†	12 mg/kg day 1; 6 mg/kg days 2-5	qd	5 days
Clindamycin	20 mg/kg/day up to 1.8 g/day	tid	10 days

*First-generation cephalosporins are preferred; dosage and frequency vary among agents. Do not use in patients with history of immediate (anaphylactic) hypersensitivity to penicillin or other β-lactam antibiotics.
†Maximum dose is 500 mg the 1st day, 250 mg subsequent days.

Table 383-1 Paradise Criteria for Tonsillectomy

CRITERION	DEFINITION
Minimum frequency of sore throat episodes	At least 7 episodes in the previous year, at least 5 episodes in each of the previous 2 yr, or at least 3 episodes in each of the previous 3 yr
Clinical features	Sore throat plus at least 1 of the following features qualifies as a counting episode: Temperature of greater than 38.3°C (100.9°F) Cervical adenopathy (tender lymph nodes or lymph node size >2 cm) Tonsillar exudate Culture positive for group A β-hemolytic streptococcus
Treatment	Antibiotics administered in the conventional dosage for proved or suspected streptococcal episodes
Documentation	Each episode of throat infection and its qualifying features substantiated by contemporaneous notation in a medical record If the episodes are not fully documented, subsequent observance by the physician of 2 episodes of throat infection with patterns of frequency and clinical features consistent with the initial history*

*Allows for tonsillectomy in patients who meet all but the documentation criterion. A 12 mo observation period is usually recommended before consideration of tonsillectomy.

Table 383-3 Risks and Potential Benefits of Tonsillectomy or Adenoidectomy or Both

RISKS
Cost*
Risk of anesthetic accidents
Malignant hyperthermia
Cardiac arrhythmia
Vocal cord trauma
Aspiration with resulting bronchopulmonary obstruction or infection
Risk of miscellaneous surgical or postoperative complications
Hemorrhage
Airway obstruction from edema of tongue, palate, or nasopharynx, or retropharyngeal hematoma
Central apnea
Prolonged muscular paralysis
Dehydration
Palatopharyngeal insufficiency
Otitis media
Nasopharyngeal stenosis
Refractory torticollis
Facial edema
Emotional upset
Unknown risks
POTENTIAL BENEFITS
Reduction in frequency of ear, nose, throat illness, and thus in
Discomfort
Inconvenience
School absence
Parental anxiety
Work missed by parents
Costs of physician visits and drugs
Reduction in nasal obstruction with improved
Respiratory function
Comfort
Sleep
Craniofacial growth and development
Appearance
Reduction in hearing impairment
Improved growth and overall well-being
Reduction in long-term parental anxiety

*Cost for tonsillectomy alone and adenoidectomy alone are somewhat lower.

Table 383-2 Comparison of American, Italian, and Scottish Guidelines for Tonsillectomy in Children and Adolescents

PARAMETER	AAO-HNS GUIDELINES	ITALIAN GUIDELINES	SCOTTISH GUIDELINES
Audience	Multidisciplinary	Multidisciplinary	Multidisciplinary
Target population	Children and adolescents 1-18 yr of age	Children and adults	Children 4-16 yr of age and adults
Scope	Treatment of children who are candidates for tonsillectomy	Appropriateness and safety of tonsillectomy	Management of sore throat and indications for tonsillectomy
Methods	Based on a priori protocol, systematic literature review, American Academy of Pediatrics scale of evidence quality	Systematic literature review, Italian National Program Guidelines scale of evidence quality	Based on a priori protocol, systematic literature review, Scottish Intercollegiate Guidelines Network scale of evidence quality
Recommendations			
Recurrent infection	Tonsillectomy is an option for children with recurrent throat infection that meets the Paradise criteria (see Table 383-1) for frequency, severity, treatment, and documentation of illness	Tonsillectomy is indicated in patients with at least 1 yr of recurrent tonsillitis (5 or more episodes per year) that is disabling and impairs normal activities, but only after an additional 6 mo of watchful waiting to assess the pattern of symptoms using a clinical diary	Tonsillectomy should be considered for recurrent, disabling sore throat caused by acute tonsillitis when the episodes are well documented, are adequately treated, and meet the Paradise criteria (see Table 383-1) for frequency of illness
Pain control	Recommendation to advocate for pain relief (e.g., provide information, prescribe) and educate caregivers about the importance of managing and reassessing pain	Recommendation for acetaminophen before and after surgery	Recommendation for adequate dose of acetaminophen for pain relief in children
Antibiotic use	Recommendation against perioperative antibiotics	Recommendation for short-term perioperative antibiotics*	NA
Steroid use	Recommendation for a single intraoperative dose of dexamethasone	Recommendation for a single intraoperative dose of dexamethasone	Recommendation for a single intraoperative dose of dexamethasone
Sleep-disordered breathing	Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with sleep-disordered breathing and comorbid conditions	Recommendation for diagnostic testing in children with suspected sleep respiratory disorders	NA
Polysomnography	Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with abnormal polysomnography	Recommendation for polysomnography when pulse oximetry results are not conclusive in agreement with Brouillette criteria	NA
Surgical technique	NA	Recommendation for "cold" technique	NA
Hemorrhage	Recommendation that the surgeon document primary and secondary hemorrhage after tonsillectomy at least annually	NA	NA
Adjunctive therapy	NA	NA	Recommendation against *Echinacea purpurea* for treatment of sore throat Recommendation for acupuncture in patients at risk of postoperative nausea and vomiting who cannot take antiemetic drugs

*Statement made prior to most recent Cochrane review.

AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; NA, not applicable.

Adapted with permission from Baugh RF, Archer SM, Mitchell RB, et al: American Academy of Otolaryngology–Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. Otolaryngol Head Neck Surg *144(1 Suppl):S23, 2011, Table 9.*

Table 384-3 Characteristics of Cough and Other Clinical Features and Possible Causes

SYMPTOMS AND SIGNS	POSSIBLE UNDERLYING ETIOLOGY*
Auscultatory findings (wheeze, crepitations/crackles, differential breath sounds)	Asthma, bronchitis, congenital lung disease, foreign body aspiration, airway abnormality
Cough characteristics (e.g., cough with choking, cough quality, cough starting from birth)	See text; congenital lung abnormalities
Cardiac abnormalities (including murmurs)	Any cardiac illness
Chest pain	Asthma, functional, pleuritis
Chest wall deformity	Any chronic lung disease
Daily moist or productive cough	Chronic bronchitis, suppurative lung disease
Digital clubbing	Suppurative lung disease, arteriovenous shunt
Dyspnea (exertional or at rest)	Compromised lung function of any chronic lung or cardiac disease
Failure to thrive	Compromised lung function, immunodeficiency, cystic fibrosis
Feeding difficulties (including choking and vomiting)	Compromised lung function, aspiration
Hemoptysis	Bronchitis, foreign body aspiration, suctioning trauma
Immune deficiency	Atypical and typical recurrent respiratory infections
Medications or drugs	Angiotensin-converting enzyme inhibitors, puffers, illicit drug use
Neurodevelopmental abnormality	Aspiration
Recurrent pneumonia	Immunodeficiency, congenital lung problem, airway abnormality
Symptoms of upper respiratory tract infection	Can coexist or be a trigger for an underlying problem

*This is not an exhaustive list; only the more common respiratory diseases are mentioned.

Table 384-1 Indicators of Serious Chronic Lower Respiratory Tract Disease in Children

Persistent fever
Ongoing limitation of activity
Failure to grow
Failure to gain weight appropriately
Clubbing of the digits
Persistent tachypnea and labored ventilation
Shortness of breath and exercise intolerance
Chronic purulent sputum
Persistent hyperinflation
Substantial and sustained hypoxemia
Refractory infiltrates on chest x-ray
Persistent pulmonary function abnormalities
Family history of heritable lung disease
Cyanosis and hypercarbia

Table 384-4 Clinical Clues About Cough

CHARACTERISTIC	THINK OF
Staccato, paroxysmal	Pertussis, cystic fibrosis, foreign body, *Chlamydia* spp., *Mycoplasma* spp.
Followed by "whoop"	Pertussis
All day, never during sleep	Habit cough
Barking, brassy	Croup, habit cough, tracheomalacia, tracheitis, epiglottitis
Hoarseness	Laryngeal involvement (croup, recurrent laryngeal nerve involvement)
Abrupt onset	Foreign body, pulmonary embolism
Follows exercise	Reactive airway disease
Accompanies eating, drinking	Aspiration, gastroesophageal reflux, tracheoesophageal fistula
Throat clearing	Postnasal drip, vocal tic
Productive (sputum)	Infection, cystic fibrosis, bronchiectasis
Night cough	Sinusitis, reactive airway disease, gastroesophageal reflux
Seasonal	Allergic rhinitis, reactive airway disease
Immunosuppressed patient	Bacterial pneumonia, *Pneumocystis jiroveci, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare,* cytomegalovirus
Dyspnea	Hypoxia, hypercarbia
Animal exposure	*Chlamydia psittaci* (birds), *Yersinia pestis* (rodents), *Francisella tularensis* (rabbits), Q fever (sheep, cattle), hantavirus (rodents), histoplasmosis (pigeons)
Geographic	Histoplasmosis (Mississippi, Missouri, Ohio River Valley), coccidioidomycosis (Southwest), blastomycosis (North and Midwest)
Workdays with clearing on days off	Occupational exposure

Table 384-2 Differential Diagnosis of Recurrent and Persistent Cough in Children

RECURRENT COUGH
Reactive airway disease (asthma)
Drainage from upper airways
Aspiration
Frequently recurring respiratory tract infections in immunocompetent or immunodeficient patients
Symptomatic Chiari malformation
Idiopathic pulmonary hemosiderosis
Hypersensitivity (allergic) pneumonitis

PERSISTENT COUGH
Hypersensitivity of cough receptors after infection
Reactive airway disease (asthma)
Chronic sinusitis
Chronic rhinitis (allergic or nonallergic)
Bronchitis or tracheitis caused by infection or smoke exposure
Bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, immunodeficiency
Habit cough
Foreign-body aspiration
Recurrent aspiration owing to pharyngeal incompetence, tracheolaryngoesophageal cleft, or tracheoesophageal fistula
Gastroesophageal reflux, with or without aspiration
Pertussis
Extrinsic compression of the tracheobronchial tract (vascular ring, neoplasm, lymph node, lung cyst)
Tracheomalacia, bronchomalacia
Endobronchial or endotracheal tumors
Endobronchial tuberculosis
Hypersensitivity pneumonitis
Fungal infections
Inhaled irritants, including tobacco smoke
Irritation of external auditory canal
Angiotensin-converting enzyme inhibitors

Table 384-5 Causes of Recurrent or Persistent Stridor in Children

RECURRENT
Allergic (spasmodic) croup
Respiratory infections in a child with otherwise asymptomatic anatomic narrowing of the large airways
Laryngomalacia
PERSISTENT
Laryngeal obstruction
• Laryngomalacia
• Papillomas, other tumors
• Cysts and laryngoceles
• Laryngeal webs
• Bilateral abductor paralysis of the cords
• Foreign body
Tracheobronchial disease
• Tracheomalacia
• Subglottic tracheal webs
• Endobronchial, endotracheal tumors
• Subglottic tracheal stenosis, congenital or acquired
Extrinsic masses
• Mediastinal masses
• Vascular ring
• Lobar emphysema
• Bronchogenic cysts
• Thyroid enlargement
• Esophageal foreign body
Tracheoesophageal fistula
OTHER
Gastroesophageal reflux
Macroglossia, Pierre Robin syndrome
Cri-du-chat syndrome
Paradoxical vocal cord dysfunction
Hypocalcemia
Vocal cord paralysis
Chiari crisis
Severe neonatal episodic laryngospasm caused by *SCN4A* mutation

Table 391-2 Pertinent Medical History in the Wheezing Infant

Did the onset of symptoms begin at birth or thereafter?
Is the infant a noisy breather and when is it most prominent?
Is the noisy breathing present on inspiration, expiration, or both?
Is there a history of cough apart from wheezing?
Was there an earlier lower respiratory tract infection?
Is there a history of recurrent upper or lower respiratory tract infections?
Have there been any emergency department visits, hospitalizations, or intensive care unit admissions for respiratory distress?
Is there a history of eczema?
Does the infant cough after crying or cough at night?
How is the infant growing and developing?
Is there associated failure to thrive?
Is there a history of electrolyte abnormalities?
Are there signs of intestinal malabsorption including frequent, greasy, or oily stools?
Is there a maternal history of genital herpes simplex virus infection?
What was the gestational age at delivery?
Was the patient intubated as a neonate?
Does the infant bottle-feed in the bed or the crib, especially in a propped position?
Are there any feeding difficulties including choking, gagging, arching, or vomiting with feeds?
Is there any new food exposure?
Is there a toddler in the home or lapse in supervision in which foreign-body aspiration could have occurred?
Change in caregivers or chance of nonaccidental trauma?

Table 384-6 Diseases Associated with Recurrent, Persistent, or Migrating Lung Infiltrates Beyond the Neonatal Period

Aspiration
Pharyngeal incompetence (e.g., cleft palate)
Laryngotracheoesophageal cleft
Tracheoesophageal fistula
Gastroesophageal reflux
Lipid aspiration
Neurologic dysphagia
Developmental dysphagia
Congenital anomalies
Lung cysts (cystic adenomatoid malformation)
Pulmonary sequestration
Bronchial stenosis or aberrant bronchus
Vascular ring
Congenital heart disease with large left-to-right shunt
Pulmonary lymphangiectasia
Genetic conditions
α_1-Antitrypsin deficiency
Cystic fibrosis
Primary ciliary dyskinesia (Kartagener syndrome)
Sickle cell disease (acute chest syndrome)
Immunodeficiency, phagocytic deficiency
Humoral, cellular, combined immunodeficiency states
Chronic granulomatous disease and related phagocytic defects
Complement deficiency states
Immunologic and autoimmune diseases
Asthma
Allergic bronchopulmonary aspergillosis
Hypersensitivity pneumonitis
Pulmonary hemosiderosis
Collagen-vascular diseases
Infection, congenital
Cytomegalovirus
Rubella
Syphilis
Infection, acquired
Cytomegalovirus
Tuberculosis
HIV
Other viruses
Chlamydia
Mycoplasma, Ureaplasma
Pertussis
Fungal organisms
Pneumocystis jiroveci
Visceral larva migrans
Inadequately treated bacterial infection
Interstitial pneumonitis and fibrosis
Usual interstitial pneumonitis
Lymphoid (AIDS)
Genetic disorders of surfactant synthesis, secretion
Desquamative
Acute (Hamman-Rich)
Alveolar proteinosis
Drug-induced, radiation-induced inflammation and fibrosis
Neoplasms and neoplastic-like conditions
Primary or metastatic pulmonary tumors
Leukemia
Histiocytosis
Eosinophilic pneumonias
Other etiologies
Bronchiectasis
Congenital
Postinfectious
Sarcoidosis

Table 391-3 Disorders with Cough as a Prominent Finding

CATEGORY	DIAGNOSES
Inflammatory	Asthma
Chronic pulmonary processes	Bronchopulmonary dysplasia Postinfectious bronchiectasis Cystic fibrosis Tracheomalacia or bronchomalacia Ciliary abnormalities Other chronic lung diseases
Other chronic disease or congenital disorders	Laryngeal cleft Swallowing disorders Gastroesophageal reflux Airway compression (such as a vascular ring or hemangioma) Congenital heart disease
Infectious or immune disorders	Immunodeficiency Eosinophilic lung disease Tuberculosis Allergy Sinusitis Tonsillitis or adenoiditis *Chlamydia, Ureaplasma* (infants) *Bordetella pertussis* *Mycoplasma pneumoniae*
Acquired	Foreign-body aspiration, tracheal or esophageal

Table 394-1 Etiology of Bronchiolitis Obliterans

POSTINFECTION
Adenovirus types 3, 7, and 21
Influenza
Parainfluenza
Measles
Respiratory syncytial virus
Varicella
Mycoplasma pneumoniae
POSTTRANSPLANTATION
Chronic rejection of lung or heart/lung transplantation
Graft-versus-host disease associated with bone marrow transplantation
CONNECTIVE TISSUE DISEASE
Juvenile idiopathic arthritis
Sjögren syndrome
Systemic lupus erythematosus
TOXIC FUME INHALATION
NO_2
NH_3
Diacetyl flavorings (microwave popcorn)
CHRONIC HYPERSENSITIVITY PNEUMONITIS
Avian antigens
Mold
ASPIRATION
Stomach contents: gastroesophageal reflux
Foreign bodies
DRUGS
Penicillamine
Cocaine
STEVENS-JOHNSON SYNDROME
Idiopathic
Drug induced
Infection related

Table 391-1 Differential Diagnosis of Wheezing in Infancy

INFECTION
Viral
Respiratory syncytial virus
Human metapneumovirus
Parainfluenza
Adenovirus
Influenza
Rhinovirus
Bocavirus
Coronavirus
Enterovirus
Other
Chlamydia trachomatis
Tuberculosis
Histoplasmosis
Papillomatosis
ASTHMA
Transient wheezer (resolved by 6 yr of age)
• Initial risk factor is primarily diminished lung size
Persistent wheezers (persists beyond 6 yr of age)
• Initial risk factors include parental asthma history, atopic dermatitis, allergen sensitization, peripheral eosinophilia (>4%) and wheezing unrelated to colds in the 1st yr of life
• At increased risk of developing clinical asthma
Late-onset wheezer (symptoms begin after age 3 yr and persist)
ANATOMIC ABNORMALITIES
Central Airway Abnormalities
Malacia of the larynx, trachea, and/or bronchi
Laryngeal or tracheal web
Tracheoesophageal fistula (specifically H-type fistula)
Laryngeal cleft (resulting in aspiration)
Extrinsic Airway Anomalies Resulting in Airway Compression
Vascular ring or sling
Mediastinal lymphadenopathy from infection or tumor
Mediastinal mass or tumor
Esophageal foreign body
Intrinsic Airway Anomalies
Airway hemangioma, other tumor
Cystic adenomatoid malformation
Bronchial or lung cyst
Congenital lobar emphysema
Aberrant tracheal bronchus
Sequestration
Congenital heart disease with left-to-right shunt (increased pulmonary edema)
Foreign body
Immunodeficiency States
Immunoglobulin A deficiency
B-cell deficiencies
AIDS
Bronchiectasis
MUCOCILIARY CLEARANCE DISORDERS
Cystic fibrosis
Primary ciliary dyskinesia
Bronchiectasis
ASPIRATION SYNDROMES
Gastroesophageal reflux disease
Pharyngeal/swallow dysfunction
OTHER
Bronchopulmonary dysplasia
Interstitial lung disease, including bronchiolitis obliterans
Heart failure
Anaphylaxis
Inhalation injury—burns

Table 398-1 Conditions Predisposing to Aspiration Lung Injury in Children

ANATOMICAL AND MECHANICAL
Tracheoesophageal fistula
Laryngeal cleft
Vascular ring
Cleft palate
Micrognathia
Macroglossia
Cysts, tumors
Achalasia
Esophageal foreign body
Tracheostomy
Endotracheal tube
Nasal or oral feeding tube
Collagen vascular disease (scleroderma, dermatomyositises)
Gastroesophageal reflux disease
Obesity
NEUROMUSCULAR
Altered consciousness
Immaturity of swallowing/Prematurity
Dysautonomia
Increased intracranial pressure
Hydrocephalus
Vocal cord paralysis
Cerebral palsy
Muscular dystrophy
Hypotonia
Myasthenia gravis
Guillain-Barré syndrome
Spinal muscular atrophy
Ataxia-telangiectasia
Cerebral vascular accident
MISCELLANEOUS
Poor oral hygiene
Gingivitis
Prolonged hospitalization
Gastric outlet or intestinal obstruction
Poor feeding techniques (bottle propping, overfeeding, inappropriate foods for toddlers)
Bronchopulmonary dysplasia
Viral infection/bronchiolitis

Table 396-1 Etiology of Pulmonary Edema

INCREASED PULMONARY CAPILLARY PRESSURE
Cardiogenic, such as left ventricular failure
Noncardiogenic, as in pulmonary venoocclusive disease, pulmonary venous fibrosis, mediastinal tumors
INCREASED CAPILLARY PERMEABILITY
Bacterial and viral pneumonia
Acute respiratory distress syndrome
Inhaled toxic agents
Circulating toxins
Vasoactive substances such as histamine, leukotrienes, thromboxanes
Diffuse capillary leak syndrome, as in sepsis
Immunologic reactions, such as transfusion reactions
Smoke inhalation
Aspiration pneumonia/pneumonitis
Drowning and near drowning
Radiation pneumonia
Uremia
LYMPHATIC INSUFFICIENCY
Congenital and acquired
DECREASED ONCOTIC PRESSURE
Hypoalbuminemia, as in renal and hepatic diseases, protein-losing states, and malnutrition
INCREASED NEGATIVE INTERSTITIAL PRESSURE
Upper airway obstructive lesions, such as croup and epiglottitis
Reexpansion pulmonary edema
MIXED OR UNKNOWN CAUSES
Neurogenic pulmonary edema
High-altitude pulmonary edema
Eclampsia
Pancreatitis
Pulmonary embolism
Heroin (narcotic) pulmonary edema

Table 396-2 Radiographic Features That May Help Differentiate Cardiogenic from Noncardiogenic Pulmonary Edema

RADIOGRAPHIC FEATURE	CARDIOGENIC EDEMA	NONCARDIOGENIC EDEMA
Heart size	Normal or greater than normal	Usually normal
Width of the vascular pedicle*	Normal or greater than normal	Usually normal or less than normal
Vascular distribution	Balanced or inverted	Normal or balanced
Distribution of edema	Even or central	Patchy or peripheral
Pleural effusions	Present	Not usually present
Peribronchial cuffing	Present	Not usually present
Septal lines	Present	Not usually present
Air bronchograms	Not usually present	Usually present

Table 398-2 Summary of Diagnostic Tests of Aspiration

EVALUATION	BENEFITS	LIMITATIONS
Chest radiograph	Inexpensive and widely available Assesses accumulation of injury over time	Insensitive to early subtle changes of lung injury
High-resolution CT	Sensitive in detecting lung injury, such as bronchiectasis, tree-in-bud opacities, and bronchial thickening Less radiation than conventional CT Assesses accumulation of injury over time	More radiation exposure than plain radiograph Expensive
Video swallow study	Evaluates all phases of swallowing Evaluates multiple consistencies Feeding recommendations made at time of study	Information limited if child consumes only small quantities Difficult to perform in child who has not been feeding by mouth Radiation exposure proportional to study duration Cannot be performed at bedside Limited evaluation of anatomy Evaluates 1 moment in time Expensive
FEES/with sensory testing	Ability to thoroughly evaluate functional anatomy Evaluates multiple consistencies Can assess risk of aspiration in non-orally feeding child; airway protective reflexes can be assessed Feeding recommendations made at time of study Visual feedback for caregivers Can be performed at bedside No radiation exposure	Blind to esophageal phase and actual swallow Invasive and may not represent physiological swallowing conditions Evaluates 1 moment in time Not widely available Expensive
BAL	Evaluates anatomy of entire upper and lower airways Samples the end-organ of damage Sample available for multiple cytological and microbiologic tests Widely available	Uncertainty regarding interpretation of lipid-laden macrophage index Index cumbersome to calculate Requires sedation or anesthesia Invasive Expensive
Esophageal pH monitoring	Current gold standard for diagnosis of Acid gastroesophageal reflux Established normative data in children	Blind to majority of reflux (nonacid) events Difficult to establish causal relationship between gastroesophageal reflux and aspiration Somewhat invasive Evaluates short time interval
Esophageal impedance monitoring	Likely gold standard for diagnosis of GERD with supraesophageal manifestations Able to detect acid and nonacid reflux events Detects proximal reflux events Able to evaluate for GERD without stopping medications	Lack of normative data for children Somewhat invasive Expensive and cumbersome to interpret Not widely available Evaluates short time interval
Gastroesophageal scintigraphy	Performed under physiologic conditions Low radiation exposure	Poor sensitivity May not differentiate between aspiration from dysphagia or GERD
Radionuclide salivagram	Child does not have to be challenged with food bolus Low radiation exposure	Unknown sensitivity Unknown relationship to disease outcomes Evaluates 1 moment in time
Dye studies	Can be constructed as screening test or confirmatory test Can evaluate aspiration of secretions or feeds Repeating over time allows for broader evaluation	Uncertainty in interpretation owing to variability of technique Can only be performed in children with tracheostomies
Other biomarkers (pepsin, bile acids) milk protein	Theoretical high specificity and sensitivity	Limited availability and standardization Variable results to date

BAL, bronchoalveolar lavage; FEES, fiberoptic-endoscopic evaluation of swallowing; GERD, gastroesophageal reflux disease.

Modified from Boesch RP, Daines C, Willging JP, et al: Advances in the diagnosis and management of chronic pulmonary aspiration in children, Eur Respir J *28:847–861, 2006; and Tutor JD, Gosa MM: Dysphagia and aspiration in children,* Pediatr Pulmonol *47(4):321–337, 2012.*

Table 399-1 Antigen Sources Associated with Specific Causes of Hypersensitivity Pneumonitis

HYPERSENSITIVITY PNEUMONITIS	ANTIGEN SOURCE
Bagassosis (mold on pressed sugar cane)	*Thermoactinomyces sacchari* *Thermoactinomyces vulgaris*
Bat lung (bat droppings)	Bat serum protein
Bible printer's lung	Moldy typesetting water
Bird fancier's lung (parakeets, budgerigars, pigeons)	Droppings, feathers, serum proteins
Byssinosis ("brown lung") (unclear if a true cause of hypersensitivity pneumonitis; asthma is common)	Cotton mill dust (carding and spinning areas of cotton, flax, and soft-hemp)
Canary fancier's lung	Serum proteins
Cheese washer's lung (moldy cheese)	*Penicillium casei* *Aspergillus clavatus*
Chemical hypersensitivity pneumonitis	Diphenylmethane diisocyanate (MDI) Toluene diisocyanate (TDI)
Coffee worker's lung	Coffee-bean dust
Composter's lung	*T. vulgaris* *Aspergillus* species
Contaminated basement (sewage) pneumonitis	*Cephalosporium*
Coptic lung (mummy handler's lung)	Cloth wrappings of mummies
Detergent worker's lung (washing powder lung)	*Bacillus subtilis* enzymes
Dry rot lung	*Merulius lacrymans*
Duck fever	Feathers, serum proteins
Epoxy resin lung	Phthalic anhydride (heated epoxy resin)
Esparto dust (mold in plaster dust)	*Aspergillus fumigatus* Thermophilic actinomycetes
Fish meal worker's lung	Fish meal
Furrier's lung (sewing furs; animal fur dust)	Animal pelts
Grain measurer's lung	Cereal grain (*Sporobolomyces*) Grain dust (mixture of dust, silica, fungi, insects, and mites)
Hot-tub lung (mists; mold on ceiling and around tub)	*Cladosporium* spp. *Mycobacterium avium* complex
Humidifier fever	*Thermoactinomyces (T. vulgaris, T. sacchari, T. candidus)* *Klebsiella oxytoca* *Naegleria gruberi* *Acanthamoeba polyphaga* *Acanthamoeba castellani*
Laboratory worker's lung (rats, gerbils)	Urine, serum, pelts, proteins
Lifeguard lung	Aerosolized endotoxin from pool-water sprays and fountains
Lycoperdonosis (*Lycoperdon* puffballs)	Puffball spores
Machine operator's lung	*Pseudomonas fluorescens* Aerosolized metal working fluid
Malt worker's disease (moldy barley)	*Aspergillus fumigatus, Aspergillus clavatus*
Maple bark disease (moldy maple bark)	*Cryptostroma corticale*
Miller's lung (dust-contaminated grain)	*Sitophilus granarius* (i.e., wheat weevil)
Moldy hay, grain, silage (farmer's lung)	Thermophilic actinomycetes Fungi (e.g., *Aspergillus umbrosus*)
Mollusk shell hypersensitivity pneumonitis	Sea-snail shell
Mushroom worker's lung	Mushroom spores Thermophilic actinomycetes
Paprika slicer's lung (moldy paprika pods)	*Mucor stolonifer*
Pauli's reagent alveolitis	Sodium diazobenzene sulfate
Pearl oyster shell pneumonitis	Oyster shells
Pituitary snuff taker's disease	Dried, powdered cattle or pig pituitary proteins)
Potato riddler's lung (moldy hay around potatoes)	Thermophilic actinomycetes *T. vulgaris* *Faenia rectivirgula* *Aspergillus* spp.
Poultry worker's lung (feather plucker's disease)	Serum proteins (chicken products)
Pyrethrum (pesticide)	Pyrethrum
Sauna taker's lung	*Aureobasidium* spp., other sources
Sequoiosis (moldy wood dust)	*Graphium* *Pullularia* *Trichoderma* spp. *Aureobasidium pullulans*
Suberosis (moldy cork dust)	*Thermoactinomyces viridis* *Penicillium glabrum* Aspergillus conidia
Summer-type pneumonitis	*Trichosporon cutaneum*
Tea grower's lung	Tea plants
Thatched-roof lung (huts in New Guinea)	*Saccharomonospora viridis* (dead grasses and leaves)
Tobacco grower's lung	*Aspergillus* spp. *Scopulariopsis brevicaulis*
Turkey handling disease	Serum proteins (turkey products)
Unventilated shower	*Epicoccum nigrum*
Upholstery fabric (nylon filament, cotton/polyester, and latex adhesive)	Aflatoxin-producing fungus, *Fusarium* spp.
Velvet worker's lung	Unknown (? nylon velvet fiber, tannic acid, potato starch)
Vineyard sprayer's lung	Copper sulfate (bordeaux mixture)
Wine maker's lung (mold on grapes)	*Botrytis cinerea*
Wood dust pneumonitis (oak, cedar, and mahogany dust, pine and spruce pulp)	*Alternaria* spp. *Bacillus subtilis*
Wood pulp worker's disease (oak and maple trees)	*Penicillium* spp.
Wood trimmer's disease (contaminated wood trimmings)	*Rhizopus* spp., *Mucor* spp.

Table 399-2 Criteria Used in the Diagnosis of Hypersensitivity Pneumonitis

1. Identified exposure to offending antigen(s) by:
   - Medical history of exposure to suspected antigen in the patient's living environment
   - Investigations of the environment confirm the presence of an inciting antigen
   - Identification of specific immune responses (immunoglobulin G serum precipitin antibodies against the identified antigen) are suggestive of the potential etiology but are insufficient in isolation to confirm a diagnosis
2. Clinical, radiographic, or physiologic findings compatible with hypersensitivity pneumonitis:
   - Respiratory and often constitutional signs and symptoms
     - Crackles on auscultation of the chest
     - Weight loss
     - Cough
     - Breathlessness
     - Episodic fever
     - Wheezing
     - Fatigue

   NOTE: These findings are especially suggestive of hypersensitivity pneumonitis when they appear or worsen several hours after antigen exposure.
   - A reticular, nodular, or ground glass opacities on chest radiograph or high-resolution CT
   - Abnormalities in the following pulmonary function tests
     - Spirometry (restrictive, obstructive, or mixed patterns)
     - Lung volumes (low or high)
     - Reduced diffusion capacity by carbon monoxide
     - Altered gas exchange either at rest or with exercise (reduced partial pressure of arterial oxygen by blood gas or pulse oximeter testing)
3. Bronchoalveolar lavage with lymphocytosis:
   - Usually with low CD4:CD8 ratio (i.e., CD8 is higher than normal)
   - Lymphocyte stimulation by offending antigen results in proliferation and cytokine production
4. Abnormal response to inhalation challenge testing to the offending antigen:
   - Reexposure to the environment
   - Inhalation challenge to the suspected antigen (rarely done any longer because of the risk of exacerbation of the disease)
5. Histopathology showing compatible changes with hypersensitivity pneumonitis by 1 of these findings:
   - Poorly formed, noncaseating granulomas (most often found closer to the respiratory epithelium where deposition of the offending antigen occurs)
   - Mononuclear cell infiltrate in the pulmonary interstitium

Table 399-3 Clinical History Clues Leading to a Diagnosis of Hypersensitivity Pneumonitis

Recurrent pneumonia
Pneumonia after repeat exposures (week, season, situation)
Cough, fever, and chest symptoms after making a job change or home change
Cough, fever, wheezing after return to school or only at school
Pet exposure (especially birds that shed dust such as pigeons, canaries, cockatiels, cockatoos)
Bird contaminant exposure (e.g., pigeon infestation)
Farm exposure to birds and hay
History of water damage despite typical cleaning
Use of hot tub, sauna, swimming pool
Other family members or workers with similar recurrent symptoms
Improvement after temporary environment change (e.g., vacation)

Table 399-5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma

OCCUPATION OR ENVIRONMENT	SOURCE
ANIMAL-DERIVED ANTIGENS	
Agricultural worker	Cow dander
Bakery	Lactalbumin
Butcher	Cow bone dust, pig, goat dander
Cook	Raw beef
Dairy industry	Lactoserum, lactalbumin
Egg producer	Egg protein
Farmer	Deer dander, mink urine
Frog catcher	Frog
Hairdresser	Sericin
Ivory worker	Ivory dust
Laboratory technician	Bovine serum albumin, laboratory animal, monkey dander
Nacre buttons	Nacre dust
Pharmacist	Endocrine glands
Pork producer	Pig gut (vapor from soaking water)
Poultry worker	Chicken
Tanner	Casein (cow's milk)
Various	Bat guano
Veterinarian	Goat dander
Zookeeper	Birds
CRUSTACEANS, SEAFOOD, FISH	
Canning factory	Octopus
Diet product	Shark cartilage
Fish food factory	Gammarus shrimp
Fish processor	Clam, shrimp, crab, prawn, salmon, trout, lobster, turbot, various fishes
Fisherman	Red soft coral, cuttlefish
Jewelry polisher	Cuttlefish bone
Laboratory grinder	Marine sponge
Oyster farm	Hoya (oyster farm prawn or sea-squirt)
Restaurant seafood handler	Scallop and shrimp
Scallop plant processor	King scallop and queen scallop
Technician	Shrimp meal *(Artemia salina)*
ARTHROPODS	
Agronomist	*Bruchus lentis*
Bottling	Ground bug
Chicken breeder	Herring worm *(Anisakis simplex)*
Engineer at electric power plant	Caddis flies *(Phryganeidae)*
Entomologist	Lesser mealworm (*Alphitobius diaperinus* Panzer), moth, butterfly
Farmer	Grain pests (*Eurygaster* and *Pyrale*)
Fish bait handler	Insect larvae *(Galleria mellonella)*, mealworm larvae *(Tenebrio molitor)*, green bottle fly larvae *(Lucila caesar)*, daphnia, fish-feed Echinodorus larva *(Echinodorus plasmosus)*, Chiromids midge *(Chironomus thummi thummi)*
Fish processing	Herring worm *(Anisakis simplex)*
Flight crew	Screw worm fly *(Cochliomyia hominivorax)*
Honey processors	Honeybee
Laboratory worker	Cricket, fruit fly, grasshopper *(Locusta migratoria)*, locust
Mechanic in a rye plant	Confused flour beetle *(Tribolium confusum)*
Museum curator	Beetles (Coleoptera)
Seed house	Mexican bean weevil *(Zabrotes subfasciatus)*
Sericulture	Silkworm, larva of silkworm
Sewage plant worker	Sewer fly *(Psychoda alternata)*
Technician	Arthropods *(Chrysoperla carnea, Leptinotarsa decemlineata, Ostrinia nubilalis, and Ephestia kuehniella)*, sheep blowfly *(Lucilia cuprina)*
Wool worker	*Dermestidae* spp.

OCCUPATION OR ENVIRONMENT	SOURCE
ACARIANS	
Apple grower	Fruit tree red spider mite *(Panonychus ulmi)*
Citrus farmer	Citrus red mite *(Panonychus citri)*
Farmer	Barn mite, two-spotted spider mite *(Tetranychus urticae)*, grain mite
Flour handler	Mites and parasites
Grain-store worker	Grain mite
Horticulturist	*Amblyseius cucumeris*
Poultry worker	Fowl mite
Vine grower	McDaniel spider mite *(Tetranychus mcdanieli)*
MOLDS	
Agriculture	*Plasmopara viticola*
Baker	*Alternaria, Aspergillus* (unspecified)
Beet sugar worker	*Aspergillus* (unspecified)
Coal miner	*Rhizopus nigricans*
Coffee maker	*Chrysonilia sitophila*
Laborer	Sooty molds (*Ascomycetes*, deuteromycetes)
Logging worker	*Chrysonilia sitophila*
Plywood factory worker	*Neurospora*
Sausage processing	*Penicillium nalgiovense*
Sawmill worker	*Trichoderma koningii*
Stucco worker	*Mucor* spp. (contaminating esparto fibers)
Technician	*Dictyostelium discoideum* (mold), *Aspergillus niger*
MUSHROOMS	
Agriculture	*Agaricus bisporus* (white mushroom)
Baker	Baker's yeast *(Saccharomyces cerevisiae), Boletus edulis*
Greenhouse worker	Sweet pea *(Lathyrus odoratus)*
Hotel manager	*Boletus edulis*
Mushroom producer	*Pleurotus cornucopiae*
Mushroom soup processor	Mushroom unspecified
Office worker	*Boletus edulis*
Seller	*Pleurotus ostreatus* (spores of white spongy rot)
ALGAE	
Pharmacist	Chlorella
Thalassotherapist	Algae (species unspecified)
FLOURS	
Animal fodder	Marigold flour *(Tagetes erecta)*
Baker	Wheat, rye, soya, and buckwheat flour; Konjac flour; white pea flour *(Lathyrus sativus)*
Food processing	White Lupin flour *(Lupinus albus)*
POLLENS	
Florist	Cyclamen, rose
Gardener	Canary island date palm *(Phoenix canariensis)*, Bell of Ireland *(Moluccella laevis)*, Bell pepper, chrysanthemum, eggplant *(Solanum melongena)*, *Brassica oleracea* (cauliflower and broccoli)
Laboratory worker	Sunflower (*Helianthus* spp.), thale cress *(Arabidopsis thaliana)*
Olive farmers	White mustard *(Sinapis alba)*
Processing worker	*Helianthus annuus*

Table 399-5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma—cont'd

OCCUPATION OR ENVIRONMENT	SOURCE
PLANTS	
Brewery chemist	Hops
Brush-makers	Tampico fiber in agave leaves
Butcher	Aromatic herb
Chemist	Linseed oilcake, *Voacanga africana* seed dust
Cosmetics	Dusts from seeds of Sacha Inchi *(Plukenetia volubilis)*, chamomile (unspecified)
Decorator	Cacoon seed (Entage gigas)
Floral worker	Decorative flower, safflower *(Carthamus tinctorius)* and yarrow *(Achillea millefolium)*, spathe flower, statice *(Limonium tataricum)*, baby's breath *(Gypsophila paniculata)*, ivy *(Hedera helix)*, flower (various), sea lavender *(Limonium sinuatum)*
Food industry	Aniseed, fenugreek, peach, garlic dust, asparagus, coffee bean, sesame seed, grain dust, carrot *(Daucus carota L.)*, green bean *(Phaseolus multiflorus)*, lima bean *(Phaseolus lunatus)*, onion, potato, swiss chard *(Beta vulgaris L.)*, courgette, carob bean, spinach powder, cauliflower, cabbage, chicory, fennel seed, onion seeds (*Allium cepa*, red onion), rice, saffron *(Crocus sativus)*, spices, grain dust
Gardener	Copperleaf *(Acalypha wilkesiana)*, grass juice, weeping fig *(Ficus benjamina)*, umbrella tree (*Schefflera* spp.), amaryllis (*Hippeastrum* spp.), Madagascar jasmine sap *(Stephanotis floribunda)*, vetch *(Vicia sativa)*
Hairdresser	Henna (unspecified)
Herbal tea processor	Herbal tea, sarsaparilla root, sanyak *(Dioscorea batatas)*, Korean ginseng *(Panax ginseng)*, tea plant dust *(Camellia sinensis)*, chamomile (unspecified)
Herbalist	Liquorice roots (*Glycyrrhiza* spp.), wonji *(Polygala tenuifolia)*, herb material
Horticulture	Freesia (Freesia hybrida), paprika *(Capsicum annuum)*, Brazil ginseng *(Pfaffia paniculata)*
Laborer	Citrus food handling (*dl*-limonene, *l*-citronellol, and dichlorophen)
Oil industry	Castor bean, olive oilcake
Pharmaceutical	Rose hip, passion flower *(Passiflora alata)*, cascara sagrada *(Rhamnus purshiana)*
Powder	Lycopodium powder
Sewer	Kapok
Sheller	Almond shell dust
Stucco handler	Esparto (*Stipa tenacissima* and *Lygeum spartum*)
Tobacco manufacturer	Tobacco leaf
PLANT-DERIVED NATURAL PRODUCTS	
Baker	Gluten, soybean lecithin
Candy maker	Pectin
Glove manufacturer	Latex
Health professional	Latex
Rose extraction	Rose oil
BIOLOGIC ENZYMES	
Baker	Fungal amylase, fungal amyloglucosidase and hemicellulase
Cheese producer	Various enzymes in rennet production (proteases, pepsine, chymosins)
Detergent industry	Esterase, *Bacillus subtilis*
Factory worker	*Bacillus subtilis*
Fruit processor	Pectinase and glucanase
Hospital personnel	Empynase (pronase B)
Laboratory worker	Xylanase, phytase from *Aspergillus niger*
Pharmaceutical	Bromelin, flaviastase, lactase, pancreatin, papain, pepsin, serratia peptidase, and lysozyme chloride; egg lysozyme, trypsin
Plastic	Trypsin
VEGETABLE GUMS	
Carpet manufacturing	Guar
Dental hygienist	*Gutta-percha*
Gum importer	Tragacanth
Hairdresser	Karaya
Printer	Acacia

Table 399-6 Low Molecular Weight Chemicals Known to Induce Occupational or Environmental Asthma

CHEMICALS	OCCUPATION OR ENVIRONMENT SOURCE
Diisocyanates	
• Diphenylmethane	Polyurethane
• Hexamethylene	Roofing materials
• Naphthalene	Insulations
• Toluene	Paint
Anhydrides	Manufacturers or users
• Trimellitic	• Paint
• Phthalic	• Plastics
	• Epoxy resins
Dyes	Personal or business use of dyes
• Anthraquinone	• Hair dye
• Carmine	• Fur dye
• Henna	• Fabric dye
• Persulfate	
Glue or resin	Plastic
• Methacrylate	• Manufacturers
• Acrylates	• Healthcare professionals
• Epoxy	• Orthopedic specialists
Metals	Metal work
• Chromic acid	• Plating
• Potassium dichromate	• Welding
• Nickel sulfate	
• Vanadium	
• Platinum salts	
Drugs	Exposure to drugs in environment
• β-Lactams	• Pharmaceutical workers
• Opioids	• Farmers
• Other	• Healthcare workers
Chemicals	Exposure in the healthcare field
• Formaldehyde	• Laboratory work
• Glutaraldehyde	• Healthcare professionals
• Ethylene oxide	
Wood dust	Workers/hobbyists
• Western red cedar (plicatic acid)	• Sawmill
• Exotic woods	• Carpentry
• Maple	• Woodworking
• Oak	

Table 399-8 Key Elements in the Medical History and Physical Exam to Raise Clinical Suspicion for Diagnostic Testing to Confirm Eosinophilic Lung Disease

Medical history and examination
- Drug exposure (especially antibiotics, NSAIDs, antiepileptics, antileukotriene modifiers in EGPA)
- Environmental inhalation exposures to dust or inhaled chemicals
- New onset of smoking cigarettes
- Travel or immigration status from areas endemic with various parasites or coccidiomycosis
- Asthma (may be severe or poorly controlled with ABPA, CSS, or is relatively new in onset with IAEP)
- ABPA concurrent in 7-10% of patients with cystic fibrosis
- Extrapulmonary symptoms suggestive of vasculitis, neuropathy, heart failure, or neoplasm)
- Rash (creeping eruption in visceral larval migrans disease or ulceration in EGPA)

Diagnostic imaging and testing
- Radiography helpful in AEP, CEP, and ABPA
- Radiography not diagnostic in EGPA or drug-induced eosinophilic disease of the lung
- Simple chest radiography findings
  - Nonlobar infiltrate
  - Classic description as mirror image of pulmonary edema with peripheral infiltrates
  - Bilateral pleural effusion in AEP
  - Central bronchiectasis in ABPA
- High-resolution computerized tomography of the chest
  - Middle and upper lobe nonlobar infiltrates with areas of ground-glass appearance
  - Mucous plugging in ABPA
  - Central bronchiectasis in ABPA (confused with cystic fibrosis)
- Blood eosinophil count
  - Elevated in many eosinophilic lung diseases
  - Magnitude of eosinophil blood count does not distinguish different pulmonary diseases
  - Usually not elevated in AEP (eosinophilic disease compartmentalized to lungs)
  - May occasionally not be elevated in CEP or after use of corticosteroids
- Total serum IgE elevated in ABPA but not always in patients with cystic fibrosis with ABPA
- Serology for helminthic infections or parasites may be diagnostic but are usually not available acutely
- P-ANCA (MPO ANCA) is positive in 40-70% of EGPA (CSS)
- BAL eosinophil percentage
  - ≥25% eosinophils diagnostic in AEP
  - ≥40% eosinophils diagnostic in CEP or tropical pulmonary eosinophilia
  - Eosinophil percentages below these criteria may require lung biopsy
  - <25% eosinophils seen in connective tissue disease, sarcoid, drug-induced disease, histiocytosis X of pulmonary Langerhans cells, and interstitial pulmonary fibrosis
- Lung biopsy
  - Open lung biopsy or video-assisted thorascopic surgery when BAL nondiagnostic
  - Transbronchial biopsy is usually insufficient with peripheral infiltrative disease
  - Histology with alveolar and interstitial infiltrates of eosinophils, non-necrotizing non-granulomatous vasculitis, multinucleated giant cells without granuloma
  - EGPA shows eosinophil rich small to medium vessel, necrotizing, granulomatous vasculitis

ABPA, allergic bronchopulmonary aspergillosis; AEP, acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; CEP, chronic eosinophilic pneumonia; CSS, Churg-Strauss syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; IAEP, idiopathic acute eosinophilic pneumonia; MPO ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; NSAID, nonsteroidal antiinflammatory drug; P-ANCA, perinuclear antineutrophil cytoplasmic antibody.

Table 399-7 Criteria for the Diagnosis of Reactive Airways Disease Syndrome

Absence of previous documented respiratory symptom
Onset of symptoms most often occur after a single specific exposure
Exposure is most often to a high concentration of gas, smoke, fume, or vapor with irritant qualities
Symptoms occur within 24 hr of exposure and persist for 3 mo or longer
Symptoms mimic asthma with cough, wheezing, shortness of breath, and/or dyspnea
Pulmonary function tests may demonstrate airflow obstruction but not always
Bronchial hyperresponsiveness is documented by methacholine challenge
Alternative pulmonary diseases are not able to be found

Table 399-10 Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis–central bronchiectasis
- Medical history of asthma*
- Immediate skin prick test reaction to *Aspergillus* antigens*
- Precipitating (IgG) serum antibodies to *Aspergillus fumigatus**
- Total IgE concentration >417 IU/mL (>1000 ng/mL)*
- Central bronchiectasis on chest CT*
- Peripheral blood eosinophilia >500/mm^3
- Lung infiltrates on chest x-ray or chest HRCT
- Elevated specific serum IgE and IgG to *A. fumigatus*

Allergic bronchopulmonary aspergillosis seropositive†
- Medical history of asthma†
- Immediate skin prick test reaction to *A. fumigatus* antigens†
- Precipitating (IgG) serum antibodies to *A. fumigatus*†
- Total IgE concentration >417 IU/mL (>1000 ng/mL)†

Staging of allergic bronchopulmonary aspergillosis

Stage 1	Acute	Upper and middle lob infiltration	High IgE
Stage 2	Remission	No infiltrate off steroids >6 mo	Normal to high IgE
Stage 3	Exacerbation	Upper and middle lobe in filtrations	High IgE
Stage 4	CSD asthma	Minimal infiltrate	Normal to high IgE
Stage 5	End stage	Fibrosis and/or bullae	Normal

*The criteria required for diagnosis of ABPA with central bronchiectasis.

†The first 4 criteria are required for a diagnosis of seropositive ABPA.
CSD, corticosteroid dependent.

Table 399-9 The Classification of the Eosinophilic Lung Diseases

IDIOPATHIC	KNOWN ETIOLOGY
Acute eosinophilic pneumonia	Drug-induced eosinophilic pneumonia
Chronic eosinophilic pneumonia	Infectious causes
Eosinophilic granulomatosis with polyangiitis	• Ascariasis (Löffler syndrome)*
Hypereosinophilic syndromes	• *Toxocara* (*canis* or *cati*)
• Myeloproliferative variant	• Filarial (tropical filarial eosinophilic pneumonia)
• Lymphocytic variant	• *Strongyloides stercoralis* Allergic bronchopulmonary aspergillosis Toxic • L-Tryptophan (eosinophilia myalgia syndrome) • Toxic oil syndrome Illicit drug use (cocaine, heroin, cannabis)

*Note: Löffler eosinophilic pneumonia has transient symptoms and is often classified as neither an acute or chronic eosinophilic pneumonia.

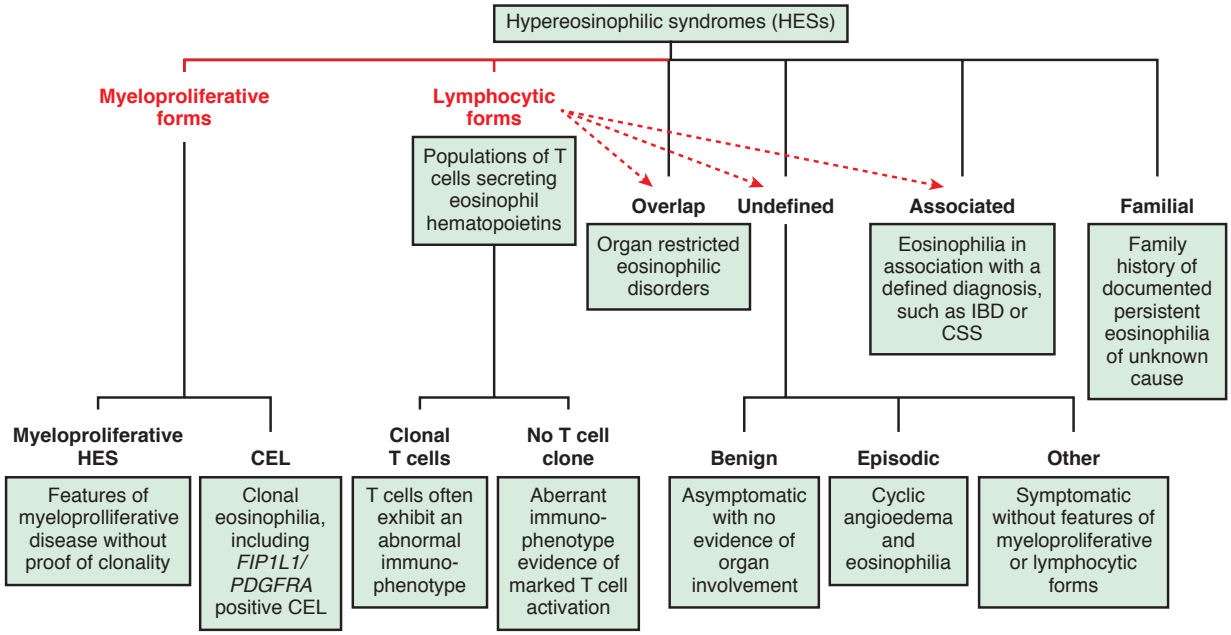


Figure 399-7 A revised classification of hypereosinophilic syndrome (HES). Changes from the previous classification are indicated in red. *Dashed arrows* identify HES forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin-producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. *(From Simon H, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome.* J Allergy Clin Immunol *126:45–49, 2010, Fig. 1.)*

Table 400-3 Etiologic Agents Grouped by Age of the Patient

AGE GROUP	FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)
Neonates (<3 wk)	Group B streptococcus, *Escherichia coli,* other Gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type b,* nontypeable)
3 wk-3 mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypeable); if patient is afebrile, consider *Chlamydia trachomatis*
4 mo-4 yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypeable), *Mycoplasma pneumoniae,* group A streptococcus
≥5 yr	*M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b,* nontypeable), influenza viruses, adenovirus, other respiratory viruses, *Legionella pneumophila*

**H. influenzae* type b is uncommon with routine *H. influenzae* type b immunization.

Table 399-11 Hypereosinophilic Syndrome Variants

Myeloproliferative	Nonclonal Clonal–F1P1L1/PDGFRA-positive chronic eosinophilic leukemia
Lymphocytic	Nonclonal T cells Clonal T-cell expansion with T-cell activation
Overlap	Organ restricted
Familial	Family history of eosinophilia without known cause
Associated	Eosinophilia in chronic disease like inflammatory bowel disease or EGPA (Churg-Strauss syndrome)
Undefined	Asymptomatic Cyclic angioedema with eosinophilia (Gleich syndrome) Symptomatic without myeloproliferation or lymphocytic form

EGPA, eosinophilic granulomatosis with polyangiitis; PDGFRA, platelet-derived growth factor receptor-α.

Table 400-2 Causes of Infectious Pneumonia

BACTERIAL	
Common	
Streptococcus pneumoniae	Consolidation, empyema
Group B streptococci	Neonates
Group A streptococci	Empyema
*Mycoplasma pneumoniae**	Adolescents; summer-fall epidemics
*Chlamydophila pneumoniae**	Adolescents
Chlamydia trachomatis	Infants
Mixed anaerobes	Aspiration pneumonia
Gram-negative enterics	Nosocomial pneumonia
Uncommon	
Haemophilus influenzae type b	Unimmunized
Staphylococcus aureus	Pneumatoceles, empyema; infants
Moraxella catarrhalis	
Neisseria meningitidis	
Francisella tularensis	Animal, tick, fly contact; bioterrorism
Nocardia species	Immunosuppressed persons
*Chlamydophila psittaci**	Bird contact (especially parakeets)
Yersinia pestis	Plague; rat contact; bioterrorism
Legionella species*	Exposure to contaminated water; nosocomial
*Coxiella burnetii**	Q fever; animal (goat, sheep, cattle) exposure
VIRAL	
Common	
Respiratory syncytial virus	Bronchiolitis
Parainfluenza types 1-3	Croup
Influenzas A, B	High fever; winter months
Adenovirus	Can be severe; often occurs between January and April
Human metapneumovirus	Similar to respiratory syncytial virus
Uncommon	
Rhinovirus	Rhinorrhea
Enterovirus	Neonates
Herpes simplex	Neonates
Cytomegalovirus	Infants, immunosuppressed persons
Measles	Rash, coryza, conjunctivitis
Varicella	Adolescents or unimmunized
Hantavirus	Southwestern United States, rodents
Coronavirus (severe acute respiratory syndrome, Middle East respiratory syndrome [MERS])	Asia, Arabian peninsula
FUNGAL	
Histoplasma capsulatum	Ohio/Mississippi River valley; bird, bat contact
Blastomyces dermatitidis	Ohio/Mississippi River valley
Coccidioides immitis	Southwest United States
Cryptococcus neoformans	Bird contact
Aspergillus species	Immunosuppressed persons; nodular lung infection
Mucormycosis	Immunosuppressed persons
Pneumocystis jiroveci	Immunosuppressed, steroids
RICKETTSIAL	
Rickettsia rickettsiae	Tick bite
MYCOBACTERIAL	
Mycobacterium tuberculosis	Travel to endemic region; exposure to high-risk persons
Mycobacterium avium complex	Immunosuppressed persons
PARASITIC	
Various parasites (e.g., Ascaris, *Strongyloides* species)	Eosinophilic pneumonia

*Atypical pneumonia syndrome; may have extrapulmonary manifestations, low-grade fever, patchy diffuse infiltrates, poor response to β-lactam antibiotics, and negative sputum Gram stain.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis & therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 29.*

Table 399-12 The Pediatric Interstitial Lung Diseases

AGE-RELATED ILDS IN INFANCY AND EARLY CHILDHOOD
Diffuse developmental disorders
• Acinar dysplasia
• Congenital alveolar dysplasia
• Alveolar capillary dysplasia with misalignment of pulmonary veins (some due to *FOXF1* mutation)
Growth abnormalities reflecting deficient alveolarization
• Pulmonary hypoplasia
• Chronic neonatal lung disease
• Chromosomal disorders
• Congenital heart disease
Neuroendocrine cell hyperplasia of infancy
Pulmonary interstitial glycogenosis (infantile cellular interstitial pneumonia)
Surfactant dysfunction disorders (pulmonary alveolar proteinosis)
• Surfactant protein–B mutation
• Surfactant protein–C mutation
• *ABCA3* mutation
• Granulocyte-macrophage colony-stimulating factor receptor (*CSF2RA*) mutation
ILD DISORDERS WITH KNOWN ASSOCIATIONS
Infectious/postinfectious processes
• Adenovirus viruses
• Influenza viruses
• *Chlamydia pneumoniae*
• *Mycoplasma pneumoniae*
Environmental agents
• Hypersensitivity pneumonitis
• Toxic inhalation
Aspiration syndromes
PULMONARY DISEASES ASSOCIATED WITH PRIMARY AND SECONDARY IMMUNE DEFICIENCY
Opportunistic infections
Granulomatous lymphocytic ILD associated with common variable immunodeficiency syndrome
Lymphoid intestinal pneumonia (HIV infection)
Therapeutic interventions: chemotherapy, radiation, transplantation, and rejection
Idiopathic ILDs
Usual interstitial pneumonitis
Desquamative interstitial pneumonitis
Lymphocytic interstitial pneumonitis and related disorders
Nonspecific interstitial pneumonitis (cellular/fibrotic)
Eosinophilic pneumonia
Bronchiolitis obliterans syndrome
Pulmonary hemosiderosis and acute idiopathic pulmonary hemorrhage of infancy
Pulmonary alveolar proteinosis
Pulmonary vascular disorders
Pulmonary lymphatic disorders
Pulmonary microlithiasis
Persistent tachypnea of infancy
Brain-thyroid-lung syndrome
SYSTEMIC DISORDERS WITH PULMONARY MANIFESTATIONS
Goodpasture disease
Gaucher disease and other storage diseases
Malignant infiltrates
Hemophagocytic lymphohistiocytosis
Langerhans cell histiocytosis
Sarcoidosis
Systemic sclerosis
Polymyositis/dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Lymphangioleiomyomatosis
Pulmonary hemangiomatosis
Neurocutaneous syndromes
Hermansky-Pudlak syndrome

Modified from Deutsch GH, Young LR, Deterding RR, et al; ChILD Research Co-operative: Diffuse lung disease in young children: application of a novel classification scheme, Am J Respir Crit Care Med *176:1120–1128, 2007.*

Table 400-4 Differential Diagnosis of Recurrent Pneumonia

HEREDITARY DISORDERS
Cystic fibrosis
Sickle cell disease
DISORDERS OF IMMUNITY
HIV/AIDS
Bruton agammaglobulinemia
Selective immunoglobulin G subclass deficiencies
Common variable immunodeficiency syndrome
Severe combined immunodeficiency syndrome
Chronic granulomatous disease
Hyperimmunoglobulin E syndromes
Leukocyte adhesion defect
DISORDERS OF CILIA
Immotile cilia syndrome
Kartagener syndrome
ANATOMIC DISORDERS
Pulmonary sequestration
Lobar emphysema
Gastroesophageal reflux
Foreign body
Tracheoesophageal fistula (H type)
Bronchiectasis
Aspiration (oropharyngeal incoordination)
Aberrant bronchus

Table 400-5 Factors Suggesting Need for Hospitalization of Children with Pneumonia

Age <6 mo
Sickle cell anemia with acute chest syndrome
Multiple lobe involvement
Immunocompromised state
Toxic appearance
Moderate to severe respiratory distress
Requirement for supplemental oxygen
Complicated pneumonia*
Dehydration
Vomiting or inability to tolerate oral fluids or medications
No response to appropriate oral antibiotic therapy
Social factors (e.g., inability of caregivers to administer medications at home or follow-up appropriately)

*Pleural effusion, empyema, abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory distress syndrome, extrapulmonary infection (meningitis, arthritis, pericarditis, osteomyelitis, endocarditis), hemolytic uremic syndrome, sepsis.

Table 400-6 Differentiation of Pleural Fluid

	TRANSUDATE	EMPYEMA
Appearance	Clear	Cloudy or purulent
Cell count (per mm^3)	<1,000	Often >50,000 (cell count has limited predictive value)
Cell type	Lymphocytes, monocytes	Polymorphonuclear leukocytes (neutrophils)
Lactate dehydrogenase	<200 U/L	More than two-thirds upper limit of normal for serum lactate dehydrogenase (LDH)
Pleural fluid:serum LDH ratio	<0.6	>0.6
Protein >3 g	Unusual	Common
Pleural fluid:serum protein ratio	<0.5	>0.5
Glucose*	Normal	Low (<40 mg/dL)
pH*	Normal (7.40-7.60)	<7.10
Gram stain	Negative	Occasionally positive (less than one-third of cases)
Cholesterol		>55 mg/dL
Pleural cholesterol:serum cholesterol ratio	<0.3	>0.3

*Low glucose or pH may be seen in malignant effusion, tuberculosis, esophageal rupture, pancreatitis (positive pleural amylase), and rheumatologic diseases (e.g., systemic lupus erythematosus).

Table 401-1 Conditions That Predispose to Bronchiectasis in Children

PROXIMAL AIRWAY NARROWING
Airway wall compression (i.e., vascular ring, adenopathy impinging on airways)
Airway intraluminal obstruction (e.g., inhaled foreign body, granulation tissue)
Airway stenosis and malacia
AIRWAY INJURY
Bronchiolitis obliterans (e.g., postviral, after lung transplantation)
Recurrent pneumonitis or pneumonia (e.g., pneumococcal pneumonia, aspiration pneumonia)
ALTERED PULMONARY HOST DEFENSES
Cystic fibrosis
Ciliary dyskinesia
Impaired cough (e.g., neuromuscular weakness conditions)
ALTERED IMMUNE STATES
Primary abnormalities (e.g., hypogammaglobulinemia)
Secondary abnormalities (e.g., HIV infection, immunosuppressive agents)
OTHER
Allergic bronchopulmonary aspergillosis
Plastic bronchitis

Table 403-1 Complications of Cystic Fibrosis

RESPIRATORY
Bronchiectasis, bronchitis, bronchiolitis, pneumonia
Atelectasis
Hemoptysis
Pneumothorax
Nasal polyps
Sinusitis
Reactive airway disease
Cor pulmonale
Respiratory failure
Mucoid impaction of the bronchi
Allergic bronchopulmonary aspergillosis
GASTROINTESTINAL
Meconium ileus, meconium plug (neonate)
Meconium peritonitis (neonate)
Distal intestinal obstruction syndrome (non-neonatal obstruction)
Rectal prolapse
Intussusception
Volvulus
Fibrosing colonopathy (strictures)
Appendicitis
Intestinal atresia
Pancreatitis
Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism)
Neonatal obstructive jaundice
Hepatic steatosis
Gastroesophageal reflux
Cholelithiasis
Inguinal hernia
Growth failure (malabsorption)
Vitamin deficiency states (vitamins A, K, E, D)
Insulin deficiency, symptomatic hyperglycemia, diabetes
Malignancy (rare)
OTHER
Infertility
Delayed puberty
Edema-hypoproteinemia
Dehydration–heat exhaustion
Hypertrophic osteoarthropathy-arthritis
Clubbing
Amyloidosis
Diabetes mellitus
Aquagenic palmoplantar keratoderma (skin wrinkling)

Table 403-4 Conditions Associated with False-Positive and False-Negative Sweat Test Results

WITH FALSE-POSITIVE RESULTS
Eczema (atopic dermatitis)
Ectodermal dysplasia
Malnutrition/failure to thrive/deprivation
Anorexia nervosa
Congenital adrenal hyperplasia
Adrenal insufficiency
Glucose-6-phosphatase deficiency
Mauriac syndrome
Fucosidosis
Familial hypoparathyroidism
Hypothyroidism
Nephrogenic diabetes insipidus
Pseudohypoaldosteronism
Klinefelter syndrome
Familial cholestasis syndrome
Autonomic dysfunction
Prostaglandin E infusions
Munchausen syndrome by proxy
WITH FALSE-NEGATIVE RESULTS
Dilution
Malnutrition
Edema
Insufficient sweat quantity
Hyponatremia
Cystic fibrosis transmembrane conductance regulator mutations with preserved sweat duct function

Table 403-3 Diagnostic Criteria for Cystic Fibrosis (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)
or
A history of CF in a sibling
or
A positive newborn screening test
plus
Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:
Two elevated sweat chloride concentrations obtained on separate days
or
Identification of two CF mutations
or
An abnormal nasal potential difference measurement

Table 403-7 Antimicrobial Agents for Cystic Fibrosis Lung Infection

ROUTE	ORGANISMS	AGENTS	DOSAGE (mg/kg/24 hr)	NO. DOSES/24 hr
Oral	*Staphylococcus aureus*	Dicloxacillin	25-50	4
		Linezolid	20	2
		Cephalexin	50	4
		Clindamycin	10-30	3-4
		Amoxicillin-clavulanate	25-45	2-3
	Haemophilus influenzae	Amoxicillin	50-100	2-3
	Pseudomonas aeruginosa	Ciprofloxacin	20-30	2-3
	Burkholderia cepacia	Trimethoprim-sulfamethoxazole	8-10*	2-4
	Empirical	Azithromycin	10, day 1; 5, days 2-5	1
		Erythromycin	30-50	3-4
Intravenous	*S. aureus*	Nafcillin	100-200	4-6
		Vancomycin	40	3-4
	P. aeruginosa	Tobramycin	8-12	1-3
		Amikacin	15-30	2-3
		Ticarcillin	400	4
		Piperacillin	300-400	4
		Ticarcillin-clavulanate	400†	4
		Piperacillin-tazobactam	240-400‡	3
		Meropenem	60-120	3
		Imipenem-cilastatin	45-100	3-4
		Ceftazidime	150	3
		Aztreonam	150-200	4
	B. cepacia	Chloramphenicol	50-100	4
		Meropenem	60-120	3
Aerosol		Tobramycin (inhaled)	300§	2
		Aztreonam (inhaled)	75	3

*Quantity of trimethoprim.
†Quantity of ticarcillin.
‡Quantity of piperacillin.
§In mg per dose.

Table 403-5 Symptoms and Signs Associated with Exacerbation of Pulmonary Infection in Patients with Cystic Fibrosis

SYMPTOMS
Increased frequency and duration of cough
Increased sputum production
Change in appearance of sputum
Increased shortness of breath
Decreased exercise tolerance
Decreased appetite
Feeling of increased congestion in the chest
SIGNS
Increased respiratory rate
Use of accessory muscles for breathing
Intercostal retractions
Change in results of auscultatory examination of chest
Decline in measures of pulmonary function consistent with the presence of obstructive airway disease
Fever and leukocytosis
Weight loss
New infiltrate on chest radiograph

Table 404-1 Clinical Manifestations of Primary Ciliary Dyskinesia

RESPIRATORY TRACT	GENITOURINARY TRACT
Lung	Male and female infertility
Neonatal respiratory distress	
Chronic cough	LEFT-RIGHT ORIENTATION DEFECTS
Recurrent pneumonia	Situs inversus
Bronchiectasis	Heterotaxy
Middle Ear	Congenital heart disease
Chronic otitis media	
Conductive hearing loss	CENTRAL NERVOUS SYSTEM
Paranasal Sinuses	Hydrocephalus
Neonatal rhinitis	Retinitis pigmentosa
Chronic mucopurulent rhinitis	
Chronic pansinusitis	
Nasal polyposis	

Table 407-2 Etiology of Pulmonary Hemorrhage (Hemoptysis)*

FOCAL HEMORRHAGE
Bronchitis and bronchiectasis (especially cystic fibrosis–related)
Infection (acute or chronic), pneumonia, abscess
Tuberculosis
Trauma
Pulmonary arteriovenous malformation
Foreign body (chronic)
Neoplasm including hemangioma
Pulmonary embolus with or without infarction
Bronchogenic cysts
DIFFUSE HEMORRHAGE
Idiopathic of infancy
Congenital heart disease (including pulmonary hypertension, venoocclusive disease, congestive heart failure)
Prematurity
Cow's milk hyperreactivity (Heiner syndrome)
Goodpasture syndrome
Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis)
Henoch-Schönlein purpura and vasculitic disorders
Granulomatous disease (granulomatosis with polyangiitis)
Celiac disease
Coagulopathy (congenital or acquired)
Malignancy
Immunodeficiency
Exogenous toxins
Hyperammonemia
Pulmonary hypertension
Pulmonary alveolar proteinosis
Idiopathic pulmonary hemosiderosis
Tuberous sclerosis
Lymphangiomyomatosis or lymphangioleiomyomatosis
Physical injury or abuse
Catamenial

Table 403-6 Complications of Therapy for Cystic Fibrosis*

COMPLICATION	AGENT
Gastrointestinal bleeding	Ibuprofen
Hyperglycemia	Corticosteroids (systemic)
Growth retardation	Corticosteroids (systemic, inhaled)
Renal dysfunction:	
Tubular	Aminoglycosides
Interstitial nephritis	Semisynthetic penicillins, nonsteroidal antiinflammatory drugs
Hearing loss, vestibular dysfunction	Aminoglycosides
Peripheral neuropathy or optic atrophy	Chloramphenicol (prolonged course)
Hypomagnesemia	Aminoglycosides
Hyperuricemia, colonic stricture	Pancreatic extracts (very large doses)
Goiter	Iodine-containing expectorants
Gynecomastia	Spironolactone
Enamel hypoplasia or staining	Tetracyclines (used in 1st 8 yr of life)

*Common hypersensitivity reactions to drugs are not included.

Table 404-2 Electron Microscopic Findings in Primary Ciliary Dyskinesia vs Acquired Cilia Abnormality

	PCD	ACQUIRED DEFECTS
EM ultrastructure	Dynein arm deficiency	Compound cilia
	Outer arms	Added peripheral tubules
	Inner arms	Deleted peripheral tubules
	Both	Added central pairs
	Translocation of central tubules	Translocation of central tubules
	Few or absent cilia (generalized)	Few or absent cilia (patchy)
Beat frequency	Hyperkinetic, slow or absent	May be normal or reduced
Wave form	Abnormal	May be normal or abnormal

EM, electron microscopy; PCD, primary ciliary dyskinesia.
From Stillwell PC, Wartchow EP, Sagel SD. Primary ciliary dyskinesia in children

Table 405-1 Comparison of Surfactant Deficiency Syndromes

	SP-B DEFICIENCY	SP-C DISEASE	ABCA3 DEFICIENCY	TTF-1 DEFICIENCY
Gene name	*SFTPB*	*SFTPC*	*ABCA3*	*NKX2-1*
Age of onset	Birth	Birth–adulthood	Birth–childhood	Birth–childhood
Inheritance	Recessive	Dominant/sporadic	Recessive	Sporadic/dominant
Mechanism	Loss of function	Gain of toxic function or dominant negative	Loss of function	Loss of function ?Gain of function
Natural history	Lethal	Variable	Generally lethal, may be chronic	Variable
Diagnosis:				
Biochemical *(tracheal aspirate)*	Absence of SP-B and presence of proSP-C	None	None	None
Genetic *(DNA)*	Sequence *SFTPB*	Sequence *SFTPC*	Sequence *ABCA3*	Sequence *NKX2-1;* deletion analysis
Ultrastructural *(lung biopsy–electron microscopy)*	Disorganized lamellar bodies	Not specific; may have dense aggregates	Small dense lamellar bodies with eccentrically placed dense cores	Variable
Treatment	Lung transplantation or compassionate care	Supportive care, lung transplantation if progressing	Consider lung transplantation	Supportive care; treat coexisting conditions (hypothyroidism)

SP, surfactant protein

Table 406-1 Diffuse Alveolar Hemorrhage Syndromes

CLASSIFICATION	SYNDROME
Disorders with pulmonary capillaritis	Idiopathic pulmonary capillaritis Granulomatosis with polyangiitis (Wegener granulomatosis) Microscopic polyangiitis Systemic lupus erythematosus Goodpasture syndrome Antiphospholipid antibody syndrome Henoch-Schönlein purpura Immunoglobulin A nephropathy Behçet syndrome Cryoglobulinemia Drug-induced capillaritis (hypersensitivity) Idiopathic pulmonary-renal syndrome Eosinophilic granulomatosis angiitis (Churg-Strauss syndrome)
Disorders without pulmonary capillaritis:	
Noncardiovascular causes	Idiopathic pulmonary hemosiderosis Heiner syndrome Acute idiopathic pulmonary hemorrhage of infancy Bone marrow transplantation Immunodeficiency Coagulation disorders Hemolytic uremic syndromes Celiac disease (Lane-Hamilton syndrome) Infanticide (child abuse) Infection (HIV, cryptococcosis, Legionnaires disease)
Cardiovascular causes	Mitral stenosis Pulmonary venoocclusive disease Arteriovenous malformations Pulmonary lymphangioleiomyomatosis Pulmonary hypertension Pulmonary capillary hemangiomatosis Chronic heart failure Vascular thrombosis with infarction

Table 407-1 Risk Factors for Pulmonary Embolism

ENVIRONMENTAL
Long-haul air travel
Obesity
Cigarette smoking
Hypertension
Immobility
WOMEN'S HEALTH
Oral contraceptives, including progesterone-only and, especially, third-generation pills
Pregnancy
Hormone replacement therapy
Septic abortion
MEDICAL ILLNESS
Previous pulmonary embolism or deep venous thrombosis
Cancer
Heart failure
Chronic obstructive pulmonary disease
Diabetes mellitus
Inflammatory bowel disease
Antipsychotic drug use
Long-term indwelling central venous catheter
Permanent pacemaker
Internal cardiac defibrillator
Stroke with limb paresis
Spinal cord injury
Nursing home confinement or current or repeated hospital admission
SURGICAL
Trauma
Orthopedic surgery
General surgery
Neurosurgery, especially craniotomy for brain tumor
THROMBOPHILIA
Factor V Leiden mutation
Prothrombin gene mutation
Hyperhomocysteinanemia (including mutation in methylenetetrahydrofolate reductase)
Antiphospholipid antibody syndrome
Deficiency of antithrombin III, protein C, or protein S
High concentrations of factor VIII or XI
Increased lipoprotein (a)
NONTHROMBOTIC
Air
Foreign particles (e.g., hair, talc, as a consequence of intravenous drug misuse)
Amniotic fluid
Bone fragments, bone marrow
Fat
Tumors (Wilms tumor)

Table 408-1 Anatomic Causes of Atelectasis

CAUSE	CLINICAL EXAMPLES
External compression on the pulmonary parenchyma	Pleural effusion, pneumothorax, intrathoracic tumors, diaphragmatic hernia
Endobronchial obstruction completely obstructing the ingress of air	Enlarged lymph node, tumor, cardiac enlargement, foreign body, mucoid plug, broncholithiasis
Intraluminal obstruction of a bronchus	Foreign body, asthma, granulomatous tissue, tumor, secretions including mucous plugs, bronchiectasis, pulmonary abscess, chronic bronchitis, acute laryngotracheobronchitis, plastic bronchitis
Intrabronchiolar obstruction	Bronchiolitis, interstitial pneumonitis, asthma
Respiratory compromise or paralysis	Neuromuscular abnormalities, osseous deformities, overly restrictive casts and surgical dressings, defective movement of the diaphragm, or restriction of respiratory effort

Table 408-2 Benefit of Airway Clearance Therapies in Pediatric Conditions

CLEAR AND PROVEN BENEFIT
Cystic fibrosis
PROBABLE BENEFIT
Neuromuscular disease
Cerebral palsy
Atelectasis in children undergoing mechanical ventilation
POSSIBLE BENEFIT
Prevention of postextubation atelectasis in neonates
MINIMAL TO NO BENEFIT
Acute asthma
Bronchiolitis
Hyaline membrane disease
Respiratory failure without atelectasis
Prevention of atelectasis immediately following surgery

Table 411-1 Causes of Pneumothorax in Children

SPONTANEOUS
Primary idiopathic—usually resulting from ruptured subpleural blebs
Secondary blebs
Congenital lung disease:
Congenital cystic adenomatoid malformation
Bronchogenic cysts
Pulmonary hypoplasia*
Birt-Hogg-Dube syndrome
Conditions associated with increased intrathoracic pressure:
Asthma
Bronchiolitis
Air-block syndrome in neonates
Cystic fibrosis
Airway foreign body
Smoking (cigarettes, marijuana, crack cocaine)
Infection:
Pneumatocele
Lung abscess
Echinococcosis
Bronchopleural fistula
Diffuse lung disease:
Langerhans cell histiocytosis
Tuberous sclerosis
Marfan syndrome
Ehlers-Danlos syndrome
Metastatic neoplasm—usually osteosarcoma (rare)
Pulmonary blastoma
TRAUMATIC
Noniatrogenic
Penetrating trauma
Blunt trauma
High-flow therapy
Loud music (air pressure)
Iatrogenic
Thoracotomy
Thoracoscopy, thoracentesis
Tracheostomy
Tube or needle puncture
Mechanical ventilation

*Associated with renal agenesis, diaphragmatic hernia, amniotic fluid leaks.

Table 416-1 Forms of Bronchopulmonary Dysplasia

FEATURES OF ALL BPD	ADDITIONAL FEATURES OF MILD BPD	ADDITIONAL FEATURES OF MODERATE BPD	ADDITIONAL FEATURES OF SEVERE BPD
<32 wk PMA Oxygen requirement 1st 28 days	Breathing room air at 36 wk PMA	<30% Supplemental oxygen at 36 wk PMA	>30% Supplemental oxygen at 36 wk PMA and mechanical support, CPAP, or ventilation
>32 wk PMA Oxygen requirement 1st 28 days of life	Breathing room air at 56 days of life	<30% Supplemental oxygen at 56 days of life	>30% Supplemental oxygen at 56 days of life and mechanical support, CPAP, or ventilation

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; PMA, postmenstrual age.

Table 418-2 Clinical Classification of Spinal Muscular Atrophy

SMA TYPE	AGE OF ONSET	HIGHEST FUNCTION	NATURAL AGE OF DEATH
Type 1 (severe)	0-6 mo	Never sits	<2 yr
Type 2 (intermediate)	7-18 mo	Never stands	<2 yr
Type 3 (mild)	Older than 18 mo	Stands and walks	Adult
Type 4 (adult)	Second or third decade	Walks during adult years	Adult

From Wang CH, Finkel RS, Bertini ES, et al: Consensus statement for standard of care in spinal muscular atrophy, J Child Neurol *22:1027–1049, 2007.*

Table 419-1 Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Chest pain	Cardiac disease	Inflammation (pericarditis), ischemia (anomalous coronary artery, vascular disease)	Precordial pain, friction rub on examination; exertional pain, radiation to arm or neck
Chest pain	Gastroesophageal reflux disease	Esophageal inflammation and/or spasm	Heartburn, abdominal pain
Cyanosis	Congenital heart disease	Right-to-left shunt	Neonatal onset, lack of response to oxygen
	Methemoglobinemia	Increased levels of methemoglobin interfere with delivery of oxygen to tissues	Drug or toxin exposure, lack of response to oxygen
Dyspnea	Toxin exposure, drug side effect, or overdose	Variable, but often metabolic acidosis	Drug or toxin exposure confirmed by history or toxicology screen, normal oxygen saturation measured by pulse oximetry
	Anxiety, panic disorder	Increased respiratory drive and increased perception of respiratory efforts	Occurs during stressful situation, other symptoms of anxiety or depression

Continued

Table 419-1 Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract—cont'd

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Exercise intolerance	Anemia	Inadequate oxygen delivery to tissues	Pallor, tachycardia, history of bleeding, history of inadequate diet
Exercise intolerance	Deconditioning	Self-explanatory	History of inactivity, obesity
Hemoptysis	Nasal bleeding	Posterior flow of bleeding causes appearance of pulmonary origin	History and physical findings suggest nasal source; normal chest examination, and chest radiography
	Upper gastrointestinal tract bleeding	Hematemesis mimics hemoptysis	History and physical examination suggest gastrointestinal source, normal chest examination and chest radiography
Wheezing, cough, dyspnea	Congenital or acquired cardiac disease	Pulmonary overcirculation (atrioseptal defect, ventriculoseptal defect, patent ductus arteriosus), left ventricular dysfunction	Murmur Refractory to bronchodilators Radiographic changes (prominent pulmonary vasculature, pulmonary edema)
Wheezing, cough	Gastroesophageal reflux disease	Laryngeal and bronchial response to stomach contents	Emesis, pain, heartburn
		Vagally mediated bronchoconstriction	Refractory to bronchodilators

Table 419-2 Disorders with Frequent Respiratory Tract Complications

UNDERLYING DISORDER(S)	RESPIRATORY COMPLICATIONS	DIAGNOSTIC TESTS
Autoimmune disorders	Pulmonary vascular disease, restrictive lung disease, pleural effusion (especially systemic lupus erythematosus), upper airway disease (Wegener granulomatosis)	Spirometry, lung volume determination, oximetry, diffusing capacity of the lung for carbon monoxide, chest radiography, upper airway endoscopy, and/or CT
Central nervous system disease (static or progressive)	Aspiration of oral or gastric contents	Chest radiography, videofluoroscopic swallowing study, esophageal pH probe, fiberoptic bronchoscopy
Immunodeficiency	Infection, bronchiectasis	Chest radiography, fiberoptic bronchoscopy, chest CT
Liver disease	Pleural effusion, hepatopulmonary syndrome	Chest radiography, assessment of orthodeoxia
Malignancy and its therapies	Infiltration, metastasis, malignant or infectious effusion, parenchymal infection, graft-versus-host disease (bone marrow transplant)	Chest radiography, chest CT, fiberoptic bronchoscopy, lung biopsy
Neuromuscular disease	Hypoventilation, atelectasis, pneumonia	Spirometry, lung volume determination, respiratory muscle force measurements
Obesity	Restrictive lung disease, obstructive sleep apnea syndrome, asthma	Spirometry, lung volume determination, nocturnal polysomnography

Table 422-1 Differential Diagnosis of Chest Pain in Pediatric Patients

MUSCULOSKELETAL (COMMON)
Trauma (accidental, abuse)
Exercise, overuse injury (strain, bursitis)
Costochondritis (Tietze syndrome)
Herpes zoster (cutaneous)
Pleurodynia
Fibrositis
Slipping rib
Precordial catch
Sickle cell anemia vasoocclusive crisis
Osteomyelitis (rare)
Primary or metastatic tumor (rare)

PULMONARY (COMMON)
Pneumonia
Pleurisy
Asthma
Chronic cough
Pneumothorax
Infarction (sickle cell anemia)
Foreign body
Embolism (rare)
Pulmonary hypertension (rare)
Tumor (rare)
Bronchiectasis

GASTROINTESTINAL (LESS COMMON)
Esophagitis (gastroesophageal reflux, infectious, pill)
Esophageal foreign body
Esophageal spasm
Cholecystitis
Subdiaphragmatic abscess
Perihepatitis (Fitz-Hugh-Curtis syndrome)
Peptic ulcer disease
Pancreatitis

CARDIAC (LESS COMMON)
Pericarditis
Postpericardiotomy syndrome
Endocarditis
Cardiomyopathy
Mitral valve prolapse
Aortic or subaortic stenosis
Arrhythmias
Marfan syndrome (dissecting aortic aneurysm)
Kawasaki disease
Cocaine, sympathomimetic ingestion
Angina (familial hypercholesterolemia, anomalous coronary artery)

IDIOPATHIC (COMMON)
Anxiety, hyperventilation
Panic disorder

OTHER (LESS COMMON)
Spinal cord or nerve root compression
Breast-related pathologic condition (mastalgia)
Castleman disease (lymph node neoplasm)

Table 418-1 Proposed Guidelines for Initial Evaluation and Follow-Up of Patients with Neuromuscular Disease

INITIAL EVALUATION	BASIC INTERVENTION/ TRAINING
History/physical/anthropometrics	Nutritional consultation and guidance
Lung function and maximal respiratory pressures (PFTs)	Regular chest physiotherapy
Arterial blood gases	Use of percussive devices
Polysomnography*	Respiratory muscle training
Exercise testing (in selected cases)	Annual influenza vaccine
If vital capacity >60% predicted or maximal respiratory pressures >60 cm H_2O	Evaluate PFTs every 6 mo CXR and polysomnography every year
If vital capacity <60% predicted or maximal respiratory pressures <60 cm H_2O	Evaluate PFTs every 3-4 mo CXR, MIP/MEP every 6 mo Polysomnography every 6 mo to year

*Please note that if polysomnography is not readily available, multichannel recordings including oronasal airflow, nocturnal oximetry, and end-tidal carbon dioxide levels may provide an adequate alternative.

CXR, chest x-ray; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PFT, pulmonary function test.

The Cardiovascular System

Table 422-2 Congenital Malformation Syndromes Associated with Congenital Heart Disease

SYNDROME	FEATURES
CHROMOSOMAL DISORDERS	
Trisomy 21 (Down syndrome)	Endocardial cushion defect, VSD, ASD
Trisomy 21p (cat eye syndrome)	Miscellaneous, total anomalous pulmonary venous return
Trisomy 18	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 13	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 9	Miscellaneous
XXXXY	PDA, ASD
Penta X	PDA, VSD
Triploidy	VSD, ASD, PDA
XO (Turner syndrome)	Bicuspid aortic valve, coarctation of aorta
Fragile X	Mitral valve prolapse, aortic root dilatation
Duplication 3q2	Miscellaneous
Deletion 4p	VSD, PDA, aortic stenosis
Deletion 9p	Miscellaneous
Deletion 5p (cri du chat syndrome)	VSD, PDA, ASD
Deletion 10q	VSD, TOF, conotruncal lesions*
Deletion 13q	VSD
Deletion 18q	VSD
SYNDROME COMPLEXES	
CHARGE association (coloboma, heart, atresia choanae, retardation, genital, and ear anomalies)	VSD, ASD, PDA, TOF, endocardial cushion defect
DiGeorge sequence, CATCH 22 (cardiac defects, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia)	Aortic arch anomalies, conotruncal anomalies
Alagille syndrome (arteriohepatic dysplasia)	Peripheral pulmonic stenosis, PS, TOF
VATER association (vertebral, anal, tracheoesophageal, radial, and renal anomalies)	VSD, TOF, ASD, PDA
FAVS (facioauriculovertebral spectrum)	TOF, VSD
CHILD (congenital hemidysplasia with ichthyosiform erythroderma, limb defects)	Miscellaneous
Mulibrey nanism (muscle, liver, brain, eye)	Pericardial thickening, constrictive pericarditis
Asplenia syndrome	Complex cyanotic heart lesions with decreased pulmonary blood flow, transposition of great arteries, anomalous pulmonary venous return, dextrocardia, single ventricle, single atrioventricular valve
Polysplenia syndrome	Acyanotic lesions with increased pulmonary blood flow, azygos continuation of inferior vena cava, partial anomalous pulmonary venous return, dextrocardia, single ventricle, common atrioventricular valve
PHACE syndrome (posterior brain fossa anomalies, facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, eye anomalies)	VSD, PDA, coarctation of aorta, arterial aneurysms
TERATOGENIC AGENTS	
Congenital rubella	PDA, peripheral pulmonic stenosis
Fetal hydantoin syndrome	VSD, ASD, coarctation of aorta, PDA
Fetal alcohol syndrome	ASD, VSD
Fetal valproate effects	Coarctation of aorta, hypoplastic left side of heart, aortic stenosis, pulmonary atresia, VSD
Maternal phenylketonuria	VSD, ASD, PDA, coarctation of aorta
Retinoic acid embryopathy	Conotruncal anomalies
OTHERS	
Apert syndrome	VSD
Autosomal dominant polycystic kidney disease	Mitral valve prolapse
Carpenter syndrome	PDA
Conradi syndrome	VSD, PDA
Crouzon disease	PDA, coarctation of aorta
Cutis laxa	Pulmonary hypertension, pulmonic stenosis
de Lange syndrome	VSD
Ellis–van Creveld syndrome	Single atrium, VSD
Holt-Oram syndrome	ASD, VSD, 1st-degree heart block
Infant of diabetic mother	Hypertrophic cardiomyopathy, VSD, conotruncal anomalies
Kartagener syndrome	Dextrocardia
Meckel-Gruber syndrome	ASD, VSD
Noonan syndrome	Pulmonic stenosis, ASD, cardiomyopathy
Pallister-Hall syndrome	Endocardial cushion defect
Rubinstein-Taybi syndrome	VSD
Scimitar syndrome	Hypoplasia of right lung, anomalous pulmonary venous return to inferior vena cava
Smith-Lemli-Opitz syndrome	VSD, PDA
TAR syndrome (thrombocytopenia and absent radius)	ASD, TOF
Treacher Collins syndrome	VSD, ASD, PDA
Williams syndrome	Supravalvular aortic stenosis, peripheral pulmonic stenosis

ASD, atrial septal defect; AV, aortic valve; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
*Conotruncal includes TOF, pulmonary atresia, truncus arteriosus, and transposition of great arteries.

Table 422-3 Cardiac Manifestations of Systemic Diseases

SYSTEMIC DISEASE	CARDIAC COMPLICATIONS
INFLAMMATORY DISORDERS	
Sepsis	Hypotension, myocardial dysfunction, pericardial effusion, pulmonary hypertension
Juvenile idiopathic arthritis	Pericarditis, rarely myocarditis
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, coronary arteritis, coronary atherosclerosis (with steroids), congenital heart block
Scleroderma	Pulmonary hypertension, myocardial fibrosis, cardiomyopathy
Dermatomyositis	Cardiomyopathy, arrhythmias, heart block
Kawasaki disease	Coronary artery aneurysm and thrombosis, myocardial infarction, myocarditis, valvular insufficiency
Sarcoidosis	Granuloma, fibrosis, amyloidosis, biventricular hypertrophy, arrhythmias
Lyme disease	Arrhythmias, myocarditis
Löffler hypereosinophilic syndrome	Endomyocardial disease
INBORN ERRORS OF METABOLISM	
Refsum disease	Arrhythmia, sudden death
Hunter or Hurler syndrome	Valvular insufficiency, heart failure, hypertension
Fabry disease	Mitral insufficiency, coronary artery disease with myocardial infarction
Glycogen storage disease IIa (Pompe disease)	Short P-R interval, cardiomegaly, heart failure, arrhythmias
Carnitine deficiency	Heart failure, cardiomyopathy
Gaucher disease	Pericarditis
Homocystinuria	Coronary thrombosis
Alkaptonuria	Atherosclerosis, valvular disease
Morquio-Ullrich syndrome	Aortic incompetence
Scheie syndrome	Aortic incompetence
CONNECTIVE TISSUE DISORDERS	
Arterial calcification of infancy	Calcinosis of coronary arteries, aorta
Marfan syndrome	Aortic and mitral insufficiency, dissecting aortic aneurysm, mitral valve prolapse
Congenital contractural arachnodactyly	Mitral insufficiency or prolapse
Ehlers-Danlos syndrome	Mitral valve prolapse, dilatated aortic root
Osteogenesis imperfecta	Aortic incompetence
Pseudoxanthoma elasticum	Peripheral arterial disease
NEUROMUSCULAR DISORDERS	
Friedreich ataxia	Cardiomyopathy
Duchenne dystrophy	Cardiomyopathy, heart failure
Tuberous sclerosis	Cardiac rhabdomyoma
Familial deafness	Occasionally arrhythmia, sudden death
Neurofibromatosis	Pulmonic stenosis, pheochromocytoma, coarctation of aorta
Riley-Day syndrome	Episodic hypertension, postural hypotension
Von Hippel–Lindau disease	Hemangiomas, pheochromocytomas
ENDOCRINE-METABOLIC DISORDERS	
Graves disease	Tachycardia, arrhythmias, heart failure
Hypothyroidism	Bradycardia, pericardial effusion, cardiomyopathy, low-voltage electrocardiogram
Pheochromocytoma	Hypertension, myocardial ischemia, myocardial fibrosis, cardiomyopathy
Carcinoid	Right-sided endocardial fibrosis
HEMATOLOGIC DISORDERS	
Sickle cell anemia	High-output heart failure, cardiomyopathy, pulmonary hypertension
Thalassemia major	High-output heart failure, hemochromatosis
Hemochromatosis (1° or 2°)	Cardiomyopathy
OTHERS	
Appetite suppressants (fenfluramine and dexfenfluramine)	Cardiac valvulopathy, pulmonary hypertension
Cockayne syndrome	Atherosclerosis
Familial dwarfism and nevi	Cardiomyopathy
Jervell and Lange-Nielsen syndrome	Prolonged QT interval, sudden death
Kearns-Sayre syndrome	Heart block
LEOPARD syndrome (lentiginosis)	Pulmonic stenosis, prolonged Q-T interval
Progeria	Accelerated atherosclerosis
Osler-Weber-Rendu disease	Arteriovenous fistula (lung, liver, mucous membrane)
Romano-Ward syndrome	Prolonged Q-T interval, sudden death
Weill-Marchesani syndrome	Patent ductus arteriosus
Werner syndrome	Vascular sclerosis, cardiomyopathy

LEOPARD, multiple *l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals, *r*etardation of growth, sensorineural *d*eafness.

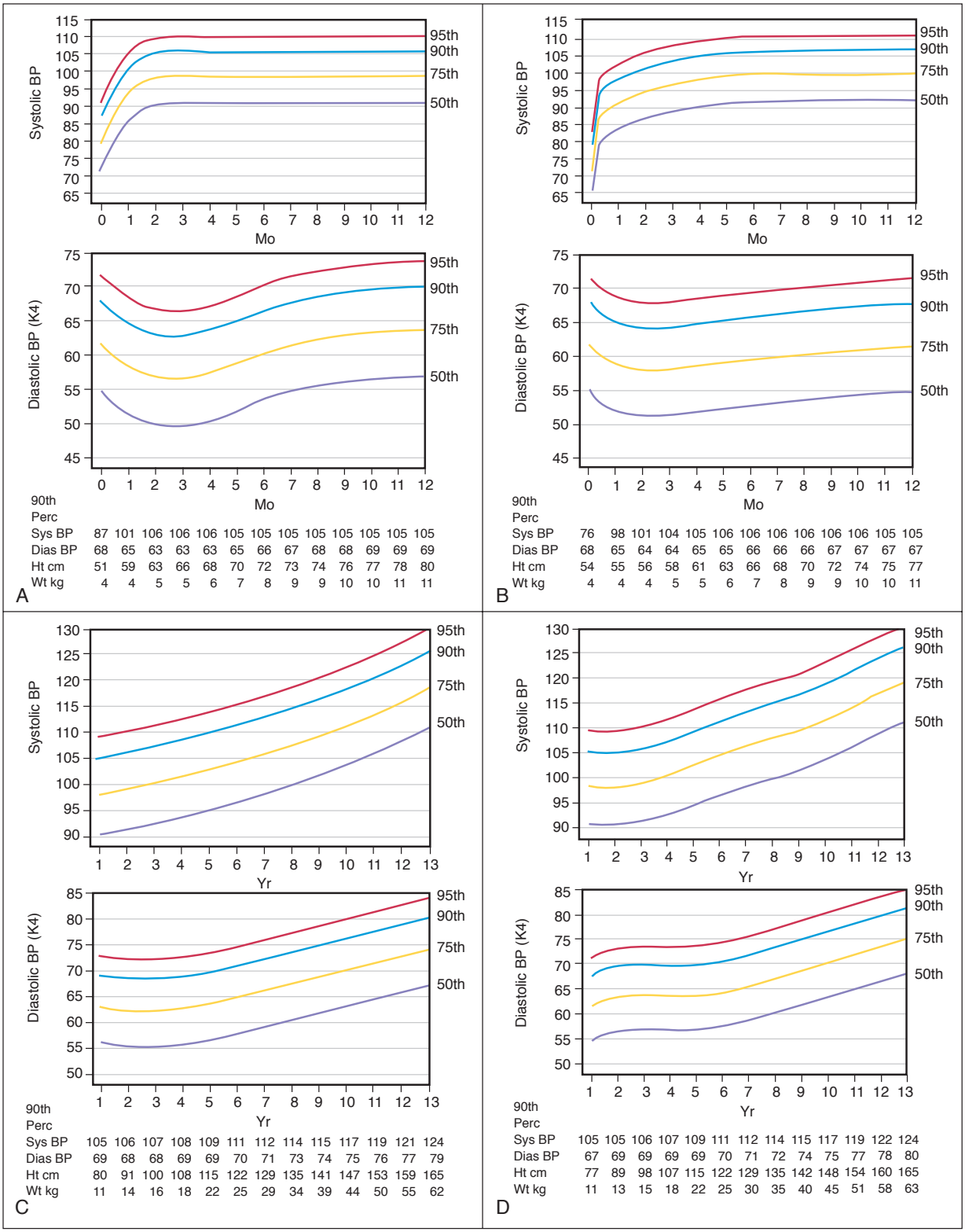


Figure 422-1 **A,** Age-specific percentiles of blood pressure (BP) measurements in boys from birth to 12 mo of age. **B,** Age-specific percentiles of BP measurements in girls from birth to 12 mo of age. **C,** Age-specific percentiles of BP measurements in boys 1-13 yr of age. **D,** Age-specific percentiles of BP measurements in girls 1-13 yr of age; Korotkoff phase IV (K4) used for diastolic BP. Dias, diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. *(From Report of the Second Task Force on Blood Pressure Control in Children—1987. National Heart, Lung, and Blood Institute, Bethesda, MD, Pediatrics 79:1–25, 1987. Copyright 1987 by the American Academy of Pediatrics.)*

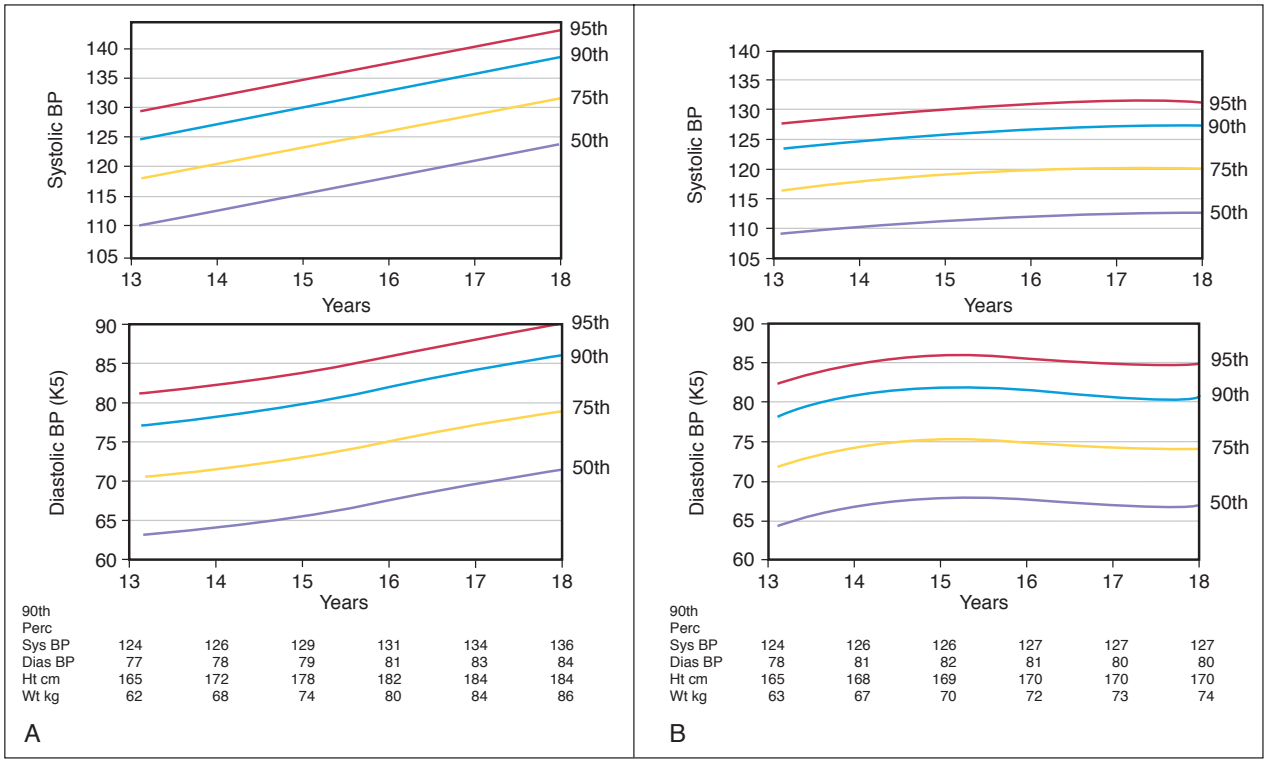


Figure 422-2 **A,** Age-specific percentiles of blood pressure (BP) measurements in boys 13-18 yr of age. **B,** Age-specific percentiles of BP measurements in girls 13-18 yr of age; Korotkoff phase V (K5) used for diastolic BP. Dias, diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. *(From Report of the Second Task Force on Blood Pressure Control in Children—1987, National Heart, Lung, and Blood Institute, Bethesda, MD, Pediatrics 79:1–25, 1987. Copyright 1987 by the American Academy of Pediatrics.)*

Table 422-4 Pulse Rates at Rest

AGE	LOWER LIMITS OF NORMAL (beats/min)		AVERAGE (beats/min)		UPPER LIMITS OF NORMAL (beats/min)	
Newborn	70		125		190	
1–11 mo	80		120		160	
2 yr	80		110		130	
4 yr	80		100		120	
6 yr	75		100		115	
8 yr	70		90		110	
10 yr	70		90		110	
	GIRLS	BOYS	GIRLS	BOYS	GIRLS	BOYS
12 yr	70	65	90	85	110	105
14 yr	65	60	85	80	105	100
16 yr	60	55	80	75	100	95
18 yr	55	50	75	70	95	90

Table 424-1 Relative Frequency of Major Congenital Heart Lesions*

LESION	% OF ALL LESIONS
Ventricular septal defect	35-30
Atrial septal defect (secundum)	6-8
Patent ductus arteriosus	6-8
Coarctation of aorta	5-7
Tetralogy of Fallot	5-7
Pulmonary valve stenosis	5-7
Aortic valve stenosis	4-7
D-Transposition of great arteries	3-5
Hypoplastic left ventricle	1-3
Hypoplastic right ventricle	1-3
Truncus arteriosus	1-2
Total anomalous pulmonary venous return	1-2
Tricuspid atresia	1-2
Single ventricle	1-2
Double-outlet right ventricle	1-2
Others	5-10

Table 424-2 Genetics of Congenital Heart Disease: Defects Associated with Syndromes

CARDIOVASCULAR DISEASE	CHROMOSOMAL LOCATION	GENE(S) IMPLICATED*	COMMON CARDIAC DEFECTS
DiGeorge syndrome, velocardiofacial syndrome	22q11.2, 11p13p14	*TBX1*	TOF, IAA, TA, VSD
Familial ASD with heart block	5q35	*NKX2.5*	ASD, heart block
Familial ASD without heart block	8p22-23	*GATA4*	ASD
Alagille syndrome (bile duct hypoplasia, right-sided cardiac lesions)	20p12, 1p12	*JAGGED1, NOTCH2*	Peripheral pulmonary hypoplasia, PS, TOF
Holt-Oram syndrome (limb defects, ASD)	12q24	*TBX5*	ASD, VSD, PDA
Trisomy 21 (Down syndrome)	21q22	Not known	AVSD
Isolated familial AV septal defect (without trisomy 21)	1p31-p21, 3p25	*CRELD1*	AVSD
Familial TAPVR	4p13-q12	Not known	TAPVR
Noonan syndrome (PS, ASD, hypertrophic cardiomyopathy)	12q24, 12p1.21, 2p212, 3p25.2, 7q34, 15q22.31, 11p15.5, 1p13.2, 10q25.2, 11q23.3,17q11.2	*PTPN11, KRAS, SOS1, RAF1, BRAF, MEK1, HRAS, NRAS, SHOC2, CBL, NF1*	PS, ASD, VSD, PDA, cardiomyopathy
Ellis–van Creveld syndrome (polydactyly, ASD)	4p16	*EVC, EVC2*	ASD, common atrium
Char syndrome (craniofacial, limb defects, PDA)	6p12-21.1	*TFAP2B*	PDA
Williams-Beuren syndrome (supravalvular AS, branch PS, hypercalcemia)	7q11.23	*ELN* (Elastin)	Supravalvar AS, peripheral PS
Marfan syndrome (connective tissue weakness, aortic root dilation)	15q21	Fibrillin	Aortic aneurysm, mitral valve disease
Familial laterality abnormalities	Xq24-2q7, 1q42, 9p13-21	*ZIC3, DNAI1*	Situs inversus, complex congenital heart disease
Turner	X	Not known	Coarctation of the aorta, Aortic stenosis
Trisomy 13 (Patau syndrome)	13	Not known	ASD, VSD, PDA, valve abnormalities
Trisomy 18 (Edwards syndrome)	18	Not known	ASD, VSD, PDA, Valve abnormalities
Cri du chat	5p15.2	*CTNND2*	ASD, VSD, PDA, TOF
Cat eye	22q11	Not known	TAPVR, TOF
Jacobsen	11q23	*JAM-3*	HLHS
Costello	11p15.5	*HRAS*	PS, hypertrophic cardiomyopathy, arrhythmias
CHARGE	8p12, 7q21.11	*CHD7, SEMA3E*	ASD, VSD, TOF
Kabuki syndrome	12q13.12	*MLL2*	ASD, VSD, TOF, coarctation, TGA
Carney syndrome	2p16	*PRKAR1A*	Atrial and ventricular myxomas

AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; AVSD, atrioventricular septal defect; HLHS, hypoplastic left-heart syndrome; IAA, interrupted aortic arch; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*In many cases, mutation of a single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

Table 424-3 Genetics of Isolated Congenital Heart Disease (Nonsyndromic)

GENE IMPLICATED*	PROTEIN ENCODED	CARDIAC DEFECTS
GENES ENCODING TRANSCRIPTION FACTORS		
ANKRD1	Ankyrin repeat domain	TAPVR
CITED2	cAMP responsive element-binding protein	ASD, VSD
FOG2/ZFPM2	Friend of GATA	TOF
GATA6	GATA6 transcription factor	ASD, VSD, TOF, PS, AVSD, PDA
HAND2	Helix-loop-helix transcription factor	TOF
IRX4	Iroquois homeobox 4	VSD
MED13L	Mediator complex subunit 13-like	TGA
NKX2-5/NKX2.5	Homeobox containing transcription factor	ASD, VSD, TOF, HLHS, CoA, TGA, IAA
TBX20	T-Box 20 transcription factor	ASD, VSD, mitral stenosis
ZIC3	Zinc finger transcription factor	TGA, PS, TAPVR, HLHS, ASD, VSD
GENES ENCODING RECEPTORS AND SIGNALING MOLECULES		
ACVR1/ALK2	BMP receptor	AVSD
ACVR2B	Activin receptor	PS, DORV, TGA
ALDH1A2	Retinaldehyde dehydrogenase	TOF
CFC1/CRYPTIC	Cryptic protein	TOF, TGA, AVSD, ASD, VSD, IAA, DORV
CRELD1	Epidermal growth factor-related proteins	ASD; AVSD
FOXH1	Forkhead activin signal transducer	TOF, TGA
GDF1	Growth differentiation factor-1	TOF, TGA, DORV, heterotaxy
GJA1	Connexin 43	ASD, HLHS, TAPVR
LEFTY2	Left-right determination factor	TGA, AVSD, IAA, CoA
NODAL	Nodal homolog (TGF-β superfamily)	TGA, PA, TOF, DORV, TAPVR, AVSD
NOTCH1	NOTCH1 (Ligand of JAG1)	Bicuspid aortic valve, AS, CoA, HLHS
PDGFRA	Platelet-derived growth factor receptor α	TAPVR
SMAD6	MAD-related protein	Bicuspid aortic valve, CoA, AS
TAB2	TGF-β activated kinase	Outflow tract defects
TDGF1	Teratocarcinoma-derived growth factor 1	TOF, VSD
VEGF	Vascular endothelial growth factor	CoA, outflow tract defects
GENES ENCODING STRUCTURAL PROTEINS		
ACTC	α Cardiac actin	ASD
MYH11	Myosin heavy chain 11	PDA, aortic aneurysm
MYH6	α-Myosin heavy chain	ASD, TA, AS, TGA
MYH7	β-Myosin heavy chain	Ebstein anomaly, ASD

AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; cAMP, cyclic adenosine monophosphate; CoA, coarctation of the aorta; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PA, pulmonary artery; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TGF, transforming growth factor; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
*In many cases, mutation of a single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

Table 431-2 Comparison of Cardiosplenic Heterotaxy Syndromes

FEATURE	ASPLENIA (RIGHT ISOMERISM)	POLYSPLENIA (LEFT ISOMERISM)
Spleen	Absent	Multiple
Sidedness (isomerism)	Bilateral right	Bilateral left
Lungs	Bilateral trilobar with eparterial bronchi	Bilateral bilobar with hyparterial bronchi
Sex	Male (65%)	Female ≥ male
Right-sided stomach	Yes	Less common
Symmetric liver	Yes	Yes
Partial intestinal rotation	Yes	Yes
Dextrocardia (%)	30-40	30-40
Pulmonary blood flow	Decreased (usually)	Increased (usually)
Severe cyanosis	Yes	No
Transposition of great arteries (%)	60-75	15
Total anomalous pulmonary venous return (%)	70-80	Rare
Common atrioventricular valve (%)	80-90	20-40
Single ventricle (%)	40-50	10-15
Absent inferior vena cava with azygos continuation	No	Characteristic
Bilateral superior vena cava	Yes	Yes
Other common defects	PA, PS	Partial anomalous pulmonary venous return, ventricular septal defect, double-outlet right ventricle
Risk of pneumococcal sepsis	Yes	Yes
Howell-Jolly and Heinz bodies, pitted erythrocytes	Yes	No
Risk of nosocomial infection	Yes	Yes
Absent gallbladder; biliary atresia	No	Yes

Table 424-4 Genetics of Cardiomyopathies

Hypertrophic cardiomyopathy	14q1	β-Myosin heavy chain
	15q2	α-Tropomyosin
	1q31	Troponin T
	19p13.2-19q13.2	Troponin I
	11p13-q13	Myosin-binding protein C
	12q23	Cardiac slow myosin regulatory light chain
	13p21	Ventricular slow myosin essential light chain
	2q31	Titin
	3p25	Caveolin-3
	Mitochondrial DNA	tRNA-glycine
	Mitochondrial DNA	tRNA-isoleucine
Hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome	7q36.1	AMP-activated protein kinase
Other genetic diseases causing cardiac hypertrophy		
Familial amyloid disease	18q12.1	Transthyretin (TTR)
Noonan syndrome	12q24.1, 2p22.1, 3p25,12p12.1	Protein tyrosine phosphatase 11 (PTPN11), son of sevenless homologue 1 (SOS1), RAF1 protooncogene, GTPase KRAS
Fabry disease	Xq22	α-Galactoside A (GLA)
Danon disease	Xq24	Lysosomal-associated membrane protein 2 (LAMP2)
Hereditary hemochromatosis	6p21.3	Hereditary hemochromatosis protein (HFE)
Pompe disease	17q25	Acid α-glucosidase (GAA)
Dilated cardiomyopathy		
X-linked	Xp21	Dystrophin
	Xp28	Tafazzin
Autosomal recessive	19p13.2-19q13.2	Troponin I

Autosomal dominant: genes encoding multiple proteins have been identified, including cardiac actin; desmin; δ-sarcoglycan; β-myosin heavy chain; cardiac troponin C and T; α-tropomyosin; titin; metavinculin; myosin-binding protein C; muscle LIM protein; α-actinin-2; phospholamban; Cypher/LIM binding domain 3; α-myosin heavy chain; SUR2A (regulatory subunit of K_{ATP} channel); and lamin A/C.
Isolated noncompaction of the left ventricle: autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns have been reported. Genes that have been implicated include: α-dystrobrevin, Cypher/ZASP, lamin A/C, Tafazzin, MIB1, and LIM domain-binding protein 3 (LDB3).
Partially adapted from Dunn KE, Caleshu C, Cirino AL, et al. A clinical approach to inherited hypertrophy: the use of family history in diagnosis, risk assessment, and management. Circ Cardiovasc Genet *6:118-131, 2013.*

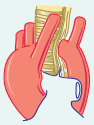
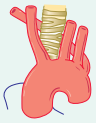
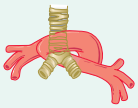
Table 424-5 Genetics of Arrhythmias

Complete heart block	19q13	Not known
Long Q-T syndrome		
LQT1 (autosomal dominant)	11p15.5	*KVLQT1* (K^+ channel)
LQT2 (autosomal dominant)	7q35	*HERG* (K^+ channel)
LQT3 (autosomal dominant)	3p21	*SCN5A* (Na^+ channel)
LQT4 (autosomal dominant)	4q25-27	Not known
LQT5 (autosomal dominant)	21q22-q22	*KCNE1* (K^+ channel)
LQT6	21q22.1	*KCNE2* (K^+ channel)
Jervell and Lange-Nielsen syndrome (autosomal recessive, congenital deafness)	11p15.5	*KVLQT1* (K^+ channel)
LQT8-13	Unknown	Private mutations (rare)
Arrhythmogenic RV dysplasia: There are now 11 genes associated with arrhythmogenic right ventricular dysplasia (ARVD1 through 11) usually with autosomal dominant inheritance, but with variable penetrance. These genes are: *TGF-β_3* (transforming growth factor β), *RyR2* (ryanodine receptor), *LAMR1* (laminin receptor-1), *PTPLA* (protein tyrosine phosphatase), *DSP* (desmoplakin), *PKP2* (plakophilin-2), *DSG2* (desmoglein), and *DSC2* (desmocollin).		
Familial atrial fibrillation (autosomal dominant)	10q22-q24, 6q14-16	Not known
	11p15.5	*KVLQT1* (K^+ channel)
	11p15.5	*KCNQ1* (K^+ channel)
	21q22	*KCNE2* (K^+ channel)
	17q23.1-q24.2	*KCNJ2* (K^+ channel)
	7q35-q36	*KCNH2* (K^+ channel)
Brugada syndrome (right bundle-branch block, ST segment elevation, unexpected sudden death)	3p21-p24	*SCN5A* (Na^+ channel)
	3p22-p24	*GPD-1L* (glycerol-3-phosphate dehydrogenase)
Catecholaminergic polymorphic ventricular tachycardia	–	*RYR2* (autosomal dominant)
	–	*CASQ2* (autosomal recessive)

Table 431-1 Total Anomalous Pulmonary Venous Return

SITE OF CONNECTION (% OF CASES)	% WITH SIGNIFICANT OBSTRUCTION
Supracardiac (50)	
Left superior vena cava (40)	40
Right superior vena cava (10)	75
Cardiac (25)	
Coronary sinus (20)	10
Right atrium (5)	5
Infracardiac (20)	95-100
Mixed (5)	

Table 432-1 Vascular Rings

LESION	SYMPTOMS	PLAIN FILM	BARIUM SWALLOW	BRONCHOSCOPY	MRI ECHOCARDIOGRAPHY	TREATMENT
DOUBLE ARCH 	Stridor Respiratory distress Swallowing dysfunction Reflex apnea	AP—wider base of heart Lat.—narrowed trachea displaced forward at C3-C4	Bilateral indentation of esophagus	Bilateral tracheal compression—both pulsatile	Diagnostic	Ligate and divide smaller arch (usually left)
RIGHT ARCH AND LIGAMENTUM/DUCTUS 	Respiratory distress Swallowing dysfunction	AP—tracheal deviation to left (right arch)	Bilateral indentation of esophagus R > L	Bilateral tracheal compression—r. pulsatile	Diagnostic	Ligate ligamentum or ductus
ANOMALOUS INNOMINATE 	Cough Stridor Reflex apnea	AP—normal Lat.—anterior tracheal compression	Normal	Pulsatile anterior tracheal compression	Unnecessary	Conservative apnea, then suspend
ABERRANT RIGHT SUBCLAVIAN 	Occasional swallowing dysfunction	Normal	AP—oblique defect upward to right Lat.—small defect on right posterior wall	Usually normal	Diagnostic	Ligate artery
PULMONARY SLING 	Expiratory stridor Respiratory distress	AP—low L. hilum, r. emphysema/atelectasis Lat.—anterior bowing of right bronchus and trachea	±Anterior indentation above carina between esophagus and trachea	Tracheal displacement to left Compression of right main bronchus	Diagnostic	Detach and reanastomose to main pulmonary artery in front of trachea

AP, anteroposterior; L and l., left; Lat., lateral; MRI, magnetic resonance imaging; R and r., right.
From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 88.*

Table 432-2 Congenital Anomalies of Coronary Arteries Unassociated with Congenital Heart Disease

Anomalous Aortic Origin
- Eccentric ostium within an aortic sinus
- Ectopic ostium above an aortic sinus
- Conus artery from the right aortic sinus
- Circumflex coronary artery from the right aortic sinus or from the right coronary artery
- Origin of left anterior descending and circumflex coronary arteries from separate ostia in the left aortic sinus (absence of left main coronary artery)
- Atresia of the left main coronary artery
- Origin of the left anterior descending coronary artery from the right aortic sinus or from the right coronary artery
- Origin of the right coronary artery from the left aortic sinus, from posterior aortic sinus, or from left coronary artery
- Origin of a single coronary artery from the right or left aortic sinus
- Anomalous origin from a noncardiac systemic artery

Anomalous Aortic Origin with Anomalous Proximal Course
- Acute proximal angulation
- Ectopic right coronary artery passing between aorta and pulmonary trunk
  - Ectopic left main coronary artery:
  - Between aorta and pulmonary trunk
  - Anterior to the pulmonary trunk
  - Posterior to the aorta
- Within the ventricular septum (intramyocardial)
- Ectopic left anterior descending coronary artery that is anterior, posterior, or between the aorta and pulmonary trunk

Anomalous Origin of a Coronary Artery from the Pulmonary Trunk
- Left main coronary artery
- Left anterior descending coronary artery
- Right coronary artery
- Both right and left coronary arteries
- Circumflex coronary artery
- Accessory coronary artery

Table 433-1 Revised World Health Organization Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)
   - 1.1. Idiopathic (IPAH)
   - 1.2. Familial (FPAH)
   - 1.3. Associated with (APAH):
     - 1.3.1. Connective tissue disorder
     - 1.3.2. Congenital systemic-to-pulmonary shunts
     - 1.3.3. Portal hypertension
     - 1.3.4. HIV infection
     - 1.3.5. Drugs and toxins
     - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
   - 1.4. Associated with significant venous or capillary involvement
     - 1.4.1. Pulmonary venoocclusive disease (PVOD)
     - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
   - 1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left-heart disease
   - 2.1. Left-sided atrial or ventricular heart disease
   - 2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   - 3.1. Chronic obstructive pulmonary disease
   - 3.2. Interstitial lung disease
   - 3.3. Sleep disordered breathing
   - 3.4. Alveolar hypoventilation disorders
   - 3.5. Chronic exposure to high altitude
   - 3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
   - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2. Thromboembolic obstruction of distal pulmonary arteries
   - 4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Table 433-2 Summary of Drugs Used to Treat Pulmonary Hypertension*

DRUG AND MECHANISM OF ACTION	DOSES USED IN PEDIATRIC STUDIES	COMMON SIDE EFFECTS
Epoprostenol (prostacyclin [PGI_2], a potent vasodilator; also inhibits platelet aggregation)	1 ng/kg/min initially. Increase based on clinical course and tolerance to 5-50 ng/kg/min. Some patients may require even higher doses. Must be given by continuous infusion that is not interrupted	Flushing, headache, nausea, diarrhea, hypotension, chest pain, jaw pain
Iloprost (synthetic analog of PGI_2)	2.5-5.0 μg 6-9 times daily (not more frequently than every 2 hr) via inhalation	Flushing, headache, diarrhea, hypotension, jaw pain, exacerbation of pulmonary symptoms (cough, wheezing)
Treprostinil (synthetic analog of PGI_2)	1 ng/kg/min initially. Target dose ranges from 20-80 ng/kg/min. Given either IV or SC via continuous infusion. Longer half-life than epoprostenol	Flushing, headache, diarrhea, hypotension, jaw pain. Pain at infusion site when given SC
Bosentan, ambrisentan, (endothelin receptor EtA and EtB antagonist)	2 mg/kg/dose bid. Use ½ dose for 1st mo and check for liver function test abnormalities prior to up-titrating	Flushing, headache, diarrhea, hypotension, fluid retention, exacerbation of heart failure, anemia, elevated liver function tests, palpitations
Sildenafil (inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase 5)	1 mg/kg/dose given 3-4 times daily. Initial dosing should be ½ final target dose to evaluate for hypotension	Flushing, headache, diarrhea, myalgia, hypotension, priapism, visual disturbance (blue coloration)
Calcium channel blockers (amlodipine, diltiazem, nifedipine)	Previously widely used. Now indicated only for patients who show a strong response to nitric oxide during cardiac catheterization	Flushing, headache, edema, arrhythmia, headache, hypotension, rash, nausea, constipation, elevated liver function tests

*These medications should only be administered under the direction of a specialist in pulmonary hypertension.

Table 434-2	Congenital Heart Defects Associated with Survival into Adulthood Without Surgery or Interventional Cardiac Catheterization
Mild pulmonary valve stenosis Bicuspid aortic valve Small to moderate size atrial septal defect Small ventricular septal defect Small patent ductus arteriosus Mitral valve prolapse Partial atrioventricular canal (ostium primum atrial septal defect and cleft mitral valve) Marfan syndrome Ebstein anomaly Congenitally corrected transposition (atrioventricular and ventriculoarterial discordance)	

Table 434-3	Most Common Congenital Heart Defects Surviving to Adulthood After Surgery or Interventional Catheterization
Aortic valve disease following balloon valvuloplasty or surgical valvotomy Pulmonary valve stenosis following balloon valvuloplasty or surgical valvotomy Tetralogy of Fallot Ventricular septal defect Complete atrioventricular canal defect Transposition of the great arteries Coarctation of the aorta Complex single ventricles after the modified Fontan procedure	

Table 434-6	Issues That Require Coordination of Care Between the Cardiologist and the Primary Care Physician
Antibiotic prophylaxis for endocarditis Medications and drug interactions Anticoagulation with prosthetic valves Exercise and sports participation Educational and vocational planning Contraception and pregnancy Drug, alcohol, and tobacco use Noncardiac surgical planning Anesthetic issues New symptoms or acute illnesses Coexistent medical conditions Travel	

Table 434-4	Risks in Adults Who Have Congenital Heart Disease
Rhythm disorder	Ventral septal defect
Supraventricular tachycardia	Atrial septal defect
Right bundle branch block	Patent ductus arteriosus
Heart block	**Acquired lesions**
Ventricular tachycardia	Subacute bacterial endocarditis
Sudden death	Subvalvular stenosis
Coarctation of aorta	Supravalvular stenosis
Essential hypertension	Valvular insufficiency
Recoarctation	Valvular restenosis
Aneurysm formation	Eisenmenger complex
Residual lesions (shunts)	**Pregnancy risk (see Table 434-5)**

Table 434-5	Lesion Specific Risks of Maternal and Neonatal Complications of Pregnancy
No additional risk	Small septal defects Surgically closed ASD, VSD, PDA Mild to moderate aortic regurgitation Mild to moderate pulmonary stenosis
Slightly increased risk	Postoperative repair of tetralogy of Fallot Transposition of the great arteries, s/p arterial switch procedure
Moderate risk	Transposition of the great arteries, s/p atrial switch procedure Congenitally corrected transposition of the great arteries Single ventricle physiology, s/p Fontan procedure
Severe risk	Cyanotic congenital heart disease, unoperated or palliated Marfan syndrome Prosthetic valves Obstructive lesions including coarctation
Pregnancy contraindicated	Severe pulmonary hypertension Severe obstructive lesions Marfan syndrome, aortic root >40 mm

ASD, atrial septal defect; PDA, patent ductus arteriosus; s/p, status post (after); VSD, ventricular septal defect.

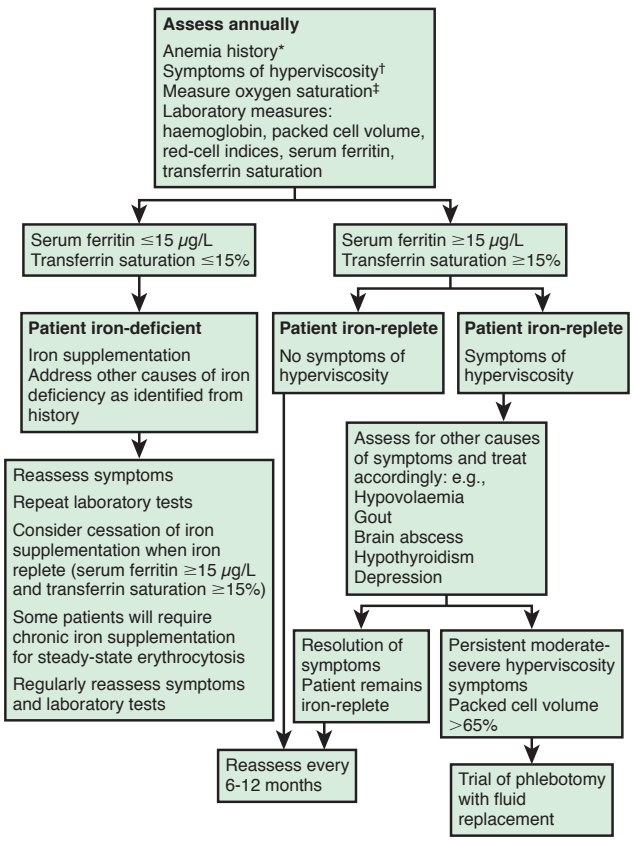


Figure 434-1 Important issues that are crucial to address at time of transition. *(From Spence MS, Balaratnam MS, Gatzoulis MA: Clinical update: cyanotic adult congenital heart disease,* Lancet *370:1530–1532, 2007, p. 1531.*

Table 435-1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS IA: INHIBITS NA^+ FAST CHANNEL, PROLONGS REPOLARIZATION					
Quinidine	SVT, atrial fibrillation, atrial flutter, VT. In atrial flutter, an AV node blocking drug (digoxin, verapamil, propranolol) must be given first to prevent 1:1 conduction	Oral: 30-60 mg/kg/24 hr divided q6h (sulfate) or q8h (gluconate) In adults, 10 mg/kg/day divided q6h Max dose: 2.4g/24 hr	Nausea, vomiting, diarrhea, fever, cinchonism, QRS and QT prolongation, AV nodal block, asystole syncope, thrombocytopenia, hemolytic anemia, SLE, blurred vision, convulsions, allergic reactions, exacerbation of periodic paralysis	Enhances digoxin, may increase PTT when given with warfarin	2-6 µg/mL
Procainamide	SVT, atrial fibrillation, atrial flutter, VT	Oral: 15-50 mg/kg/24 hr divided q4h Max dose: 4 g/24 hr IV: 10-15 mg/kg over 30-45 min load followed by 20-80 µg/kg/min Max dose: 2 g/24 hr	PR, QRS, QT interval prolongation, anorexia, nausea, vomiting, rash, fever, agranulocytosis, thrombocytopenia, Coombs-positive hemolytic anemia, SLE, hypotension, exacerbation of periodic paralysis, proarrhythmia	Toxicity increased by amiodarone and cimetidine	4-8 µg/mL With NAPA <40 µg/mL
Disopyramide	SVT, atrial fibrillation, atrial flutter	Oral: <2 yr: 20-30 mg/kg/24 hr divided q6h or q12h (long-acting form); 2-10 yr: 9-24 mg/kg/24 hr divide q6h or q12h (long-acting form); 11 yr: 5-13 mg/kg/24 hr divided q6h or q12h (long-acting) Max dose: 1.2 g/24 hr	Anticholinergic effects, urinary retention, blurred vision, dry mouth, QT and QRS prolongation, hepatic toxicity, negative inotropic effects, agranulocytosis, psychosis, hypoglycemia, proarrhythmia		2-5 µg/ml
CLASS IB: INHIBITS NA^+ FAST CHANNEL, SHORTENS REPOLARIZATION					
Lidocaine	VT, VF	IV: 1 mg/kg repeat q 5 min 2 times followed by 20-50 µg/kg/min (max dose: 3 mg/kg)	CNS effects, confusion, convulsions, high grade AV block, asystole, coma, paresthesias, respiratory failure	Propranolol, cimetidine, increases toxicity	1-5 µg/mL
Mexiletine	VT	Oral: 6-15 mg/kg/24 hr divided q8h	GI upset, skin rash, neurologic	Cimetidine	0.8-2 µg/mL
Phenytoin	Digitalis intoxication	Oral: 3-6 mg/kg/24 hr divided q12h Max dose: 600 mg IV: 10-15 mg/kg over 1 hr load	Rash, gingival hyperplasia, ataxia, lethargy, vertigo, tremor, macrocytic anemia, bradycardia with rapid push	Amiodarone, oral anticoagulants, cimetidine, nifedipine, disopyramide, increase toxicity	10-20 µg/mL
CLASS IC: INHIBITS NA^+ CHANNEL					
Flecainide	SVT, atrial tachycardia, VT	Oral: 6.7-9.5 mg/kg/24 hr divided q8h In older children, 50-200 mg/m^2/day divided q12h	Blurred vision, nausea, decrease in contractility, proarrhythmia	Amiodarone increases toxicity	0.2-1 µg/mL
Propafenone	SVT, atrial tachycardia, atrial fibrillation, VT	Oral: 150-300 mg/m^2/24 hr divided q6h	Hypotension, decreased contractility, hepatic toxicity, paresthesia, headache, proarrhythmia	Increases digoxin levels	0.2-1 µg/mL

Continued

Table 435-1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class—cont'd

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS II: β-BLOCKERS					
Propranolol	SVT, long QT	Oral: 1-4 mg/kg/24 hr divided q6h Max dose 60 mg/24 hr IV: 0.1-0.15 mg/kg over 5 min Max IV dose: 10 mg	Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
Atenolol	SVT	Oral: 0.5-1 mg/kg/24 hr once daily or divided q12h	Bradycardia, loss of concentration, school performance problems	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
Nadolol	SVT, long QT	Oral: 1-2 mg/kg/24 hr given once daily	Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
CLASS III: PROLONGS REPOLARIZATION					
Amiodarone	SVT, JET, VT	Oral: 10 mg/kg/24 hr in 1-2 divided doses for 4-14 days; reduce to 5 mg/kg/24 hr for several weeks; if no recurrence, reduce to 2.5 mg/kg/24 hr IV: 2.5-5 mg/kg over 30-60 min, may repeat 3 times, then 2-10 mg/kg/24 hr continuous infusion	Hypothyroidism or hyperthyroidism, elevated triglycerides, hepatic toxicity, pulmonary fibrosis	Digoxin (increases levels), flecainide, procainamide, quinidine, warfarin, phenytoin	0.5-2.5 mg/L
CLASS IV AND MISCELLANEOUS MEDICATIONS					
Digoxin	SVT (not WPW), atrial flutter, atrial fibrillation	Oral/load instructions: Premature: 20 μg/kg Newborn: 30 μg/kg >6 mo: 40 μg/kg Give ½ total dose followed by ¼ q8-12h × 2 doses Maintenance: 10 μg/kg/24 hr divide q12h Max dose: 0.5 mg IV: ¾ PO dose Max dose: 0.5 mg	PAC, PVC, bradycardia, AV block, nausea, vomiting, anorexia, prolongs PR interval	Quinidine Amiodarone, verapamil, increase digoxin levels	1-2 mg/mL
Verapamil	SVT (not WPW)	Oral: 2-7 mg/kg/24 hr divided q8h Max dose: 480 mg IV: 0.1-0.2 mg/kg q 20 min × 2 doses Max dose: 5-10 mg	Bradycardia, asystole, high degree AV block, PR prolongation, hypotension, CHF	Use with β-blocker or disopyramide exacerbates CHF, increases digoxin level and toxicity	
Adenosine	SVT	IV: 50-300 μg/kg by need rapid IV push Begin with 50 μg/kg and increase by 50-100 μg/kg/dose Max dose: 18 mg	Chest pain, flushing, dyspnea, bronchospasm, atrial fibrillation, bradycardia, asystole		

AV, atrioventricular; CHF, congestive heart failure; CNS, central nervous systems; GI, gastrointestinal; IV, intravenous; JET, junctional ectopic tachycardia; NAPA, *N*-acetyl procainamide; PAC, premature atrial contraction; PTT, partial thromboplastin time; PVC, premature ventricular contraction; SLE, systemic lupus erythematosus–like illness; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

Table 435-2 Diagnosis of Tachyarrhythmias: Electrocardiographic Findings

	HEART RATE (BEATS/MIN)	P WAVE	QRS DURATION	REGULARITY
Sinus tachycardia	<230	Always present, normal axis	Normal	Rate varies with respiration
Atrial tachycardia	180-320	Present Abnormal P wave morphology and axis	Normal or prolonged (with aberration)	Usually regular but ventricular response may be variable because of Wenckebach conduction
Atrial fibrillation	120-180	Fibrillatory waves	Normal or prolonged (with aberration)	Irregularly irregular (no 2 R-R intervals alike)
Atrial flutter	Atrial: 250-400 Ventricular response variable: 100-320	Sawtoothed flutter waves	Normal or prolonged (with aberration)	Regular ventricular response (e.g., 2:1, 3:1, 3:2, and so on)
Junctional tachycardia	120-280	Atrioventricular dissociation with no fusion, and normal QRS capture beats	Normal or prolonged (with aberration)	Regular (except with capture beats)
Ventricular tachycardia	120-300	Atrioventricular dissociation with capture beats and fusion beats	Prolonged for age	Regular (except with capture beats)

Table 435-3 Inherited Channel Mutations in Long and Short QT Syndromes

	CHROMOSOME	GENE	PROTEIN	ION CURRENT AFFECTED	TRIGGER	SPECIAL FEATURES/ OCCURRENCE
LQTS TYPE						
1	11p15.5	*KCNQ1*	KvLQT1 (Kv7.1)	I_{Ks}	Exercise (swimming), emotion	42-54%
2	7q35-36	*KCNH2*	HERG, (Kv11.1)	I_{Kr}	Rest, emotion, exercise (acoustic, postpartum), surprise (sudden loud noise)	35-45%
3	3p24-21	*SCN5A*	Nav1.5	I_{Na}	Rest, sleep, emotion	1.7-8%; high lethality
4	4q24-27	*ANK2*	Ankyrin-B	$I_{Na\text{-}K}$, $I_{Na\text{-}Ca}$, I_{Na}	Exercise	<1%
5	21q22	*KCNE1*	MinK	I_{Ks}	Exercise, emotion	<1%
6	21q22	*KCNE2*	MiRP1	I_{Kr}	Rest, exercise	<1%
7	17q23	*KCNJ2*	Kir2.1	I_{K1}	Rest, exercise	Periodic paralysis, dysmorphic feature
8	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}	Exercise, emotion	Rare, syndactyly
9	3p25.3	*CAV3*	Caveolin-3	I_{Na}	Nonexertional, sleep	Rare
10	11q23.3	*SCN4B*	NaVβ4	I_{Na}	Exercise, postpartum	<0.1%
11	7q21-22	*AKAP9*	Yotiao	I_{Ks}	Poorly characterized	<1%
12	2q11.2	*SNTA1*	Syntrophin α1	I_{Na}	Poorly characterized	<1%
13	11q24	*KCNJ5*	Kir3.4	K_{Ir}	Poorly characterized	<1%
SHORT QT SYNDROME TYPE						
1	7q35-36	*KCNH2*	HERG (Kv11.1)	I_{Kr}	Exercise, rest (acoustic)	—
2	11p15.5	*KCNQ1*	KvLQT1 (Kv7.1)	I_{Ks}	—	—
3	17q23	*KCNJ2*	Kir2.1	I_{K1}	Sleep	—
4	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}	—	—
5	10p12.33	*CACNB2b*	CaV β2b	I_{Ca}	—	—
JERVELL AND LANGE-NIELSEN SYNDROME TYPE						
1	11p15.5	*KCNQ1*	KvLQT1 (Kv7.1)	I_{Ks}	Exercise (swimming), emotion	1-7%; deafness
2	21q22	*KCNE1*	MinK	I_{Ks}	Exercise (swimming), emotion	<1%; deafness

From Morita H, Wu J, Zipes DP: The QT syndromes: long and short, Lancet *372:750–762, 2008, p. 751, Table 1.*

Table 435-4 Acquired Causes of QT Prolongation*

DRUGS
Antibiotics—erythromycin, clarithromycin, azithromycin, telithromycin, trimethoprim/sulfamethoxazole, fluoroquinolones†
Antifungal agents†—fluconazole, itraconazole, ketoconazole
Antiprotozoal agents—pentamidine isethionate
Antihistamines—astemizole, terfenadine (Seldane; Seldane has been removed from the market for this reason)
Antidepressants—tricyclics such as imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), and doxepin (Sinequan)
Antipsychotics—haloperidol, risperidone, phenothiazines such as thioridazine (Mellaril) and chlorpromazine (Thorazine), selective serotonin uptake inhibitors
Antiarrhythmic agents
Class 1A (sodium channel blockers)—quinidine, procainamide, disopyramide
Class III (prolong depolarization)—amiodarone (rare), bretylium, dofetilide, *N*-acetyl-procainamide, sotalol
Lipid-lowering agents—probucol
Antianginals—bepridil
Diuretics (through K^+ loss)—furosemide (Lasix), ethacrynic acid (bumetanide [Bumex])
Opiates—methadone, oxycodone
Oral hypoglycemic agents—glibenclamide, glyburide
Organophosphate insecticides
Motility agents—cisapride, domperidone
Vasodilators—prenylamine
Other drugs—Ondansetron, HIV protease inhibitors, Chinese herbs
ELECTROLYTE DISTURBANCES
Hypokalemia—diuretics, hyperventilation
Hypocalcemia
Hypomagnesemia
UNDERLYING MEDICAL CONDITIONS
Bradycardia—complete atrioventricular block, severe bradycardia, sick sinus syndrome
Myocardial dysfunction—anthracycline cardiotoxicity, congestive heart failure, myocarditis, cardiac tumors
Endocrinopathy—hyperparathyroidism, hypothyroidism, pheochromocytoma
Neurologic—encephalitis, head trauma, stroke, subarachnoid hemorrhage
Nutritional—alcoholism, anorexia nervosa, starvation

*A more exhaustive updated list of medications that can prolong the QTc interval is available at the University of Arizona Center for Education and Research of Therapeutics website (www.azcert.org).
†Combinations of quinolones plus azoles increase the risk of prolonged QT intervals.
From Park MY: Pediatric cardiology for practitioners, *ed 5, Philadelphia, 2008, Mosby/Elsevier, p. 433, Box 24-1.*

Table 434-1 Extracardiac Complications of Cyanotic Congenital Heart Disease and Eisenmenger Physiology

PROBLEM	ETIOLOGY	THERAPY
Polycythemia	Persistent hypoxia	Phlebotomy
Relative anemia	Nutritional deficiency	Iron replacement
CNS abscess	Right-to-left shunting	Antibiotics, drainage
CNS thromboembolic stroke	Right-to-left shunting or polycythemia	Phlebotomy
Low-grade DIC, thrombocytopenia	Polycythemia	None for DIC unless bleeding, then phlebotomy
Hemoptysis	Pulmonary infarct, thrombosis, or rupture of pulmonary artery plexiform lesion	Embolization
Gum disease	Polycythemia, gingivitis, bleeding	Dental hygiene
Gout	Polycythemia, diuretic agent	Allopurinol
Arthritis, clubbing	Hypoxic arthropathy	None
Pregnancy complications: abortion, fetal growth retardation, prematurity increase, maternal illness	Poor placental perfusion, poor ability to increase cardiac output	Bed rest, pregnancy prevention counseling
Infections	Associated asplenia, DiGeorge syndrome, endocarditis	Antibiotics
	Fatal RSV pneumonia with pulmonary hypertension	Ribavirin; RSV immunoglobulin (prevention)
Failure to thrive	Increased oxygen consumption, decreased nutrient intake	Treat heart failure; correct defect early; increase caloric intake
Protein-losing enteropathy	S/P Fontan; high right-sided pressures	Oral budesonide or sildenafil
Chylothorax	Injury to thoracic duct	Medium chain triglyceride diet Octreotide Surgical ligation of thoracic duct
Psychosocial adjustment	Limited activity, cyanotic appearance, chronic disease, multiple hospitalizations	Counseling

CNS, central nervous system; DIC, disseminated intravascular coagulation; RSV, respiratory syncytial virus; S/P, status post (after).

Table 436-1 Potential Causes of Sudden Death in Infants, Children, and Adolescents

SIDS AND SIDS "MIMICS"
SIDS
Long QT syndromes*
Inborn errors of metabolism
Child abuse
Myocarditis
Ductal-dependent congenital heart disease
CORRECTED OR UNOPERATED CONGENITAL HEART DISEASE
Aortic stenosis
Tetralogy of Fallot
Transposition of great vessels (postoperative atrial switch)
Mitral valve prolapse
Hypoplastic left-heart syndrome
Eisenmenger syndrome
CORONARY ARTERIAL DISEASE
Anomalous origin*
Anomalous tract (tunneled)
Kawasaki disease
Periarteritis
Arterial dissection
Marfan syndrome (rupture of aorta)
Myocardial infarction
MYOCARDIAL DISEASE
Myocarditis
Hypertrophic cardiomyopathy*
Dilated cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Lyme carditis
CONDUCTION SYSTEM ABNORMALITY/ARRHYTHMIA
Long QT syndromes*
Brugada syndrome
Proarrhythmic drugs
Preexcitation syndromes
Heart block
Commotio cordis
Idiopathic ventricular fibrillation
Arrhythmogenic right ventricular dysplasia
Catecholaminergic polymorphic ventricular tachycardia
Heart tumor
MISCELLANEOUS
Pulmonary hypertension
Pulmonary embolism
Heat stroke
Cocaine and other stimulant drugs or medications
Anorexia nervosa
Electrolyte disturbances

SIDS, sudden infant death syndrome.
*Common.

Table 437-1 Bacterial Agents in Pediatric Infective Endocarditis

COMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS
Viridans group streptococci *(Streptococcus mutans, Streptococcus sanguinis, Streptococcus mitis)*
Staphylococcus aureus
Group D streptococcus (enterococcus) *(Streptococcus bovis, Streptococcus faecalis)*
UNCOMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS
Streptococcus pneumoniae
Haemophilus influenzae
Coagulase-negative staphylococci
Abiotrophia defectiva (nutritionally variant streptococcus)
Coxiella burnetii (Q fever)*
Neisseria gonorrhoeae
*Brucella**
*Chlamydia psittaci**
*Chlamydia trachomatis**
*Chlamydia pneumoniae**
*Legionella**
*Bartonella**
*Tropheryma whipplei** (Whipple disease)
HACEK group†
*Streptobacillus moniliformis**
*Pasteurella multocida**
Campylobacter fetus
Culture negative (6% of cases)
PROSTHETIC VALVE
Staphylococcus epidermidis
Staphylococcus aureus
Viridans group streptococcus
Pseudomonas aeruginosa
Serratia marcescens
Diphtheroids
Legionella species*
HACEK group†
Fungi‡

*These fastidious bacteria plus some fungi may produce culture-negative endocarditis. Detection may require special media, incubation for more than 7 days, polymerase chain reaction on blood or valve for 16SrRNA (bacteria) or 18SrRNA (fungi), or serologic tests.
†The HACEK group includes *Haemophilus* species *(H. paraphrophilus, H. parainfluenzae, H. aphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species.
‡*Candida* species, *Aspergillus* species, *Pseudallescheria boydii, Histoplasma capsulatum.*

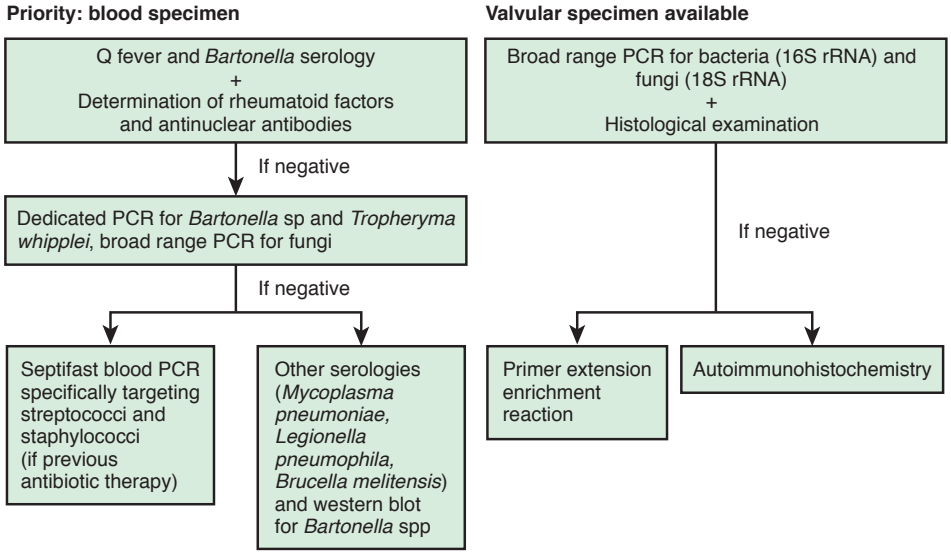


Figure 437-1 Diagnostic tests applied to clinical specimens for the identification of the causative agents of blood culture–negative endocarditis. Septifast, LightCycler SeptiFast (Roche). Serum should be considered a priority specimen, with Q fever and *Bartonella* serologic analysis being routinely done. We also suggest that detection of antinuclear antibodies and rheumatoid factor should be routinely done for diagnosis of noninfective endocarditis.

Table 437-2 Manifestations of Infective Endocarditis

HISTORY
Prior congenital or rheumatic heart disease
Preceding dental, urinary tract, or intestinal procedure
Intravenous drug use
Central venous catheter
Prosthetic heart valve
SYMPTOMS
Fever
Chills
Chest and abdominal pain
Arthralgia, myalgia
Dyspnea
Malaise, weakness
Night sweats
Weight loss
CNS manifestations (stroke, seizures, headache)
SIGNS
Elevated temperature
Tachycardia
Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions)
Janeway lesions
New or changing murmur
Splenomegaly
Arthritis
Heart failure
Arrhythmias
Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli)
Clubbing
LABORATORY
Positive blood culture
Elevated erythrocyte sedimentation rate; may be low with heart or renal failure
Elevated C-reactive protein
Anemia
Leukocytosis
Immune complexes
Hypergammaglobulinemia
Hypocomplementemia
Cryoglobulinemia
Rheumatoid factor
Hematuria
Renal failure: azotemia, high creatinine (glomerulonephritis)
Chest radiograph: bilateral infiltrates, nodules, pleural effusions
Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, myocardial abscess, new-onset valve insufficiency

Table 440-1 Etiology of Pericardial Disease

CONGENITAL
Absence (partial, complete)
Cysts
Mulibrey nanism (*TRIM 37* gene mutation)
Camptodactyly-arthropathy-coxa vara-pericarditis syndrome (*PRG4* gene mutation)
INFECTIOUS
Viral (coxsackievirus B, Epstein-Barr virus, influenza, adenovirus, parvovirus, HIV, mumps)
Bacterial (*Haemophilus influenzae*, streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma, tularemia, listeria, leptospirosis, tuberculosis, Q-fever, salmonella)
Immune complex (meningococcus, *H. influenzae*)
Fungal (actinomycosis, histoplasmosis)
Parasitic (toxoplasmosis, echinococcosis)
NONINFECTIOUS
Idiopathic
Systemic inflammatory diseases (acute rheumatic fever, juvenile idiopathic arthritis, systemic lupus erythematosus, mixed connective tissue disorders, systemic sclerosis, Kawasaki disease, Churg-Strauss syndrome, Behçet syndrome, sarcoidosis, familial Mediterranean fever and other recurrent fever syndromes, pancreatitis, granulomatosis with polyangiitis)
Metabolic (uremia, hypothyroidism, Gaucher disease, very-long-chain acyl-CoA dehydrogenase deficiency)
Traumatic (surgical, catheter, blunt)
Lymphomas, leukemia, radiation therapy
Primary pericardial tumors

Table 437-3 Diagnostic Approach to Uncommon Pathogens Causing Endocarditis

PATHOGEN	DIAGNOSTIC PROCEDURE
Brucella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Coxiella burnetii	Serology (IgG phase I >1 in 800); tissue culture, immunohistology, and PCR of surgical material
Bartonella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Chlamydia spp.	Serology; culture, immunohistology, and PCR of surgical material
Mycoplasma spp.	Serology; culture, immunohistology, and PCR of surgical material
Legionella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Tropheryma whipplei	Histology and PCR of surgical material

Table 437-6 2007 Statement of the American Heart Association (AHA): Cardiac Conditions Associated with the Highest Risk of an Adverse Outcome from Infective Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
CONGENITAL HEART DISEASE (CHD)*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired CHD with prosthetic material or device, whether placed by surgery or catheter intervention, during the 1st 6 mo after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch, or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed here, antibiotic prophylaxis is no longer recommended by the AHA for any other form of CHD.

†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.

From Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis. Guidelines from the American Heart Association, Circulation *116:1736–1754, 2007.*

Table 437-4 Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

REGIMEN	DOSAGE* AND ROUTE	DURATION, WK	COMMENTS
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in 4 or 6 equally divided doses	4	Preferred in patients with impairment of 8th cranial nerve function or renal function
or			
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose ***Pediatric dose***[†]: penicillin 200,000 U/kg per 24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 hr IV/IM in 1 dose	4	
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in 6 equally divided doses	2	2 wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or *Abiotrophia*, *Granulicatella*, or *Gemella* spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 μg/mL and trough serum concentration of <1 μg/mL when 3 divided doses are used; nomogram used for single daily dosing
or			
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose	2	
plus			
Gentamicin sulfate[‡]	3 mg/kg per 24 hr IV/IM in 1 dose, or 3 equally divided doses ***Pediatric dose:*** penicillin 200,000 U/kg per 24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 hr IV/IM in 1 dose; gentamicin 3 mg/kg per 24 hr IV/IM in 1 dose or 3 equally divided doses[§]	2	
Vancomycin hydrochloride[¶]	30 mg/kg per 24 hr IV in 2 equally divided doses not to exceed 2 g/24 hr unless concentrations in serum are inappropriately low ***Pediatric dose:*** 40 mg/kg per 24 hr IV in 2-3 equally divided doses	4	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hr after infusion completed) serum concentration of 30-45 μg/mL and a trough concentration range of 10-15 μg/mL

Minimum inhibitory concentration ≤0.12 μg/mL.
*Dosages recommended are for patients with normal renal function.
[†]Pediatric dose should not exceed that of a normal adult.
[‡]Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy.
[§]Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.
[¶]Vancomycin dosages should be infused during course of at least 1 hr to reduce risk of histamine-release "red man" syndrome.
From Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications, Circulation *111:e394–*

Table 439-3 Causes of Myocarditis

INFECTIOUS		IMMUNE-MEDIATED		TOXIC
Viral	Adenovirus Parvovirus Coxsackie B virus Epstein-Barr virus Hepatitis C virus Measles virus Human herpes virus Varicella-zoster virus Human immunodeficiency virus Influenza viruses	Autoantigens	Churg-Strauss syndrome Inflammatory bowel disease Giant cell myocarditis Diabetes mellitus Sarcoidosis Systemic lupus erythematosus Thyrotoxicosis Takayasu arteritis Kawasaki syndrome Celiac disease Whipple disease	Anthracyclines Cocaine Interleukin-2 Ethanol Heavy metals Spider bite Snake bite Scorpion bite Electric shock
Bacterial	*Mycobacteria* *Streptococcus* spp. *Mycoplasma pneumoniae* *Treponema pallidum* *Corynebacterium diphtheriae* *Borrelia burgdorferi* *Ehrlichia*			
Fungal	*Aspergillus* *Candida* *Coccidioides* *Cryptococcus* *Histoplasma*	Hypersensitivity	Granulomatosis with polyangiitis Sulfonamides Cephalosporins Diuretics Tricyclic antidepressants Dobutamine	
Protozoal	*Trypanosoma cruzi* *Toxoplasma gondii* *Babesia*			
Parasitic	Schistosomiasis Larva migrans (visceral)			

Data from Feldman AM, McNamara D: Myocarditis, N Engl J Med *343:1388–1398, 2000; Magnani JW, Dec GW: Myocarditis: current trends in diagnosis and treatment,* Circulation *113:876–990, 2006.*

Table 437-5 Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

REGIMEN	DOSAGE* AND ROUTE	DURATION	COMMENTS
OXACILLIN-SUSCEPTIBLE STRAINS			
Nafcillin or oxacillin[†]	12 g/24 hr IV in 4-6 equally divided doses	6 wk	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk
with			
Optional addition of gentamicin sulfate[‡]	3 mg/kg per 24 hr IV/IM in 2 or 3 equally divided doses	3-5 day	
	Pediatric dose[§]: Nafcillin or oxacillin 200 mg/kg per 24 hr IV in 4-6 equally divided doses; gentamicin 3 mg/kg per 24 hr IV/IM in 3 equally divided doses		Clinical benefit of aminoglycosides has not been established
For penicillin-allergic (nonanaphylactoid-type) patients:			Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Cefazolin	6 g/24 hr IV in 3 equally divided doses	6 wk	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases[§]
with			
Optional addition of gentamicin sulfate	3 mg/kg per 24 hr IV/IM in 2 or 3 equally divided doses	3-5 day	Clinical benefit of aminoglycosides has not been established
	Pediatric dose: cefazolin 100 mg/kg per 24 hr IV in 3 equally divided doses; gentamicin 3 mg/kg per 24 hr IV/IM in 3 equally divided doses		
OXACILLIN-RESISTANT STRAINS			
Vancomycin[¶]	30 mg/kg per 24 hr IV in 2 equally divided doses	6 wk	Adjust vancomycin dosage to achieve 1 hr serum concentration of 30-45 μg/mL and trough concentration of 10-15 μg/mL
	Pediatric dose: 40 mg/kg per 24 hr IV in 2 or 3 equally divided doses		

IE, infective endocarditis.
*Dosages recommended are for patients with normal renal function.
[†]Penicillin G 24 million U/24 hr IV in 4-6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 μg/mL) and does not produce β-lactamase.
[‡]Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing.
[§]Pediatric dose should not exceed that of a normal adult.
[¶]For specific dosing adjustment and issues concerning vancomycin, see Table 437-4 footnotes.
From Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications, Circulation *111:e394–*

Table 437-7 2007 Statement of the American Heart Association (AHA): Prophylactic Antibiotic Regimens for a Dental Procedure

SITUATION	AGENT	ADULTS	CHILDREN
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin *or* cefazolin or ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin*[†] *or* Clindamycin *or* Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† *or* clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

IM, intramuscular; IV, intravenous.
*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
[†]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, urticaria with penicillins or ampicillin.
From Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis. Guidelines from the American Heart Association, Circulation *116:1736–1754, 2007.*

Table 439-1 Etiology of Pediatric Myocardial Disease

CARDIOMYOPATHY	
Dilated Cardiomyopathy (DCM)	
Neuromuscular diseases	Muscular dystrophies (Duchenne, Becker, limb girdle, Emery-Dreifuss, congenital muscular dystrophy, etc.), myotonic dystrophy, myofibrillar myopathy
Inborn errors of metabolism	Fatty acid oxidation disorders (trifunctional protein, VLCAD), carnitine abnormalities (carnitine transport, CPTI, CPTII), mitochondrial disorders (including Kearns-Sayre syndrome), organic acidemias (propionic acidemia)
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic DCM
Genetic syndromes	Alstrom syndrome, Barth syndrome (phospholipid disorders)
Ischemic	Most common in adults
Chronic tachyarrhythmias	
Hypertrophic Cardiomyopathy (HCM)	
Inborn errors of metabolism	Mitochondrial disorders (including Friedreich ataxia, mutations in nuclear or mitochondrial genome), storage disorders (glycogen storage disorders, especially Pompe; mucopolysaccharidoses; Fabry disease; sphingolipidoses; hemochromatosis; Danon disease)
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic HCM
Genetic syndromes	Noonan, Costello, cardiofaciocutaneous, Beckwith-Wiedemann syndrome
Infant of a diabetic mother	Transient hypertrophy
Restrictive Cardiomyopathy (RCM)	
Neuromuscular disease	Myofibrillar myopathies
Metabolic	Storage disorders
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic RCM
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic ARVC
LVNC	X-linked (Barth syndrome), autosomal dominant, autosomal recessive, mitochondrial inheritance, or sporadic LVNC
SECONDARY OR ACQUIRED MYOCARDIAL DISEASE	
Myocarditis (see also Table 439-3)	**Viral:** parvovirus B19, adenovirus, coxsackievirus A and B, echovirus, rubella, varicella, influenza, mumps, Epstein-Barr virus, cytomegalovirus, measles, poliomyelitis, smallpox vaccine, hepatitis C virus, human herpesvirus 6, HIV virus, or opportunistic infections **Rickettsial:** psittacosis, *Coxiella*, Rocky Mountain spotted fever, typhus **Bacterial:** diphtheria, mycoplasma, meningococcus, leptospirosis, Lyme disease, typhoid fever, tuberculosis, streptococcus, listeriosis **Parasitic:** Chagas disease, toxoplasmosis, *Loa loa, Toxocara canis,* schistosomiasis, cysticercosis, echinococcus, trichinosis **Fungal:** histoplasmosis, coccidioidomycosis, actinomycosis
Systemic inflammatory disease	SLE, infant of mother with SLE, scleroderma, Churg-Strauss vasculitis, rheumatoid arthritis, rheumatic fever, sarcoidosis, dermatomyositis, periarteritis nodosa, hypereosinophilic syndrome (Löffler syndrome), acute eosinophilic necrotizing myocarditis, giant cell myocarditis, Kawasaki disease
Nutritional deficiency	Beriberi (thiamine deficiency), kwashiorkor, Keshan disease (selenium deficiency)
Drugs, toxins	Doxorubicin (Adriamycin), cyclophosphamide, chloroquine, ipecac (emetine), sulfonamides, mesalazine, chloramphenicol, alcohol, hypersensitivity reaction, envenomations, irradiation, herbal remedy (blue cohosh)
Coronary artery disease	Kawasaki disease, medial necrosis, anomalous left coronary artery from the pulmonary artery, other congenital coronary anomalies (anomalous right coronary, coronary ostial stenosis), familial hypercholesterolemia
Hematology-oncology	Anemia, sickle cell disease, leukemia
Endocrine-neuroendocrine	Hyperthyroidism, carcinoid tumor, pheochromocytoma

CPTI/CPTII, carnitine palmitoyltransferase 1/2; LVNC, left ventricular noncompaction; SLE, systemic lupus erythematosus; VLCAD, very long chain acyl coenzyme A dehydrogenase.

Table 442-2 Dosage of Drugs Commonly Used for the Treatment of Congestive Heart Failure

DRUG	DOSAGE
DIGOXIN	
Digitalization (½ initially, followed by ¼ q12h × 2)	Premature: 20 µg/kg Full-term neonate (up to 1 mo): 20-30 µg/kg Infant or child: 25-40 µg/kg Adolescent or adult: 0.5-1 mg in divided doses NOTE: These doses are PO; IV dose is 75% of PO dose
Maintenance digoxin	5-10 µg/kg/day, divided q12h Trough serum level: 1.5-3.0 ng/mL <6 mo old; 1-2 ng/mL >6 mo old NOTE: These doses are PO; IV dose is 75% of PO dose
DIURETICS	
Furosemide (Lasix)	IV: 0.5-2 mg/kg/dose PO: 1-4 mg/kg/day, divided qd-qid
Bumetanide (Bumex)	IV: 0.01-0.1 mg/kg/dose PO: 0.01-0.1 mg/kg/day q24-48h
Chlorothiazide (Diuril)	PO: 20-40 mg/kg/day, divided bid or tid
Spironolactone (Aldactone)	PO: 1-3 mg/kg/day, divided bid or tid
Nesiritide (B-type natriuretic peptide)	IV: 0.001-0.03 µg/kg/min
ADRENERGIC AGONISTS (ALL IV)	
Dobutamine	2-20 µg/kg/min
Dopamine	2-30 µg/kg/min
Isoproterenol	0.01-0.5 µg/kg/min
Epinephrine	0.1-1.0 µg/kg/min
Norepinephrine	0.1-2.0 µg/kg/min
PHOSPHODIESTERASE INHIBITORS (ALL IV)	
Milrinone	0.25-1.0 µg/kg/min
AFTERLOAD-REDUCING AGENTS	
Captopril (Capoten), all PO	Prematures: start at 0.01 mg/kg/dose; 0.1-0.4 mg/kg/day, divided q6-24h Infants: 1.5-6 mg/kg/day, divided q6-12h Children: 2.5-6 mg/kg/day, divided q6-12h
Enalapril (Vasotec), all PO	0.08-0.5 mg/kg/day, divided q12-24h
Hydralazine (Apresoline)	IV: 0.1-0.5 mg/kg/dose (maximum: 20 mg) PO: 0.75-5 mg/kg/day, divided q6-12h
Nitroglycerin	IV: 0.25-0.5 µg/kg/min start; increase to 20 µg/kg/min maximum
Nitroprusside (Nipride)	IV: 0.5-8 µg/kg/min
β-ADRENERGIC BLOCKERS	
Carvedilol (Coreg)	PO: initial dose 0.1 mg/kg/day (maximum: 6.25 mg) divided bid, increase gradually (usually 2 wk intervals) to maximum of 0.5-1 mg/kg/day over 8-12 wk as tolerated; adult maximal dose: 50-100 mg/day
Metoprolol (Lopressor, Toprol-XL)	PO, nonextended release form: 0.2 mg/kg/day divided bid, increase gradually (usually 2 wk intervals) to maximum dose of 1-2 mg/kg/day PO, extended release form (Toprol-XL) is given once daily; adult initial dose 25 mg/day, maximum dose is 200 mg/day

Note: Pediatric doses based on weight should not exceed adult doses. Because recommendations may change, these doses should always be double-checked. Doses may also need to be modified in any patient with renal or hepatic dysfunction.

Maintenance digitalis therapy is started ≈12 hr after full digitalization. The daily dosage, one quarter of the total digitalizing dose, is divided in 2 and given at 12-hr intervals. The oral maintenance dose is usually 20-25% higher than when digoxin is used parenterally (see Table 442-2). The normal daily dose of digoxin for older children (>5 yr of age) calculated by body weight should not exceed the usual adult dose of 0.125-0.5 mg/24 hr.

Table 442-3 Treatment of Cardiogenic Shock*

	DETERMINANTS OF STROKE VOLUME		
	Preload	**Contractility**	**Afterload**
Parameters measured	CVP, PCWP, LAP, cardiac chamber size on echocardiography	CO, BP, fractional shortening or ejection fraction on echocardiography, MV O_2 saturation	BP, peripheral perfusion, SVR
Treatment to improve cardiac output	Volume expansion (crystalloid, colloid, blood)	β-Adrenergic agonists, phosphodiesterase inhibitors	Afterload-reducing agents: milrinone, nitroprusside, ACE inhibitors

ACE, angiotensin-converting enzyme; BP, blood pressure; CO, cardiac output (measured with a thermodilation catheter); CVP, central venous pressure; LAP, left atrial pressure (measured with an indwelling LA line); MV O_2 saturation, mixed venous oxygen saturation (measured with a central venous catheter); PCWP, pulmonary capillary wedge pressure (measured with a thermodilation catheter); SVR, systemic vascular resistance (calculated from CO and mean BP).

*The goal is to improve peripheral perfusion by increasing cardiac output, where: cardiac output = heart rate × stroke volume.

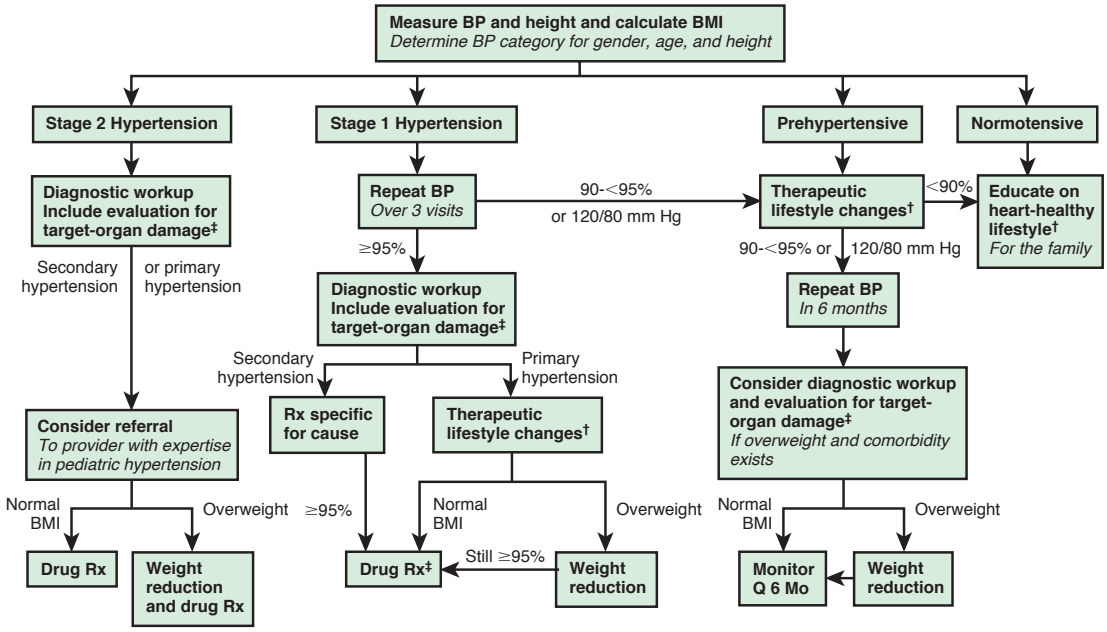


Figure 445-1 Management algorithm. BMI, body mass index; BP, blood pressure; Q, every; Rx, prescription; † diet modification and physical activity; ‡ especially if younger, very high BP, little or no family history, diabetic, or other risk factors. *(From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents,* Pediatrics *114[2 Suppl 4th Report]:571, 2004.)*

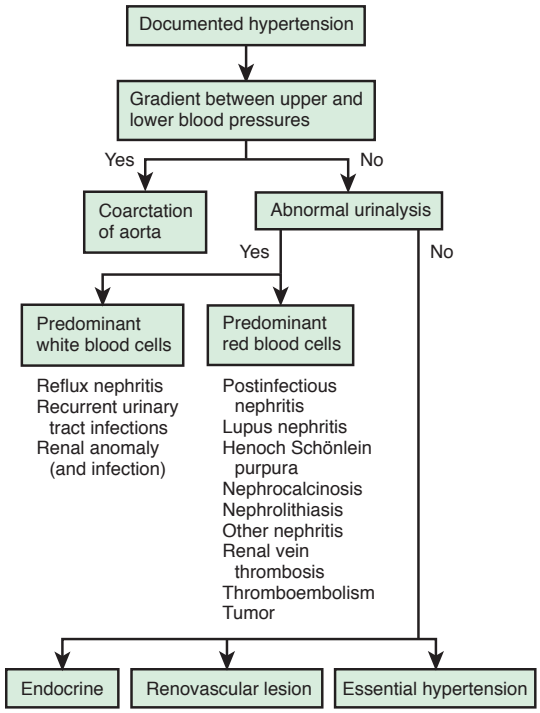


Figure 445-3 Initial diagnostic algorithm in the evaluation of hypertension. *(From Kliegman RM, Greenbaum LA, Lye PS:* Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 222.)*

Table 442-1 Etiology of Heart Failure

FETAL
Severe anemia (hemolysis, fetal-maternal transfusion, parvovirus B19–induced anemia, hypoplastic anemia)
Supraventricular tachycardia
Ventricular tachycardia
Complete heart block
Severe Ebstein anomaly or other severe right-sided lesions
Myocarditis
PREMATURE NEONATE
Fluid overload
Patent ductus arteriosus
Ventricular septal defect
Cor pulmonale (bronchopulmonary dysplasia)
Hypertension
Myocarditis
Genetic cardiomyopathy
FULL-TERM NEONATE
Asphyxial cardiomyopathy
Arteriovenous malformation (vein of Galen, hepatic)
Left-sided obstructive lesions (coarctation of aorta, hypoplastic left heart syndrome)
Large mixing cardiac defects (single ventricle, truncus arteriosus)
Myocarditis
Genetic cardiomyopathy
INFANT-TODDLER
Left-to-right cardiac shunts (ventricular septal defect)
Hemangioma (arteriovenous malformation)
Anomalous left coronary artery
Genetic or metabolic cardiomyopathy
Acute hypertension (hemolytic-uremic syndrome)
Supraventricular tachycardia
Kawasaki disease
Myocarditis
CHILD-ADOLESCENT
Rheumatic fever
Acute hypertension (glomerulonephritis)
Myocarditis
Thyrotoxicosis
Hemochromatosis-hemosiderosis
Cancer therapy (radiation, doxorubicin)
Sickle cell anemia
Endocarditis
Cor pulmonale (cystic fibrosis)
Genetic or metabolic cardiomyopathy (hypertrophic, dilated)

Table 445-1 Conditions Associated with Chronic Hypertension in Children

RENAL
Chronic pyelonephritis
Chronic glomerulonephritis
Hydronephrosis
Congenital dysplastic kidney
Multicystic kidney
Solitary renal cyst
Vesicoureteral reflux nephropathy
Segmental hypoplasia (Ask-Upmark kidney)
Ureteral obstruction
Renal tumors
Renal trauma
Rejection damage following transplantation
Postirradiation damage
Systemic lupus erythematosus (other connective tissue diseases)
VASCULAR
Coarctation of thoracic or abdominal aorta
Renal artery lesions (stenosis, fibromuscular dysplasia, thrombosis, aneurysm)
Umbilical artery catheterization with thrombus formation
Neurofibromatosis (intrinsic or extrinsic narrowing for vascular lumen)
Renal vein thrombosis
Vasculitis
Arteriovenous shunt
Williams-Beuren syndrome
Moyamoya disease
Takayasu arteritis
ENDOCRINE
Hyperthyroidism
Hyperparathyroidism
Congenital adrenal hyperplasia (11β-hydroxylase and 17-hydroxylase defect)
Cushing syndrome
Primary aldosteronism
Apparent mineralcorticoid excess
Glucocorticoid remedial aldosteronism (familial aldosteronism type 1)
Glucocorticoid resistance (Chrousos syndrome)
Pseudohypoaldosteronism type 2 (Gordon syndrome)
Pheochromocytoma
Other neural crest tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)
Liddle syndrome
Geller syndrome
CENTRAL NERVOUS SYSTEM
Intracranial mass
Hemorrhage
Residual following brain injury
Quadriplegia

Table 445-2 Conditions Associated with Transient or Intermittent Hypertension in Children

RENAL
Acute postinfectious glomerulonephritis
Anaphylactoid (Henoch-Schönlein) purpura with nephritis
Hemolytic-uremic syndrome
Acute tubular necrosis
After renal transplantation (immediately and during episodes of rejection)
After blood transfusion in patients with azotemia
Hypervolemia
After surgical procedures on the genitourinary tract
Pyelonephritis
Renal trauma
Leukemic infiltration of the kidney
Obstructive uropathy associated with Crohn disease
DRUGS AND POISONS
Cocaine
Oral contraceptives
Sympathomimetic agents
Amphetamines
Phencyclidine
Corticosteroids and adrenocorticotropic hormone
Cyclosporine or sirolimus treatment posttransplantation
Licorice (glycyrrhizic acid)
Lead, mercury, cadmium, thallium
Antihypertensive withdrawal (clonidine, methyldopa, propranolol)
Vitamin D intoxication
CENTRAL AND AUTONOMIC NERVOUS SYSTEM
Increased intracranial pressure
Guillain-Barré syndrome
Burns
Familial dysautonomia
Stevens-Johnson syndrome
Posterior fossa lesions
Porphyria
Poliomyelitis
Encephalitis
Spinal cord injury (autonomic storm)
MISCELLANEOUS
Preeclampsia
Fractures of long bones
Hypercalcemia
After coarctation repair
White cell transfusion
Extracorporeal membrane oxygenation
Chronic upper airway obstruction

Table 445-3 Clinical Findings in Patients with Mineralocorticoid Excess

CONDITION	CLINICAL PRESENTATION
CAH: 11β-hydroxylase deficiency	Early growth spurt initially, then short adult stature, advanced bone age, premature adrenarche, acne, precocious puberty in males, amenorrhea/hirsutism/virilism in females
CAH: 17α-hydroxylase deficiency	Pseudohermaphroditism (male), sexual infantilism (female)
Apparent mineralocorticoid excess	Growth retardation/short stature, nephrocalcinosis
Liddle syndrome	Severe hypertension, hypokalemia, and metabolic alkalosis, muscle weakness
Geller syndrome	Early onset of hypertension (before age 20 years), exacerbated in pregnancy
Glucocorticoid remediable aldosteronism (GRA) (familial aldosteronism type 1)	Early onset of hypertension, presence of family history of mortality or morbidity from early hemorrhagic stroke
Pseudohypaldosteronism type 2 (Gordon syndrome)	Short stature, hyperkalemic and hyperchloremic metabolic acidosis, borderline blood pressure
Glucocorticoid resistance (children) (Chrousos syndrome)	Ambiguous genitalia, precocious puberty; women may have acne, excessive hair, oligo/anovulation, infertility

Table 445-4 Findings to Look for on Physical Examination in Patients with Hypertension

PHYSICAL FINDINGS	POTENTIAL RELEVANCE
GENERAL	
Pale mucous membranes, edema, growth retardation	Chronic renal disease
Elfin facies, poor growth, retardation	Williams syndrome
Webbing of neck, low hairline, widespread nipples, wide carrying angle	Turner syndrome
Moon face, buffalo hump, hirsutism, truncal obesity, striae, acne	Cushing syndrome
HABITUS	
Thinness	Pheochromocytoma, renal disease, hyperthyroidism
Virilization	Congenital adrenal hyperplasia
Rickets	Chronic renal disease
SKIN	
Café-au-lait spots, neurofibromas	Neurofibromatosis, pheochromocytoma
Tubers, "ash-leaf" spots	Tuberous sclerosis
Rashes	Systemic lupus erythematosus, vasculitis (Henoch-Schönlein purpura), impetigo with acute nephritis
Pallor, evanescent flushing, sweating	Pheochromocytoma
Needle tracks	Illicit drug use
Bruises, striae	Cushing syndrome
Acanthosis nigricans	Type 2 diabetes, insulin resistance
EYES	
Extraocular muscle palsy	Nonspecific, chronic, severe
Fundal changes	Nonspecific, chronic, severe
Proptosis	Hyperthyroidism
HEAD AND NECK	
Goiter	Thyroid disease
Adenotonsillar hypertrophy	Sleep disordered breathing
CARDIOVASCULAR SIGNS	
Absent of diminished femoral pulses, low leg pressure relative to arm pressure	Aortic coarctation
Heart size, rate, rhythm; murmurs; respiratory difficulty, hepatomegaly	Aortic coarctation, congestive heart failure
Bruits over great vessels	Arteritis or arteriopathy
Rub	Pericardial effusion secondary to chronic renal disease
PULMONARY SIGNS	
Pulmonary edema	Congestive heart failure, acute nephritis
Picture of bronchopulmonary dysplasia	Bronchopulmonary dysplasia-associated hypertension
ABDOMEN	
Epigastric bruit	Primary renovascular disease or in association with Williams syndrome, neurofibromatosis, fibromuscular dysplasia, or arteritis
Abdominal masses	Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidneys, hydronephrosis, dysplastic kidneys
NEUROLOGIC SIGNS	
Neurologic deficits	Chronic or severe acute hypertension with stroke
Muscle weakness	Hyperaldosteronism, Liddle syndrome
GENITALIA	
Ambiguous, virilized	Congenital adrenal hyperplasia

Table 445-5 Clinical Evaluation of Confirmed Hypertension

STUDY OR PROCEDURE	PURPOSE	TARGET POPULATION
EVALUATION FOR IDENTIFIABLE CAUSES		
History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination	History and physical examination help focus subsequent evaluation	All children with persistent BP ≥95th percentile
Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture	R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states	All children with persistent BP ≥95th percentile
Complete blood count	R/O anemia, consistent with chronic renal disease	All children with persistent BP ≥95th percentile
Renal ultrasound	R/O renal scar, congenital anomaly, or disparate renal size	All children with persistent BP ≥95th percentile
EVALUATION FOR COMORBIDITY		
Fasting lipid panel, fasting glucose	Identify hyperlipidemia, identify metabolic abnormalities	Overweight patients with BP at 90th-94th percentile; all patients with BP ≥95th percentile; family history of hypertension or cardiovascular disease; child with chronic renal disease
Drug screen	Identify substances that might cause hypertension	History suggestive of possible contribution by substances or drugs.
Polysomnography	Identify sleep disorder in association with hypertension	History of loud, frequent snoring
EVALUATION FOR TARGET-ORGAN DAMAGE		
Echocardiogram	Identify left ventricular hypertrophy and other indications of cardiac involvement	Patients with comorbid risk factors* and BP 90th-94th percentile; all patients with BP ≥95th percentile
Retinal exam	Identify retinal vascular changes	Patients with comorbid risk factors and BP 90th-94th percentile; all patients with BP ≥95th percentile
ADDITIONAL EVALUATION AS INDICATED		
Ambulatory blood pressure monitoring	Identify white coat hypertension, abnormal diurnal BP pattern, BP load	Patients in whom white coat hypertension is suspected, and when other information on BP pattern is needed
Plasma renin determination	Identify low renin, suggesting mineralocorticoid-related disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension Positive family history of severe hypertension
Renovascular imaging Isotopic scintigraphy (renal scan) Magnetic resonance angiography Duplex Doppler flow studies 3-Dimensional CT Arteriography: digital subtraction arteriography or classic	Identify renovascular disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine steroid levels	Identify steroid-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine catecholamines	Identify catecholamine-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension

R/O, rule out.
*Comorbid risk factors also include diabetes mellitus and kidney disease.
From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics *114(2 Suppl 4th Report):562, 2004.*

Table 445-6 Causes of Renovascular Hypertension in Children

Fibromuscular dysplasia

Syndromic
- Neurofibromatosis type 1
- Tuberous sclerosis
- Williams syndrome
- Marfan syndrome
- Other syndromes

Vasculitis
- Takayasu disease
- Polyarteritis nodosa
- Kawasaki disease
- Other systemic vasculitides

Extrinsic compression
- Neuroblastoma
- Wilms tumor
- Other tumors

Other causes
- Radiation
- Umbilical artery catheterization
- Trauma
- Congenital rubella syndrome
- Transplant renal artery stenosis

From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, Lancet *371:1453–1463, 2008, p. 1454, Panel 1.*

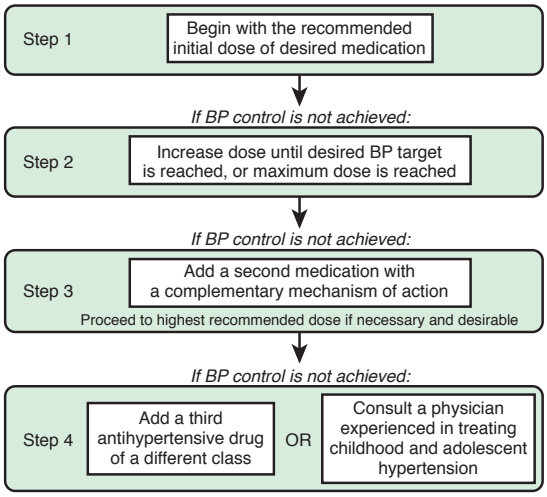


Figure 445-5 Stepped-care approach to antihypertensive therapy in children and adolescents. BP, blood pressure. *(From Flynn JT, Daniels SR: Pharmacologic treatment of hypertension in children and adolescents,* J Pediatr *149:746–754, 2006, p. 751, Fig. 2.)*

Table 445-7 Recommended Doses for Selected Antihypertensive Agents for Use in Hypertensive Children and Adolescents

CLASS	DRUG	STARTING DOSE	INTERVAL	MAXIMUM DOSE*
Aldosterone receptor antagonist	Eplerenone	25 mg/day	qd-bid	100 mg/day
	Spironolactone†	1 $mg \cdot kg^{-1} \cdot day^{-1}$	qd-bid	3.3 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 100 mg/day
Angiotensin-converting enzyme inhibitors	Benazepril†	0.2 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 10 mg/day	qd	0.6 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 40 mg/day
	Captopril†	0.3-0.5 mg/kg/dose	bid-tid	6 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 450 mg/day
	Enalapril†	0.08 $mg \cdot kg^{-1} \cdot day^{-1}$	qd	0.6 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 40 mg/day
	Fosinopril	0.1 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Lisinopril†	0.07 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 5 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Quinapril	5-10 mg/day	qd	80 mg/day
Angiotensin receptor blockers	Candesartan	1-6 yr, 0.2 $mg \cdot kg^{-1} \cdot day^{-1}$ 6-17 yr, <50 kg 4-8 mg once daily >50 kg 8-16 mg qdqd	qd	1-6 yr, 0.4 mg/kg; 6-17 yr, <50 kg 16 mg qd; >50 kg 32 mg qd
	Losartan†	0.75 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 50 mg/day	qd	1.4 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 100 mg/day
	Olmesartan	20 to <35 kg 10 mg qd; ≥35 kg 20 mg qd	qd	20 to <35 kg 20 mg qd ≥35 kg 40 mg qd
	Valsartan†	6-17 yr, 1.3 mg/kg/day up to 40 mg/day; <6 yr: 5-10 mg/day	qd	6-17 yr, 2.7 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 160 mg/day; <6 yr: 80 mg/day
α- and β-Adrenergic antagonists	Labetalol†	2-3 $mg \cdot kg^{-1} \cdot day^{-1}$	bid	10-12 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 1.2 g/day
	Carvedilol	0.1 mg/kg/dose up to 12.5 mg bid	bid	0.5 mg/kg/dose up to 25 mg bid
β-adrenergic antagonists	Atenolol†	0.5-1 $mg \cdot kg^{-1} \cdot day^{-1}$	qd-bid	2 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 100 mg/day
	Bisoprolol/HCTZ	0.04 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 2.5/6.25 mg/day	qd	10/6.25 mg/day
	Metoprolol	1-2 $mg \cdot kg^{-1} \cdot day^{-1}$	bid	6 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 200 mg/day
	Propranolol	1 $mg \cdot kg^{-1} \cdot day^{-1}$	bid-tid	16 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 640 mg/day
Calcium channel blockers	Amlodipine†	0.06 $mg \cdot kg^{-1} \cdot day^{-1}$	qd	0.3 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 10 mg/day
	Felodipine	2.5 mg/day	qd	10 mg/day
	Isradipine†	0.05-0.15 mg/kg/dose	tid-qid	0.8 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 20 mg/day
	Extended-release nifedipine	0.25-0.5 $mg \cdot kg^{-1} \cdot day^{-1}$	qd-bid	3 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 120 mg/day
Central α-agonist	Clonidine†	5-10 μg/kg/day	bid-tid	25 μg/kg/day up to 0.9 mg/day
Diuretics	Amiloride	5-10 mg/day	qd	20 mg/day
	Chlorthalidone	0.3 $mg \cdot kg^{-1} \cdot day^{-1}$	qd	2 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 50 mg/day
	Furosemide	0.5-2.0 mg/kg/dose	qd-bid	6 $mg \cdot kg^{-1} \cdot day^{-1}$
	HCTZ	0.5-1 $mg \cdot kg^{-1} \cdot day^{-1}$	qd	3 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 50 mg/day
Vasodilators	Hydralazine	0.25 mg/kg/dose	tid-qid	7.5 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 200 mg/day
	Minoxidil	0.1-0.2 $mg \cdot kg^{-1} \cdot day^{-1}$	bid-tid	1 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 50 mg/day

bid, Twice-daily; HCTZ, hydrochlorothiazide; qd, once daily; qid, 4 times daily; tid, 3 times daily.
*The maximum recommended adult dose should never be exceeded.
†Information on preparation of a stable extemporaneous suspension is available for these agents.
From Flynn JT. Management of hypertension in the young: role of antihypertensive medications. J Cardiovasc Pharmacol *2011:58(2)111–120.*

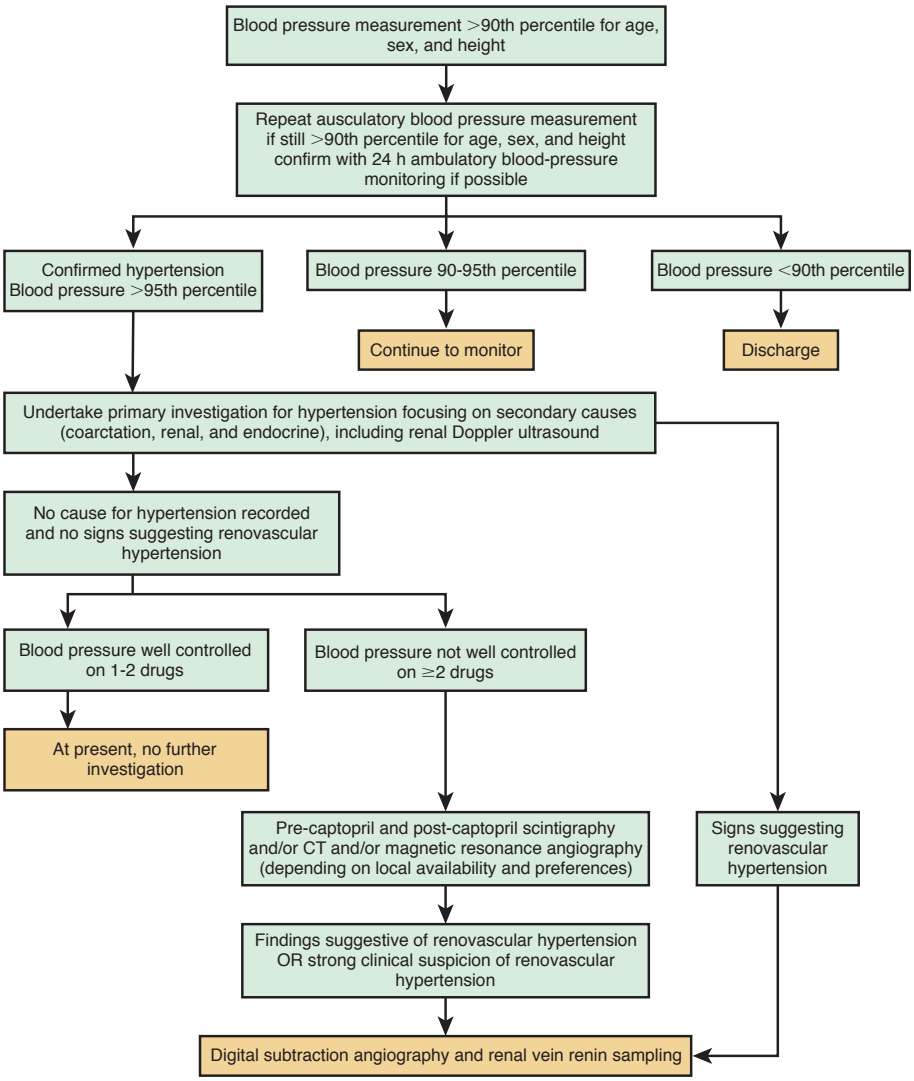


Figure 445-6 Diagnostic pathway for renovascular hypertension. *(From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children,* Lancet *371:1453–1463, 2008, p. 1458, Fig. 6.)*

Table 445-8 Antihypertensive Drugs for Management of Severe Hypertension in Children 1–17 Yr

DRUG	CLASS	DOSE	ROUTE	COMMENTS
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LIFE-THREATENING SYMPTOMS				
Esmolol	β-Adrenergic blocker	100-500 μg/kg/min	IV infusion	Very short acting—constant infusion preferred. May cause profound bradycardia
Hydralazine	Direct vasodilator	0.2-0.6 mg/kg/dose	IV, IM	Should be given q4h when given IV bolus
Labetalol	α- and β-adrenergic blocker	bolus: 0.20-1.0 mg/kg/dose, up to 40 mg/dose infusion: 0.25-3.0 mg/kg/hr	IV bolus or infusion	Asthma and overt heart failure are relative contraindications
Nicardipine	Calcium channel blocker	Bolus: 30 mcg/kg up to 2 mg/dose Infusion: 0.5-4 μg/kg/min	IV bolus or infusion	May cause reflex tachycardia
Sodium nitroprusside	Direct vasodilator	0.5-10 μg/kg/min	IV infusion	Monitor cyanide levels with prolonged (>72 hr) use or in renal failure; or coadminister with sodium thiosulfate
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LESS-SIGNIFICANT SYMPTOMS				
Clonidine	Central α-agonist	0.05-0.1 mg/dose, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness
Enalaprilat	ACE inhibitor	5-10 μg/kg/dose up to 1.25 mg/dose	IV bolus	May cause prolonged hypotension and acute renal failure, especially in neonates
Fenoldopam	Dopamine receptor agonist	0.2-0.8 μg/kg/min	IV infusion	Produced modest reductions in BP in a pediatric clinical trial in patients up to 12 yr
Hydralazine	Direct vasodilator	0.25 mg/kg/dose up to 25 mg/dose	PO	Extemporaneous suspension stable for only 1 wk
Isradipine	Calcium channel blocker	0.05-0.1 mg/kg/dose up to 5 mg/dose	PO	Stable suspension can be compounded
Minoxidil	Direct vasodilator	0.1-0.2 mg/kg/dose up to 10 mg/dose	PO	Most potent oral vasodilator; long acting

ACE, angiotensin-converting enzyme, IM, intramuscular, IV, intravenous, PO, oral.
From Flynn JT: Correction to severe hypertension in children and adolescents: pathophysiology and treatment, Pediatr Nephrol *27(3):503–504, 2012.*

Table 446-1 Characteristics of Hematopoietic Growth Factors

GROWTH FACTOR	MOLECULAR MASS (kDa)	CHROMOSOMAL LOCATION	PRINCIPAL TARGET CELL
ERYTHROPOIETIN	30-39	7q11-12	CFU-E, fetal BFU-E, endothelial cells, neurons, astrocytes, oligodendrocytes
COLONY-STIMULATING FACTORS			
G-CSF	18-22	17q11.2-21	CFU-G, CFU-MIX, mature neutrophils
GM-CSF	18-30	5q23-31	CFU-MIX, CFU-GM, BFU-E, monocytes, mature neutrophils
M-CSF	45-70 (Dimer of 2 subunits)	5q33.1	CFU-M, macrophages
SCF	36	12q21.32	CFU-MIX, BFU-E, CFU-GM, mast cells
TGF-β	25 Homodimeric protein	19q13.2	BL-CFC
CSF-1	192 Amino acid protein	1p13.3	Monocytes, macrophages, dendritic cells, Langerhans cells
INTERLEUKINS			
IL-1	17	Alpha 2q13 Beta 2q13-21	Hepatocytes, macrophages, lymphocytes
IL-2	15-20	4q26-27	T cells, cytotoxic lymphocytes
IL-3	14-30	5q23-31	CFU-MIX, CFU-Meg, CFU-GM, BFU-E, macrophage
IL-4	16-20	5q23-31	T cells, B cells, dendritic cells
IL-5	46 (Dimer of 2 subunits)	5q23-31	CFU-Eo, B cells
IL-6	19-26	7p21-24	CFU-MIX, CFU-GM, BFU-E, monocytes, B cells, T cells, cytotoxic lymphocytes
IL-7	35	8q12-13	B cells
IL-8	8-10	4q13.3	Neutrophils, endothelial cells, T cells
IL-9	16	5q31-32	BFU-E, CFU-MIX
IL-10	18.7	1q32.1	Macrophages, lymphocytes
IL-11	23	19q13	CFU-Meg, B cells, keratinocytes
IL-12	70-75 (Dimer of 2 subunits)	p35/p40	3 (p35) and 11 (p40) T cells, NK cells, macrophages
IL-13	9	5q23-31	Pre-B lymphocytes, macrophages
IL-14	53	5q31	B cells
IL-15	14-15	4q25-35	B cells, T cells
IL-16	12-14	15q23-26	T cells
IL-17	20-30	2q31	Marrow stromal cells
IL-18	24	9p13	CD4+ T cells, NK cells
IL-21		4q26-q27	T cells
IL-23	Dimer of subunits	p19/IL-12p40	CD4+ T cells
IL-25		14q11.2	T cells, monocytes, marrow stromal cells
IL-31	4-Helix bundle	12q24.31	T cells, hematopoietic progenitors
IL-34	222 Amino acid protein	16q22.1	Monocytes, macrophages
THROMBOPOIETIN	35-38	3q27–28	Megakaryocyte progenitors, megakaryocytes

BFU-E, burst-forming units–erythroid; BL-CFU, blast colony-forming cell; CFU-E, colony-forming units–erythroid; CFU-Eo, colony-forming units–eosinophil; CFU-G, colony-forming units–granulocyte; CFU-GM, colony-forming units–granulocyte macrophage; CFU-M, colony-forming units–macrophage; CFU-Meg, colony-forming units–megakaryocyte; CFU-MIX, colony-forming units–mixed; CSF-1, colony-stimulating factor-1; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; NK, natural killer; SCF, stem cell factor; TGF-β, transforming growth factor-beta.

Diseases of the Blood

Table 447-1 Normal Mean and Lower Limits of Normal for Hemoglobin, Hematocrit, and Mean Corpuscular Volume

	HEMOGLOBIN (g/dL)		HEMATOCRIT (%)		MEAN CORPUSCULAR VOLUME (μM^3)	
Age (yr)	**Mean**	**Lower Limit**	**Mean**	**Lower Limit**	**Mean**	**Lower Limit**
0.5-1.9	12.5	11.0	37	33	77	70
2-4	12.5	11.0	38	34	79	73
5-7	13.0	11.5	39	35	81	75
8-11	13.5	12.0	40	36	83	76
12-14 female	13.5	12.0	41	36	85	78
12-14 male	14.0	12.5	43	37	84	77
15-17 female	14.0	12.0	41	36	87	79
15-17 male	15.0	13.0	46	38	86	78
18-49 female	14.0	12.0	42	37	90	80
18-49 male	16.0	14.0	47	40	90	80

From Brugnara C, Oski FJ, Nathan DG: Nathan and Oski's hematology of infancy and childhood, *ed 7, Philadelphia, 2009, WB Saunders, p. 456.*

Table 447-2 NHANES III Hemoglobin Values for Non-Hispanic Whites and African-Americans Ages 2-18 Yr

	WHITE NON-HISPANIC		AFRICAN-AMERICAN	
Age (yr)	**Mean**	**–2 SD**	**Mean**	**–2 SD**
2-5	12.21	10.8	11.95	10.37
6-10	12.87	11.31	12.40	10.74
11-15 male	13.76	11.76	13.06	10.88
11-15 female	13.32	11.5	12.61	10.85
16-18 male	15.00	13.24	14.18	12.42
16-18 female	13.39	11.61	12.37	10.37

Sample size is 5,142 (white, 2,264; African-American, 2,878).
Modified from Robbins EB, Blum S: Hematologic reference values for African American children and adolescents, Am J Hematol *82:611–614, 2007.*

Table 450-1 Comparison of Diamond-Blackfan Anemia and Transient Erythroblastopenia of Childhood

FEATURE	DBA	TEC
Male : female	1.1	1.3
AGE AT DIAGNOSIS, MALE (MO)		
Mean	10	26
Median	2	23
Range	0-408	1-120
AGE AT DIAGNOSIS, FEMALE (MO)		
Mean	14	26
Median	3	23
Range	0-768	1-192
Boys >1 yr	9%	82%
Girls >1 yr	12%	80%
Etiology	Genetic	Acquired
Antecedent history	None	Viral illness
Physical examination abnormal (congenital anomalies present)	25%	0%
LABORATORY		
Hemoglobin (g/dL)	1.2-14.8	2.2-12.5
WBCs <5,000/μL	15%	20%
Platelets >400,000/μL	20%	45%
Adenosine deaminase	Increased	Normal
MCV increased at diagnosis	80%	5%
MCV increased during recovery	100%	90%
MCV increased in remission	100%	0%
HbF increased at diagnosis	100%	20%
HbF increased during recovery	100%	100%
HbF increased in remission	85%	0%
i Antigen increased	100%	20%
i Antigen increased during recovery	100%	60%
i Antigen increased in remission	90%	0%

DBA, Diamond-Blackfan anemia; HbF, fetal hemoglobin; MCV, mean cell volume; TEC, transient erythroblastopenia of childhood; WBC, white blood cell.
From Nathan DG, Orkin SH, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, *ed 6, vol 1, Philadelphia, 2003, WB Saunders, p. 329. Adapted from Alter BP: The bone marrow failure syndromes. In Nathan DG, Oski FA, editors:* Hematology of infancy and childhood, *ed 3, Philadelphia, 1987, WB Saunders, p. 159; and Link MP, Alter BP: Fetal erythropoiesis during recovery from transient erythroblastopenia of childhood (TEC),* Pediatr Res *15:1036–1039, 1981.*

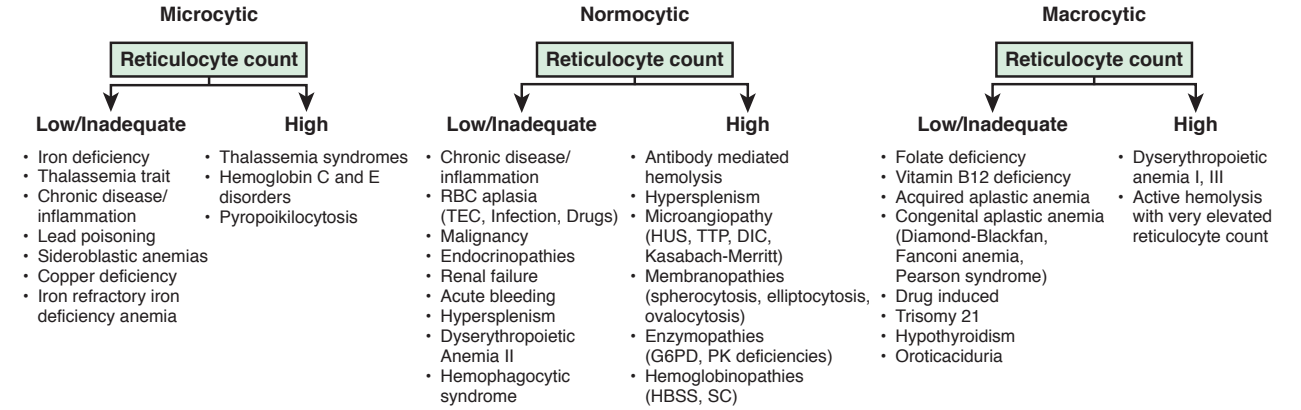


Figure 447-3 Use of the mean corpuscular volume (MCV) and reticulocyte count in the diagnosis of anemia. *(Adapted from Brunetti M, Cohen J:* The Harriet Lane handbook, *ed 17, Philadelphia, 2005, Elsevier Mosby, p 338.)*

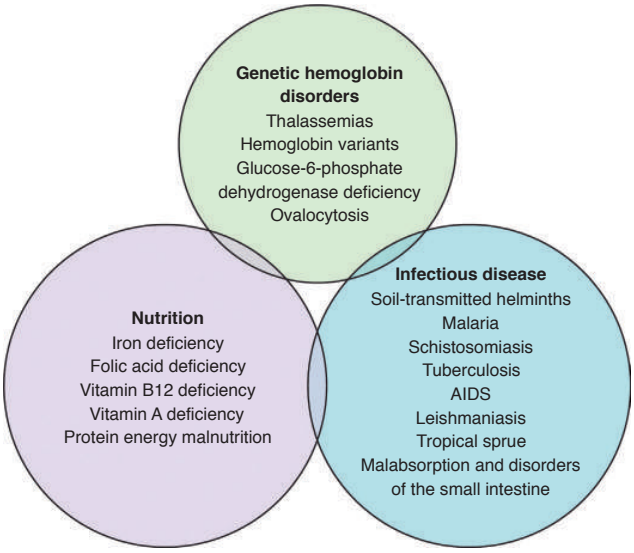


Figure 447-2 Causes of anaemia in countries with low or middle incomes. *(From Balarajan Y, Ramakrishnan U, Özaltin E, et al: Anaemia in low-income and middle-income countries.* Lancet *378:2123–2134, 2011, Fig. 3.)*

Table 448-1 Range of Congenital Anomalies Observed in Diamond-Blackfan Anemia

Craniofacial	Hypertelorism Broad, flat nasal bridge Cleft palate High arched palate Microcephaly Micrognathia Microtia Low-set ears Low hair line Epicanthus Ptosis
Ophthalmologic	Congenital glaucoma Strabismus Congenital cataract
Neck	Short neck Webbed neck Sprengel deformity Klippel-Feil deformity
Thumbs	Triphalangeal Duplex or bifid Hypoplastic Flat thenar eminence Absent radial artery
Urogenital	Absent kidney Horseshoe kidney Hypospadias
Cardiac	Ventricular septal defect Atrial septal defect Coarctation of the aorta Complex cardiac anomalies
Other musculoskeletal	Growth retardation Syndactyly
Neuromotor	Learning difficulties

The list includes the anomalies that are most characteristic of DBA but is not exhaustive. Multiple anomalies, most commonly including craniofacial, are present in up to 25% of affected individuals.

Table 455-1 Indicators of Iron-Deficiency Anemia

INDICATOR	SELECTED CUTOFF VALUES TO DEFINE IRON DEFICIENCY	COMMENTS
Hemoglobin (g/dL)	<11.0 for non-Hispanic whites ages 0.5-4 yr	When used alone, it has low specificity and sensitivity. Use appropriate age specific normal values found in Table 447-1. Normal values for African-Americans are found in Table 447-2.
Mean corpuscular volume (MCV) (μm^3)	<70 from 6-24 months	A reliable, but late indicator of iron deficiency (ID) Low values can also be a result of thalassemia and other causes of microcytosis. Normal values are found in Table 447-1.
Serum ferritin (SF) (μg/L)	≤5 yr <12 Children >5 yr <15 In all age groups in the presence of infection <30	It is probably the most useful laboratory measure of iron stores and helps identify ID; a low value of SF is diagnostic of iron-deficiency anemia (IDA) in a patient with anemia. SF is an acute phase reactant that increases in many acute or chronic inflammatory conditions independent of iron status. Combining SF with a measurement of C-reactive protein (CRP) helps to identify these false-negative SF results.
Reticulocyte hemoglobin content (CHr) (pg)	In infants and young children <27.5 In adults ≤28.0	A sensitive indicator that falls within days of onset of iron-deficient erythropoiesis and is unaffected by inflammation. It is an excellent tool to recognize ID as well as IDA. False normal values can occur when MCV is increased and in thalassemia. It is not yet widely available on hematology analyzers.
Serum transferrin receptor (sTfR)	Cutoff varies with assay and with patient's age and ethnic origin	This soluble receptor is upregulated in ID and is found in increased amounts in serum. It also increased during enhanced erythropoiesis. sTfR is not substantially affected by the acute-phase response, but it might be affected by malaria, age, and ethnicity. Its application is limited by high cost of commercial assays and lack of an international standard, but it has great promise as an indicator of ID.
Transferrin saturation	<16%	It is inexpensive, but its use is limited by diurnal variation in serum iron and by many clinical disorders that affect transferrin concentrations including in inflammatory conditions.
Erythrocyte zinc protoporphyrin (ZPP) (μmol/mol heme)	≤5 yr >70 Children >5 yr >80 Children >5 yr on washed red cells >40	It can be measured directly on a drop of blood with a portable hematofluorometer. A useful screening test in field surveys, particularly in children, in whom uncomplicated ID is the primary cause of anemia. Lead poisoning can increase values, particularly in urban and industrial settings.
Hepcidin	To be defined; usually ≤10 ng/mL	Extremely elevated in anemia of inflammation and suppressed in iron deficiency anemia

Modified from Zimmermann MB, Hurrell RF: Nutritional iron deficiency, Lancet *370:511–520, 2007.*

Table 455-2 Laboratory Studies Differentiating the Most Common Microcytic Anemias

STUDY	IRON-DEFICIENCY ANEMIA	α- OR β-THALASSEMIA	ANEMIA OF CHRONIC DISEASE
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal-decreased
RDW	Increased	Normal or minimally increased	Normal-increased
RBC	Decreased	Normal-increased	Normal-decreased
Serum ferritin	Decreased	Normal	Increased
Total Fe binding capacity	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
FEP	Increased	Normal	Increased
Transferrin receptor	Increased	Normal	Increased
Reticulocyte hemoglobin concentration	Decreased	Normal	Normal-decreased

FEP, free erythrocyte protoporphyrin; MCV, mean corpuscular volume; RBC, red blood cell count; RDW, red cell distribution width.
Modified from Zimmermann MB, Hurrell RF: Nutritional iron deficiency, Lancet *370:511–520, 2007.*

Table 462-2 Clinical Factors Associated with Increased Risk of Bacteremia Requiring Admission in Febrile Children with Sickle Cell Disease

Seriously ill appearance
Hypotension: systolic blood pressure <70 mm Hg at 1 yr of age or <70 mm Hg + 2 × the age in yr for older children
Poor perfusion: capillary-refill time >4 sec
Temperature >40.0°C (104°F)
A corrected white-cell count >30,000/mm^3 or <5000/mm^3
Platelet count <100,000/mm^3
History of pneumococcal sepsis
Severe pain
Dehydration: poor skin turgor, dry mucous membranes, history of poor fluid intake, or decreased output of urine
Infiltration of a segment or a larger portion of the lung
Hemoglobin level <5.0 g/dL

Table 467-1 Differential Diagnosis of Polycythemia

CLONAL (PRIMARY)
Polycythemia vera
NONCLONAL
Congenital
High-oxygen affinity hemoglobinopathy (e.g., hemoglobin Chesapeake, Malmo, San Diego)
Erythropoietin receptor mutations (primary familial and congenital polycythemia [PFCP])
Methemoglobin reductase deficiency
Hemoglobin M disease
2,3-Diphosphoglycerate deficiency
Acquired
Hormonal
Adrenal disease
Virilizing hyperplasia, Cushing syndrome
Anabolic steroid therapy
Malignant tumors
Adrenal, cerebellar, hepatic, other
Renal disease
Cysts, hydronephrosis, renal artery stenosis
Hypoxia
Altitude
Cardiac disease
Lung disease
Central hypoventilation
Chronic carbon monoxide exposure
Neonatal
Delayed cord clamping (placental-fetal transfusion)
Normal intrauterine environment
Placental insufficiency (preeclampsia, maternal chronic hypertension, placental abruption)
Twin–twin or maternal–fetal hemorrhage
Perinatal asphyxia
Infants of diabetic mothers
Intrauterine growth retardation
Trisomy 13, 18, or 21
Adrenal hyperplasia
Thyrotoxicosis
Spurious
Plasma volume decrease

Table 455-3 Differential Diagnosis of Microcytic Anemia That Fails to Respond to Oral Iron

Poor compliance (true intolerance of Fe is uncommon)
Incorrect dose or medication
Malabsorption of administered iron
Ongoing blood loss, including gastrointestinal, menstrual, and pulmonary
Concurrent infection or inflammatory disorder inhibiting the response to iron
Concurrent vitamin B_{12} or folate deficiency
Diagnosis other than iron deficiency
Thalassemias
Hemoglobins C and E disorders
Anemia of chronic disease
Lead poisoning
Sickle thalassemias, hemoglobin SC disease
Iron refractory iron deficiency anemia (IRIDA)
Rare microcytic anemias (see Chapter 456)

Table 455-4 Responses to Iron Therapy in Iron-Deficiency Anemia

TIME AFTER IRON ADMINISTRATION	RESPONSE
12-24 hr	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite
36-48 hr	Initial bone marrow response; erythroid hyperplasia
48-72 hr	Reticulocytosis, peaking at 5-7 days
4-30 days	Increase in hemoglobin level
1-3 mo	Repletion of stores

Table 462-6 Known Etiologies of Acquired Methemoglobinemia

MEDICATIONS
Benzocaine
Chloroquine
Dapsone
EMLA (eutectic mixture of local anesthetics) topical anesthetic (lidocaine 2.5% and prilocaine 2.5%)
Flutamide
Lidocaine
Metoclopramide
Nitrates
Nitric oxide
Nitroglycerin
Nitroprusside
Nitrous oxide
Phenazopyridine
Prilocaine
Primaquine
Riluzole
Silver nitrate
Sodium nitrate
Sulfonamides
MEDICAL CONDITIONS
Pediatric gastrointestinal infection, sepsis
Recreational drug overdose with amyl nitrate ("poppers")
Sickle cell disease–related painful episode
MISCELLANEOUS
Aniline dyes
Fume inhalation (automobile exhaust, burning of wood and plastics)
Herbicides
Industrial chemicals: nitrobenzene, nitroethane (found in nail polish, resins, rubber adhesives)
Pesticides
Gasoline octane booster

Table 457-1 Hemolytic Anemias and Their Treatment

DIAGNOSIS	DEFECT	LABORATORY TESTS	TREATMENT
CELLULAR DEFECTS			
Membrane Defects			
Hereditary spherocytosis	Cytoskeletal protein defects Often involve vertical interactions of spectrin ankyrin, protein 3	Spherocytes on blood film Negative Coombs test eliminates immune hemolysis Increased incubated osmotic fragility Abnormal cytoskeletal protein analysis	If Hb >10 g/dL and reticulocyte count <10%: none If severe anemia, poor growth, aplastic crises, and age <2 yr: transfusion Folic acid, 1 mg qd Splenectomy (see text)
Hereditary elliptocytosis	Cytoskeletal protein defects Often involve horizontal interactions of spectrin, protein 4.1, and glycophorin c	Elliptocytes on blood film RBCs mildly heat-sensitive Abnormal cytoskeletal protein analysis	Mild types: no treatment Chronic hemolysis: transfusion and splenectomy as recommended for spherocytosis (see above) Folic acid, 1 mg qd
Hereditary pyropoikilocytosis	Cytoskeletal protein defects Homozygous or double heterozygous abnormality in horizontal interactions of α-spectrin	Extreme variation in RBC size and shape on blood film Thermal sensitivity-fragmentation at 45°C (113°F) for 15 min	Transfusion and splenectomy as recommended for spherocytosis (see above) Folic acid, 1 mg qd
Hereditary stomatocytosis	Cytoskeletal protein defects Decreased protein 7.2b (1 subset) Abnormal RBC cation and water content	Stomatocytes on blood film	Splenectomy should be avoided (see text) Folic acid, 1 mg qd
Paroxysmal nocturnal hemoglobinuria	Primary acquired marrow disorder RBCs unusually sensitive to complement-mediated lysis	Decreased WBC CD55 and CD59 or decreased RBC CD59 by flow cytometry Marrow aspirate and biopsy to assess cellularity Decreased decay-accelerating factor	Folic acid, 1 mg qd Mild cytopenias: no treatment Chronic hemolysis and other cytopenias: prednisone, qd initially, and then qod for maintenance therapy Iron for secondary iron deficiency Eculizumab (inhibits C5) Anticoagulation Marrow transplant for pancytopenia
Enzyme Deficiencies			
Pyruvate kinase deficiency	Decreased or abnormal enzyme	Pyruvate kinase assay: decreased V_{max} or, rarely, high K_m variant	In severe anemia with symptoms, poor growth and age <2 yr: transfusion Splenectomy age >6 yr, but earlier if necessary Folic acid, 1 mg qd
G6PD deficiency	A^- type: age-labile enzyme Mediterranean type: no enzyme activity in circulating RBCs	G6PD assay	Avoid oxidant stress to RBCs Transfusion if acute anemia is symptomatic
Hemoglobin Abnormalities			
For discussion of hemoglobinopathies, see sections on these topics.			

Table 458-2 Hereditary Spherocytosis Disease Classification

	TRAIT	MILD	MODERATE	SEVERE
Hemoglobin (g/dL)	Normal	11-15	8-12	<6-8
Reticulocytes (%)	Normal (<3)	3-6	>6	>10
Bilirubin	<17	17-34	>34	>51
Transfusions	0	0	0-2	Regular
Typical heredity	AD	AD	AD or de novo mutation	AR
Splenectomy	Not indicated	Not indicated	May be indicated*	Indicated

*Splenectomy indicated if patient requires frequent transfusions for hypoplastic crises or shows poor growth or cardiomegaly.
AD, autodominant; AR, autorecessive.

Table 464-2 Selected Drugs That Cause Immune-Mediated Hemolysis

MECHANISM	DRUG ADSORPTION (HAPTEN)	TERNARY (IMMUNE) COMPLEX	AUTOANTIBODY INDUCTION
Direct antiglobulin test	Positive (anti-IgG)	Positive (anti-C3)	Positive (anti-IgG)
Site of hemolysis	Extravascular	Intravascular	Extravascular
Medications	Penicillins Cephalosporins 6-mercaptopurine Tetracycline Oxaliplatin Hydrocortisone	Cephalosporins Quinidine Amphotericin B Hydrocortisone Rifampin (Rifadin) Metformin Quinine Probenecid Chlorpromazine Oxaliplatin	α-Methyldopa Cephalosporins Oxaliplatin L-Dopa Procainamide Ibuprofen Diclofenac (Voltaren) Interferon alfa

Table 457-1 Hemolytic Anemias and Their Treatment—cont'd

DIAGNOSIS	DEFECT	LABORATORY TESTS	TREATMENT
EXTRACELLULAR DEFECTS			
Autoimmune			
"Warm" antibody	Alteration in membrane surface antigen (Rh) or abnormal response of B lymphocytes, causing autoantibody formation "Molecular mimicry" to viral antigen	Spherocytes on blood film Positive direct antiglobulin (Coombs) test to IgG "warm" antibody or anti-C3d directed against RBCs Positive indirect Coombs test and antibody detectable in plasma Thermal amplitude 35-40°C (95-104°F) Some complement (C3b) may be detected on RBCs Tests for underlying disease	If Hb >10 g/dL and reticulocyte count <10%—none Severe anemia may require transfusion; prednisone, 2 mg/kg/24 hr IVIG ***Rituximab*** Splenectomy Immunosuppressives Folic acid, 1 mg/24 hr if chronic
"Cold" antibody	"Cold" or IgM autoantibody directed against I/i antigen system	Agglutination or rouleaux on blood film Positive direct Coombs test to complement (C3b) Tests for underlying disease Serology for infectious mononucleosis; anti-i present Serology for *Mycoplasma pneumoniae;* anti-I present	If Hb >10 g/dL and reticulocyte count <10%: none Severe anemia might require transfusion Avoid exposure to cold If severe: ***Rituximab*** Immunosuppressives and plasmapheresis Prednisone is less effective Splenectomy is not useful Folic acid, 1 mg/24 hr if chronic
Fragmentation Hemolysis			
DIC, TTP, HUS, aHUS, pneumococcal-induced HUS See Table 465-1	Direct damage to RBC membrane	Fragments on blood film	Treat underlying condition Transfusion, but transfused cells also will have shortened life span
Extracorporeal membrane oxygenation	Direct damage to RBC membrane	Fragments on blood film	Supportive Transfusion until ECMO is discontinued
Prosthetic heart valve	Direct damage to RBC membrane	Fragments on blood film	Folic acid, 1 mg/24 hr Iron for secondary iron deficiency
Burns, thermal injury	Direct damage to RBC membrane	Spherocytes on blood film	Supportive Transfusion
Hypersplenism	Effects of sequestration, ↓ pH, lipases and other enzymes, and macrophages on RBCs	Thrombocytopenia and neutropenia	Treat underlying condition: cytopenias all usually mild Splenectomy if complicating other anemia (e.g., thalassemia major) Folic acid, 1 mg/24 hr
Plasma Factors			
Liver disease	Alteration in plasma cholesterol and phospholipids	Target cells or spiculated RBCs on blood film Abnormal liver function tests	Treat underlying condition Transfusion, but transfused cells also will have shortened life span Folic acid, 1 mg/24 hr
Abetalipoproteinemia	Absence of apolipoprotein β Vitamin E deficiency and heightened sensitivity to oxidative damage	Acanthocytes on blood film Absent chylomicrons, VLDL, and LDL	Vitamin E (A, K, and D) Folic acid, 1 mg/24 hr Dietary restriction of triglycerides
Infections	Toxic effects on RBCs	Associated symptoms and signs Cultures	Antibiotics Supportive
Wilson disease	Effect of copper on RBC membrane, usually self-limited	Spherocytes on blood film Copper, ceruloplasmin Kaiser Fleischer rings Penicillamine challenge and urine copper excretion Liver biopsy for Cu content Gene analysis for mutation of ATP7B	Penicillamine Supportive Transfusion if acute anemia is symptomatic

aHUS, atypical hemolytic uremic syndrome; Cu, copper; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; HUS, hemolytic uremic syndrome; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; LDL, low-density lipoprotein; K_m, Michaelis constant; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura; VLDL, very-low-density lipoprotein; V_{max}, maximal velocity; WBC, white blood cell.

Modified from Asselin BL, Segel GB: In Rakel R, editor: Conn's current therapy, *Philadelphia, 1994, Saunders, pp 338–339.*

Table 462-4 Overall Strategies for the Management of Acute Chest Syndrome

PREVENTION
Incentive spirometry and periodic ambulation in patients admitted for sickle cell pain, surgery, or febrile episodes
Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)
Cautious use of intravenous fluids
Intense education and optimum care of patients who have sickle cell anemia and asthma
DIAGNOSTIC TESTING AND LABORATORY MONITORING
Blood cultures
Nasopharyngeal samples for viral culture (respiratory syncytial virus, influenza)
Blood counts every day and appropriate chemistries
Continuous pulse oximetry
Chest radiographs
TREATMENT
Blood transfusion (simple or exchange)
Supplemental O_2 for drop in pulse oximetry by 4% over baseline, or values <90%
Empirical antibiotics (third-generation cephalosporin and macrolide)
Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)
Bronchodilators and steroids for patients with asthma
Optimum pain control and fluid management

Table 462-5 Complications Associated with Sickle Cell Trait

DEFINITE ASSOCIATIONS
Renal medullary cancer
Hematuria
Renal papillary necrosis
Hyposthenuria
Splenic infarction
Exertional rhabdomyolysis
Exercise-related sudden death
Protection against severe falciparum malaria
Microalbuminuria (adults)

Table 462-3 Summary of the Chronology of Pain in Children with Sickle Cell Disease

PHASE	PAIN CHARACTERISTICS	SUGGESTED COMFORT MEASURES USED
1 (Baseline)	No vasoocclusive pain; pain of complications may be present, such as that connected with avascular necrosis of the hip	No comfort measures used
2 (Prepain)	No vasoocclusive pain; pain of complications may be present; prodromal signs of impending vasoocclusive episode may appear, e.g., "yellow eyes" and/or fatigue	No comfort measures used; caregivers may encourage child to increase fluids to prevent pain event from occurring
3 (Pain start point)	First signs of vasoocclusive pain appear, usually in mild form	Mild oral analgesic often given; fluids increased; child usually maintains normal activities
4 (Pain acceleration)	Intensive of pain increases from mild to moderate Some children skip this level or move quickly from phase 3 to phase 5	Stronger oral analgesic are given; rubbing, heat, or other activities are often used; child usually stays in school until the pain becomes more severe, then stays home and limits activities; is usually in bed; family searches for ways to control the pain
5 (Peak pain experience)	Pain accelerates to high moderate or severe levels and plateaus; pain can remain elevated for extended period Child's appearance, behavior, and mood are significantly different from normal	Oral analgesics are given around the clock at home; combination of comfort measures is used; family might avoid going to the hospital; if pain is very distressing to the child, parent takes the child to the emergency department After child enters the hospital, families often turn over comforting activities to healthcare providers and wait to see if the analgesics work Family caregivers are often exhausted from caring for the child for several days with little or no rest
6 (Pain decrease start point)	Pain finally begins to decrease in intensity from the peak pain level	Family caregivers again become active in comforting the child but not as intensely as during phases 4 and 5
7 (Steady pain decline)	Pain decreases more rapidly, become more tolerable for the child Child and family are more relaxed	Healthcare providers begin to wean the child from the IV analgesic; oral opioids given; discharge planning is started Children may be discharged before they are pain free
8 (Pain resolution)	Pain intensity is at a tolerable level, and discharge is imminent Child looks and acts like "normal" self; mood improves	May receive oral analgesics

Adapted from Beyer JE, Simmons LE, Woods GM, et al: A chronology of pain and comfort in children with sickle cell disease, Arch Pediatr Adolesc Med *153:913–920, 1999.*

Table 462-7 The Thalassemias

THALASSEMIA	GLOBIN GENOTYPE	FEATURES	EXPRESSION	HEMOGLOBIN ANALYSIS
α-THALASSEMIA				
1 Gene allele deletion	–,α/α,α	Normal	Normal	Newborn: Bart 1-2%
2 Gene allele deletion trait	–,α/–,α –, –/α,α	Microcytosis, mild hypochromasia	Normal, mild anemia	Newborn: Bart: 5-10%
3 Gene allele deletion hemoglobin H	–,–/–,α	Microcytosis, hypochromic	Mild anemia, transfusions not required	Newborn: Bart: 20-30%
2 Gene allele deletion + Constant Spring	–,–/α,$\alpha^{Constant\ Spring}$	Microcytosis, hypochromic	Moderate to severe anemia, transfusion, splenectomy.	2-3% Constant Spring, 10-15% HbH
4 Gene allele deletion	–,–/–,–	Anisocytosis, poikilocytosis	Hydrops fetalis	Newborn: 89-90% Bart with Gower 1 and 2 and Portland
Nondeletional	α,α/α,$\alpha^{variant}$	Microcytosis, mild anemia	Normal	1-2% variant hemoglobin
β-THALASSEMIA				
β^0 or β^+ heterozygote: trait	β^0/A,β^+/A	Variable microcytosis	Normal	Elevated A_2, variable elevation of F
β^0-Thalassemia	β^0/β^0, β^+/β^0, E/β^0	Microcytosis, nucleated RBC	Transfusion dependent	F 98% and A_2 2%, E 30-40%
β^+-Thalassemia severe	β^+/β^+	Microcytosis nucleated RBC	Transfusion dependent/ thalassemia intermedia	F 70-95%, A_2 2%, trace A
Silent	β^+/A	Microcytosis	Normal with only microcytosis	A_2 3.3-3.5%
β^+/β^+	Hypochromic, microcytosis	Mild to moderate anemia	A_2 2-5%, F 10-30%	
Dominant (rare)	B^0/A	Microcytosis, abnormal RBCs	Moderately severe anemia, splenomegaly	Elevated F and A_2
δ-Thalassemia	A/A	Normal	Normal	A_2 absent
$(\delta\beta)^0$-Thalassemia	$(\delta\beta)^0$/A	Hypochromic	Mild anemia	F 5-20%
$(\delta\beta)^+$-Thalassemia Lepore	β^{Lepore}/A	Microcytosis	Mild anemia	Lepore 8-20%
Lepore	$\beta^{Lepore}/\beta^{Lepore}$	Microcytic, hypochromic	Thalassemia intermedia	F 80%, Lepore 20%
γδβ-Thalassemia	$(\gamma^A\delta\beta)^0$/A	Microcytosis, microcytic, hypochromic	Moderate anemia, splenomegaly, homozygote: thalassemia intermedia	Decreased F and A2 compared with δβ-thalassemia
γ-Thalassemia	$(\gamma^A\gamma^G)^0$/A	Microcytosis	Insignificant unless homozygote	Decreased F
HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN				
Deletional	A/A	Microcytic	Mild anemia	F 100% homozygotes
Nondeletional	A/A	Normal	Normal	F 20-40%

Table 463-1 Agents Precipitating Hemolysis in Glucose-6-Phosphate Dehydrogenase Deficiency

MEDICATIONS

Antibacterials
Sulfonamides
Dapsone
Trimethoprim-sulfamethoxazole
Nalidixic acid
Chloramphenicol
Nitrofurantoin

Antimalarials
Primaquine
Pamaquine
Chloroquine
Quinacrine

Antihelminths
β-Naphthol
Stibophen
Niridazole

Others
Acetanilide
Vitamin K analogs
Methylene blue
Toluidine blue
Probenecid
Dimercaprol
Acetylsalicylic acid
Phenazopyridine
Rasburicase

CHEMICALS
Phenylhydrazine
Benzene
Naphthalene (moth balls)
2,4,6-Trinitrotoluene

ILLNESS
Diabetic acidosis
Hepatitis
Sepsis

Table 464-1 Diseases Characterized by Immune-Mediated Red Blood Cell Destruction

AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY WARM REACTIVE AUTOANTIBODIES
Primary (idiopathic)
Secondary
- Lymphoproliferative disorders
- Connective tissue disorders (especially systemic lupus erythematosus)
- Nonlymphoid neoplasms (e.g., ovarian tumors)
- Chronic inflammatory diseases (e.g., ulcerative colitis)
- Immunodeficiency disorders

AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY COLD REACTIVE AUTOANTIBODIES (CRYOPATHIC HEMOLYTIC SYNDROMES)
Primary (idiopathic) cold agglutinin disease
Secondary cold agglutinin disease
- Lymphoproliferative disorders
- Infections (*Mycoplasma pneumoniae*, Epstein-Barr virus)
- Paroxysmal cold hemoglobinuria
- Primary (idiopathic)
- Viral syndromes (most common)
- Congenital or tertiary syphilis

DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA
(see Table 464-2)
Hapten/drug adsorption (e.g., penicillin)
Ternary (immune) complex (e.g., quinine or quinidine)
True autoantibody induction (e.g., methyldopa)

Table 466-1 WHO Diagnostic Criteria for Polycythemia Vera

MAJOR CRITERIA 1. Hb >18.5 g/dL (men) or Hb >16.5 g/dL (women) *or* Hb or Hct >99th percentile of reference range for age, sex, or altitude of residence *or* Hb >17 g/dL (men) or Hb >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency *or* elevated red cell mass >25% above mean normal predicted value 2. Presence of *JAK2* or similar mutation
MINOR CRITERIA 1. Bone marrow trilineage myeloproliferation 2. Subnormal serum erythropoietin level 3. Endogenous erythroid colony growth
DIAGNOSIS Both major criteria and one minor criteria *or* first major criteria and 2 minor criteria.

Hb, hemoglobin; Hct, hematocrit.
From Tefferi A, Vardiman JW: Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia *22:14–22, 2008.*

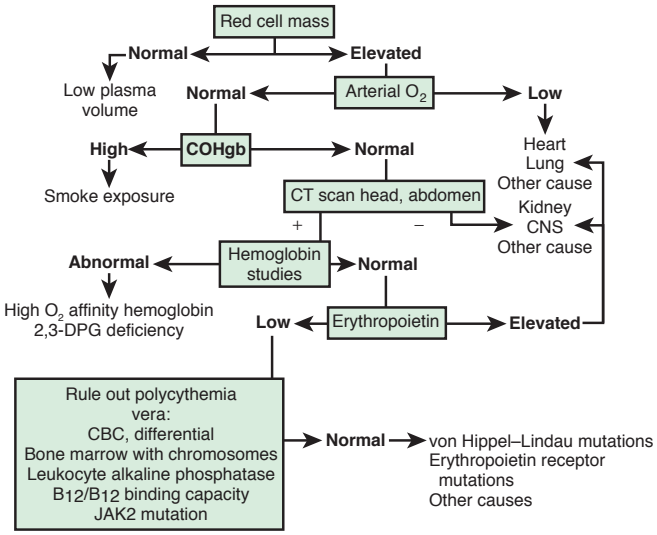


Figure 466-1 Sequential studies to evaluate polycythemia. CBC, complete blood count; CNS, central nervous system; COHgb, carboxy-hemoglobin; 2,3-DPG, 2,3-diphosphoglycerate.

Table 472-1 Guidelines for Pediatric Granulocyte Transfusions*

CHILDREN AND ADOLESCENTS 1. Severe neutropenia (blood neutrophil count <0.5 × 10^9/L) and infection (bacterial, yeast, or fungal) *unresponsive or progressive* despite appropriate antimicrobial therapy 2. Qualitative neutrophil defect, neutropenia not required, and infection (bacterial or fungal) *unresponsive or progressive* to appropriate antimicrobial therapy
INFANTS ≤4 MO OLD† Blood neutrophil count <3.0 × 10^9/L in 1st wk of life or <1.0 × 10^9/L thereafter and *fulminant* bacterial infection.

*Words in italics must be defined for local transfusion guidelines.
†No longer commonly used.

Table 473-1 Guidelines for Pediatric Plasma Transfusions*

1. *Severe* clotting factor deficiency AND bleeding 2. *Severe* clotting factor deficiency AND an invasive procedure 3. *Emergency reversal* of warfarin effects 4. Dilutional coagulopathy and bleeding (e.g., massive transfusion) 5. Anticoagulant protein (antithrombin III, proteins C and S) replacement 6. Plasma exchange replacement fluid for thrombotic thrombocytopenic purpura or for disorders with overt bleeding or in which there is risk of bleeding because of clotting protein abnormalities (e.g., liver failure)

*Words in *italics* must be defined for local transfusion guidelines.

Table 465-1 Thrombotic Microangiopathies

DISEASE*	PATHOPHYSIOLOGY	LAB FINDINGS	MANAGEMENT
TTP	Ab to AdamTS13	AdamTS13 <10%† Ab to AdamTS13	PLEX with plasma
HUS	*E. coli* 0157, *Shiga* toxin	*E. coli* 0157, *Shiga* toxin	Supportive ? value of PLEX
aHUS	Complement-mediated alternative pathway	AdamTS13 >10% Decreased factors H and I (inhibitors of complement)‡	Eculizumab (ab to C5) PLEX not indicated
Pneumococcal-induced HUS	Neuraminidase-induced RBC, platelet, and kidney damage Exposure of T-antigen on RBC and kidney	Pneumococcal infection AdamTS13 >10%	PLEX with albumin for neuraminidase and endogenous T ab removal
DIC	Sepsis, shock, endotoxin	Decreased fibrinogen, increased fibrin split products, decreased clotting factors and platelets	Treat underlying condition; replace factors and platelets if bleeding

*All show fragmentation hemolytic anemia, thrombocytopenia and potential renal and other organ damage. An elevated lactate dehydrogenase and reduced haptoglobin usually are present secondary to hemolysis.
†Rarely a congenital defect in AdamTS13.
‡May be related to inherited defect in factor H or I.
Ab/ab, antibody; aHUS, atypical hemolytic uremic syndrome; DIC, disseminated intravascular coagulation; *E. coli*, *Escherichia coli*; HUS, hemolytic uremic syndrome; PLEX, plasmapheresis; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura

Table 468-1 Inherited Pancytopenia Syndromes

Fanconi anemia
Shwachman-Diamond syndrome
Dyskeratosis congenita
Congenital amegakaryocytic thrombocytopenia
Reticular dysgenesis
Unclassified inherited bone marrow failure syndromes
Other genetic syndromes
  Down syndrome
  Dubowitz syndrome
  Seckel syndrome
  Schimke immunoosseous dysplasia
  Cartilage-hair hypoplasia
  Noonan syndrome

Table 468-3 Characteristic Physical Anomalies in Fanconi Anemia

ANOMALY	APPROXIMATE FREQUENCY (% OF PATIENTS)
Skin pigment changes ± café-au-lait spots	55
Short stature	51
Upper limb abnormalities (thumbs, hands, radii, ulnas)	43
Hypogonadal and genital changes (mostly male)	35
Other skeletal findings (head/face, neck, spine)	30
Eye/lid/epicanthal fold anomalies	23
Renal malformations	21
Gastrointestinal/cardiopulmonary malformations	11
Hip, leg, foot, toe abnormalities	10
Ear anomalies (external and internal), deafness	9

Table 468-2 Distinguishing Clinical Features of the Inherited Bone Marrow Failure Syndromes That May Be Initially Diagnosed in Adulthood

Distinguishing Features	DISEASES		
	Fanconi Anemia	Dyskeratosis Congenita	Schwachman-Diamond Anemia
History	Skeletal and renal malformations, low birthweight, pancytopenia, family member with bone marrow failure, MDS, acute myelogenous leukemia (AML), or squamous cell carcinoma at an early age; family member with Fanconi anemia	Intrauterine growth retardation, developmental delay, and short stature. Family history of MDS, AML, marrow failure, abnormal fingernails or toenails, leukoplakia, head and neck cancer, or pulmonary fibrosis	Pancreatic insufficiency, low birth weight, metaphyseal dysostosis, initial neutropenia, delayed development
Physical findings	Thumb and radial malformations, hyperpigmented skin lesions (café-au-lait spots), short stature, MDS, AML, squamous cell carcinoma at young age, renal and cardiac malformations, microcephaly, hypogonadism	Lacy reticular pigmentation of skin, dystrophic fingernails and toenails, premature graying of hair, hair loss, short stature, oral leukoplakia, squamous cell cancer of head and neck, pulmonary fibrosis, osteopenia, hypogonadism	Short stature, abnormal thorax
Genes inactivated	*FANCA, FANCB, FANCC, FANCD1* (aka *BRCA2), FANCD2, FANCE, FANCF, FANCG* (aka *XRCC9), FANCI, FANCJ* (aka *BACH1* and *BRIP1), FANCL* (aka *PHF9* and *POG), FANCM* (aka *Hef*), and *FANCN* (aka *PALB2*) These genes encode proteins known to protect the genome from excessive damage induced by chemical crosslinking agents. These genes account for most cases of Fanconi anemia	*DKC1, TERC, TERT, TINF2, NOLA2,* and *NOLA3* These genes encode proteins known to participate in maintenance of telomeres. They account for only half of dyskeratosis cases, so there are additional genes to be discovered	*SBDS* autosomal recessive marrow clonal expansion in ~15%
Screening and diagnostic tests	1. Chromosomal breakage test (in response to mitomycin C or diepoxybutane) 2. Complementation analysis (flow cytometric analysis of G_2 arrest in melphalan-exposed cells after transduction with retroviral vectors expressing normal Fanconi anemia genes) 3. Gene sequencing	1. Quantitative analysis of telomere length ("flow FISH") 2. Gene sequencing	CT demonstrates fatty infiltration of pancreas Gene testing May evolve to myelodysplasia or leukemia Absence of pancreatic lipomatosis, fecal fat, or dysostosis does not rule out diagnosis

ADA, adenosine deaminase; FISH, fluorescent in situ hybridization.
Modified from Bagby GC: Aplastic anemia and related bone marrow failure states. In Goldman L, Schafer AI, editors, Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, WB Saunders, Table 168-3, p. 1086.*

Table 468-4 Canadian Inherited Marrow Failure Registry Criteria for Unclassified Inherited Bone Marrow Failure Syndromes

FULFILLS CRITERIA 1 AND 2: 1. Does not fulfill criteria for any categorized inherited bone marrow failure syndrome* 2. Fulfills both of the following
FULFILLS AT LEAST 2 OF THE FOLLOWING: a. Chronic cytopenia(s) detected on at least 2 occasions over at least 3 mo† b. Reduced marrow progenitors or reduced clonogenic potential of hematopoietic progenitor cells or evidence of ineffective hematopoiesis‡ c. High fetal hemoglobin for age‡ d. Red blood cell macrocytosis (not caused by hemolysis or a nutritional deficiency)
FULFILLS AT LEAST 1 OF THE FOLLOWING: a. Family history of bone marrow failure b. Presentation at age <1 yr c. Anomalies involving multiple systems to suggest an inherited syndrome

*The Canadian Inherited Marrow Failure Registry diagnostic guidelines for selected syndromes were adapted from the literature and are available at http://www.sickkids.ca/cimfr.

†Cytopenia was defined as follows: neutropenia, neutrophil count of $<1.5 \times 10^9$/L; thrombocytopenia, platelet count of $<150 \times 10^9$/L; anemia, hemoglobin concentration of <2 standard deviations below mean, adjusted for age.

‡Hemoglobinopathies with ineffective erythropoiesis and high hemoglobin F should be excluded by clinical or laboratory testing.

Table 469-1 Etiology of Acquired Aplastic Anemia

Radiation, drugs, and chemicals:
- Predictable: chemotherapy, benzene
- Idiosyncratic: chloramphenicol, antiepileptics, gold; 3,4-methylenedioxymethamphetamine

Viruses:
- Cytomegalovirus
- Epstein-Barr
- Hepatitis B
- Hepatitis C
- Hepatitis non-A, non-B, non-C (seronegative hepatitis)
- HIV

Immune diseases:
- Eosinophilic fasciitis
- Hypoimmunoglobulinemia
- Thymoma

Pregnancy

Paroxysmal nocturnal hemoglobinuria

Marrow replacement:
- Leukemia
- Myelodysplasia
- Myelofibrosis

Autoimmune

Other:
- Cryptic dyskeratosis congenita (no physical stigmata)
- Telomerase reverse transcriptase haploinsufficiency

Table 470-1 Guidelines for Pediatric Red Blood Cell Transfusions*†

CHILDREN AND ADOLESCENTS 1. Maintain stable status with acute loss of >25% of circulating blood volume 2. Maintain hemoglobin >7.0 g/dL† in the perioperative period 3. Maintain hemoglobin >12.0 g/dL with *severe* cardiopulmonary disease 4. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation 5. Maintain hemoglobin >7.0 g/dL and *symptomatic* chronic anemia 6. Maintain hemoglobin >7.0 g/dL and *marrow failure*
INFANTS ≤4 MO OLD 1. Maintain hemoglobin >12.0 g/dL and *severe* pulmonary disease 2. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation 3. Maintain hemoglobin >10.0 g/dL and *moderate* pulmonary disease 4. Maintain hemoglobin >12.0 g/dL and *severe* cardiac disease 5. Maintain hemoglobin >10.0 g/dL preoperatively and during *major* surgery 6. Maintain hemoglobin >7.0 g/dL postoperatively 7. Maintain hemoglobin >7.0 g/dL and *symptomatic* anemia

*Words in *italics* must be defined for local transfusion guidelines.

†Pretransfusion blood hemoglobin level (convert to hematocrit values if preferred by multiplying hemoglobin values by 3) "triggering" an RBC transfusion. Hemoglobin values to maintain vary among published reports, and the guideline values to maintain should be determined locally to fit the practices judged to be optimal by local MDs.

Table 471-1 Guidelines for Pediatric Platelet Transfusion*

CHILDREN AND ADOLESCENTS 1. Maintain PLT count $>50 \times 10^9$/L with bleeding 2. Maintain PLT count $>50 \times 10^9$/L with *major invasive* procedure; $>25 \times 10^9$/L with minor 3. Maintain PLT count $>20 \times 10^9$/L and *marrow failure* WITH hemorrhagic risk factors 4. Maintain PLT count $>10 \times 10^9$/L and *marrow failure* WITHOUT hemorrhagic risk factors 5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding or invasive procedure
INFANTS ≤4 MO OLD 1. Maintain PLT count $>100 \times 10^9$/L with bleeding or during extracorporeal membrane oxygenation 2. Maintain PLT count $>50 \times 10^9$/L and an invasive procedure 3. Maintain PLT count $>20 \times 10^9$/L and *clinically stable* 4. Maintain PLT count $>50 \times 10^9$/L and *clinically unstable and/or bleeding or not when on indomethacin, nitric oxide, antibiotics, etc. affecting PLT function* 5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding invasive procedure

*Words in *italics* must be defined for local transfusion guidelines.
PLT, platelet.

Table 475-1 Coagulation Factors

CLOTTING FACTOR	SYNONYM	DISORDER
I	Fibrinogen	Congenital deficiency (afibrinogenemia) or dysfunction (dysfibrinogenemia)
II	Prothrombin	Congenital deficiency or dysfunction
V	Labile factor, proaccelerin	Congenital deficiency (parahemophilia)
VII	Stable factor or proconvertin	Congenital deficiency
VIII	Antihemophilic factor	Congenital deficiency is hemophilia A (classic hemophilia)
IX	Christmas factor	Congenital deficiency is hemophilia B (sometimes referred to as Christmas disease)
X	Stuart-Prower factor	Congenital deficiency
XI	Plasma thromboplastin antecedent	Congenital deficiency (sometimes referred to as hemophilia C)
XII	Hageman factor	Congenital deficiency is not associated with clinical symptoms
XIII	Fibrin-stabilizing factor	Congenital deficiency

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XI	Plasma thromboplastin antecedent	Congenital deficiency (sometimes referred to as hemophilia C)
XII	Hageman factor	Congenital deficiency is not associated with clinical symptoms
XIII	Fibrin-stabilizing factor	Congenital deficiency

Table 475-2 Reference Values for Coagulation Tests in Healthy Children*

TEST	28-31 Wk GESTATION	30-36 Wk GESTATION	FULL TERM	1-5 Yr	6-10 Yr	11-18 Yr	ADULT
SCREENING TESTS							
Prothrombin time (sec)	15.4 (14.6-16.9)	13.0 (10.6-16.2)	13.0 (10.1-15.9)	11 (10.6-11.4)	11.1 (10.1-12.0)	11.2 (10.2-12.0)	12 (11.0-14.0)
Activated partial thromboplastin time (sec)	108 (80-168)	53.6 (27.5-79.4)‡§	42.9 (31.3-54.3)‡	30 (24-36)	31 (26-36)	32 (26-37)	33 (27-40)
Bleeding time (min)				6 (2.5-10)‡	7 (2.5-13)‡	5 (3-8)‡	4 (1-7)
PROCOAGULANTS							
Fibrinogen	256 (160-550)	243 (150-373)‡§	283 (167-399)	276 (170-405)	279 (157-400)	300 (154-448)	278 (156-40)
Factor II	31 (19-54)	45 (20-77)‡	48 (26-70)‡	94 (71-116)‡	88 (67-107)‡	83 (61-104)‡	108 (70-146)
Factor V	65 (43-80)	88 (41-144)§	72 (34-108)‡	103 (79-127)	90 (63-116)‡	77 (55-99)‡	106 (62-150)
Factor VII	37 (24-76)	67 (21-113)‡	66 (28-104)‡	82 (55-116)‡	86 (52-120)‡	83 (58-115)‡	105 (67-143)
Factor VIII procoagulant	79 (37-126)	111 (5-213)	100 (50-178)	90 (59-142)	95 (58-132)	92 (53-131)	99 (50-149)
von Willebrand factor	141 (83-223)	136 (78-210)	153 (50-287)	82 (60-120)	95 (44-144)	100 (46-153)	92 (50-158)
Factor IX	18 (17-20)	35 (19-65)‡§	53 (15-91)†‡	73 (47-104)‡	75 (63-89)‡	82 (59-122)‡	109 (55-163)
Factor X	36 (25-64)	41 (11-71)‡	40 (12-68)‡	88 (58-116)‡	75 (55-101)‡	79 (50-117)	106 (70-152)
Factor XI	23 (11-33)	30 (8-52)‡§	38 (40-66)‡	30 (8-52)‡	38 (10-66)	74 (50-97)‡	97 (56-150)
Factor XII	25 (5-35)	38 (10-66)‡§	53 (13-93)‡	93 (64-129)	92 (60-140)	81 (34-137)‡	108 (52-164)
Prekallikrein	26 (15-32)	33 (9-89)‡	37 (18-69)‡	95 (65-130)	99 (66-131)	99 (53-145)	112 (62-162)
High-molecular-weight kininogen	32 (19-52)	49 (9-89)‡	54 (6-102)‡	98 (64-132)	93 (60-130)	91 (63-119)	92 (50-136)
Factor XIIIa‖		70 (32-108)‡	79 (27-131)‡	108 (72-143)	109 (65-151)	99 (57-140)	105 (55-155)
Factor XIIIb‖		81 (35-127)‡	76 (30-122)‡	113 (69-156)‡	116 (77-154)‡	102 (60-143)	98 (57-137)
ANTICOAGULANTS							
Antithrombin-III	28 (20-38)	38 (14-62)‡§	63 (39-87)‡	111 (82-139)	111 (90-131)	106 (77-132)	100 (74-126)
Protein C		28 (12-44)‡§	35 (17-53)‡	66 (40-92)‡	69 (45-93)‡	83 (55-111)‡	96 (64-128)
Protein S:							
Total (units/mL)		26 (14-38)‡§	36 (12-60)‡	86 (54-118)	78 (41-114)	72 (52-92)	81 (61-113)
Free (units/mL)				45 (21-69)	42 (22-62)	38 (26-55)	45 (27-61)
Plasminogen (units/mL)		170 (112-248)	195 (125-265)	98 (78-118)	92 (75-108)	86 (68-103)	99 (77-122)
Tissue-type plasminogen activator (ng/mL)		8.48 (3.00-16.70)	9.6 (5.0-18.9)	2.15 (1.0-4.5)‡	2.42 (1.0-5.0)‡	2.16 (1.0-4.0)‡	1.02 (0.68-1.36)
Antiplasmin (units/mL)		78 (40-116)	85 (55-115)	105 (93-117)	99 (89-110)	98 (78-118)	102 (68-136)
Plasminogen activator inhibitor-I		5.4 (0.0-12.2)‡	6.4 (2.0-15.1)	5.42 (1.0-10.0)	6.79 (2.0-12.0)‡	6.07 (2.0-10.0)‡	3.60 (0.0-11.0)

*All factors except fibrinogen are expressed as units/mL (fibrinogen in mg/mL), in which pooled normal plasma contains 1 unit/mL. All data are expressed as the mean, followed by the upper and lower boundaries encompassing 95% of the normal population (shown in parentheses). Normal ranges above vary based on the reagents and instruments used.

†Levels for 19-27 wk and 28-31 wk gestation are from multiple sources and cannot be analyzed statistically.

‡Values are significantly different from those of adults.

§Values are significantly different from those of full-term infants.

‖Value given as CTA (Committee on Thrombolytic Agents) units/mL. Normal ranges above vary based on the reagents and instruments used.

Data from Andrew M, Paes B, Johnston M: Development of the hemostatic system in the neonate and young infant, Am J Pediatr Hematol Oncol *12:95, 1990; and Andrew M, Vegh P, Johnston M, et al: Maturation of the hemostatic system during childhood,* Blood *80:1998, 1992.*

Table 476-1 Treatment of Hemophilia

TYPE OF HEMORRHAGE	HEMOPHILIA A	HEMOPHILIA B
Hemarthrosis*	50-60 IU/kg factor VIII concentrate† on day 1; then 20-30 IU/kg on days 2, 3, 5 until joint function is normal or back to baseline. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.	80-100 IU/kg on day 1; then 40 IU/kg on days 2, 4. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.
Muscle or significant subcutaneous hematoma	50 IU/kg factor VIII concentrate; 20 IU/kg every-other-day treatment may be needed until resolved	80 IU/kg factor IX concentrate‡; treatment every 2-3 days may be needed until resolved
Mouth, deciduous tooth, or tooth extraction	20 IU/kg factor VIII concentrate; antifibrinolytic therapy; remove loose deciduous tooth	40 IU/kg factor IX concentrate‡; antifibrinolytic therapy§; remove loose deciduous tooth
Epistaxis	Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy; 20 IU/kg factor VIII concentrate if this treatment fails‖	Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy; 30 IU/kg factor IX concentrate‡ if this treatment fails
Major surgery, life-threatening hemorrhage	50-75 IU/kg factor VIII concentrate, then initiate 25 IU/kg q8-12h to maintain trough level >50 IU/dL for 5-7 days, then 50 IU/kg q24h to maintain trough >25 IU/dL for 7 days	120 IU/kg factor IX concentrate‡, then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dL for 5-7 days, and then at >30 IU/dL for 7 days
Iliopsoas hemorrhage	50 IU/kg factor VIII concentrate, then 25 IU/kg every 12 hr until asymptomatic, then 20 IU/kg every other day for a total of 10-14 days**	120 IU/kg factor IX concentrate‡; then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dL until patient is asymptomatic; then 40-50 IU every other day for a total of 10-14 days**††
Hematuria	Bed rest; 1.5× maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected)	Bed rest; 1.5× maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate‡; if not controlled, give prednisone (unless patient is HIV-infected)
Prophylaxis	20-40 IU/kg factor VIII concentrate every other day to achieve a trough level ≥1%	30-50 IU/kg factor IX concentrate‡ every 2-3 days to achieve a trough level ≥1%

*For hip hemarthrosis, orthopedic evaluation for possible aspiration is advisable to prevent avascular necrosis of the femoral head.
†For mild or moderate hemophilia, desmopressin, 0.3 μg/kg, should be used instead of factor VIII concentrate, if the patient is known to respond with a hemostatic level of factor VIII; if repeated doses are given, monitor factor VIII levels for tachyphylaxis.
‡Stated doses apply for recombinant factor IX concentrate; for plasma-derived factor IX concentrate, use 70% of the stated dose.
§Do not give antifibrinolytic therapy until 4-6 hr after a dose of prothrombin complex concentrate.
‖Nonprescription coagulation-promoting products may be helpful.
**Repeat radiologic assessment should be performed before discontinuation of therapy.
††If repeated doses of factor IX concentrate are required, use highly purified, specific factor IX concentrate.
Adapted from Montgomery RR, Gill JC, Scott JP: Hemophilia and von Willebrand disease. In Nathan DG, Orkin SH, editors: Nathan and Oski's hematology of

Table 477-2 VWD Classification

	TYPE 1	TYPE 3	TYPE 2A	TYPE 2B*	TYPE 2M	TYPE 2N
VWF:Ag	↓	Absent	↓	↓	↓	Normal or ↓
VWF:RCo	↓	Absent	↓↓	↓↓	↓↓	Normal or ↓
FVIII	Normal	↓↓	Normal or ↓	Normal or ↓	Normal or ↓	↓↓
Multimer distribution	Normal	Absent	Loss of HMWM	Loss of HMWM	Normal	Normal

*Platelet count is also usually decreased in type 2B VWD.
FVIII, factor VIII; HMWM, high-molecular-weight multimers; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor activity.

Table 477-3 VWD Treatment

TREATMENT	VWD TYPES	ADMINISTRATION	DOSING
Desmopressin*	Type 1 VWD Some type 2 VWD (use with caution)	IV or IN	0.3 μg/kg IV† 1 spray IN (<50 kg) 2 sprays IN (>50 kg)
von Willebrand factor concentrates‡	Type 3 VWD Type 2 VWD Severe type 1 VWD (or type 1 clearance defects)	IV	40-60 ristocetin cofactor activity units/kg (adjust dose depending on baseline VWF level and desired peak VWF level)
Antifibrinolytics	Mucosal bleeding, all types of VWD	PO or IV	Aminocaproic acid: 100 mg/kg PO loading dose followed by 50 mg/kg q 6 hours§ Tranexamic acid: 1300 mg PO tid × 5 days

*Recommended treatment with Stimate brand nasal spray, as this form is concentrated to give 150 μg/spray. Other forms are much more dilute and will not result in desired increase in VWF.
†Maximum recommended dose is 20-30 μg/day.
‡Currently both Humate-P and Wilate are approved for treatment of VWD. A recombinant VWF preparation is currently undergoing clinical trials.
§Maximum recommended dose is 24 g/day.
IN, intranasal; IV, intravenous; PO, oral administration.

Table 478-1 Common Inherited Thrombophilias and Accompanying Diagnostic Laboratory Studies

THROMBOPHILIA	PREVALENCE IN WHITE POPULATION %	ODDS RATIO FOR FIRST EPISODE VTE IN CHILDHOOD*	LABORATORY STUDIES
Factor V Leiden mutation Heterozygote Homozygote	 3-7 0.06-0.25	 3.8 80-100	DNA-based PCR assay (or screen with activated protein C resistance)
Prothrombin 20210 mutation Heterozygote Homozygote	 1-3 –	 2.6 –	DNA-based PCR assay
Antithrombin deficiency	0.02-0.04	9.4	Antithrombin activity via chromogenic or clotting assay
Protein S deficiency	0.03-0.13	5.8	Protein S activity via assay or immunologic assay of free and total protein S antigen
Protein C deficiency	0.2	7.7	Protein C activity via chromogenic or clotting assay
Hyperhomocystinemia	–	–	Fasting homocysteine
Elevated VIII	–	–	Factor VIII activity via one-stage clotting or chromogenic assay

*Data from Young G, Albisetti M, Bonduel M, et al: Impact of inherited thrombophilia on venous thromboembolism in children. *Circulation* 118:1373–1382, 2008.
PCR, polymerase chain reaction; VTE, venous thromboembolism.

Table 479-1 Risk Factors for Thrombosis

General	Indwelling catheter including PICC (peripherally inserted central venous catheter) lines Infection Trauma Surgery Cancer Immobility Cardiac disease/prosthetic valve Systemic lupus Rheumatoid arthritis Inflammatory bowel disease Polycythemia/dehydration Nephrotic syndrome Diabetes Pregnancy Obesity Prematurity Paroxysmal nocturnal hemoglobinuria Antiphospholipid antibody syndrome Thrombotic thrombocytopenic purpura
Inherited thrombophilia	Factor V Leiden mutation Prothrombin mutation Antithrombin deficiency Protein C deficiency Protein S deficiency Homocystinuria Elevated factor VIII Dysfibrinogenemia
Anatomic	Thoracic outlet obstruction (Paget-Schroetter syndrome) May-Thurner syndrome Absence of the inferior vena cava
Medications	Estrogen-containing contraceptives Asparaginase Heparin (heparin-induced thrombocytopenia) Corticosteroids

Table 474-1 Estimated Risks in Transfusion Per Unit Transfused in the United States

ADVERSE EFFECT	ESTIMATED RISK
Febrile reaction	1/300
Urticaria or other cutaneous reaction	1/50-100
Red blood cell alloimmunization	1/100
Mistranfusion	1/14,000-19,000
Hemolytic reaction	1/6,000
Fatal hemolysis	1/1,000,000
Transfusion-related acute lung injury (TRALI)	1/5,000
HIV1 and HIV2	1/2,000,000-3,000,000
Hepatitis B	1/100,000-200,000
Hepatitis C	1/1,000,000-2,000,000
Human T-cell lymphotrophic virus (HTLV) I and II	1/641,000
Bacterial contamination (usually platelets)	1/5,000,000
Malaria	1/4,000,000
Anaphylaxis	1/20,000-50,000
Graft-versus-host disease	Uncommon
Immunomodulation	Unknown
Hepatitis A	Unknown
Parvovirus	Unknown
Dengue fever	Unknown
Babesiosis	Unknown
West Nile virus	Unknown
Trypanosoma cruzi	Unknown
Leishmania spp.	Unknown
Variant Creutzfeldt-Jakob prion disease	Unknown

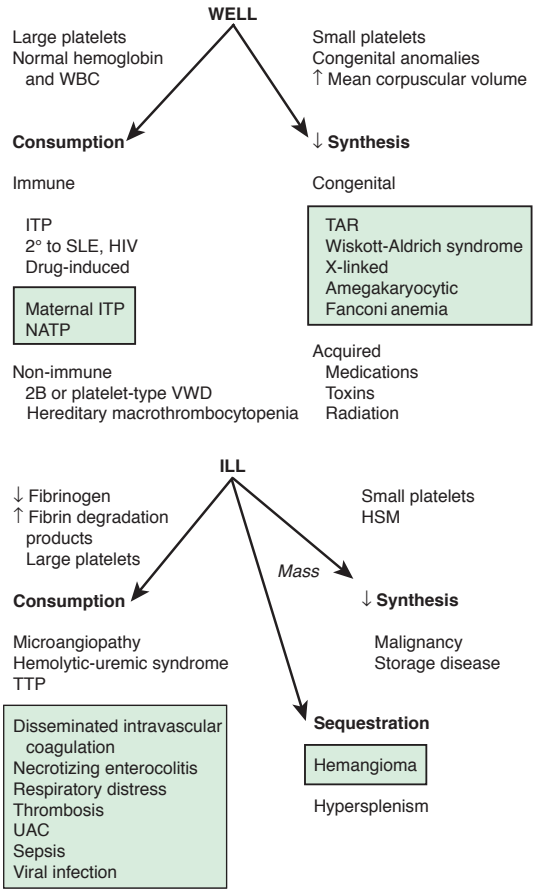

Table 487-1 Diseases Associated with Hyposplenism or Splenic Atropy

CONGENITAL FORMS	**AUTOIMMUNE DISORDERS**
Normal and premature neonates	Systematic lupus erythematosus
Isolated congenital hypoplasia	Rheumatoid arthritis
Ivemark syndrome	Glomerulonephritis
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome	Wegener granulomatosis
	Goodpasture syndrome
	Sjögren syndrome
Hypoparathyroidism syndrome	Nodous polyarteritis
Stormorken syndrome	Thyroiditis
Heterotaxia syndromes	Sarcoidosis
GASTROINTESTINAL DISORDERS	**INFECTIOUS DISEASES**
Coeliac disease	HIV/AIDS
Inflammatory bowel disease	Pneumococcal meningitis
Whipple disease	Malaria
Dermatitis herpetiformis	
Intestinal lymphangiectasia	
Idiopathic chronic ulcerative enteritis	
HEPATIC DISORDERS	**IATROGENIC FORMS**
Active chronic hepatitis	Exposure to methyldopa
Primary biliary cirrhosis	High-dose steroids
Hepatic cirrhosis and portal hypertension	Total parenteral nutrition
	Splenic irradiation
Alcoholism and alcoholic hepatopathy	
ONCOHEMATOLOGIC DISORDERS	**ALTERATION IN SPLENIC CIRCULATION**
Hemoglobin S diseases	Thrombosis of splenic artery
Bone marrow transplantation	Thrombosis of splenic vein
Chronic graft-versus-host disease	Thrombosis of coeliac artery
Acute leukemia	**MISCELLANEOUS**
Chronic myeloproliferative disorders	Amyloidosis
Fanconi syndrome	
Splenic tumors	
Mastocytosis	

Table 483-1 Causes of Disseminated Intravascular Coagulation

INFECTIOUS
Meningococcemia (purpura fulminans)
Bacterial sepsis (staphylococcal, streptococcal, *Escherichia coli*, *Salmonella*)
Rickettsia (Rocky Mountain spotted fever)
Virus (cytomegalovirus, herpes simplex, hemorrhagic fevers)
Malaria
Fungus
TISSUE INJURY
Central nervous system trauma (massive head injury)
Multiple fractures with fat emboli
Crush injury
Profound shock or asphyxia
Hypothermia or hyperthermia
Massive burns
MALIGNANCY
Acute promyelocytic leukemia
Acute monoblastic or promyelocytic leukemia
Widespread malignancies (neuroblastoma)
VENOM OR TOXIN
Snake bites
Insect bites
MICROANGIOPATHIC DISORDERS
"Severe" thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome
Giant hemangioma (Kasabach-Merritt syndrome)
GASTROINTESTINAL DISORDERS
Fulminant hepatitis
Ischemic bowel
Pancreatitis
HEREDITARY THROMBOTIC DISORDERS
Antithrombin III deficiency
Homozygous protein C deficiency
NEWBORN
Maternal toxemia
Bacterial or viral sepsis (group B streptococcus, herpes simplex)
Abruptio placenta
Severe respiratory distress syndrome
Necrotizing enterocolitis
Erythroblastosis fetalis
Fetal demise of a twin
MISCELLLANEOUS
Severe acute graft rejection
Acute hemolytic transfusion reaction
Severe collagen-vascular disease
Kawasaki disease
Heparin-induced thrombosis
Infusion of "activated" prothrombin complex concentrates
Hyperpyrexia/encephalopathy, hemorrhagic shock syndrome

Table 490-1 Differential Diagnosis of Systemic Generalized Lymphadenopathy

INFANT	CHILD	ADOLESCENT
COMMON CAUSES		
Syphilis	Viral infection	Viral infection
Toxoplasmosis	EBV	EBV
CMV	CMV	CMV
HIV	HIV	HIV
	Toxoplasmosis	Toxoplasmosis
		Syphilis
RARE CAUSES		
Chagas disease (congenital)	Serum sickness	Serum sickness
Leukemia	SLE, JIA	SLE, JIA
Tuberculosis	Leukemia/lymphoma	Leukemia/lymphoma/Hodgkin disease
Reticuloendotheliosis	Tuberculosis	Lymphoproliferative disease
Lymphoproliferative disease	Measles	Tuberculosis
Metabolic storage disease	Sarcoidosis	Histoplasmosis
Histiocytic disorders	Fungal infection	Sarcoidosis
	Plague	Fungal infection
	Langerhans cell histiocytosis	Plague
	Chronic granulomatous disease	Drug reaction
		Castleman disease
	Sinus histiocytosis	
	Drug reaction	

Table 484-1 Differential Diagnosis of Thrombocytopenia in Children and Adolescents

DESTRUCTIVE THROMBOCYTOPENIAS
Primary Platelet Consumption Syndromes
Immune thrombocytopenias
- Acute and chronic ITP
- Autoimmune diseases with chronic ITP as a manifestation
  - Cyclic thrombocytopenia
  - Autoimmune lymphoproliferative syndrome and its variants
  - Systemic lupus erythematosus
  - Evans syndrome
  - Antiphospholipid antibody syndrome
  - Neoplasia-associated immune thrombocytopenia
- Thrombocytopenia associated with HIV
- Neonatal immune thrombocytopenia
  - Alloimmune
  - Autoimmune (e.g., maternal ITP)
- Drug-induced immune thrombocytopenia (including heparin-induced thrombocytopenia)
- Posttransfusion purpura
- Allergy and anaphylaxis
- Posttransplant thrombocytopenia

Nonimmune thrombocytopenias
- Thrombocytopenia of infection
  - Bacteremia or fungemia
  - Viral infection
  - Protozoan
- Thrombotic microangiopathic disorders
  - Hemolytic-uremic syndrome
  - Eclampsia, HELLP syndrome
  - Thrombotic thrombocytopenic purpura
  - Bone marrow transplantation-associated microangiopathy
  - Drug-induced
  - Platelets in contact with foreign material
  - Congenital heart disease
  - Drug-induced via direct platelet effects (ristocetin, protamine)
  - Type 2B VWD or platelet-type VWD

Combined Platelet and Fibrinogen Consumption Syndromes
- Disseminated intravascular coagulation
- Kasabach-Merritt syndrome
- Virus-associated hemophagocytic syndrome

IMPAIRED PLATELET PRODUCTION
- Hereditary disorders
- Acquired disorders
  - Aplastic anemia
  - Myelodysplastic syndrome
  - Marrow infiltrative process—neoplasia
  - Osteopetrosis
  - Nutritional deficiency states (iron, folate, vitamin B_{12}, anorexia nervosa)
  - Drug- or radiation-induced thrombocytopenia
  - Neonatal hypoxia or placental insufficiency

SEQUESTRATION
- Hypersplenism
- Hypothermia
- Burns

HELLP, hemolysis, elevated liver enzymes, and low platelets; HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; VWD, von Willebrand disease.

From Wilson DB: Acquired platelet defects. In Orkin SH, Nathan DG, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, *ed 7, Philadelphia, 2009, WB Saunders, p. 1555, Box 33-1.*

Table 484-2 Classification of Fetal and Neonatal Thrombocytopenias*

	CONDITION		CONDITION
Fetal	**Alloimmune thrombocytopenia** **Congenital infection** (e.g., CMV, toxoplasma, rubella, HIV) **Aneuploidy** (e.g., trisomy 18, 13, or 21, or triploidy) **Autoimmune condition** (e.g., ITP, SLE) Severe Rh hemolytic disease Congenital/inherited (e.g., Wiskott-Aldrich syndrome)		Thrombosis (e.g., aortic, renal vein) Bone marrow replacement (e.g., congenital leukemia) Kasabach-Merritt syndrome Metabolic disease (e.g., proprionic and methylmalonic acidemia) Congenital/inherited (e.g., TAR, CAMT)
Early-onset neonatal (<72 hr)	**Placental insufficiency** (e.g., PET, IUGR, diabetes) **Perinatal asphyxia** **Perinatal infection** (e.g., *Escherichia coli*, GBS, herpes simplex) **DIC** **Alloimmune thrombocytopenia** **Autoimmune condition** (e.g., ITP, SLE) Congenital infection (e.g., CMV, toxoplasma, rubella, HIV)	Late-onset neonatal (>72 hr)	**Late-onset sepsis** NEC Congenital infection (e.g., CMV, toxoplasma, rubella, HIV) Autoimmune Kasabach-Merritt syndrome Metabolic disease (e.g., proprionic and methylmalonic acidemia) Congenital/inherited (e.g., TAR, CAMT)

*The most common conditions are shown in bold.
CAMT, congenital amegakaryocytic thrombocytopenia; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; GBS, group B streptococcus; ITP, idiopathic thrombocytopenic purpura; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; PET, preeclampsia; SLE, systemic lupus erythematosus; TAR, thrombocytopenia with absent radii.

Table 487-2 Diagnostic Techniques for and Features of Spleen Dysfunction

	DESCRIPTION	COMMENTS
Immunoglobulin M memory B cells	Cells dependent on spleen for survival. Produced in marginal zone	Special tests required
Technetium-99m–labeled sulphur colloidal scintiscan	Quantitation of splenic uptake of colloidal sulphur particles enables a fairly accurate static assessment of spleen function	Hypertrophy of the left hepatic lobe might be a limiting factor (this technique does not clearly show whether the mass originated in the liver or the spleen in the presence of an overlapping hypertropic left hepatic lobe)
Technetium-99m–labeled or rubidium-81–labeled heat-damaged autologous erythrocyte clearance	Measurement of clearance time allows a dynamic evaluation of spleen function	Preexisting erythrocyte defects, difficult erythrocyte incorporation of the radioisotope, false-positive or false-negative results in relation to excessive or insufficient heat damage make the test not suitable for clinical practice
Detection of Howell-Jolly bodies by staining	Erythrocytes with nuclear remnants Flow cytometry	No need for special equipment; inaccurate in the quantitation of splenic hypofunction
Detection of pitted erythrocytes by phase-interference microscopy	Erythrocytes with membrane indentations (4% upper limit of the normal range)	Need for phase-interference microscopy; counts enable a wide range of measurements and correlate with radioisotopic methods

Table 486-1 Differential Diagnosis of Splenomegaly by Pathophysiology

ANATOMIC LESIONS
Cysts, pseudocysts
Hamartomas
Polysplenia syndrome
Hemangiomas and lymphangiomas
Hematoma or rupture (traumatic)
Peliosis

HYPERPLASIA CAUSED BY HEMATOLOGIC DISORDERS
Acute and Chronic Hemolysis*
Hemoglobinopathies (sickle cell disease in infancy with or without sequestration crisis and sickle variants, thalassemia major, unstable hemoglobins)
Erythrocyte membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)
Erythrocyte enzyme deficiencies (severe G6PD deficiency, pyruvate kinase deficiency)
Immune hemolysis (autoimmune and isoimmune hemolysis)
Paroxysmal nocturnal hemoglobinuria
Chronic Iron Deficiency
Extramedullary Hematopoiesis
Myeloproliferative diseases: CML, juvenile CML, myelofibrosis with myeloid metaplasia, polycythemia vera
Osteopetrosis
Patients receiving granulocyte and granulocyte-macrophage colony-stimulating factors

INFECTIONS†
Bacterial
Acute sepsis: *Salmonella typhi, Streptococcus pneumoniae, Haemophilus influenzae* type b, *Staphylococcus aureus*
Chronic infections: infective endocarditis, chronic meningococcemia, brucellosis, tularemia, cat-scratch disease
Local infections: splenic abscess (*S. aureus*, streptococci, less often *Salmonella* species, polymicrobial infection), pyogenic liver abscess (anaerobic bacteria, Gram-negative enteric bacteria), cholangitis
Viral*
Acute viral infections, especially in children
Congenital CMV, herpes simplex, rubella
Hepatitides A, B, and C; CMV
EBV
Viral hemophagocytic syndromes: CMV, EBV, HHV-6
HIV
Spirochetal
Syphilis, especially congenital syphilis
Leptospirosis
Rickettsial
Rocky Mountain spotted fever
Q fever
Typhus
Fungal/Mycobacterial
Miliary tuberculosis
Disseminated histoplasmosis
South American blastomycosis
Systemic candidiasis (in immunosuppressed patients)
Parasitic
Malaria
Toxoplasmosis, especially congenital
Toxocara canis, Toxocara cati (visceral larva migrans)
Leishmaniasis (kala-azar)
Schistosomiasis (hepatic-portal involvement)
Trypanosomiasis
Fascioliasis
Babesiosis

IMMUNOLOGIC AND INFLAMMATORY PROCESSES*
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disease
Systemic vasculitis
Serum sickness
Drug hypersensitivity, especially to phenytoin
Graft-versus-host disease
Sjögren syndrome
Cryoglobulinemia
Amyloidosis
Sarcoidosis
Autoimmune lymphoproliferative syndrome
Posttransplant lymphoproliferative disease
Large granular lymphocytosis and neutropenia
Histiocytosis syndromes
Hemophagocytic syndromes (nonviral, familial)

MALIGNANCIES
Primary: leukemia (acute, chronic), lymphoma, angiosarcoma, Hodgkin disease, mastocytosis
Metastatic

STORAGE DISEASES
Lipidosis (Gaucher disease, Niemann-Pick disease, infantile GM1 gangliosidosis)
Mucopolysaccharidoses (Hurler, Hunter-type)
Mucolipidosis (I-cell disease, sialidosis, multiple sulfatase deficiency, fucosidosis)
Defects in carbohydrate metabolism: galactosemia, fructose intolerance, glycogen storage disease IV
Sea-blue histiocyte syndrome
Tangier disease
Wolman disease
Hyperchylomicronemia type I, IV

CONGESTIVE*
Heart failure
Intrahepatic cirrhosis or fibrosis
Extrahepatic portal (thrombosis), splenic, and hepatic vein obstruction (thrombosis, Budd-Chiari syndrome)

*Common.
†Chronic or recurrent infection suggests underlying immunodeficiency.
CML, chronic myelogenous leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus.

Table 479-2 Comparison of Antithrombotic Agents

	rTPA	UNFRACTIONATED HEPARIN*	WARFARIN	LMW HEPARIN (ENOXAPARIN)
Indication	Recent onset of life- or limb-threatening thrombus	Acute or chronic thrombus, prophylaxis	Subacute or chronic thrombosis, thromboprophylaxis for cardiac valves	Acute or chronic thrombus, prophylaxis
Administration	IV, Continuous infusion	IV, Continuous infusion	PO, once daily	SC injection, twice daily
Monitoring	"Lytic state": FDP or D-dimer	PTT	INR	Anti-Xa activity
Other	Higher risk of bleeding	Difficult to titrate, requires frequent dose adjustments	Heavily influenced by drug and diet	More stable and easy to titrate; concern of osteopenia with long-term use

FDP, fibrin degradation product; INR, international normalized ratio; LMW, low-molecular-weight; PTT, partial thromboplastin time; rTPA, recombinant tissue-type plasminogen activator.
*Higher dose is required in newborns.

Table 490-2 Sites of Local Lymphadenopathy and Associated Diseases

CERVICAL
Oropharyngeal infection (viral or group A streptococcal, staphylococcal)
Scalp infection/infestation (head lice)
Mycobacterial lymphadenitis (tuberculosis and nontuberculous mycobacteria)
Viral infection (EBV, CMV, HHV-6)
Cat-scratch disease
Toxoplasmosis
Kawasaki disease
Thyroid disease
Kikuchi disease
Sinus histiocytosis (Rosai-Dorfman disease)
Autoimmune lymphoproliferative disease
Periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy (PFAPA) syndrome
ANTERIOR AURICULAR
Conjunctivitis
Other eye infection
Oculoglandular tularemia
Facial cellulitis
Otitis media
Viral infection (especially rubella, parvovirus)
SUPRACLAVICULAR
Malignancy or infection in the mediastinum (right)
Metastatic malignancy from the abdomen (left)
Lymphoma
Tuberculosis
EPITROCHLEAR
Hand infection, arm infection*
Lymphoma†
Sarcoid
Syphilis
INGUINAL
Urinary tract infection
Venereal disease (especially syphilis or lymphogranuloma venereum)
Other perineal infections
Lower extremity suppurative infection
Plague
HILAR (NOT PALPABLE, FOUND ON CHEST RADIOGRAPH OR CT)
Tuberculosis†
Histoplasmosis†
Blastomycosis†
Coccidioidomycosis†
Leukemia/lymphoma†
Hodgkin disease†
Metastatic malignancy*
Sarcoidosis†
Castleman disease
AXILLARY
Cat-scratch disease
Arm or chest wall infection
Malignancy of chest wall
Leukemia/lymphoma
Brucellosis
ABDOMINAL
Malignancies
Mesenteric adenitis (measles, tuberculosis, *Yersinia*, group A streptococcus)

*Unilateral.
†Bilateral.
CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6.
From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 864.*

Table 495-1 Factors Predisposing to Childhood Leukemia

GENETIC CONDITIONS
Down syndrome
Fanconi anemia
Bloom syndrome
Diamond-Blackfan anemia
Shwachman-Diamond syndrome
Kostmann syndrome
Neurofibromatosis type 1
Ataxia-telangiectasia
Severe combined immune deficiency
Paroxysmal nocturnal hemoglobinuria
Li-Fraumeni syndrome
ENVIRONMENTAL FACTORS
Ionizing radiation
Drugs
Alkylating agents
Epipodophyllotoxin
Benzene exposure

Cancer and Benign Tumors

Table 491-2 Known Risk Factors for Selected Childhood Cancers

CANCER TYPE	RISK FACTOR	COMMENTS
Acute lymphoid leukemia	Ionizing radiation	Although primarily of historical significance, prenatal diagnostic x-ray exposure increases risk. Therapeutic irradiation for cancer treatment also increases risk.
	Race	White children have a 2-fold higher rate than black children in the United States.
	Genetic factors*	Down syndrome is associated with an estimated 10-20–fold increased risk. NF1, Bloom syndrome, ataxia-telangiectasia, and Langerhans cell histiocytosis, among others, are associated with an elevated risk.
Acute myeloid leukemias	Chemotherapeutic agents	Alkylating agents and epipodophyllotoxins increase risk.
	Genetic factors*	Down syndrome and NF1 are strongly associated. Familial monosomy 7 and several other genetic syndromes are also associated with increased risk.
Brain cancers	Therapeutic ionizing radiation to the head	With the exception of cancer radiation therapy, higher risk from radiation treatment is essentially of historical importance.
	Genetic factors*	NF1 is strongly associated with optic gliomas, and, to a lesser extent, with other central nervous system tumors. Tuberous sclerosis and several other genetic syndromes are associated with increased risk.
Hodgkin disease	Family history	Monozygotic twins and siblings are at increased risk.
	Infections	EBV is associated with increased risk.
Non-Hodgkin lymphoma	Immunodeficiency	Acquired and congenital immunodeficiency disorders and immunosuppressive therapy increase risk.
	Infections	EBV is associated with Burkitt lymphoma in Africa.
Osteosarcoma	Ionizing radiation	Cancer radiation therapy and high radium exposure increase risk.
	Chemotherapy	Alkylating agents increase risk.
	Genetic factors*	Increased risk is apparent with Li-Fraumeni syndrome and hereditary retinoblastoma.
Ewing sarcoma	Race	White children have about a 9-fold higher incidence rate than black children in the United States.
Neuroblastoma		Neurocristopathies.
Retinoblastoma	Genetic factors*	No established other risk factors.
Wilms tumor	Congenital anomalies	Aniridia, Beckwith-Wiedemann syndrome, and other congenital and genetic conditions are associated with increased risk.
	Race	Asian children reportedly have about half the rates of white and black children.
Renal medullary carcinoma	Sickle cell trait	Etiology unknown.
Rhabdomyosarcoma	Congenital anomalies and genetic conditions	Li-Fraumeni syndrome and NF1 are believed to be associated with increased risk. There is some concordance with major birth defects.
Hepatoblastoma	Genetic factors*	Beckwith-Wiedemann syndrome, hemihypertrophy, Gardner syndrome, and family history of adenomatous polyposis are associated with increased risk.
Leiomyosarcoma	Immunosuppression and EBV infection	EBV is associated with leiomyosarcoma for all forms of congenital and acquired immunosuppression but not leiomyosarcoma among immunocompetent persons.
Malignant germ cell tumors	Cryptorchidism	Cryptorchidism is a risk factor for testicular germ cell tumors.

*See Chapter 492, Table 492-2.
EBV, Epstein-Barr virus; NF1, neurofibromatosis type 1.
Scheurer ME, Bondy ML, Gurney JG: Epidemiology of childhood cancer. In Pizzo PA, Poplack DG, editors: Principles and practice of pediatric oncology, *ed 6, Philadelphia, 2011, Lippincott Williams & Wilkins, p. 15.*

Table 492-2 Familial or Genetic Susceptibility to Malignancy

DISORDER	TUMOR/CANCER	COMMENT
CHROMOSOMAL SYNDROMES		
Chromosome 11p deletion syndrome with sporadic aniridia	Wilms tumor	Associated with genitourinary anomalies, mental retardation, *WT1* gene
Chromosome 13q deletion syndrome	Retinoblastoma, sarcoma	Associated with intellectual disability, skeletal malformations; autosomal dominant (bilateral) or sporadic new mutations, *RB1* gene
Trisomy 21	Lymphocytic or nonlymphocytic leukemia, especially megakaryocytic leukemia; transient leukemoid reaction	Risk of ALL is increased 20%; risk of AML is increased 400%; patients have an increased sensitivity to chemotherapy
Klinefelter syndrome (47,XXY)	Breast cancer, extragonadal germ cell tumors	
Trisomy 8	Preleukemia	
Noonan syndrome	JMML	Autosomal dominant; mutations in *PTPN11* gene
Monosomy 5 or 7	Myelodysplastic syndrome	Recurrent infections may precede neoplasia
CHROMOSOMAL INSTABILITY		
Xeroderma pigmentosum	Basal cell and squamous cell carcinomas; melanoma	Autosomal recessive; failure to repair UV-damaged DNA. Mutations in *XP* gene on chromosome 3p25
Fanconi anemia	Leukemia, myelodysplastic syndrome, liver neoplasias, rare head and neck tumors, GI and GU cancers	Autosomal recessive; chromosome fragility; positive diepoxybutane test result. Mutations in *FANCX* gene family
Bloom syndrome	Leukemia, lymphoma, and solid tumors	Autosomal recessive; increase sister chromatid exchange; mutations in *BLM* gene; member of the RecQ helicase gene
Ataxia-telangiectasia	Lymphoma, leukemia, less commonly central nervous system and nonneural solid tumors	Autosomal recessive; sensitive to X-irradiation, radiomimetic drugs; mutation in *ATM* tumor-suppressor gene
Dysplastic nevus syndrome	Melanoma	Autosomal dominant; some cases associated with mutations in *CDKN2A* gene
Rothmund-Thompson syndrome	Osteosarcoma; skin cancers	Autosomal recessive; mutation in RecQ helicase gene family
Werner syndrome (premature aging)	Soft tissue sarcomas	Autosomal recessive; mutation in the *WRN* gene; member of the RecQ helicase gene family
IMMUNODEFICIENCY SYNDROMES		
Wiskott-Aldrich syndrome	Lymphoma, leukemia	X-linked recessive; *WAS* gene mutation (Xp11.22-23); WASP protein functions in signal transduction associated with cytoskeletal actin filament rearrangement
X-linked immunodeficiency (Duncan syndrome)	Lymphoproliferative disorder	X-linked; Epstein-Barr viral infection can result in fatal outcome; mutation in *SH2D1A* gene locus
X-linked agammaglobulinemia (Bruton disease)	Lymphoma, leukemia	X-linked; mutation in *BKT* gene resulting in absence of mature B cells
Severe combined immunodeficiency	Leukemia, lymphoma	X-linked; mutations in *ADA* gene

Table 492-2 Familial or Genetic Susceptibility to Malignancy—cont'd

DISORDER	TUMOR/CANCER	COMMENT
OTHERS		
Neurofibromatosis 1	Neurofibroma, optic glioma, acoustic neuroma, astrocytoma, meningioma, pheochromocytoma, sarcoma	Autosomal dominant; mutation in tumor-suppressor gene, *NF1*
Neurofibromatosis 2	Bilateral acoustic neuromas, meningiomas	Autosomal dominant; mutation in tumor-suppressor gene, *NF2*
Tuberous sclerosis	Fibroangiomatous nevi, myocardial rhabdomyoma	Autosomal dominant
Gorlin-Goltz syndrome (nevus basal cell carcinoma syndrome)	Multiple basal cell carcinomas; medulloblastoma	Autosomal dominant; mutation in *PTCH* gene
Li-Fraumeni syndrome	Bone, soft tissue sarcoma, breast	Mutation of *P53* tumor-suppressor gene, autosomal dominant
Retinoblastoma	Sarcoma	Autosomal recessive; increased risk of secondary malignancy 10-20 yr later; mutation in *RB* tumor-suppressor gene
Hemihypertrophy ± Beckwith syndrome	Wilms tumor, hepatoblastoma, adrenal carcinoma	*WT1* gene; 25% develop tumor, most in 1st 5 yr of life
von Hippel-Landau disease	Hemangioblastoma of the cerebellum and retina, pheochromocytoma, renal cancer	Autosomal dominant; mutation of tumor-suppressor gene, *VHL* gene
Multiple endocrine neoplasia syndrome, type 1 (Wermer syndrome)	Parathyroid, pancreatic islet, and pituitary tumors	Autosomal dominant; mutation in *PYGM* tumor-suppressor gene
Multiple endocrine neoplasia syndrome, type 2A (Sipple syndrome)	Medullary carcinoma of the thyroid, hyperparathyroidism, pheochromocytoma	Autosomal dominant; mutations in CYS-rich regions of the *RET* gene activate this protooncogene; *RET* codes for a tyrosine kinase; monitor calcitonin and calcium levels
Multiple endocrine neoplasia type 2B (multiple mucosal neuroma syndrome)	Mucosal neuroma, pheochromocytoma, medullary thyroid carcinoma, Marfan habitus; neuropathy	Autosomal dominant; mutation in catalytic site (codon 883 or 914) activates protooncogene; *RET* codes for a tyrosine kinase
Familial adenomatous polyposis	Colorectal, thyroid carcinoma, duodenal and periampullar carcinomas; pediatric hepatoblastoma	Autosomal dominant; mutation in *APC* gene
Familial juvenile polyposis	Colorectal carcinoma	Autosomal dominant; mutation in *SMAD4* gene
Hereditary nonpolyposis colon cancer (Lynch syndrome, NHPCC)	Colon cancer	Autosomal dominant; mutation in mismatch repair genes; *hMSH2, hMLH1, PMS1, PMS2, hMSH6, hMSG3*
Turcot syndrome	Pediatric brain tumors and increased risk of colon carcinoma and polyps	Mutation in *APC* gene
Familial adenomatous polyposis coli	Adenocarcinoma of colon	Autosomal dominant, *APC* gene
Gardner syndrome	Adenocarcinoma of colon, skull and soft tissue tumors	Autosomal dominant, *APC* gene
Peutz-Jeghers syndrome	Gastrointestinal carcinoma, ovarian neoplasia	Autosomal dominant, *LKB1* gene codes for a Ser/Thr kinase that regulates cell cycle, metabolism, cell polarity
Hemochromatosis	Hepatocellular carcinoma	Autosomal dominant; malignancy associated with cirrhotic liver
Glycogen storage disease 1 (von Gierke disease)	Hepatocellular carcinoma	Autosomal recessive; malignancy associated with cirrhotic liver Mutation in glucose-6-phosphatase or glucose-6-phosphatase translocase genes
Tyrosinemia, galactosemia	Hepatocellular carcinoma	Autosomal recessive; tumor associated with cirrhotic liver
BRCA1 and *BRCA2*	Breast, ovarian	DNA repair defect
Diamond-Blackfan anemia	AML, myelodysplastic syndrome, osteogenic sarcoma	Autosomal dominant; family 9 genes encoding ribosomal proteins
Shwachman-Diamond syndrome	AML, myelodysplasia	Autosomal recessive; *SBDS* gene; chromosome 7q11.21
Hereditary diffuse gastric cancer	Gastric cancer	Autosomal dominant; *CDH1* gene
Pleuropulmonary blastoma family tumor and dysplasia syndrome (DICER1)	Pulmonary blastoma	Encoded protein is a ribonuclease required for microRNA processing
Hereditary neuroblastoma	Neuroblastoma	Two genes have been identified: • Anaplastic lymphoma kinase *(ALK)* at chromosome 2p23 • Paired-like homeobox 2b *(PHOX2B)* at chromosome 4q12
Hereditary paraganglioma–pheochromocytoma syndrome	Paraganglioma Pheochromocytomas	Mutation in the mitochondrial enzyme succinate dehydrogenase protein (SDH)
Congenital or cyclic neutropenia	Myelodysplastic syndrome AML	*ELANE* mutation at 19p13.3; elastase; neutrophil expressed

ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; GI, gastrointestinal; GU, genitourinary; JMML, juvenile myelomonocytic leukemia; NHPCC, nonhereditary polyposis colon cancer.

Table 493-1 Common Manifestations of Childhood Malignancies

	SIGNS AND SYMPTOMS	POTENTIAL ETIOLOGY	POSSIBLE ONCOLOGIC DIAGNOSIS
Constitutional/Systemic	Fever, persistent or recurrent infection, neutropenia	Bone marrow infiltration	Leukemia, neuroblastoma
	Fever of unknown origin, weight loss, night sweats	Lymphoma	Hodgkin and non-Hodgkin lymphoma
	Painless lymphadenopathy	Lymphoma, metastatic solid tumor	Leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, thyroid carcinoma
	Hypertension	Renal or adrenal tumor	Neuroblastoma, pheochromocytoma, Wilms tumor
	Soft tissue mass	Local or metastatic tumor	Ewing sarcoma, osteosarcoma, neuroblastoma, thyroid carcinoma, rhabdomyosarcoma, Langerhans cell histiocytosis
Neurologic/Ophthalmologic	Headache with emesis, visual disturbances, ataxia, papilledema, cranial nerve palsies	Increased intracranial pressure	Primary brain tumor; metastasis
	Leukokoria (white pupil)	Retinal mass	Retinoblastoma
	Periorbital ecchymosis	Metastasis	Neuroblastoma
	Miosis, ptosis, heterochromia	Horner syndrome: compression of cervical sympathetic nerves	Neuroblastoma
	Opsoclonus myoclonus, ataxia	Neurotransmitters? Autoimmunity?	Neuroblastoma
	Exophthalmos, proptosis	Orbital tumor	Rhabdomyosarcoma, lymphoma, Langerhans cell histiocytosis
Respiratory/Thoracic	Cough, stridor, pneumonia, tracheal-bronchial compression; superior vena cava syndrome	Anterior mediastinal mass	Germ cell tumor, non-Hodgkin lymphoma, Hodgkin lymphoma
	Vertebral or nerve root compression; dysphagia	Posterior mediastinal mass	Neuroblastoma, neuroenteric cyst
Gastrointestinal	Abdominal mass	Adrenal, renal, or lymphoid tumor	Neuroblastoma, Wilms tumor, lymphoma
	Diarrhea	Vasoactive intestinal polypeptide	Neuroblastoma, ganglioneuroma
Hematologic	Pallor, anemia	Bone marrow infiltration	Leukemia, neuroblastoma
	Petechiae, thrombocytopenia	Bone marrow infiltration	Leukemia, neuroblastoma
Musculoskeletal	Bone pain, limp, arthralgia	Primary bone tumor, metastasis to bone	Osteosarcoma, Ewing sarcoma, leukemia, neuroblastoma
Endocrine	Diabetes insipidus, galactorrhea, poor growth	Neuroendocrine involvement of hypothalamus or pituitary gland	Adenoma, craniopharyngioma, prolactinoma, Langerhans cell histiocytosis

Table 493-2 Work-up of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases

MALIGNANCY	BONE MARROW ASPIRATE OR BIOPSY	CHEST X-RAY	CT SCAN	MRI	PET SCAN	BONE SCAN	CSF ANALYSIS	SPECIFIC MARKERS	OTHER TESTS
Leukemia	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	—	—	—	—	Yes	—	—
Non-Hodgkin lymphoma	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	Yes	—	Yes	Yes (selected cases)	Yes	—	—
Hodgkin lymphoma	Yes (in advanced stage)	Yes	Yes	—	Yes	Yes (selected cases)	—	—	—
CNS tumors	—	—	—	Yes	—	—	Yes (selected tumors)	—	—
Neuroblastoma	Yes (includes cytogenetics, molecular studies)	—	Yes	—	—	Yes	—	VMA, HVA	MIBG scan; bone x-rays
Wilms tumor	—	Yes	Yes	—	—	—	—	—	—

Continued

Table 493-2 Work-up of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases—cont'd

MALIGNANCY	BONE MARROW ASPIRATE OR BIOPSY	CHEST X-RAY	CT SCAN	MRI	PET SCAN	BONE SCAN	CSF ANALYSIS	SPECIFIC MARKERS	OTHER TESTS
Rhabdomyosarcoma	Yes	Yes	Yes	Yes (selected sites)	—	Yes	Yes (for parameningeal tumors only)	—	—
Osteosarcoma	—	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes	—	—	—
Ewing sarcoma	Yes	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes	—	—	—
Germ cell tumors	—	Yes	Yes	Consider MRI of brain	—	—	—	AFP, HCG	—
Liver tumors	—	Yes	Yes	—	—	—	—	AFP	—
Retinoblastoma	Selected cases	—	Yes	Yes (includes brain)	—	Selected cases	Selected cases	—	—

AFP, α-Fetoprotein; CNS, central nervous system; CSF, cerebrospinal fluid; HCG, human chorionic gonadotropin; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; VMA, vanillylmandelic acid.

Table 494-2 Common Chemotherapeutic Agents Used in Children

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Methotrexate	Folic acid antagonist; inhibits dihydrofolate reductase	ALL, non-Hodgkin lymphoma, osteosarcoma, Hodgkin lymphoma, medulloblastoma	Myelosuppression, mucositis, stomatitis, dermatitis, hepatitis With long-term administration; osteopenia and bone fractures With high-dose administration; renal and CNS toxicity With intrathecal administration; arachnoiditis, leukoencephalopathy, leukomyelopathy	Systemic administration may be PO, IM, or IV; also may be administered intrathecally Plasma methotrexate levels must be monitored with high-dose therapy and when low doses are administered to patients with renal dysfunction, and leucovorin rescue applied accordingly
6-Mercaptopurine (Purinethol)	Purine analog; inhibits purine synthesis	ALL	Myelosuppression, hepatic necrosis, mucositis; allopurinol increases toxicity	Allopurinol inhibits metabolism
Cytarabine (cytosine arabinoside; Ara-C)	Pyrimidine analog; inhibits DNA polymerase	ALL, AML, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, myelosuppression, conjunctivitis, mucositis, CNS dysfunction With intrathecal administration; arachnoiditis, leukoencephalopathy, leukomyelopathy	Systemic administration may be PO, IM, or IV; may also be administered intrathecally
Cyclophosphamide (Cytoxan)	Alkylates guanine; inhibits DNA synthesis	ALL, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, Ewing sarcoma, Wilms tumor, neuroblastoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, bladder cancer, anaphylaxis	Requires hepatic activation and thus is less effective in presence of liver dysfunction. Mesna prevents hemorrhagic cystitis
Ifosfamide (Ifex)	Alkylates guanine; inhibits DNA synthesis	Non-Hodgkin lymphoma, Wilms tumor, soft tissue sarcoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, CNS dysfunction, cardiac toxicity, anaphylaxis	Mesna prevents hemorrhagic cystitis

Continued

Table 494-2 Common Chemotherapeutic Agents Used in Children—cont'd

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Doxorubicin (Adriamycin), daunorubicin (Cerubidine), and idarubicin (Idamycin)	Binds to DNA, intercalation	ALL, AML, osteosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma	Nausea, vomiting, cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia	Dexrazoxane reduces risk of cardiotoxicity
Dactinomycin	Binds to DNA, inhibits transcription	Wilms tumor, rhabdomyosarcoma, Ewing sarcoma	Nausea, vomiting tissue necrosis on extravasation, myelosuppression, radiosensitizer, mucosal ulceration	
Bleomycin (Blenoxane)	Binds to DNA, cleaves DNA strands	Hodgkin disease, non-Hodgkin lymphoma, germ cell tumors	Nausea, vomiting, pneumonitis, stomatitis, Raynaud phenomenon, pulmonary fibrosis, dermatitis	
Vincristine (Oncovin)	Inhibits microtubule formation	ALL, non-Hodgkin lymphoma, Hodgkin disease, Wilms tumor, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma	Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression	IV administration only; must not be allowed to extravasate
Vinblastine (Velban)	Inhibits microtubule formation	Hodgkin lymphoma, non-Hodgkin lymphoma, Langerhans cell histiocytosis, CNS tumors	Local cellulitis, leukopenia	IV administration only; must not be allowed to extravasate
L-Asparaginase	Depletion of L-asparagine	ALL; AML, when used in combination with cytarabine	Allergic reaction pancreatitis, hyperglycemia, platelet dysfunction and coagulopathy, encephalopathy	PEG-asparaginase now preferred to L-asparaginase
Pegaspargase (Oncaspar)	Polyethylene glycol conjugate of L-asparagine	ALL	Indicated for prolonged asparagine depletion and for patients with allergy to L-asparaginase	
Prednisone and dexamethasone (Decadron)	Lymphatic cell lysis	ALL; Hodgkin lymphoma, non-Hodgkin lymphoma	Cushing syndrome, cataracts, diabetes, hypertension, myopathy, osteoporosis, avascular necrosis, infection, peptic ulceration, psychosis	
Carmustine (BiCNU)	Carbamylation of DNA; inhibits DNA synthesis	CNS tumors, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, delayed myelosuppression (4-6 wk); pulmonary fibrosis, carcinogenic stomatitis	Phenobarbital increases metabolism, decreases activity
Carboplatin and cisplatin (Platinol)	Inhibits DNA synthesis	Osteosarcoma, neuroblastoma, CNS tumors, germ cell tumors	Nausea, vomiting, renal dysfunction, myelosuppression, ototoxicity, tetany, neurotoxicity, hemolytic-uremic syndrome, anaphylaxis	Aminoglycosides may increase nephrotoxicity
Etoposide (VePesid)	Topoisomerase inhibitor	ALL, non-Hodgkin lymphoma, germ cell tumor, Ewing sarcoma	Nausea, vomiting, myelosuppression, secondary leukemia	
Tretinoin (all *trans*-retinoic acid); and isotretinoin (cis-retinoic acid; Accutane)	Enhances normal differentiation	Acute promyelocytic leukemia; neuroblastoma	Dry mouth, hair loss, pseudotumor cerebri, premature epiphyseal closure, birth defects	

ADH, antidiuretic hormone; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CNS, central nervous system; PEG, polyethylene glycol.

Table 494-3 Infectious Complications of Malignancy

PREDISPOSING FACTOR	ETIOLOGY	SITE OF INFECTION	INFECTIOUS AGENTS
Neutropenia	Chemotherapy, bone marrow infiltration	Sepsis, shock, pneumonia, soft tissue, proctitis, mucositis	*Streptococcus viridans, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Candida, Aspergillus,* anaerobic oral and rectal bacteria
Immunosuppression, lymphopenia, lymphocyte-monocyte dysfunction	Chemotherapy, corticosteroid	Pneumonia, meningitis, disseminated viral infection	*Pneumocystis jiroveci, Cryptococcus neoformans, Mycobacterium, Nocardia, Listeria monocytogenes, Candida, Aspergillus, Strongyloides, Toxoplasma,* varicella-zoster virus, cytomegalovirus, herpes simplex
Indwelling central venous catheter	Nutrition, administration of chemotherapy	Line sepsis, tract of tunnel, exit site	*S. epidermidis, S. aureus, Candida albicans, P. aeruginosa, Aspergillus, Corynebacterium, Streptococcus faecalis, Mycobacterium fortuitum, Propionibacterium acnes*

Table 494-4 Oncologic Emergencies

CONDITION	MANIFESTATIONS	ETIOLOGY	MALIGNANCY	TREATMENT
METABOLIC				
Hyperuricemia	Uric acid nephropathy	Tumor lysis syndrome	Lymphoma, leukemia	Allopurinol, alkalinize urine; hydration and diuresis, rasburicase
Hyperkalemia	Arrhythmias, cardiac arrest	Tumor lysis syndrome	Lymphoma, leukemia	Kayexalate, sodium bicarbonate, glucose, and insulin; check for pseudohyperkalemia from leukemic cell lysis in test tube
Hyperphosphatemia	Hypocalcemic tetany; metastatic calcification, photophobia, pruritus	Tumor lysis syndrome	Lymphoma, leukemia	Hydration, forced diuresis; stop alkalinization; oral aluminum hydroxide to bind phosphate
Hyponatremia	Seizure, lethargy (may also be asymptomatic)	SIADH; fluid, sodium losses in vomiting	Leukemia, CNS tumor	Restrict free water for SIADH; replace sodium if depleted
Hypercalcemia	Anorexia, nausea, polyuria, pancreatitis, gastric ulcers; prolonged PR, shortened QT interval	Bone resorption; ectopic parathormone, vitamin D, or prostaglandins	Metastasis to bone, rhabdomyosarcoma, leukemia	Hydration and furosemide diuresis; corticosteroids; calcitonin, bisphosphonates
HEMATOLOGIC				
Anemia	Pallor, weakness, heart failure	Bone marrow suppression or infiltration; blood loss	Any with chemotherapy	Packed red blood cell transfusion
Thrombocytopenia	Petechiae, hemorrhage	Bone marrow suppression or infiltration	Any with chemotherapy	Platelet transfusion
Disseminated intravascular coagulation	Shock, hemorrhage	Sepsis, hypotension, tumor factors	Promyelocytic leukemia, others	Fresh-frozen plasma; platelets, cryoprecipitate, treat underlying disorder
Neutropenia	Infection	Bone marrow suppression or infiltration	Any with chemotherapy	If febrile, administer broad-spectrum antibiotics, and filgrastim (G-CSF) if appropriate
Hyperleukocytosis (>100,000/mm^3)	Hemorrhage, thrombosis; pulmonary infiltrates, hypoxia; tumor lysis syndrome	Leukostasis; vascular occlusion	Leukemia	Leukapheresis; chemotherapy; hydroxyurea
Graft-versus-host disease	Dermatitis, diarrhea, hepatitis	Immunosuppression and nonirradiated blood products; bone marrow transplantation	Any with immunosuppression	Corticosteroids; cyclosporine; tacrolimus; antithymocyte globulin
SPACE-OCCUPYING LESIONS				
Spinal cord compression	Back pain ± radicular *Cord above T10:* symmetric weakness, increased deep tendon reflex; sensory level present; toes up *Conus medullaris (T10-L2):* symmetric weakness, increased knee reflexes; decreased ankle reflexes; saddle sensory loss; toes up or down *Cauda equina (below L2):* asymmetric weakness; loss of deep tendon reflex and sensory deficit; toes down	Metastasis to vertebra and extramedullary space	Neuroblastoma; medulloblastoma	MRI or myelography for diagnosis; corticosteroids; radiotherapy; laminectomy; chemotherapy
Increased intracranial pressure	Confusion, coma, emesis, headache, hypertension, bradycardia, seizures, papilledema, hydrocephalus; cranial nerves III and VI palsies	Primary or metastatic brain tumor	Neuroblastoma, astrocytoma; glioma	CT or MRI for diagnosis; corticosteroids; phenytoin; ventriculostomy tube; radiotherapy; chemotherapy
Superior vena cava syndrome	Distended neck veins plethora, edema of head and neck, cyanosis, proptosis, Horner syndrome	Superior mediastinal mass	Lymphoma	Chemotherapy; radiotherapy
Tracheal compression	Respiratory distress	Mediastinal mass compressing trachea	Lymphoma	Radiation, corticosteroids

CNS, Central nervous system; G-CSF, granulocyte colony-stimulating factor; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: Nelson essentials of pediatrics, *ed 6, Philadelphia, 2011, WB Saunders, p. 590.*

Table 494-5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
NEUROCOGNITIVE			
Neurocognitive deficits Functional deficits in: • Executive function • Sustained attention • Memory • Processing speed • Visual-motor integration Learning deficits Diminished IQ Behavioral change	Chemotherapy: • Methotrexate Radiation affecting brain: • Cranial • Ear/infratemporal • Total-body irradiation (TBI)	Age <3 yr at time of treatment Female sex Supratentorial tumor Premorbid or family history of learning or attention problems Radiation doses >24 Gy Whole-brain irradiation	Acute lymphoblastic leukemia Brain tumor Sarcoma (head and neck or osteosarcoma)
NEUROSENSORY			
Hearing loss, sensorineural	Chemotherapy: • Cisplatin • Carboplatin Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher cisplatin dose (360 mg/m^2) Higher radiation dose impacting ear (>30 Gy) Concurrent radiation and cisplatin	Brain tumor Germ cell tumor Sarcoma (head and neck) Neuroblastoma Hepatoblastoma
Hearing loss, conductive Tympanosclerosis Otosclerosis Eustachian tube dysfunction	Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher radiation dose affecting ear (>30 Gy)	Brain tumor Sarcoma (head and neck)
Visual impairment Cataracts Lacrimal duct atrophy Xerophthalmia Retinopathy Glaucoma	Chemotherapy: • Busulfan • Glucocorticoids Radiation affecting eye: • Cranial • Orbital/eye • TBI	Higher radiation dose impacting eye (≥15 Gy for cataracts; >45 Gy for retinopathy and visual impairment)	Brain tumor Acute lymphoblastic leukemia Retinoblastoma Rhabdomyosarcoma (orbital) Allogeneic HSCT
Peripheral neuropathy, sensory	Chemotherapy: • Vincristine • Vinblastine • Cisplatin • Carboplatin	Higher cisplatin dose (≥300 mg/m^2)	Acute lymphoblastic leukemia Brain tumor Hodgkin lymphoma Germ cell tumor Non-Hodgkin lymphoma Sarcoma Neuroblastoma Wilms tumor Carcinoma
NEUROMOTOR			
Peripheral neuropathy, motor	Chemotherapy: • Vincristine • Vinblastine		Acute lymphoblastic leukemia Hodgkin lymphoma Non-Hodgkin lymphoma Sarcoma Brain tumor Neuroblastoma Wilms tumor
ENDOCRINE			
GH deficiency Precocious puberty	Radiation affecting HPA: • Cranial • Orbital/eye	Female sex Radiation dose to HPA >18 Gy	Acute lymphoblastic leukemia Sarcoma (facial) Carcinoma (nasopharyngeal)
Obesity	Ear/infratemporal Nasopharyngeal	Female sex Younger age (<4 yr)	Acute lymphoblastic leukemia
Hypothyroidism, central Gonadotropin deficiency Adrenal insufficiency, central	TBI	Radiation dose to HPA >18 Gy	Brain tumor Sarcoma (facial) Carcinoma (nasopharyngeal)
Hypothyroidism, primary	Neck, mantle irradiation	Radiation dose to thyroid >20 Gy	Hodgkin lymphoma

Table 494-5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment—cont'd

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
REPRODUCTIVE			
Gonadal dysfunction Delayed or arrested puberty Premature menopause Germ cell dysfunction or failure Infertility	Chemotherapy, alkylating: • Busulfan • Carmustine (BCNU) • Chlorambucil • Cyclophosphamide • Ifosfamide • Lomustine (CCNU) • Mechlorethamine • Melphalan • Procarbazine Radiation affecting reproductive system: • Whole abdomen (girls) • Pelvic • Lumbar/sacral spine (girls) • Testicular (boys) • TBI	Higher alkylating agent dose Alkylating agent conditioning for HSCT Radiation dose ≥15 Gy in prepubertal girls Radiation dose ≥10 Gy in pubertal girls For germ cell failure in boys, any pelvic irradiation For androgen insufficiency, gonadal irradiation, ≥20-30 Gy in boys	Acute lymphoblastic leukemia, high risk Brain tumor Hodgkin lymphoma, advanced or unfavorable Non-Hodgkin lymphoma, advanced or unfavorable Sarcoma Neuroblastoma Wilms tumor, advanced Autologous or allogeneic HSCT
CARDIAC			
Cardiomyopathy Arrhythmias	Chemotherapy: • Daunorubicin • Doxorubicin • Idarubicin	Female sex Age <5 yr at time of treatment Higher doses of chemotherapy (≥300 mg/m^2) Higher doses of cardiac radiation (≥30 Gy) Combined-modality therapy with cardiotoxic chemotherapy and irradiation	Hodgkin lymphoma Leukemia Non-Hodgkin lymphoma Sarcoma Wilms tumor Neuroblastoma
Cardiomyopathy Arrhythmias Pericardial fibrosis Valvular disease Myocardial infarction Atherosclerotic heart disease	Radiation affecting heart: • Chest • Mantle • Mediastinum • Axilla • Spine • Upper abdomen		
PULMONARY			
Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	Chemotherapy: • Bleomycin • Busulfan • Carmustine (BCNU) • Lomustine (CCNU) Radiation impacting lungs: • Mantle • Mediastinum • Whole lung • TBI	Higher doses of chemotherapy Combined modality therapy with pulmonary toxic chemotherapy and irradiation	Brain tumor Germ cell tumor Hodgkin lymphoma Sarcoma (chest wall or intrathoracic) Autologous or allogeneic HCST
GASTROINTESTINAL			
Chronic enterocolitis Strictures Bowel obstruction	Radiation affecting gastrointestinal tract (≥30 Gy) Abdominal surgery	Higher radiation dose to bowel (≥45 Gy) Combined modality therapy with abdominal irradiation and radiomimetic chemotherapy (dactinomycin or anthracyclines) Combined modality therapy with abdominal surgery and irradiation	Sarcoma (retroperitoneal or pelvic primary)
HEPATIC			
Hepatic fibrosis Cirrhosis	Radiation affecting liver	Higher radiation dose or treatment volume (20-30 Gy to entire liver or ≥40 Gy to at least one third of liver)	Sarcoma Neuroblastoma
RENAL			
Renal insufficiency Hypertension Glomerular injury Tubular injury	Chemotherapy: • Ifosfamide • Cisplatin • Carboplatin Radiation affecting kidneys: • Whole abdomen • Upper abdominal fields • TBI		

GH, Growth hormone; HPA, hypothalamic–pituitary–adrenal axis; HSCT, hematopoietic stem cell transplantation; TBI, total-body irradiation.
From Kurt BA, Armstrong GT, Cash DK, et al: Primary care management of the childhood cancer survivor, J Pediatr *152:458–466, 2008.*

Table 496-3 Chemotherapy Regimens Commonly Used for Children, Adolescents, and Young Adults with Hodgkin Lymphoma

CHEMOTHERAPY REGIMEN	CORRESPONDING AGENTS
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine
ABVD-Rituxan	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine, rituximab
ABVD	Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine
ABVE (DBVE)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide
VAMP	Vincristine, doxorubicin (Adriamycin), methotrexate, prednisone
OPPA ± COPP (females)	Vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
OEPA ± COPP (males)	Vincristine (Oncovin), etoposide, prednisone, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP/ABV	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), bleomycin, vinblastine
BEACOPP (advanced stage)	Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
CHOP	Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), prednisone
ABVE-PC (DBVE-PC)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, cyclophosphamide
ICE ± (Brentuximab)	Ifosfamide, carboplatin, etoposide ± brentuximab
Ifos/Vino ± (Brentuximab)	Ifosfamide, vinorelbine ± brentuximab

Table 496-1 New World Health Organization/Revised European–American Classification of Lymphoid Neoplasms Classification System for Hodgkin Lymphoma

Nodular lymphocyte predominance
Classical Hodgkin lymphoma
Lymphocyte rich
Mixed cellularity
Nodular sclerosis
Lymphocyte depletion

Table 495-3 WHO Classification of Acute Myeloid Neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- APL with t(15;17)(q22;q12); *PML-RARA*
- AML with t(9;11)(p22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- *Provisional entity: AML with mutated NPM1*
- *Provisional entity: AML with mutated CEBPA*

Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma
Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia.

Table 496-2 Ann Arbor Staging Classification for Hodgkin Lymphoma*

STAGE	DEFINITION
I	Involvement of a single lymph node (I) or of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and 1 or more lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (IIIS) or by localized involvement of an extralymphatic organ or site (IIIE) or both (IIISE)
IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues with or without associated lymph node involvement

Table 496-4 Treatment Regimens and Outcome by Disease Staging

		LOCALIZED/LOW STAGE	INTERMEDIATE	ADVANCED
Hodgkin lymphoma	Treatment	*POG study 9426/GPOH-HD 95:* ABVD-type therapy ± IFRT (risk adapted based on early response to chemotherapy)	*Stanford/DAL-HD-90:* COPP-based or dose-intense multiagent chemotherapy + low-dose RT *POG 9426/CCG 5942:* ABVD-type therapy ± IFRT (risk adapted)	*POG 8725/DAL-HD-90:* Dose-intense multiagent chemotherapy + low-dose RT *HD9/HD12/CCG 59704:* Dose-intense BEACOPP ± IFRT
	Prognosis	5 yr EFS: 85-90% 5 yr OS: 95%	*Stanford/DAL-HD-90:* 5 yr EFS: 89-92%*POG 9426/CCG 5942:* 5 yr EFS: 84% 5 yr OS: 91%	*POG 8725:* 5-yr EFS: 72-89% (age based) *DAL-HD-90:* 5 yr EFS: 86% 5 yr OS: 85-90% *HD9/HD12/CCG 59704:* 5 yr EFS/OS: 88-93/~100%

Table 496-4 Treatment Regimens and Outcome by Disease Staging—cont'd

		LOCALIZED/LOW STAGE	INTERMEDIATE	ADVANCED
Burkitt lymphoma and diffuse large B-cell lymphoma	Treatment	*FAB/LMB 96 Group A therapy:* Complete surgical resection followed by 2 cycles of chemotherapy	*FAB/LMB 96 Group B* therapy with reduced cyclophosphamide and no maintenance therapy; *COG ANHL01P1*: FAB/LMB Group B therapy + rituximab	*FAB/LMB 96:* standard-intensity Group C therapy: Reduction, induction, intensification, and maintenance therapy *COG ANHL01P1*: FAB/LMB Group C therapy + rituximab
	Prognosis	4 yr EFS: 98% (CI_{95} 94-99.5%) 4 yr OS: 99% (CI_{95} 96-99.9%)	*FAB/LMB96:* 4 yr EFS: 92% (CI_{95} 90-94%) 4 yr OS: 95% (CI_{95} 93-96%) *PMB DLBCL has worse prognosis (EFS/OS: 66/73%) *COG ANHL01P1:* 3 yr EFS 93% (CI_{95} 79-98%) 3 yr OS 95% (CI_{95} 83-99%)	*FAB/LMB96:* 4 yr EFS: BM+/CNS–: 91% ± 3% BM–/CNS+: 85% ± 6% BM+/CNS+: 66% ± 7% *COG ANHL01P1:* 3 yr EFS/OS: BM+ or CNS+: 90% (CI_{95} 75-96%) CNS+: 93% (CI_{95} 61-99%)
Lymphoblastic lymphoma	Treatment	*NHL-BFM86/90/95: COG A5971:* ALL-type therapy × 2 yr without prophylactic cranial RT	No intermediate group; disease classified as localized (stages I/II) or advanced (stages III/IV)	*NHL-BFM86/90/95:* ALL-type therapy × 2 yr ± px CRT *CCG 5941:* Intensive chemotherapy × 1 yr + cranial RT if CNS + at diagnosis
	Prognosis	*COG A5971:* 5 yr EFS: 90 (CI_{95} 78-96%) 5 yr OS: 96 (CI_{95} 84-99%)	No intermediate group; see above	*NHL-BFM95:* 5 yr EFS: 90% ± 3% (III), 95 ± 5% (IV) *CCG 5941:* 5 yr EFS/OS: 78% ± 5%/85% ± 4%
Anaplastic large cell lymphoma	Treatment	*EICHNL ALCL 99:* Short intensive chemotherapy + HD MTX Completely resected stage I disease may be treated with surgery alone	No intermediate group; disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)	*ALCL 99, CCG 5941:* Short intensive chemotherapy + HD MTX *COG ANHL0131*: APO (doxorubicin, prednisone, vincristine) ± vinblastine
	Prognosis	*EICHNL database:* 5 yr PFS: 89% (CI_{95} 82-96%) 5 yr OS: 94% (CI_{95} 89-99%)	No intermediate group; see above	*ALCL99:* 2 yr EFS: 71% (CI_{95} 75-77%) 2 yr OS: 94% (CI_{95} 89-95%) *COG5941:* 5 yr EFS 68% (CI_{95} 57-78%) 5 yr OS: 80% (CI_{95} 69-87%) *COH ANHL0131:* 2 yr EFS 79% (CI_{95} 71-88%) 2 yr OS 89% (CI_{95} 83-95%)

ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; BM, bone marrow (involvement); CCG, Children's Cancer Group; CI_{95}, 95% confidence interval; CNS, central nervous system (involvement); COG, Children's Oncology Group; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; CRT, chemoradiotherapy; EFS, event-free survival; EICHNL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB, French-American-British; HD MTX, high-dose methotrexate; IFRT, involved field radiation therapy; LMB, Lymphome Malins de Burkit; MTX, methotrexate; NHL-BFM, non-Hodgkin lymphoma Berlin-Frankfurt-Munster; OS, overall survival; PFS, progression-free survival; PMB DLBCL, primary mediastinal B-cell diffuse large B-cell lymphoma; POG, Pediatric Oncology Group; px, prophylactic; RT, radiation therapy.

Table 496-5 St. Jude Staging System for Childhood Non-Hodgkin Lymphoma

STAGE	DESCRIPTION
I	A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen
II	A single tumor (extranodal) with regional node involvement Two or more nodal areas on the same side of the diaphragm Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, which must be grossly (>90%) resected
III	Two single tumors (extranodal) on opposite sides of the diaphragm Two or more nodal areas above and below the diaphragm Any primary intrathoracic tumor (mediastinal, pleural, or thymic) Any extensive primary intraabdominal disease
IV	Any of the above, with initial involvement of central nervous system or bone marrow at time of diagnosis

From Murphy SB: Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults, Semin Oncol *7:332–339, 1980.*

Table 496-6 Risk Stratification Groups for Pediatric B-Cell NHL

	Berlin-Frankfurt-Munster (BFM)	French-American-British (FAB)
Low Risk ↓ High Risk	**R1** Stage I or II, completely resected	**Group A** Resected stage I and abdominal completely resected stage II
	R2 Stage I or II, not resected Stage III with LDH <500 U/L	**Group B** All patients not in Group A or C
	R3 Stage III with LDH ≥500 to <1000 U/L or Stage IV with LDH <1000 U/L and CNS-negative	**Group C** Bone marrow disease (≥25% L3 blasts) and/or CNS-positive
	R4 Stage III or IV with LDH ≥1000 U/L and/or CNS-positive	

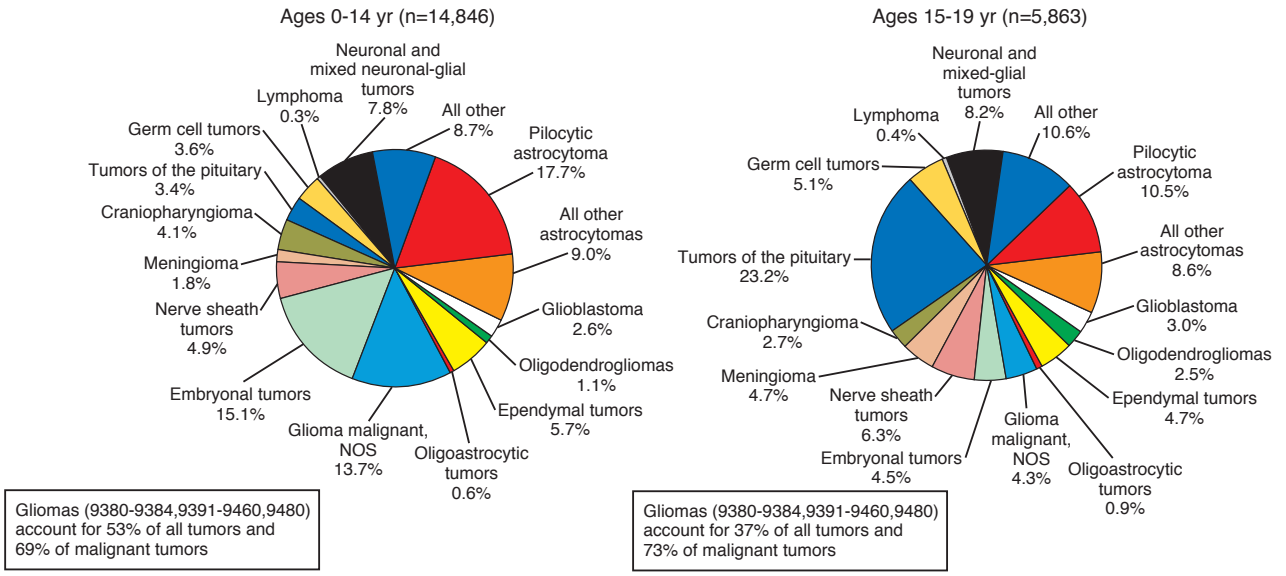

Figure 497-1 Distribution of childhood primary brain and CNS tumors by histology. *(From Dolecek TA, Propp JM, Stroup NE, Kruchko C: CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009,* Neuro Oncol *14:v1-v49, 2012.)*

Table 497-1 Familial Syndromes Associated with Pediatric Brain Tumors

SYNDROME	CENTRAL NERVOUS SYSTEM MANIFESTATIONS	CHROMOSOME	GENE
Neurofibromatosis type 1 (autosomal dominant)	Optic pathway gliomas, astrocytoma, malignant peripheral nerve sheath tumors, neurofibromas	17q11	*NF1*
Neurofibromatosis type 2 (autosomal dominant)	Vestibular schwannomas, meningiomas, spinal cord ependymoma, spinal cord astrocytoma, hamartomas	22q12	*NF2*
von Hippel–Lindau (autosomal dominant)	Hemangioblastoma	3p25-26	*VHL*
Tuberous sclerosis (autosomal dominant)	Subependymal giant cell astrocytoma, cortical tubers	9q34 16q13	*TSC1* *TSC2*
Li-Fraumeni (autosomal dominant)	Astrocytoma, primitive neuroectodermal tumor	17q13	*TP53*
Cowden (autosomal dominant)	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease)	10q23	*PTEN*
Turcot (autosomal dominant)	Medulloblastoma Glioblastoma	5q21 3p21 7p22	*APC* *hMLH1* *hPSM2*
Nevoid basal cell carcinoma Gorlin (autosomal dominant)	Medulloblastoma	9q31	*PTCH1*

Modified from Kleihues P, Cavenee WK: World Health Organization classification of tumors: pathology and genetics of tumors of the nervous system, *Lyon, 2000, IARC Press.*

Table 497-2 Posterior Fossa Tumors of Childhood

TUMOR	RELATIVE INCIDENCE (%)	PRESENTATION	DIAGNOSIS	PROGNOSIS
Medulloblastoma	35-40	2-3 mo of headaches, vomiting, truncal ataxia	Heterogeneously or homogeneously enhancing fourth ventricular mass; may be disseminated	65-85% survival; dependent on stage/type; poorer (20-70%) in infants
Cerebellar astrocytoma	35-40	3-6 mo of limb ataxia; secondary headaches, vomiting	Cerebellar hemisphere mass, usually with cystic and solid (mural nodule) components	90-100% survival in totally resected pilocytic type
Brainstem glioma	10-15	1-4 mo of double vision, unsteadiness, weakness, and cranial nerve dysfunction, including facial weakness, swallowing dysfunction, and oculomotor abnormalities	Diffusely expanded, minimally or partially enhancing mass in 80%; 20% more focal tectal or cervicomedullary lesion	>90% mortality in diffuse tumors; better in localized
Ependymoma	10-15	2-5 mo of unsteadiness, headaches, double vision, and facial asymmetry	Usually enhancing, fourth ventricular mass with cerebellopontine predilection	>75% survival in totally resected lesions
Atypical teratoid/ rhabdoid	>5 (10-15% of infantile malignant tumors)	As in medulloblastoma, but primarily in infants; often associated facial weakness and strabismus	As in medulloblastoma, but often more laterally extended	≤20% survival in infants

Modified from Packer RJ, MacDonald T, Vezina G: Central nervous system tumors, Pediatr Clin North Am *55:121–145, 2008.*

Table 498-2 Children's Oncology Group Neuroblastoma Risk Stratification

RISK GROUP	STAGE	AGE	*MYCN* AMPLIFICATION STATUS	PLOIDY	SHIMADA
Low risk	1	Any	Any	Any	Any
Low risk	2A/2B	Any	Not amplified	Any	Any
High risk	2A/2B	Any	Amplified	Any	Any
Intermediate risk	3	<547 days	Not amplified	Any	Any
Intermediate risk	3	≥547 days	Not amplified	Any	FH
High risk	3	Any	Amplified	Any	Any
High risk	3	≥547 days	Not amplified	Any	UH
High risk	4	<365 days	Amplified	Any	Any
Intermediate risk	4	<365 days	Not amplified	Any	Any
High risk	4	365 to <547 days	Amplified	Any	Any
High risk	4	365 to <547 days	Any	DNA index = 1	Any
High risk	4	365 to <547 days	Any	Any	UH
Intermediate risk	4	365 to <547 days	Not amplified	DNA index > 1	FH
High risk	4	≥547 days	Any	Any	Any
Low risk	4S	<365 days	Not amplified	DNA index > 1	FH
Intermediate risk	4S	<365 days	Not amplified	DNA index = 1	Any
Intermediate risk	4S	<365 days	Not amplified	Any	UH
High risk	4S	<365 days	Amplified	Any	Any

FH, Favorable histology; UH, unfavorable histology.
Courtesy of Children's Oncology Group; from Park JR, Eggert A, Caron H: Neuroblastoma: biology, prognosis, and treatment, Pediatr Clin North Am *55:97–120, 2008.*

Table 498-3 International Neuroblastoma Staging System

STAGE	DEFINITION	INCIDENCE (%)	SURVIVAL AT 5 YR* (%)
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)	5	≥90
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically	10	70-80
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically	10	70-80
3	Unresectable unilateral tumor infiltrating across the midline,† with or without regional lymph node involvement; *or* localized unilateral tumor with contralateral regional lymph node involvement; *or* midline tumor with bilateral extension by infiltration (resectable) or by lymph node involvement	25	40-70
4	Any primary tumor with dissemination to distant lymph nodes; bone, bone marrow, liver, skin, and other organs (except as defined for stage 4S)	60	85-90 if age at diagnosis is <18 mo 30-40 if age at diagnosis is >18 mo
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and bone marrow‡ (limited to infants <1 yr of age)	5	>80

*Survival is influenced by other characteristics, such as *MYCN* amplification. Percentages are approximate.
†The *midline* is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the other side of the vertebral column.
‡Marrow involvement in stage 4S should be minimal (i.e., <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate). More extensive marrow involvement would be considered stage 4. Results of the metaiodobenzylguanidine (MIBG) scan (if performed) should be negative in the marrow.
Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: Nelson essentials of pediatrics, *ed 5, Philadelphia, 2006, WB Saunders, p. 746; and Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment,* J Clin Oncol *11:1466–1477, 1993.*

symptoms because of the mass itself, including spinal cord compression, bowel obstruction, and superior vena cava syndrome.

Children with neuroblastoma can also present with neurologic signs and symptoms. Neuroblastoma originating in the superior cervical ganglion can result in **Horner syndrome.** Paraspinal neuroblastoma tumors can invade the neural foramina, causing spinal cord and nerve root compression. Neuroblastoma can also be associated with a paraneoplastic syndrome of autoimmune origin, termed *opsoclonus–myoclonus–ataxia syndrome,* in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination,

Table 498-4 Phenotypic and Genetic Features of Neuroblastoma, Treatment, and Survival According to Prognostic Category

	PROGNOSTIC CATEGORY*			
VARIABLE	**Low Risk**	**Intermediate Risk**	**High Risk**	**Tumor Stage 4S**
Pattern of disease	Localized tumor	Localized tumor with locoregional lymph node extension; metastases to bone marrow and bone in infants	Metastases to bone marrow and bone (except in infants)	Metastases to liver and skin (with minimal bone marrow involvement) in infants
Tumor genomics	Whole-chromosome gains	Whole-chromosome gains	Segmental chromosomal aberrations	Whole-chromosome gains
Treatment	Surgery†	Moderate-intensity chemotherapy; surgery†	Dose-intensive chemotherapy, surgery, and external-beam radiotherapy to primary tumor and resistant metastatic sites; myeloablative chemotherapy with autologous hematopoietic stem cell rescue; isotretinoin with anti–ganglioside GD2 immunotherapy	Supportive care‡
Survival rate	>98%	90-95%	40-50%	>90%

*Patients are assigned to prognostic groups according to risk, as described by the Children's Oncology Group, with the level of risk defining the likelihood of death from disease. Stage 4S disease is considered separately here because of the unique phenotype of favorable biologic features and relentless early progression but ultimately full and complete regression of the disease.

†The goal of surgery is to safely debulk the tumor mass and avoid damage to surrounding normal structures while also obtaining sufficient material for molecular diagnostic studies. Some localized tumors may spontaneously regress without surgery.

‡Low-dose chemotherapy or radiation therapy, or both, is used in patients with life-threatening hepatic involvement, especially in infants <2 mo of age, who are at much higher risk for life-threatening complications from massive hepatomegaly.

Table 499-3 Differential Diagnosis of Abdominal and Pelvic Tumors in Children

TUMOR	PATIENT AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Wilms	Preschool	Unilateral flank mass, aniridia, hemihypertrophy	Hematuria, polycythemia, thrombocytosis, elevated partial thromboplastin time value
Neuroblastoma	Preschool	Gastrointestinal/genitourinary obstruction, raccoon eyes, myoclonus opsoclonus, diarrhea, skin nodules	Increased urinary vanillylmandelic acid, or homovanillic acid, or ferritin, stippled calcification in the mass
Non-Hodgkin lymphoma	>1 yr	Intussusception in patients >2 yr old	Increased lactic dehydrogenase, blood cytopenia from bone marrow involvement
Rhabdomyosarcoma	All	Gastrointestinal/genitourinary obstruction, abdominal pain, vaginal bleeding, paratesticular mass	Hypercalcemia, blood cytopenia from bone marrow involvement
Germ cell tumor/teratoma	Preschool, teenage	Girls: abdominal pain, vaginal bleeding Boys: testicular mass, new-onset hydrocele, sacrococcygeal mass/dimple	Increased human chorionic gonadotropin, increased α-fetoprotein
Hepatoblastoma	Birth-3 yr	Large firm liver	Increased α-fetoprotein
Hepatoma	School age, teenage	Large firm nodule, hepatitis B, cirrhosis	Increased α-fetoprotein

Table 499-4 Staging of Wilms Tumor

Stage I	Tumor *confined to the kidney* and completely resected. Renal capsule or sinus vessels not involved. Tumor not ruptured or biopsied. Regional lymph nodes examined and negative.
Stage II	Tumor extends *beyond the kidney* but is completely resected with negative margins and lymph nodes. At least 1 of the following has occurred: (a) penetration of renal capsule, (b) invasion of renal sinus vessels.
Stage III	*Residual tumor* present following surgery confined to the abdomen, including gross or microscopic tumor; spillage of tumor preoperatively or intraoperatively; biopsy prior to nephrectomy, regional lymph node metastases; tumor implants on the peritoneal surface; extension of tumor thrombus into the inferior vena cava including thoracic vena cava and heart.
Stage IV	*Hematogenous metastases* (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region.
Stage V	*Bilateral* renal involvement by tumor.

Table 500-3 Features of Most Common Types of Nonrhabdomyosarcoma Soft Tissue Sarcomas

TISSUE TYPE	TUMOR	NATURAL HISTORY AND BIOLOGY
Adipose	Liposarcoma	A very rare tumor. Usually arises in the extremities or retroperitoneum; associated with a nonrandom translocation, t(12;16)(q13;p11). Tends to be locally invasive and rarely metastasizes; wide local excision is the treatment of choice. The role of radiation therapy and chemotherapy in treating gross residual or metastatic disease is not established.
Fibrous	Fibrosarcoma	Most common soft tissue sarcoma in children younger than 1 yr. Congenital fibrosarcoma is a low-grade malignancy that commonly arises in the extremities or trunk and rarely metastasizes. Surgical excision is treatment of choice; dramatic responses to preoperative chemotherapy may occur. In children older than 4 yr, the natural history is similar to that in adults (a 5 yr survival rate of 60%); wide surgical excision and preoperative chemotherapy are commonly used. Associated with t(12;15)(p13;q25) or trisomy 11, also +8, +17, +20.
	Malignant fibrous histiocytoma	Most commonly arises in the trunk and extremities, deep in the subcutaneous layer. Histologically subdivided into storiform, giant cell, myxoid, and angiomatoid variants. The angiomatoid type tends to affect younger patients and is curable with surgical resection alone. Wide surgical excision is the treatment of choice. Chemotherapy has produced objective tumor regressions.
Vascular	Hemangiopericytoma	Often arises in the lower extremities or retroperitoneum; may manifest as hypoglycemia and hypophosphatemic rickets. Both benign and malignant histology. Nonrandom translocations t(12;19)(q13;q13) and t(13;22)(q22;q13.3) have been described. Complete surgical excision is the treatment of choice. Chemotherapy and radiation therapy may produce responses.
	Angiosarcoma	Rare in children; 33% arise in skin, 25% in soft tissue, and 25% in liver, breast, or bone. Associated with chronic lymphedema and exposure to vinyl chloride in adults. Survival rate is poor (12% at 5 yr) despite some responses to chemotherapy/radiation therapy.
	Hemangioendothelioma	Can occur in soft tissue, liver, and lung. Localized lesions have a favorable outcome; lesions in lung and liver often are multifocal and have a poor prognosis.
Peripheral nerves	Neurofibrosarcoma	Also known as the malignant peripheral nerve sheath tumor. Develops in up to 16% of patients with neurofibromatosis type 1 (NF1); almost 50% occur in patients with NF1. Deletions of chromosome 22q11-q13 or 17q11 and p53 mutations have been reported. Commonly arises in trunk and extremities and is usually locally invasive. Complete surgical excision is necessary for survival; response to chemotherapy is suboptimal.
Synovium	Synovial sarcoma	The most common nonrhabdomyosarcoma soft tissue sarcoma in some series. Often manifesting in the 3rd decade, but 33% of patients are younger than age 20 yr. Typically arises around the knee or thigh and is characterized by a nonrandom translocation t(X;18)(p11;q11). Wide surgical excision is necessary. Radiation therapy is effective in microscopic residual disease, and ifosfamide-based therapy is active in advanced disease.
Unknown	Alveolar soft part sarcoma	Slow-growing tumor; tends to recur or to metastasize to lung and brain years after diagnosis. Often arises in the extremities and head and neck.
Smooth muscle	Leiomyosarcoma	Often arises in the gastrointestinal tract and may be associated with a t(12;14)(q14;q23) translocation. Associated with Epstein-Barr virus in immunodeficiency syndromes (including AIDS). Complete surgical excision is the treatment of choice.

Table 501-1 Comparison of Features of Osteosarcoma and the Ewing Family of Tumors

FEATURE	OSTEOSARCOMA	EWING FAMILY OF TUMORS
Age	Second decade	Second decade
Race	All races	Primarily whites
Sex (M:F)	1.5:1	1.5:1
Cell	Spindle cell–producing osteoid	Undifferentiated small round cell, probably of neural origin
Predisposition	Retinoblastoma, Li-Fraumeni syndrome, Paget disease, radiotherapy	None known
Site	Metaphyses of long bones	Diaphyses of long bones, flat bones
Presentation	Local pain and swelling; often, history of injury	Local pain and swelling; fever
Radiographic findings	Sclerotic destruction (less commonly lytic); sunburst pattern	Primarily lytic, multilaminar periosteal reaction ("onion-skinning")
Differential diagnosis	Ewing sarcoma, osteomyelitis	Osteomyelitis, eosinophilic granuloma, lymphoma, neuroblastoma, rhabdomyosarcoma
Metastasis	Lungs, bones	Lungs, bones
Treatment	Chemotherapy Ablative surgery of primary tumor	Chemotherapy Radiotherapy and/or surgery of primary tumor
Outcome	Without metastases, 70% cured; with metastases at diagnosis, ≤20% survival	Without metastases, 60% cured; with metastases at diagnosis, 20-30% survival

Table 507-5 Spectrum of Diseases Characterized By Hemophagocytosis

PRIMARY HLH (see Table 507-3)
HLH WITH IMMUNODEFICIENCY, AUTOINFLAMMATORY STATES (see Table 507-3)
INFECTION-ASSOCIATED HLH (see Table 507-2)
MALIGNANCY-ASSOCIATED HLH Lymphoma Leukemia
MACROPHAGE ACTIVATION SYNDROME (MAS) ASSOCIATED WITH AUTOIMMUNE DISEASE
Systemic-onset juvenile idiopathic arthritis Systemic lupus erythematosus Enthesitis-related arthritis Inflammatory bowel disease

Table 507-4 Diagnostic Guidelines for Hemophagocytic Lymphohistiocytosis

The diagnosis of HLH is established by fulfilling one of the following two criteria:

1. A molecular diagnosis consistent with HLH (e.g., PRF mutations, SAP mutations)

or

2. Having 5 of the following 8 signs or symptoms:
   a. Fever
   b. Splenomegaly
   c. Cytopenia (affecting ≥2 cell lineages; hemoglobin ≤9 g/dL [or ≤10 g/dL for infants <4 wk of age], platelets <100,000/μL, neutrophils <1,000/μL)
   d. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL)
   e. Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
   f. Low or absent natural killer cell cytotoxicity
   g. Hyperferritinemia (≥500 ng/mL)
   h. Elevated soluble CD25 (interleukin-2Rα chain; ≥2,400 U/mL)

Table 507-2 Infections Associated with Hemophagocytic Syndrome

VIRAL Adenovirus Cytomegalovirus Dengue virus Epstein-Barr virus Enteroviruses Herpes simplex viruses (HSV1, HSV2) Human herpesviruses (HHV6, HHV8) Human immunodeficiency virus Influenza viruses Parvovirus B19 Varicella-zoster virus Hepatitis viruses Measles Parechovirus
BACTERIAL *Babesia microti* *Brucella abortus* Enteric Gram-negative rods *Haemophilus influenzae* *Mycoplasma pneumoniae* *Staphylococcus aureus* *Streptococcus pneumoniae*
Candida albicans *Cryptococcus neoformans* *Histoplasma capsulatum* *Fusarium*
MYCOBACTERIAL *Mycobacterium tuberculosis*
RICKETTSIAL *Coxiella burnetii* Other rickettsial diseases
PARASITIC *Leishmania donovani* *Plasmodium*

	DISEASE	CELLULAR CHARACTERISTICS OF LESIONS	TREATMENT
LCH	Langerhans cell histiocytosis	Langerhans-like cells (CD1a-positive, CD207-positive) with Birbeck granules (LCH cells)	Local therapy for isolated lesions; chemotherapy for disseminated disease
HLH	Familial hemophagocytic lymphohistiocytosis Infection-associated hemophagocytic syndrome† Associated with albinism syndromes* Associated with immunocompromised states Associated with autoimmune/autoinflammatory states	Morphologically normal reactive macrophages with prominent erythrophagocytosis, and CD8-positive T cells	Chemotherapy; allogeneic bone marrow transplantation
Other	Juvenile xanthogranuloma	Characteristic vacuolated lesional histiocytes with foamy cytoplasm	None or excisional biopsy for localized disease; chemotherapy, radiotherapy for disseminated disease
	Rosai-Dorfman disease	Hemophagocytic histiocytes	None if localized; surgery for bulk reduction; chemotherapy if organ systems involvement
	Malignant histiocytosis	Neoplastic proliferation of cells with characteristics of monocytes/macrophages or their precursors	Antineoplastic chemotherapy, including anthracyclines
Other	Acute monocytic leukemia‡	M5 by FAB classification	Antineoplastic chemotherapy

*Chediak-Higashi and Hermansky-Pudlak syndromes.
†Also called secondary hemophagocytic lymphohistiocytosis.
‡See Chapter 495.2.
FAB, French-American-British; LCH, Langerhans cell histiocytosis; HLH, hemophagocytic lymphohistiocytosis.

Nephrology

Table 509-1 Other Causes of Red Urine

HEME POSITIVE	**Dyes (Vegetable/Fruit)**
Hemoglobin	Beets
Myoglobin	Blackberries
HEME NEGATIVE	Food and candy coloring
Drugs	Rhubarb
Chloroquine	**Metabolites**
Deferoxamine	Homogentisic acid
Ibuprofen	Melanin
Iron sorbitol	Methemoglobin
Metronidazole	Porphyrin
Nitrofurantoin	Tyrosinosis
Phenazopyridine (Pyridium)	Urates
Phenolphthalein	
Phenothiazines	
Rifampin	
Salicylates	
Sulfasalazine	

Table 509-2 Causes of Hematuria in Children

UPPER URINARY TRACT DISEASE
Isolated renal disease
Immunoglobulin (Ig) A nephropathy (Berger disease)
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane nephropathy
Postinfectious GN (poststreptococcal GN)*
Membranous nephropathy
Membranoproliferative GN*
Rapidly progressive GN
Focal segmental glomerulosclerosis
Anti–glomerular basement membrane disease
Multisystem disease
Systemic lupus erythematosus nephritis*
Henoch-Schönlein purpura nephritis
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
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)
Crystalluria
Anatomic
Hydronephrosis
Cystic-syndromic kidney disease
Polycystic kidney disease
Multicystic dysplasia
Tumor (Wilms tumor, rhabdomyosarcoma, angiomyolipoma, medullary carcinoma)
Trauma

LOWER URINARY TRACT DISEASE
Inflammation (infectious and noninfectious)
Cystitis
Urethritis
Urolithiasis
Trauma
Coagulopathy
Heavy exercise
Bladder tumor
Factitious syndrome, factitious syndrome by proxy†

*Denotes glomerulonephritides presenting with hypocomplementemia.
†Formerly Munchausen syndrome and Munchausen syndrome by proxy.
GN, glomerulonephritis.

Table 509-3 Common Causes of Gross Hematuria

Urinary tract infection
Meatal stenosis
Perineal irritation
Trauma
Urolithiasis
Hypercalciuria
Coagulopathy
Tumor
Glomerular
Postinfectious glomerulonephritis
Henoch-Schönlein purpura nephritis
IgA nephropathy
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane disease
Systemic lupus erythematosus nephritis

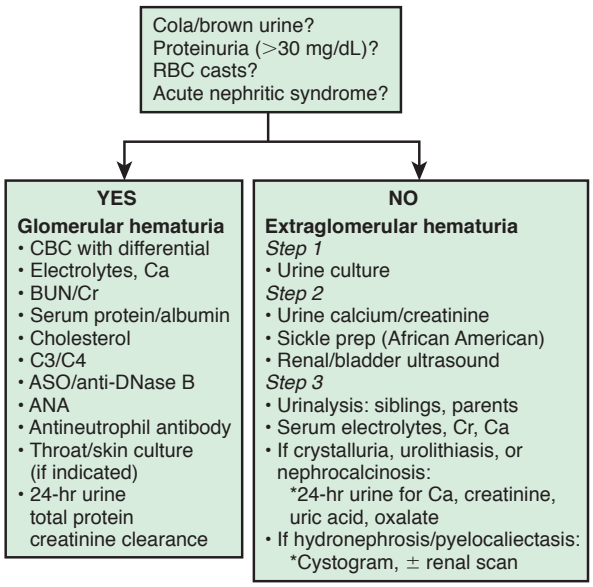

Figure 509-1 Algorithm of the general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. ANA, antinuclear antibody; ASO, antistreptolysin O; BUN, blood urea nitrogen; C3/C4, complement; CBC, complete blood cell count; Cr, creatinine; RBC, red blood cell.

Table 511-1 Summary of Primary Renal Diseases That Manifest as Acute Glomerulonephritis

DISEASES	POSTSTREPTOCOCCAL GLOMERULONEPHRITIS	IgA NEPHROPATHY	GOODPASTURE SYNDROME	IDIOPATHIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS
CLINICAL MANIFESTATIONS				
Age and sex	All ages, mean 7 yr, 2:1 male	10-35 yr, 2:1 male	15-30 yr, 6:1 male	Adults, 2:1 male
Acute nephritic syndrome	90%	50%	90%	90%
Asymptomatic hematuria	Occasionally	50%	Rare	Rare
Nephrotic syndrome	10-20%	Rare	Rare	10-20%
Hypertension	70%	30-50%	Rare	25%
Acute renal failure	50% (transient)	Very rare	50%	60%
Other	Latent period of 1-3 wk	Follows viral syndromes	Pulmonary hemorrhage; iron deficiency anemia	None
Laboratory findings	↑ ASO titers (70%) Positive streptozyme (95%) ↓C3-C9; normal C1, C4	↑ Serum IgA (50%) IgA in dermal capillaries	Positive anti-GBM antibody	Positive ANCA in some
Immunogenetics	HLA-B12, D "EN" (9)*	HLA-Bw 35, DR4 (4)*	HLA-DR2 (16)*	None established
RENAL PATHOLOGY				
Light microscopy	Diffuse proliferation	Focal proliferation	Focal → diffuse proliferation with crescents	Crescentic GN
Immunofluorescence	Granular IgG, C3	Diffuse mesangial IgA	Linear IgG, C3	No immune deposits
Electron microscopy	Subepithelial humps	Mesangial deposits	No deposits	No deposits
Prognosis	95% resolve spontaneously 5% RPGN or slowly progressive	Slow progression in 25-50%	75% stabilize or improve if treated early	75% stabilize or improve if treated early
Treatment	Supportive	Uncertain (options include steroids, fish oil, and ACE inhibitors)	Plasma exchange, steroids, cyclophosphamide	Steroid pulse therapy

*Relative risk.
ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ASO, anti-streptolysin O; GBM, glomerular basement membrane; GN, glomerulonephritis; HLA, human leukocyte antigen; Ig, immunoglobulin; RPGN, idiopathic rapidly progressive glomerulonephritis.

Table 516-1 Classification of Rapidly Progressive ("Crescentic") Glomerulonephritis

PRIMARY
Type I: Anti–glomerular basement membrane antibody disease, Goodpasture syndrome (with pulmonary disease)
Type II: Immune complex mediated
Type III: Pauciimmune (usually antineutrophil cytoplasmic antibody-positive)
SECONDARY
Membranoproliferative glomerulonephritis
Immunoglobulin A nephropathy, Henoch-Schönlein purpura
Poststreptococcal glomerulonephritis
Systemic lupus erythematosus
Polyarteritis nodosa, hypersensitivity angiitis

Table 527-5 Causes of Nephrotic Syndrome in Infants Younger Than 1 Year

SECONDARY CAUSES
Infections
Syphilis
Cytomegalovirus
Toxoplasmosis
Rubella
Hepatitis B
HIV
Malaria
Drug reactions
Toxins
Mercury
Systemic lupus erythematosus
Syndromes with associated renal disease
Syndromes with associated renal disease
Nail-patella syndrome
Lowe syndrome
Nephropathy associated with congenital brain malformation
Denys-Drash syndrome: Wilms tumor
Hemolytic-uremic syndrome
PRIMARY CAUSES
Congenital nephrotic syndrome
Diffuse mesangial sclerosis
Minimal change disease
Focal segmental sclerosis
Membranous nephropathy

Table 514-1 Classification of Lupus Nephritis

CLASS	CLINICAL FEATURES
I. Minimal mesangial LN	No renal findings
II. Mesangial proliferative LN	Mild clinical renal disease; minimally active urinary sediment; mild to moderate proteinuria (never nephrotic) but may have active serology
III. Focal proliferative LN <50% glomeruli involved A. Active A/C. Active and chronic C. Chronic	More active sediment changes; often active serology; increased proteinuria (approximately 25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment, chronic do not
IV. Diffuse proliferative LN (>50% glomeruli involved); all may be with segmental or global involvement (S or G) A. Active A/C. Active and chronic C. Chronic	Most severe renal involvement with active sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), often reduced glomerular filtration rate; serology very active. Active lesions require treatment
V. Membranous LN glomerulonephritis	Significant proteinuria (often nephrotic) with less active lupus serology
VI. Advanced sclerosing LN	More than 90% glomerulosclerosis; no treatment prevents renal failure

LN, lupus nephritis.

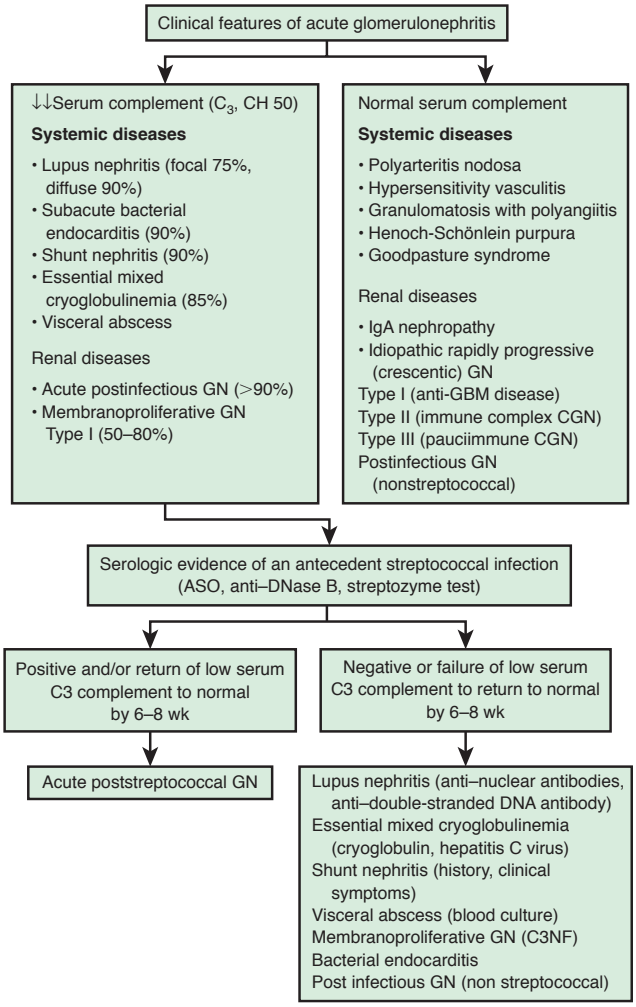

Figure 511-3 Differential diagnosis of acute glomerulonephritis (GN). ASO, anti–streptolysin O; GBM, glomerular basement membrane; NF, nuclear factor.

Table 518-1 Thrombotic Microangiopathies Overview and Classification

TMA associated with genetic or immune-mediated abnormalities of the complement system
Genetically determined factor H deficiency
Genetic membrane cofactor protein (CD46) abnormalities
Complement factor 1 deficiency
Gain-of-function mutations of complement factor B
Complement C3 mutations
Acquired anti-C3 autoantibodies
Immune-mediated factor H deficiency
TTP associated with genetic or immune-mediated ADAMTS13 abnormalities
Infectious disease–associated TMA
STEC-HUS
Neuraminidase (pneumococcal)–associated TMA
HIV infection
Systemic disease–associated TMA
Antiphospholipid syndrome
Systemic lupus erythematosus
Scleroderma
Malignant hypertension
Malignancy
Pregnancy-associated TMA
TTP
Hemolysis, elevated liver enzymes, and low platelet count syndrome
Postpartum HUS
Drug-associated TMA (>50 substances reported)
Mitomycin
Quinidine
Ticlopidine
Clopidogrel
Calcineurin inhibitors
Oral contraception
Gemcitabine
Anti-VEGF
Metabolic disease–associated TMA
Deficiency in cobalamin C metabolism HUS
Transplant-associated TMA
De novo HUS
Recurrent posttransplantation HUS

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HIV, human immunodeficiency virus; HUS, hemolytic-uremic syndrome; STEC-HUS, Shiga toxin–producing *Escherichia coli* hemolytic-uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VEGF, vascular endothelial growth factor.

Table 521-2 Autosomal Recessive Polycystic Kidney Disease and Hepatorenal Fibrocystic Disease Phenocopies

DISEASE	GENE(S)	RENAL DISEASE	HEPATIC DISEASE	SYSTEMIC FEATURES
ARPKD	*PKHD1*	Collecting duct dilation	CHF; Caroli disease	No
ADPKD	*PKD1; PKD2*	Cysts along entire nephron	Biliary cysts; CHF (rare)	Yes: adults
NPHP	*NPHP1-NPHP16*	Cysts at the corticomedullary junction	CHF	+/–
Joubert syndrome and related disorders	*JBTS1-JBTS20*	Cystic dysplasia; NPHP	CHF; Caroli disease	Yes
Bardet-Biedel syndrome	*BBS1-BBS18*	Cystic dysplasia; NPHP	CHF	Yes
Meckel-Gruber syndrome	*MKS1-MKS10*	Cystic dysplasia	CHF	Yes
Oral-facial-digital syndrome, type I	*OFD1*	Glomerular cysts	CHF (rare)	Yes
Glomerulocystic disease	*PKD1; HNF1B; UMOD*	Enlarged; normal or hypoplastic kidneys	CHF (with PKD1 mutations)	+/–
Jeune syndrome (asphyxiating thoracic dystrophy)	*IFT80 (ATD2) DYNC2H1 (ADT3) ADT1, ADT4, ADT5*	Cystic dysplasia	CHF; Caroli disease	Yes
Renal-hepatic-pancreatic dysplasia (Ivemark II)	*NPHP3, NEK8*	Cystic dysplasia	Intrahepatic biliary dysgenesis	Yes
Zellweger syndrome	*PEX1-3;5-6;10-11;13;14;16;19;26*	Renal cortical microcysts	Intrahepatic biliary dysgenesis	Yes

NPHP, Nephronophthisis. CHF, congenital hepatic fibrosis.
Modified from Guay-Woodford LM, Bissler JJ, Braun MC, et al: Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: Report of an international conference. J Pediatr *165:611-617, 2014.*

Table 521-1 Comparison of Clinical Features of Cystic Kidney Diseases

DISEASE	INHERITANCE	FREQUENCY	GENE PRODUCT	AGE OF ONSET	CYST ORIGIN	RENOMEGALY	CAUSE OF ESRD	OTHER MANIFESTATIONS
ADPKD	AD	400-1,000	Polycystin 1 Polycystin 2	20s and 30s; <2% before age 15 Occasional perinatal onset	Anywhere (including the Bowman capsule)	Yes	Yes	Liver cysts Cerebral aneurysms Hypertension Mitral valve prolapse Kidney stones UTIs
ARPKD	AR	6,000-10,000	Fibrocystin/ polyductin	First yr of life; perinatal onset	Distal nephron, CD	Yes	Yes	Hepatic fibrosis Pulmonary hypoplasia Hypertension
ACKD	No	90% of ESRD patients at 8 yr	None	Years after onset of ESRD	Proximal and distal tubules	Rarely	No	None
Simple cysts	No	50% in those older than 40 yr	None	Adulthood	Anywhere (usually cortical)	No	No	None
Nephronophthisis	AR	80,000	Nephrocystins (NPHP1-9)	Childhood or adolescence	Medullary DCT	No	Yes	Retinal degeneration; neurologic, skeletal, hepatic, cardiac malformations
MCKD	AD	Rare	Uromodulin, others	Adulthood	Medullary DCT	No	Yes	Hyperuricemia, gout
MSK	No	5,000-20,000	None	30s	Medullary CD	No	No	Kidney stones Hypercalciuria
Tuberous sclerosis	AD	10,000	Hamartin (TSC1) Tuberin (TSC2)	Childhood	Loop of Henle, DCT	Rarely	Rarely	Renal cell carcinoma Tubers, seizures Angiomyolipoma Hypertension
VHL syndrome	AD	40,000	VHL protein	20s	Cortical nephrons	Rarely	Rarely	Retinal angioma, CNS hemangioblastoma, renal cell carcinoma, pheochromocytoma
Oral-facial-digital syndrome	XD	250,000	OFD1 protein	Childhood or adulthood	Renal glomeruli	Rarely	Yes	Malformation of the face, oral cavity, and digits; liver cysts; mental retardation
Bardet-Biedl syndrome	AR	65,000-160,000	BBS 14	Adulthood	Renal calyces	Rarely	Yes	Syndactyly and polydactyly, obesity, retinal dystrophy, male hypogenitalism, hypertension, mental retardation

ACKD, acquired cystic kidney disease; AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; ARPKD, autosomal recessive polycystic kidney disease; CD, collecting duct; CNS, central nervous system; DCT, distal convoluted tubule; ESRD, end-stage renal disease; MCKD, medullary cystic kidney disease; MSK, medullary sponge kidney; UTI, urinary tract infection; VHL, von Hippel-Lindau; XD, X-linked dominant.

From Arnaout MA: Cystic kidney disease. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Elsevier Saunders, Table 129-1, p. 796.*

Table 523-1 Methods Available to Test for Proteinuria

METHOD	INDICATIONS	NORMAL RANGE	COMMENTS
Dipstick testing	Routine screening for proteinuria performed in the office	Negative or trace in a concentrated urine specimen (specific gravity: ≥1.020)	False-positive test can occur if urine is very alkaline (pH > 8.0) or very concentrated (specific gravity: >1.025)
24 hr urine for protein and creatinine* excretion	Quantitation of proteinuria (as well as creatinine clearances)	<100 mg/m^2/24 hr or <150 mg/24 hr in a documented 24 hr collection	More accurate than spot urine analysis; inconvenient for patient; limited use in pediatric practice
Spot urine for protein/creatinine ratio—preferably on first morning urine specimen	Semiquantitative assessment of proteinuria	<0.2 mg protein/mg creatinine in children >2 yr old <0.5 mg protein/mg creatinine in those 6–24 mo old	Simplest method to quantitate proteinuria; less accurate than measuring 24 hr proteinuria
Microalbuminuria	Assess risk of progressive glomerulopathy in patients with diabetes mellitus	<30 mg urine albumin per gram of creatinine on first morning urine	Therapy should be intensified in diabetics with microalbuminuria

*Note that in a 24 hr urine specimen, the creatinine content should be measured to determine whether the specimen is truly a 24 hr collection. The amount of creatinine in a 24 hr specimen can be estimated as follows: females, 15-20 mg/kg; males, 20-25 mg/kg.

Adapted from Hogg RJ, Portman RJ, Milliner D, et al, Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk Assessment, Detection, and Elimination (PARADE), Pediatrics *105(6):1242–1249, 2000.*

Table 527-1 Causes of Childhood Nephrotic Syndrome

IDIOPATHIC NEPHROTIC SYNDROME
- Minimal change disease
- Focal segmental glomerulosclerosis
- Membranous nephropathy
- Glomerulonephritis associated with nephrotic syndrome–membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy

GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME
- Nephrotic Syndrome (Typical)
  - Finnish-type congenital nephrotic syndrome (absence of nephrin)
  - Focal segmental glomerulosclerosis (mutations in nephrin, podocin, *MYO1E*, α-actinin 4, TRPC6)
  - Diffuse mesangial sclerosis (mutations in laminin β_2 chain)
  - Denys-Drash syndrome (mutations in WT1 transcription factor)
  - Congenital nephrotic syndrome with lung and skin involvement (integrin α-3 mutation)
  - Mitochondrial disorders)
- Proteinuria With or Without Nephrotic Syndrome
  - Nail-patella syndrome (mutation in LMX1B transcription factor)
  - Alport syndrome (mutation in collagen biosynthesis genes)
- Multisystem Syndromes With or Without Nephrotic Syndrome
  - Galloway-Mowat syndrome
  - Charcot-Marie-Tooth disease
  - Jeune syndrome
  - Cockayne syndrome
  - Laurence-Moon-Biedl-Bardet syndrome
- Metabolic Disorders With or Without Nephrotic Syndrome
  - Alagille syndrome
  - α_1-Antitrypsin deficiency
  - Fabry disease
  - Glutaric acidemia
  - Glycogen storage disease
  - Hurler syndrome
  - Partial lipodystrophy
  - Mitochondrial cytopathies
  - Sickle cell disease

SECONDARY CAUSES OF NEPHROTIC SYNDROME
- Infections
  - Endocarditis
  - Hepatitides B, C
  - HIV-1
  - Infectious mononucleosis
  - Malaria
  - Syphilis (congenital and secondary)
  - Toxoplasmosis
  - Schistosomiasis
  - Filariasis
- Drugs
  - Captopril
  - Penicillamine
  - Gold
  - Nonsteroidal antiinflammatory drugs
  - Pamidronate
  - Interferon
  - Mercury
  - Heroin
  - Lithium
- Immunologic or Allergic Disorders
  - Vasculitis syndromes
  - Castleman disease
  - Kimura disease
  - Beesting
  - Food allergens
  - Serum sickness
- Associated With Malignant Disease
  - Lymphoma
  - Leukemia
  - Solid tumors
- Glomerular Hyperfiltration
  - Oligomeganephronia
  - Morbid obesity
  - Adaptation to nephron reduction

Adapted from Eddy AA, Symons JM: Nephrotic syndrome in childhood, Lancet *362:629–638, 2003.*

Table 527-2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				Type I	Type II
DEMOGRAPHICS					
Age (yr)	2-6, some adults	2-10, some adults	40-50	5-15	5-15
Sex	2:1 male	1.3:1 male	2:1 male	Male-female	Male-female
CLINICAL MANIFESTATIONS					
Nephrotic syndrome	100%	90%	80%	60%*	60%*
Asymptomatic proteinuria	0	10%	20%	40%	40%
Hematuria (microscopic or gross)	10-20%	60-80%	60%	80%	80%
Hypertension	10%	20% early	Infrequent	35%	35%
Rate of progression to renal failure	Does not progress	10 yr	50% in 10-20 yr	10-20 yr	5-15 yr
Associated conditions	Usually none	HIV, heroin use, sickle cell disease, reflux nephropathy	Renal vein thrombosis; medications; SLE; hepatitides B, C; lymphoma; tumors	None	Partial lipodystrophy
GENETICS	None except in congenital nephrotic syndrome (see Table 527-3)	Podocin, α-actinin 4, TRPC6 channel, INF-2, MYH-9	None	None	None
LABORATORY FINDINGS	Manifestations of nephrotic syndrome ↑ BUN in 15-30% Normal complement levels	Manifestations of nephrotic syndrome ↑ BUN in 20-40% Normal complement levels	Manifestations of nephrotic syndrome Normal complement levels	Low complement levels—C1, C4, C3-C9	Normal complement levels—C1, C4, low C3-C9
RENAL PATHOLOGY					
Light microscopy	Normal	Focal sclerotic lesions	Thickened GBM, spikes	Thickened GBM, proliferation	Lobulation
Immunofluorescence	Negative	IgM, C3 in lesions	Fine granular IgG, C3	Granular IgG, C3	C3 only
Electron microscopy	Foot process fusion	Foot process fusion	Subepithelial deposits	Mesangial and subendothelial deposits	Dense deposits
REMISSION ACHIEVED AFTER 8 WK OF ORAL CORTICOSTEROID THERAPY	90%	15-20%	Resistant	Not established/ resistant	Not established/ resistant

*Approximate frequency as a cause of idiopathic nephrotic syndrome. Approximately 10% of cases of adult nephrotic syndrome are a result of various diseases that usually manifest as acute glomerulonephritis.

↑, Elevated; BUN, blood urea nitrogen; C, complement; GBM, glomerular basement membrane; Ig, immunoglobulin; SLE, systemic lupus erythematosus.

Modified from Couser WG: Glomerular disorders. In Wyngaarden JB, Smith LH, Bennett JC, editors: Cecil textbook of medicine, *ed 19, Philadelphia, 1992, WB Saunders, p. 560.*

Table 526-1 Causes of Proteinuria

TRANSIENT PROTEINURIA
Fever
Exercise
Dehydration
Cold exposure
Congestive heart failure
Seizure
Stress

ORTHOSTATIC (POSTURAL) PROTEINURIA

GLOMERULAR DISEASES CHARACTERIZED BY ISOLATED PROTEINURIA
Idiopathic (minimal change) 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 (streptococcal, endocarditis, hepatitis B or C virus, HIV)
Immunoglobulin A nephropathy
Henoch-Schönlein purpura nephritis
Lupus nephritis
Serum sickness
Alport syndrome
Vasculitic disorders
Reflux nephropathy

TUBULAR DISEASES
Cystinosis
Wilson disease
Lowe syndrome
Dent disease (X-linked recessive nephrolithiasis)
Galactosemia
Tubulointerstitial nephritis
Acute tubular necrosis
Renal dysplasia
Polycystic kidney disease
Reflux nephropathy
Drugs (penicillamine, lithium, NSAID)
Heavy metals (lead, gold, mercury)

NSAID, nonsteroidal antiinflammatory drug.

Table 529-1 Common Causes of Renal Tubular Acidosis

PROXIMAL RENAL TUBULAR ACIDOSIS

Primary

Sporadic

Inherited

- Inherited renal disease (idiopathic Fanconi)
  - Sporadic (most common)
  - Autosomal dominant
  - Autosomal recessive
  - X-linked (Dent disease)
- Inherited syndromes
  - Cystinosis
  - Tyrosinemia type 1
  - Galactosemia
  - Oculocerebral dystrophy (Lowe syndrome)
  - Wilson disease
- Hereditary fructose intolerance

Secondary

Intrinsic renal disease

- Autoimmune diseases (Sjögren syndrome)
- Hypokalemic nephropathy
- Renal transplant rejection

Hematologic disease

- Myeloma

Drugs

- Gentamicin
- Cisplatin
- Ifosfamide
- Sodium valproate

Heavy metals

- Lead
- Cadmium
- Mercury

Organic compounds

- Toluene

Nutritional

- Kwashiorkor

Hormonal

- Primary hyperparathyroidism

DISTAL RENAL TUBULAR ACIDOSIS

Primary

Sporadic

Inherited

- Inherited renal diseases
  - Autosomal dominant
  - Autosomal recessive
  - Autosomal recessive with early-onset hearing loss
  - Autosomal recessive with later-onset hearing loss
- Inherited syndromes associated with type I renal tubular acidosis
  - Marfan syndrome
  - Wilson syndrome
  - Ehlers-Danlos syndrome
- Familial hypercalciuria

Secondary

Intrinsic renal

- Interstitial nephritis
- Pyelonephritis
- Transplant rejection
- Sickle cell nephropathy
- Lupus nephritis
- Nephrocalcinosis
- Medullary sponge kidney

Urologic

- Obstructive uropathy
- Vesicoureteral reflux

- Hepatic
- Cirrhosis

Toxins or medications

- Amphotericin B
- Lithium
- Toluene
- Cisplatin

HYPERKALEMIC RENAL TUBULAR ACIDOSIS

Primary

Sporadic

Genetic

- Hypoaldosteronism
- Addison disease
- Congenital adrenal hyperplasia
- Pseudohypoaldosteronism (type I or II)

Secondary

Urologic

- Obstructive uropathy

Intrinsic renal

- Pyelonephritis
- Interstitial nephritis

Systemic

- Diabetes mellitus
- Sickle cell nephropathy

Drugs

- Trimethoprim/sulfamethoxazole
- Angiotensin-converting enzyme inhibitors
- Cyclosporine
- Prolonged heparinization

Addison disease

Table 535-6 Standardized Terminology for Stages of Chronic Kidney Disease (NKF KDOQI Guidelines)

STAGE	DESCRIPTION	GFR (mL/min/1.73 m²)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	5-29
5	Kidney failure	<15 or on dialysis

GFR, glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Table 535-8 Merits of Peritoneal Dialysis in Pediatric Patients with End-Stage Renal Disease

ADVANTAGES

Ability to perform dialysis treatment at home
Technically easier than hemodialysis, especially in infants
Ability to live a greater distance from medical center
Freedom to attend school and after-school activities
Less-restrictive diet
Less expensive than hemodialysis
Independence (adolescents)

DISADVANTAGES

Catheter malfunction
Catheter-related infections (peritonitis, exit site)
Impaired appetite (due to full peritoneal cavity)
Negative body image
Caregiver burnout

Table 529-1 Common Causes of Renal Tubular Acidosis

PROXIMAL RENAL TUBULAR ACIDOSIS

Primary

Sporadic

Inherited

- Inherited renal disease (idiopathic Fanconi)
  - Sporadic (most common)
  - Autosomal dominant
  - Autosomal recessive
  - X-linked (Dent disease)
- Inherited syndromes
  - Cystinosis
  - Tyrosinemia type 1
  - Galactosemia
  - Oculocerebral dystrophy (Lowe syndrome)
  - Wilson disease
- Hereditary fructose intolerance

Secondary

Intrinsic renal disease

- Autoimmune diseases (Sjögren syndrome)
- Hypokalemic nephropathy
- Renal transplant rejection

Hematologic disease

- Myeloma

Drugs

- Gentamicin
- Cisplatin
- Ifosfamide
- Sodium valproate

Heavy metals

- Lead
- Cadmium
- Mercury

Organic compounds

- Toluene

Nutritional

- Kwashiorkor

Hormonal

- Primary hyperparathyroidism

DISTAL RENAL TUBULAR ACIDOSIS

Primary

Sporadic

Inherited

- Inherited renal diseases
  - Autosomal dominant
  - Autosomal recessive
  - Autosomal recessive with early-onset hearing loss
  - Autosomal recessive with later-onset hearing loss
- Inherited syndromes associated with type I renal tubular acidosis
  - Marfan syndrome
  - Wilson syndrome
  - Ehlers-Danlos syndrome
- Familial hypercalciuria

Secondary

Intrinsic renal

- Interstitial nephritis
- Pyelonephritis
- Transplant rejection
- Sickle cell nephropathy
- Lupus nephritis
- Nephrocalcinosis
- Medullary sponge kidney

Urologic

- Obstructive uropathy
- Vesicoureteral reflux
- Hepatic
- Cirrhosis

Toxins or medications

- Amphotericin B
- Lithium
- Toluene
- Cisplatin

HYPERKALEMIC RENAL TUBULAR ACIDOSIS

Primary

Sporadic

Genetic

- Hypoaldosteronism
- Addison disease
- Congenital adrenal hyperplasia
- Pseudohypoaldosteronism (type I or II)

Secondary

Urologic

- Obstructive uropathy

Intrinsic renal

- Pyelonephritis
- Interstitial nephritis

Systemic

- Diabetes mellitus
- Sickle cell nephropathy

Drugs

- Trimethoprim/sulfamethoxazole
- Angiotensin-converting enzyme inhibitors
- Cyclosporine
- Prolonged heparinization

Addison disease

Table 531-1 Bartter and Gitelman Syndromes

	TYPE I BARTTER SYNDROME	TYPE II BARTTER SYNDROME	TYPE III BARTTER SYNDROME	TYPE IV BARTTER SYNDROME	TYPE V BARTTER SYNDROME	GITELMAN SYNDROME
Inheritance	AR	AR	AR	AR	AD	AR
Affected tubular region	TAL	TAL + CCD	TAL + DCT	TAL + DCT	TAL	DCT
Gene	*SLC12A2*	*KCNJ1*	*CLCBRK*	*BSND*	*CASR*	*SLC12A3* Few have *CLCNKB*
Onset	Prenatal, postnatal	Prenatal, postnatal	Variable	Prenatal, postnatal	Variable	Adolescent, adult
Urine PGE2	Very high	Very high	Slightly elevated	Elevated	Elevated	Normal
Hypokalemic metabolic alkalosis	Present	Present	Present	Present	Present	Present
Features	Polyhydramnios, prematurity, nephrocalcinosis, dehydration, hyposthenuria, polyuria, failure to thrive	Same as type I	Failure to thrive, dehydration, salt craving, low serum magnesium in 20%, mildest form	Same as type I, with sensorineural hearing loss and no nephrocalcinosis	Hypocalcemia, low parathyroid hormone levels, hypercalciuria, uncommon cause of Bartter syndrome	Hypomagnesemia in 100%, mild dehydration, occasional growth retardation, tetany

AD, autosomal dominant; AR, autosomal recessive; CCD, cortisol collecting duct; DCT, descending convoluted tubule; PGE_2, prostaglandin E_2; TAL, thick ascending loop of Henle.

Table 532-1 Etiology of Interstitial Nephritis

ACUTE
Drugs
- Antimicrobials
  - Penicillin derivatives
  - Cephalosporins
  - Sulfonamides
  - Trimethoprim-sulfamethoxazole
  - Ciprofloxacin
  - Tetracyclines
  - Vancomycin
  - Erythromycin derivatives
  - Rifampin
  - Amphotericin B
  - Acyclovir
- Anticonvulsants
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Sodium valproate
- Other drugs
  - Allopurinol
  - All-*trans*-retinoic acid
  - 5-Aminosalicylic acid
  - Cimetidine
  - Cyclosporine
  - Diuretics
  - Escitalopram
  - Interferon
  - Mesalazine
  - Quetiapine
  - Olanzapine
  - Nonsteroidal antiinflammatory drugs
  - Protease inhibitors
  - Proton pump inhibitors
  - Aristolochic acid (traditional Chinese herb)

Infections
- Adenovirus
- Bacteria associated with acute pyelonephritis
- BK virus
- *Brucella*
- Streptococcal species
- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis B virus
- Histoplasmosis
- Human immunodeficiency virus
- Hantavirus
- Leptospirosis
- *Toxoplasma gondii*

Disease-associated
- Glomerulonephritis (e.g., systemic lupus erythematosus)
- Acute allograft rejection
- Tubulointerstitial nephritis and uveitis (TINU) syndrome

Idiopathic

CHRONIC
Drugs and toxins
- Analgesics
- Cyclosporine
- Lithium
- Heavy metals

Infections (see Acute)
Disease-associated
- Metabolic and hereditary
- Cystinosis
- Oxalosis
- Fabry disease
- Wilson disease
- Sickle cell nephropathy
- Alport syndrome
- Juvenile nephronophthisis, medullary cystic disease

Immunologic
- Systemic lupus erythematosus
- Crohn disease
- Chronic allograft rejection
- Tubulointerstitial nephritis and uveitis (TINU) syndrome
- Antitubular basement disease

Urologic
- Posterior urethral valves
- Eagle-Barrett syndrome
- Ureteropelvic junction obstruction
- Vesicoureteral reflux

Miscellaneous
- Balkan nephropathy
- Radiation
- Sarcoidosis
- Neoplasm

Idiopathic

Table 538-2 Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination

TEST	SENSITIVITY (RANGE) %	SPECIFICITY (RANGE) %
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy (white blood cells)	73 (32-100)	81 (45-98)
Microscopy (bacteria)	81 (16-99)	83 (11-100)
Leukocyte esterase test, nitrite test, or microscopy positive	99.8 (99-100)	70 (60-92)

From Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management: Clinical practice guideline. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in Febrile infants and children 2 to 24 months. Pediatrics *128:595–610, 2011.*

Table 533-1 Renal Syndromes Produced by Nephrotoxins

NEPHROTIC SYNDROME
Angiotensin-converting enzyme inhibitors
Gold salts
Interferon
Mercury compounds
Nonsteroidal antiinflammatory drugs
Penicillamine
NEPHROGENIC DIABETES INSIPIDUS
Amphotericin B
Cisplatin
Colchicine
Demeclocycline
Lithium
Methoxyflurane
Propoxyphene
Vinblastine
RENAL VASCULITIS
Hydralazine
Isoniazid
Penicillins
Propylthiouracil
Sulfonamides
Numerous other drugs that can cause a hypersensitivity reaction
THROMBOTIC MICROANGIOPATHY
Cyclosporine A
Oral contraceptive agents
Mitomycin C
NEPHROCALCINOSIS OR NEPHROLITHIASIS
Allopurinol
Bumetanide
Ethylene glycol
Furosemide
Melamine
Methoxyflurane
Topiramate
Vitamin D
ACUTE RENAL FAILURE
Acetaminophen
Acyclovir
Aminoglycosides
Amphotericin B
Angiotensin-converting enzyme inhibitors
Biologic toxins (snake, spider, bee, wasp)
Cisplatin
Cyclosporine
Ethylene glycol
Halothane
Heavy metals
Ifosfamide
Lithium
Methoxyflurane
Nonsteroidal antiinflammatory drugs
Radiocontrast agents
Tacrolimus
Vancomycin
OBSTRUCTIVE UROPATHY
Sulfonamides
Acyclovir
Methotrexate
Protease inhibitors
Ethylene glycol
Methoxyflurane
FANCONI SYNDROME
Aminoglycosides
Chinese herbs (aristolochic)
Cisplatin
Heavy metals (cadmium, lead, mercury, and uranium)
Ifosfamide
Lysol
Outdated tetracycline
RENAL TUBULAR ACIDOSIS
Amphotericin B
Lead
Lithium
Toluene
INTERSTITIAL NEPHRITIS
Amidopyrine
p-Aminosalicylate
Carbon tetrachloride
Cephalosporins
Cimetidine
Cisplatin
Colistin
Copper
Cyclosporine
Ethylene glycol
Foscarnet
Gentamicin
Gold salts
Indomethacin
Interferon-α
Iron
Kanamycin
Lithium
Mannitol
Mercury salts
Mitomycin C
Neomycin
Nonsteroidal antiinflammatory drugs
Penicillins (especially methicillin)
Pentamidine
Phenacetin
Phenylbutazone
Poisonous mushrooms
Polymyxin B
Radiocontrast agents
Rifampin
Salicylate
Streptomycin
Sulfonamides
Tacrolimus
Tetrachloroethylene
Trimethoprim-sulfamethoxazole

Table 535-2 Common Causes of Acute Kidney Injury

PRERENAL
Dehydration
Hemorrhage
Sepsis
Hypoalbuminemia
Cardiac failure
INTRINSIC RENAL
Glomerulonephritis
• Postinfectious/poststreptococcal
• Lupus erythematosus
• Henoch-Schönlein purpura
• Membranoproliferative
• Anti–glomerular basement membrane
Hemolytic-uremic syndrome
Acute tubular necrosis
Cortical necrosis
Renal vein thrombosis
Rhabdomyolysis
Acute interstitial nephritis
Tumor infiltration
Tumor lysis syndrome
POSTRENAL
Posterior urethral valves
Ureteropelvic junction obstruction
Ureterovesicular junction obstruction
Ureterocele
Tumor
Urolithiasis
Hemorrhagic cystitis
Neurogenic bladder

Table 535-5 Criteria for Definition of Chronic Kidney Disease (NKF KDOQI Guidelines)

Patient has CKD if either of the following criteria are present:

1. Kidney damage for ≥3 mo, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by 1 or more of the following features:
   - Abnormalities in the composition of the blood or urine
   - Abnormalities in imaging tests
   - Abnormalities on kidney biopsy
2. GFR <60 mL/min/1.73 m^2 for ≥3 mo, with or without the other signs of kidney damage described above

NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Table 535-1 Pediatric-Modified Rifle (pRIFLE) Criteria

CRITERIA	ESTIMATED CCL	URINE OUTPUT
Risk	eCCl decrease by 25%	<0.5 mL/kg/hr for 8 hr
Injury	eCCl decrease by 50%	<0.5 mL/kg/hr for 16 hr
Failure	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m^2	<0.3 mL/kg/hr for 24 hr or anuric for 12 hr
Loss	Persistent failure >4 wk	
End-stage	End-stage renal disease (persistent failure >3 mo)	

CCl, creatinine clearance; eCCl, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss, and end-stage renal disease.

Table 535-4 Comparison of Peritoneal Dialysis, Intermittent Hemodialysis, and Continual Renal Replacement Therapy

	PD	IHD	CRRT
BENEFITS			
Fluid removal	+	++	++
Urea and creatinine clearance	+	++	+
Potassium clearance	++	++	+
Toxin clearance	+	++	+
COMPLICATIONS			
Abdominal pain	+	–	–
Bleeding	–	+	+
Dysequilibrium	–	+	–
Electrolyte imbalance	+	+	+
Need for heparinization	–	+	+/–
Hyperglycemia	+	–	–
Hypotension	+	++	+
Hypothermia	–	–	+
Central line infection	–	+	+
Inguinal or abdominal hernia	+	–	–
Peritonitis	+	–	–
Protein loss	+	–	–
Respiratory compromise	+	–	–
Vessel thrombosis	–	+	+

PD, peritoneal dialysis; IHD, intermittent hemodialysis; CRRT, continual renal replacement therapy.

Adapted from Rogers MC: Textbook of pediatric intensive care, *Baltimore, 1992, Williams & Wilkins.*

Table 535-3 Urinalysis, Urine Chemistries, and Osmolality in Acute Kidney Injury

	HYPOVOLEMIA	ACUTE TUBULAR NECROSIS	ACUTE INTERSTITIAL NEPHRITIS	GLOMERULONEPHRITIS	OBSTRUCTION
Sediment	Bland	Broad, brownish granular casts	White blood cells, eosinophils, cellular casts	Red blood cells, red blood cell casts	Bland or bloody
Protein	None or low	None or low	Minimal but may be increased with NSAIDs	Increased, >100 mg/dL	Low
Urine sodium, mEq/L*	<20	>30	>30	<20	<20 (acute) >40 (few days)
Urine osmolality, mOsm/kg	>400	<350	<350	>400	<350
Fractional excretion of sodium %†	<1	>1	Varies	<1	<1 (acute) >1 (few days)

*The sensitivity and specificity of urine sodium of <20 mEq/L in differentiating prerenal azotemia from acute tubular necrosis are 90% and 82%, respectively.

†Fractional excretion of sodium is the urine:plasma (U:P) ratio of sodium divided by U:P of creatinine ×100. The sensitivity and specificity of fractional excretion of sodium of <1% in differentiating prerenal azotemia from acute tubular necrosis are 96% and 95%, respectively.

NSAIDs, nonsteroidal antiinflammatory drugs.

From Singri N, Ahya SN, Levin ML: Acute renal failure, JAMA *289:747–751, 2003.*

Table 536-2 Common Causes of ESRD in Pediatric Transplant Recipients (N = 9854)

CAUSES	% OF RECIPIENTS
Aplasia, hypoplasia, dysplasia	15.9
Obstructive uropathy	15.6
Focal segmental glomerulosclerosis	11.7
Reflux nephropathy	5.2
Chronic glomerulonephritis	3.3
Polycystic disease	2.9
Medullary cystic disease	2.8
Hemolytic-uremic syndrome	2.6
Prune belly syndrome	2.6
Congenital nephrotic syndrome	2.6
Familial nephritis	2.3
Cystinosis	2.0
Idiopathic crescentic glomerulonephritis	1.7
MPGN type I	1.7
Berger (IgA) nephritis	1.3
Henoch-Schönlein nephritis	1.1
MPGN type II	0.8

Table 539-1 Classification of Vesicoureteral Reflux

TYPE	CAUSE
Primary	Congenital incompetence of the valvular mechanism of the vesicoureteral junction
Primary associated with other malformations of the ureterovesical junction	Ureteral duplication Ureterocele with duplication Ureteral ectopia Paraureteral diverticula
Secondary to increased intravesical pressure	Neuropathic bladder Nonneuropathic bladder dysfunction Bladder outlet obstruction
Secondary to inflammatory processes	Severe bacterial cystitis Foreign bodies Vesical calculi Clinical cystitis
Secondary to surgical procedures involving the ureterovesical junction	Surgery

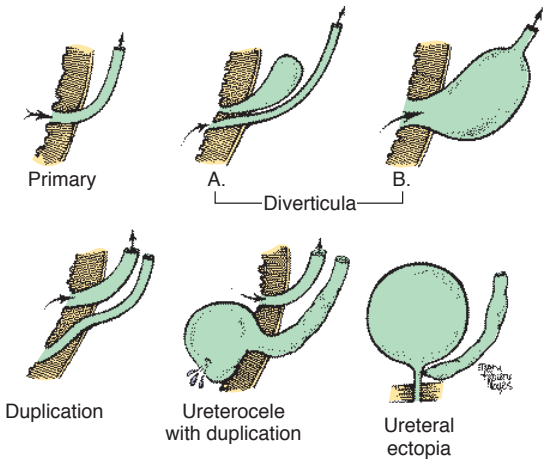

Figure 539-5 Various anatomic defects of the ureterovesical junction associated with vesicoureteral reflux.

Table 535-7 Pathophysiology of Chronic Kidney Disease

MANIFESTATION	MECHANISMS
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium retention	Excessive renin production Oliguria
Sodium wasting	Solute diuresis Tubular damage
Urinary concentrating defect	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron deficiency Folate deficiency Vitamin B_{12} deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy)	Uremic factor(s) Aluminum toxicity Hypertension
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility Serositis (uremia)
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity
Pericarditis, cardiomyopathy	Uremic factor(s) Hypertension Fluid overload
Glucose intolerance	Tissue insulin resistance

Table 538-3 Guideline Recommendations for Diagnostic Evaluation Following a Febrile Urinary Tract Infection in Infants

GUIDELINE	ULTRASONOGRAPHY	VCUG	LATE DMSA SCAN
National Institute for Health And Care Excellence (NICE)*	(see Table 538-4)		
American Academy of Pediatrics	Yes	If abnormal ultrasonogram	No
Italian Society for Paediatric Nephrology (ISPN)	Yes	If abnormal ultrasonogram or if risk factors are present†	If abnormal ultrasonogram or VUR

*Upper urinary tract dilation on ultrasonography, poor urinary flow, infection with organism other than *E. coli*, or family history of vesicoureteral reflux.
†Abnormal antenatal ultrasonogram of fetal urinary tract, family history of reflux, septicemia, renal failure, age younger than 6 mo in a male infant, likely family noncompliance, incomplete bladder emptying, no clinical response to appropriate antibiotic therapy within 72 hr, or infection with organism other than *E. coli*.
DMSA, dimercaptosuccinic acid; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

Table 538-4 Recommended Imaging Schedule for Children with Urinary Tract Infection

	Type of Infection		
CHILD AGE AND TESTS	RESPONDS WELL TO TREATMENT WITHIN 48 HR	ATYPICAL INFECTION	RECURRENT INFECTION
CHILDREN YOUNGER THAN 6 MO OLD			
Ultrasound scan during acute infection	No	Yes	Yes
Ultrasound scan within 6 wk of infection	Yes	No	No
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	Consider if ultrasound scan abnormal	Yes	Yes
CHILDREN 6 MO-3 YR OLD			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	No	Not routine, consider if dilation on ultrasound, poor urine flow, non–*E. coli* infection, or family history of vesicoureteric reflux	
CHILDREN OLDER THAN AGE 3 YR			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	No	No	No

DMSA, dimercaptosuccinic acid.
Adapted from National Institute for Health and Clinical Excellence. Urinary tract infection in children: diagnosis, treatment, and long-term management. *NICE clinical guidelines, no. 54. London, 2007, RCOG Press, Tables 6-13, 6-14, and 6-15.*

Table 540-3 The Etiology of Antenatal Hydronephrosis

ETIOLOGY	INCIDENCE
Transient hydronephrosis	41-88%
Ureteropelvic junction obstruction	10-30%
Vesicoureteral reflux	10-20%
Ureterovesical junction obstruction/megaureters	5-10%
Multicystic dysplastic kidney	4-6%
Posterior urethral valve/urethral atresia	1-2%
Ureterocele/ectopic ureter/duplex system	5-7%
Others: prune belly syndrome, cystic kidney disease, congenital ureteric strictures, and megalourethra	Uncommon

From Nguyen HT, Herndon CDA, Cooper C, et al: The society for fetal urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol *6:212–231, 2010, Table 5, p. 217.*

Table 540-4 Society for Fetal Urology Grading System for Hydronephrosis

	Renal Image	
GRADE OF HYDRONEPHROSIS	CENTRAL RENAL COMPLEX	RENAL PARENCHYMAL THICKNESS
0	Intact	Normal
1	Slight splitting	Normal
2	Evident splitting, complex confined within renal border	Normal
3	Wide splitting pelvis dilated outside renal border, calyces uniformly dilated	Normal
4	Further dilation of pelvis and calyces (calyces may appear convex)	Thin

After Maizels M, Mitchell B, Kass E, et al: Outcome of nonspecific hydronephrosis in the infant: a report from the registry of the Society for Fetal Urology, J Urol *152:2324–2327, 1994.*

Table 543-1 Causes of Urinary Incontinence in Childhood

Overactive bladder (urge incontinence or diurnal urge syndrome)
Infrequent voiding (underactive bladder)
Voiding postponement
Detrusor–sphincter dyssynergia
Nonneurogenic neurogenic bladder (Hinman syndrome)
Vaginal voiding
Giggle incontinence
Cystitis
Bladder outlet obstruction (posterior urethral valves)
Ectopic ureter and fistula
Sphincter abnormality (epispadias, exstrophy; urogenital sinus abnormality)
Neuropathic
Overflow incontinence
Traumatic
Iatrogenic
Behavioral
Combinations

Table 540-2 Definition of Antenatal Hydronephrosis by Anterior-Posterior Diameter

DEGREE OF ANTENATAL HYDRONEPHROSIS	SECOND TRIMESTER	THIRD TRIMESTER
Mild	4 to <7 mm	7 to <9 mm
Moderate	7 to ≤10 mm	9 to ≤15 mm
Severe	>10 mm	>15 mm

From Nguyen HT, Herndon CDA, Cooper C, et al: The society for fetal urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol *6:212–231, 2010, Table 2, p. 215.*

Table 540-1 Types and Causes of Urinary Tract Obstruction

LOCATION	CAUSE
Infundibula	Congenital Calculi Inflammatory (tuberculosis) Traumatic Postsurgical Neoplastic
Renal pelvis	Congenital (infundibulopelvic stenosis) Inflammatory (tuberculosis) Calculi Neoplasia (Wilms tumor, neuroblastoma)
Ureteropelvic junction	Congenital stenosis Calculi Neoplasia Inflammatory Postsurgical Traumatic
Ureter	Congenital obstructive megaureter Midureteral structure Ureteral ectopia Ureterocele Retrocaval ureter Ureteral fibroepithelial polyps Ureteral valves Calculi Postsurgical Extrinsic compression Neoplasia (neuroblastoma, lymphoma, and other retroperitoneal or pelvic tumors) Inflammatory (Crohn disease, chronic granulomatous disease) Hematoma, urinoma Lymphocele Retroperitoneal fibrosis
Bladder outlet and urethra	Neurogenic bladder dysfunction (functional obstruction) Posterior urethral valves Anterior urethral valves Diverticula Urethral strictures (congenital, traumatic, or iatrogenic) Urethral atresia Ectopic ureterocele Meatal stenosis (males) Calculi Foreign bodies Phimosis Extrinsic compression by tumors Urogenital sinus anomalies

Table 540-5 Classification of Megaureter

Refluxing		Obstructed		Nonrefluxing and Nonobstructed	
PRIMARY	**SECONDARY**	**PRIMARY**	**SECONDARY**	**PRIMARY**	**SECONDARY**
Primary reflux	Neuropathic bladder	Intrinsic (primary obstructed megaureter)	Neuropathic bladder	Nonrefluxing, nonobstructive	Diabetes insipidus
Megacystic-megaureter syndrome	Hinman syndrome	Ureteral valve	Hinman syndrome		Infection
Ectopic ureter	Posterior urethral valves	Ectopic ureter	Posterior urethral valves		Persistent after relief of obstruction
Prune-belly syndrome	Bladder diverticulum Postoperative	Ectopic uterocele	Ureteral calculus Extrinsic Postoperative		

Patient name:
Hospital number:
Reason for referral:
Date:

Over the last month	Almost never	Less than half the time	About half the time	Almost every time	Not available
1. I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2. When I wet myself, my underwear is soaked.	0	1	2	3	NA
3. I miss having a bowel movement every day.	0	1	2	3	NA
4. I have to push for my bowel movements to come out.	0	1	2	3	NA
5. I only go to the bathroom one or two times each day.	0	1	2	3	NA
6. I can hold onto my pee by crossing my legs, squatting or doing the "pee dance."	0	1	2	3	NA
7. When I have to pee, I cannot wait.	0	1	2	3	NA
8. I have to push to pee.	0	1	2	3	NA
9. When I pee it hurts.	0	1	2	3	NA
10. Parents to answer. Has your child experienced something stressful like the example below?	No (0)			Yes (3)	
Total*					

- New baby.
- New home.
- New school.
- School problems.
- Abuse (sexual/physical).
- Home problems (divorce/death).
- Special events (birthday).
- Accident/injury.
- Others.

*Females with a score ≥6 and males with a score ≥9 are most likely to have dysfunctional voiding.

Figure 543-1 Dysfunctional Voiding Symptom Score questionnaire. *(From Farhat W, Bagli DJ, Capolicchio G, et al: The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children,* J Urol *164:1011–1015, 2000.)*

Table 545-3 Differential Diagnosis of Scrotal Swelling in Newborn Boys

Hydrocele	Scrotal hematoma
Inguinal hernia (reducible)	Testicular tumor
Inguinal hernia (incarcerated)*	Meconium peritonitis
Testicular torsion*	Epididymitis*

Table 546-1 Grading of Renal Injuries

GRADE	DESCRIPTION
1	Renal contusion or subcapsular hematoma
2	Nonexpanding perirenal hematoma, <1 cm parenchymal laceration, no urinary extravasation; all renal fragments viable; confined to renal retroperitoneum
3	Nonexpanding perirenal hematoma, >1 cm parenchymal laceration, no urinary extravasation; renal fragments may be viable or devitalized
4	Laceration extending into the collecting system with urinary extravasation; renal fragments may be vital or devitalized *or* Injury to the main renal vasculature with contained hemorrhage
5	Completely shattered kidney; by definition multiple major lacerations >1 cm associated with multiple devitalized fragments *or* Injury to the main renal vasculature with uncontrolled hemorrhage, renal hilar avulsion

Table 543-2 Nocturnal Enuresis

CAUSES
- Delayed maturation of the cortical mechanisms that allow voluntary control of the micturition reflex
- Defective sleep arousal
- Reduced antidiuretic hormone production at night, resulting in an increased urine output (nocturnal polyuria)
- Genetic factors, with chromosomes 12 and 13q the likely sites of the gene for enuresis
- Bladder factors (lack of inhibition, reduced capacity, overactive)
- Constipation
- Organic factors, such as urinary tract infection or obstructive uropathy
- Sleep disorders
- Sleep disordered breathing secondary to enlarged adenoids
- Psychologic factors more often implicated in secondary enuresis

OTHER FEATURES
- Enuresis can occur in any stage of sleep (but usually non–rapid eye movement sleep)
- All children are most difficult to arouse in the first third of the night and easiest to awaken in the last third, but enuretic children are more difficult to arouse than those with normal bladder control
- Enuretic children often are described as "soaking the bed"
- Family history in enuretic children often positive for enuresis
- Risk increased with developmental delay, attention-deficit/hyperactivity disorder, autism spectrum disorders

Table 547-1 Classification of Urolithiasis

CALCIUM STONES (CALCIUM OXALATE AND CALCIUM PHOSPHATE)*
Hypercalciuria
Absorptive: increased Ca absorption from gut; types I and II
Renal leak: decreased tubular reabsorption of Ca
Resorptive
Primary hyperparathyroidism (rare in children)
Iatrogenic
Loop diuretics
Ketogenic diet
Corticosteroids
Adrenocorticotropic hormone administration
Methylxanthines (theophylline, aminophylline)
Distal renal tubular acidosis, type 1 (calcium phosphate)
Hypocitraturia—citrate most important inhibitor of Ca crystallization
Vitamin D excess
Immobilization
Sarcoidosis
Cushing disease
Hyperuricosuria
Heterozygous cystinuria
Hyperoxaluria (calcium oxalate)
Primary hyperoxaluria, types 1 and 2
Secondary hyperoxaluria
Enteric hyperoxaluria
CYSTINE STONES
Cystinuria
STRUVITE STONES (MAGNESIUM AMMONIUM PHOSPHATE)
Urinary tract infection (urea-splitting organism)
Foreign body
Urinary stasis
URIC ACID STONES
Hyperuricosuria
Lesch-Nyhan syndrome
Myeloproliferative disorders
After chemotherapy
Inflammatory bowel disease
INDINAVIR STONES
MELAMINE
NEPHROCALCINOSIS

Table 547-2 Laboratory Tests Suggested for Evaluation of Urolithiasis

SERUM	URINE
Calcium	Urinalysis
Phosphorus	Urine culture
Uric acid	Calcium : creatinine ratio
Electrolytes and anion gap	Spot test for cystinuria
Creatinine	24 hr collection for:
Alkaline phosphatase	Creatinine clearance
	Calcium
	Phosphate
	Oxalate
	Uric acid
	Dibasic amino acids (if cystine spot test result is positive)

Table 545-2 Differential Diagnosis of Scrotal Masses in Boys and Adolescents

PAINFUL	PAINLESS
Testicular torsion	Hydrocele
Torsion of appendix testis	Inguinal hernia*
Epididymitis	Varicocele*
Trauma: ruptured testis, hematocele	Spermatocele*
	Testicular tumor*
Inguinal hernia (incarcerated)	Henoch-Schönlein purpura*
Mumps orchitis	Idiopathic scrotal edema
Testicular vasculitis	

*May be associated with discomfort.

Table 545-1 American Urological Association Guidelines for Evaluation and Treatment of Boys with an Undescended Testis

DIAGNOSIS
Primary care providers should palpate testes for quality and position at each recommended well-child visit. (Standard)
Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by 6 mo (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. (Standard)
Providers should refer boys with the possibility of newly diagnosed (acquired) cryptorchidism after 6 mo. (Standard)
Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD). (Standard)
Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of boys with cryptorchidism before referral because these studies rarely assist in decision making. (Standard)
Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. (Recommendation)
In boys with retractile testes, providers should monitor the position of the testes at least annually to monitor for secondary ascent. (Standard)
TREATMENT
Providers should not use hormonal therapy to induce testicular descent, since evidence shows low response rates and lack of evidence for long-term efficacy. (Standard)
In the absence of spontaneous testicular descent by 6 mo (corrected for gestational age), specialists should perform surgery within the next year. (Standard)
In prepubertal boys with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchidopexy should be performed. (Standard)
In boys with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a boy has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age. (Clinical Principle)
Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. (Clinical Principle)

Adapted from Kolon TF, Herndon CDA, Baker LA, et al: Evaluation and treatment of cryptorchidism: AUA Guideline. http://www.auanet.org/common/pdf/education/clinical-guidance/Cryptorchidism.pdf

URINE CONSTITUENT	AGE	RANDOM	TIMED	COMMENTS
Calcium	0-6 mo 7-12 mo ≥2 yr	<0.8 mg/mg creat <0.6 mg/mg creat <0.21 mg/mg creat	<4 mg/kg/24 hr	Prandial variation Sodium-dependent
Oxalate*	<1 yr 1-<5 yr 5-12 yr >12 yr	0.15-0.26 mmol/mmol creat 0.11-0.12 mmol/mmol creat 0.006-0.15 mmol/mmol creat 0.002-0.083 mmol/mmol creat	≥2 yr: <0.5 mmol/1.73 m^2/24 hr	Random urine mmol/mmol highly age-dependent Excretion rate/1.73 m^2 constant through childhood and adulthood
Uric acid	Term infant >3 yr	3.3 mg/dL GFR† <0.53 mg/dL GFR	<815 mg/1.73 m^2/24 hr	Excretion rate/1.73 m^2 from >1 yr age; constant through childhood
Magnesium	>2 yr	<0.12 mg/mg creat	<88 mg/1.73 m^2/24 hr	Excretion rate/1.73 m^2 constant through childhood
Citrate		>400 mg/g creat		Limited data available for children
Cystine		<75 mg/g creat	<60 mg/1.73 m2/24 hr	Cystine >250 mg/g creat suggests homozygous cystinuria

*Oxalate oxidase assay.
†(mg/dL uric acid) (serum creatinine concentration/urine creatinine concentration).
creat, Creatinine; GFR, glomerular filtration rate.
From Milliner DS: Urolithiasis. In Avner ED, Harmon WE, Naiudet P, editors: Pediatric nephrology, *ed 5, Philadelphia, 2004, Lippincott Williams & Wilkins, p. 1103, with permission.*

Table 547-4 Metabolic Evaluation of Children with Hypercalciuria

TYPE	SERUM CALCIUM	RESTRICTED CALCIUM (URINE)	FASTING CALCIUM (URINE)	CALCIUM LOAD (URINE)	PARATHYROID HORMONE (SERUM)
Absorptive	N	N or I	N	I	I
Renal	N	I	I	I	N
Resorptive	I	I	I	I	I

I, increased; N, normal.

Table 547-5 Primary Surgical Treatment Options vs Stone Size and Location

STONES	SHOCK WAVE LITHOTRIPSY	URETEROSCOPY	PERCUTANEOUS NEPHROLITHOTOMY
RENAL			
<1 cm	Most common	Optional	Optional
1-2 cm	Most common	Optional	Optional
>2 cm	Optional	Rare	Most common
LOWER POLE			
<1 cm	Most common	Optional	Optional
>1 cm	Optional	Optional	Most common
URETERAL			
Proximal	Most common	Optional	Occasional
Distal	Optional	Most common	Rare

Table 548-1 Suggested Indications for Pelvic Examination in Adolescents

Age 21 yr for initial Pap test
Unexplained menstrual irregularities, including pubertal aberrations
Severe dysmenorrhea
Unexplained abdominal pain
Unexplained dysuria
Abnormal vaginal discharge
Placement of intrauterine device
Removal of foreign body

Modified from The initial reproductive visit. Committee Opinion No. 460. American College of Obstetricians and Gynecologists. Obstet Gynecol *116:240–243, 2010.*

Table 548-2 Recommendations for First Gynecologic Evaluation

Between 13 and 15 yr of age
First gynecologic encounter focuses on patient education; pelvic examination is generally not indicated
First pelvic examination with Pap test at 21 yr of age, unless otherwise indicated by Table 548-1

Table 547-6 Suggested Therapy for Urolithiasis Caused by Metabolic Abnormalities

METABOLIC ABNORMALITY	INITIAL TREATMENT	SECOND-LINE TREATMENT
Hypercalciuria	Reduction of dietary Na+ Dietary calcium at RDA Thiazides	Potassium citrate Neutral phosphate
Hyperoxaluria	Adjustment of dietary oxalate Potassium citrate	Neutral phosphate* Magnesium Pyridoxine*
Hypocitric aciduria	Potassium citrate Bicarbonate	
Hyperuricosuria	Alkalinization	Allopurinol
Cystinuria	Alkalinization Reduction of dietary Na+	Tiopronin (Thiola) D-Penicillamine Captopril

*Initial therapy in primary hyperoxaluria.

Gynecologic Problems of Childhood

Table 549-1 Specific Vulvar Disorders in Children

ORGANISM	PRESENTATION	DIAGNOSIS	TREATMENT
Molluscum contagiosum (Fig. 549-7)	1-5 mm discrete, skin-colored, dome-shaped, umbilicated lesions with a central cheesy plug	Diagnosis usually is made by visual inspection	The disease generally is self-limited and the lesions can resolve spontaneously Treatment choices in children may include cryosurgery, laser, application of topical anesthetic and curettage, podophyllotoxin, and topical silver nitrate Use of topical 5% imiquimod cream and 10% potassium hydroxide has been reported with similar effects
Condyloma acuminata	Skin-colored papules, some with a shaggy, cauliflower-like appearance	Diagnosis usually is made by visual inspection. Biopsy should be reserved for when the diagnosis is in question. Human papillomavirus DNA testing is not helpful	Many lesions in children resolve spontaneously, "wait and see" often utilized in children (60 days). Topical treatment with imiquimod cream and podophyllotoxin is the most studied (daily qhs 3 times/wk × 16 wk, wash 6-10 hr after application). General anesthesia is usually required for surgical/ablative procedures (cryotherapy, laser therapy, electrocautery)–reserve for symptomatic or large lesions. Other treatments have been utilized in adults, including trichloroacetic acid, 5-fluorouracil, sinecatechins, topical cidofovir, and cimetidine. The efficacy and safety of these treatments in children has not been established
Herpes simplex	Blisters that break, leaving tender ulcers	Visual inspection confirmed by culture from lesion	*Infants:* Acyclovir 20 mg/kg body weight IV q8 hr × 21 days for disseminated and central nervous system disease or × 14 days for disease limited to the skin and mucous membranes *Genital/mucocutaneous disease:* Age 3 mo–2 yr: 15 mg/kg/day IV divided in q8h × 5-7 days Age 2-12 yr (1st episode): Same as above or 1,200 mg/day divided in q8h dosing × 7-10 days Age 2-12 yr (Reoccurrence): 1,200 mg/day in q8h dosing or 1,600 mg/day in bid dosing × 5 days (give 3-5 days for children older than 12 yr)

Table 552-4 Causes of Hirsutism

PERIPHERAL
Idiopathic
Partial androgen insensitivity (5α-reductase deficiency)
HAIR-AN syndrome (*h*irsutism, *a*ndrogenization, *i*nsulin *r*esistance, and *a*canthosis *n*igricans)
Hyperprolactinemia
GONADAL
Polycystic ovary syndrome (polycystic ovaries, chronic anovulation)
Ovarian neoplasm (Sertoli-Leydig cell, granulosa cell, thecoma, gynandroblastoma, lipoid cell, luteoma, hypernephroma, Brenner tumor)
Gonadal dysgenesis (Turner mosaic with XY or H-Y antigen–positive)
ADRENAL
Cushing syndrome
Adrenal hyperresponsiveness
Congenital adrenal hyperplasia (classic, cryptic, adult onset)
21-Hydroxylase deficiency
11-Hydroxylase deficiency
3β-Hydroxysteroid deficiency
17β-Hydroxylase deficiency
Adrenal neoplasm (adenoma, cortical carcinoma)
EXOGENOUS
Minoxidil
Dilantin
Cyclosporine
Anabolic steroids
Acetazolamide (Diamox)
Penicillamine
Oral contraceptives with androgenic progestins
Danazol
Androgenic steroids
Psoralens
Hydrochlorothiazide
Phenothiazines
CONGENITAL ANOMALIES
Trisomy 18 (Edwards syndrome)
Cornelia de Lange syndrome
Hurler syndrome
Juvenile hypothyroidism

Table 549-1 Specific Vulvar Disorders in Children—cont'd

ORGANISM	PRESENTATION	DIAGNOSIS	TREATMENT
Labial agglutination (see Fig. 549-1)	May be asymptomatic or can cause vulvitis, urinary dribbling, urinary tract infection, or urethritis	Diagnosis is made by visual inspection of the adherent labia, often with a central semitranslucent line	Does not require treatment if the patient is asymptomatic *Symptomatic patients:* Topical estrogen cream or betamethasone ointment applied alone or in combination daily for 6 wk directly to the line of adhesion, using a cotton swab while applying gentle labial traction Estrogen should be interrupted if breast budding occurs Mechanical or surgical separation of the adhesions is rarely indicated The adhesions usually resolve in 6-12 wk; unless good hygiene measures are followed, reoccurrence is common To decrease the risk of recurrence, an emollient (petroleum jelly, A and D ointment) should be applied to the inner labia for 1 mo or longer at bedtime
Lichen sclerosus (Fig. 549-4)	A sclerotic, atrophic, parchment-like plaque with an hourglass or keyhole appearance of vulvar, perianal, or perineal skin, subepithelial hemorrhages may be misinterpreted as sexual abuse or trauma The patient can experience perineal itching, soreness, or dysuria	Diagnosis usually is made by visual inspection Biopsy should be reserved for when the diagnosis is in question	Ultrapotent topical corticosteroids are the first-line therapy (clobetasol propionate ointment 0.05%) once or twice a day for 4-8 wk Once symptoms are under control, the patient should be tapered off the drug unless therapy is required for a flare-up In many girls, the condition resolves with puberty; however, this is not always the case and patients may require long-term follow-up
Psoriasis	Children are more likely than adults to have vulvar psoriasis noted as pruritic, well-demarcated, nonscaly, brightly erythematous, symmetrical plaques. The classic extragenital lesion are similar but with a silver scaly appearance	Diagnosis may be confirmed by locating other affected areas on the scalp or in nasolabial folds or behind the ears	Vulvar lesions may be treated with low to medium potency topical corticosteroids, increasing strength as necessary
Atopic dermatitis	Chronic cases can result in crusty, weepy lesions that are accompanied by intense pruritus and erythema Scratching often results in excoriation of the lesions and secondary bacterial or candidal infection	It may be seen in the vulvar area but characteristically affects the face, neck, chest, and extremities	Children with this condition should avoid common irritants and use topical corticosteroids (such as 1% hydrocortisone) for flare-ups If dry skin is present, lotion or bath oil can be used to seal in moisture after bathing
Contact dermatitis	Erythematous, edematous, or weepy vulvar vesicles or pustules can result, but more often the skin appears inflamed	Associated with exposure to an irritant, such as perfumed soaps, bubble bath, talcum powder, lotions, elastic bands of undergarments, or disposable diaper components	Avoidance of irritant Topical corticosteroids for flare-ups
Seborrheic dermatitis	Erythematous and greasy, yellowish scaling on vulva and labial crural folds associated with greasy dandruff-type rash of scalp, behind ears and face	Diagnosis usually is made by visual inspection	Gentle cleaning, topical clotrimazole with 1% hydrocortisone added
Vitiligo (Fig. 549-5)	Sharply demarcated hypopigmented patches, often symmetric in vaginal and anal regions. May be present in periphery at body orifices and extensor surfaces	Clinical. Test for associated illness if clinically warranted (thyroid disease, Addison disease, pernicious anemia, diabetes mellitus)	If desired, treat limited lesions with low-potency corticosteroids or tacrolimus. See dermatologist for extensive lesions.

Table 549-2 Antibiotic Recommendations for Specific Vulvovaginal Infections

ETIOLOGY	TREATMENT
Streptococcus pyogenes *Streptococcus pneumoniae*	Penicillin V, 250 mg PO bid-tid ×10 days Amoxicillin 50 mg/kg/day (max: 500 mg/dose) divided into 3 doses daily × 10 days Erythromycin ethyl succinate, 30-50 mg/kg/day (max: 400 mg/dose) divided into 4 doses daily TMP-SMX 6-10 mg/kg/day (TMP component) divided into 2 doses daily × 10 days Clarithromycin 7.5 mg/kg bid (max: 1 g/day) × 5-10 days Reoccurrence most likely from asymptomatic pharyngeal carriage in child or family member. However, failure of penicillin regimens can occur For penicillin resistance: Rifampin 10 mg/kg every 12 hr × 2 days
Staphylococcus aureus	Topical mupirocin 2% 3 times daily to the affected skin area If systemic therapy required: Amoxicillin-clavulanate, 45 mg/kg/day (amoxicillin) PO divided into 2 or 3 doses daily × 7 days (first-line treatment because of high penicillin resistance) Extensive resistance to common antibiotics noted, recommend susceptibility testing for further antibiotic use MRSA: TMP-SMX double-strength 8-10 mg/kg/day; culture abscesses, incision and drainage
Haemophilus influenzae	Amoxicillin, 40 mg/kg/day divided into 3 doses daily × 7 days Cases of treatment failure or non-encapsulated *H. influenzae*, amoxicillin–clavulanate is recommended
Yersinia	TMP-SMX 6 mg/kg (TMP component) daily for 3 days
Shigella	TMP-SMX 10/50 mg/kg/day (max: 160/600) divided into 2 doses daily × 5 days Ampicillin 50-100 mg/kg/day divided into 4 doses daily (adult max: 4 g/day) × 5 days Azithromycin 12 mg/kg (max: 500) × 1 day, then 6 mg/kg/day (max: 250 mg) × 4 days (in areas of high resistance to above regimens or when sensitivities are unknown) For resistant organisms: Ceftriaxone 50-75 mg/kg/day IV or IM divided into 1 or 2 doses (max: 2 g/day) × 2-5 days
Chlamydia trachomatis	*Children weighing <45 kg:* Erythromycin base or ethylsuccinate 50 mg/kg/day PO divided into 4 daily doses × 14 days *Children weighing >45 kg but age younger than 8 yr:* azithromycin 1 g PO in a single dose *Children age older than 8 yr (treat per adult regimens):* *Preferred regimens:* Azithromycin 1 g PO in a single dose *or* Doxycycline 100 mg PO twice daily × 7 days *Alternative regimens:* Erythromycin base 500 mg PO 4 times daily × 7 days Erythromycin ethylsuccinate 800 mg PO 4 times daily × 7 days Levofloxacin 500 mg PO daily × 7 days Ofloxacin 300 mg PO twice daily for 7 days
Neisseria gonorrhoeae	*Children weighing <45 kg:* Ceftriaxone, 125 mg IM in a single dose *Children weighing ≥45 kg:* Treat with adult regimen of 250 mg IM in a single dose *Children with bacteremia or arthritis:* Ceftriaxone, 50 mg/kg (max dose for children weighing <45 kg: 1 g) IM or IV in a single dose daily × 7 days *Dual treatment:* Addition of either azithromycin 1 g PO in a single dose or doxycycline 100 mg PO twice daily × 7 days to the above regimens may assist in hindering the development of antibiotic resistance. *Note:* The CDC removed cefixime 400 mg PO in a single dose from recommended medications because of increasing resistance; however, can be used as part of a dual therapy if ceftriaxone is unavailable
Trichomonas	Metronidazole, 15-30 mg/kg/day tid (max: 250 mg tid) × 5-7 days *or* Tinidazole 50 mg/kg (≤2 g) as a single dose for children older than 3 yr
Pinworms (*Enterobius vermicularis*)	Mebendazole (Vermox), 1 chewable 100 mg tablet, repeated in 2 wk *or* Albendazole, 100 mg for child younger than age 2 yr or 400 mg for older child, repeated in 2 wk Pyrantel pamoate 10 mg/kg in a single administration

MRSA, methicillin-resistant *Staphylococcus aureus;* TMP-SMX, trimethoprim-sulfamethoxazole.

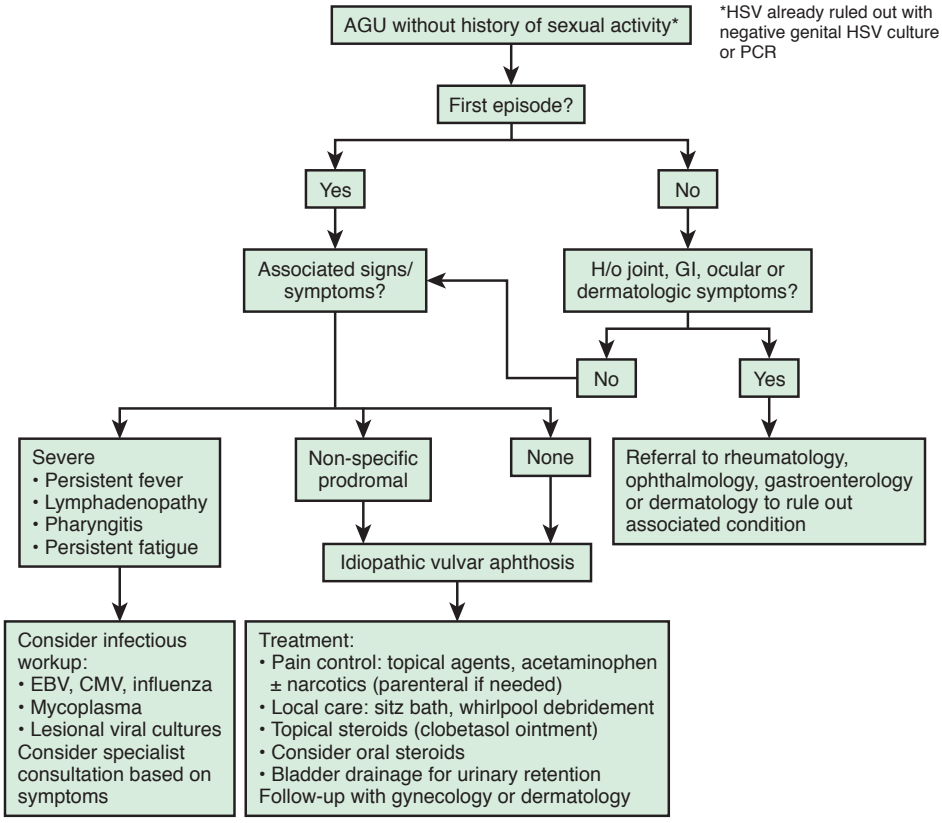

Figure 549-3 Algorithm for evaluation and management of acute genital ulcers in nonsexually active young girls. *(From Rosman IS, Berk DR, Bayliss SJ, et al: Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations.* Pediatr Dermatol *29(2);147–153, 2012.)*

Table 551-2 Common Causes of Nipple Discharge

Pregnancy
Medicines
Hormones (oral contraceptives, estrogen, progesterone)
Blood pressure drugs (methyldopa, verapamil)
Tricyclic antidepressants
Tranquilizers (antipsychotics)
Antinausea drugs (metoclopramide)
Herbs (nettle, fennel, blessed thistle, anise, fenugreek seed)
Illicit drugs (marijuana, opiates)
Stimulation of the breast (sexual or from exercise)
Thyroid abnormalities
Chronic emotional stress
Hypothalamic tumors
Chest wall conditions
Herpes zoster
Trauma
Burns
Tumors
Breast conditions
Mammary duct ectasia
Chronic cystic mastitis
Intraductal cysts
Intraductal papillomas

Table 551-3 Breast Masses in the Adolescent Girl

BENIGN
Fibroadenoma
Fibrocystic changes or cysts
Unilateral thelarche
Hemangioma
Intramammary lymph node
Fat necrosis
Abscess
Mastitis
Lipoma
Hematoma
Hamartoma
Macromastia (juvenile hypertrophy)
Galactocele
Intraductal papilloma
Juvenile papillomatosis
Lymphangioma
MALIGNANT
Malignant cystosarcoma phyllodes
Breast carcinoma
Metastatic disease
Lymphoma, neuroblastoma, sarcoma, rhabdomyosarcoma, acute leukemia

Table 553-2 Malignant Ovarian Tumors in Children and Adolescents

TUMOR	OVERALL 5-YR SURVIVAL	CLINICAL FEATURES
GERM CELL TUMORS		
Dysgerminoma	85%	10-20% bilateral Most common ovarian malignancy Gonadal dysgenesis/androgen insensitivity Sensitive to chemotherapy/radiation
Immature teratoma	97-100%	All 3 germ layers present
Endodermal sinus tumor	80%	Almost always large (>15 cm) Schiller-Duval bodies
Choriocarcinoma	30%	Rare Can mimic ectopic pregnancy
Embryonal carcinoma	25%	Endocrinologic symptoms (precocious puberty) Highly malignant
Gonadoblastoma	100%	Primary amenorrhea Virilization 45,X or 45,X/46,XY mosaicism
SEX CORD STROMAL TUMORS		
Juvenile granulosa stroma cell tumor	92%	Produce estrogen Menstrual irregularities Isosexual precious pseudopuberty Call-Exner bodies rare
Sertoli-Leydig cell tumor	70-90%	Virilization in 40% Produce testosterone
Lipoid cell tumors	~80%	Rare heterogenous group with lipid-filled parenchyma
Gynandroblastoma	90% or greater	Rare low-grade mixed tumors that produce either estrogen or androgen

Table 553-3 Serum Tumor Markers

TUMOR	CA-125	AFP	hCG	LDH	E2	T	INHIBIN	MIS	VEGF	DHEA
Epithelial tumor	+									
Immature teratoma	+	+			+					+
Dysgerminoma			+	+	+					
Endodermal sinus tumor		+								
Embryonal carcinoma		+	+		+					
Choriocarcinoma			+							
Mixed germ cell		+	+	+						
Granulosa cell tumor	+				+		+	+		
Sertoli-Leydig						+	+			
Gonadoblastoma					+	+	+			+
Theca-fibroma									+	

AFP, α-fetoprotein; CA-125, cancer antigen 125; DHEA, dehydroepiandrostenedione; E2, estradiol; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; T, testosterone, MIS, müllerian inhibiting substance; VEGF, vascular endothelial growth factor.

Table 554-1 Common Müllerian Anomalies

ANOMALY	DESCRIPTION
Hydrocolpos	Accumulation of mucus or nonsanguineous fluid in the vagina
Hemihematometra	Atretic segment of vagina with menstrual fluid accumulation
Hydrosalpinx	Accumulation of serous fluid in the fallopian tube, often an end result of pyosalpinx
Didelphic uterus	Two cervices, each associated with 1 uterine horn
Bicornuate uterus	One cervix associated with 2 uterine horns
Unicornuate uterus	Result of failure of 1 müllerian duct to descend

Table 555-1 Health Consequences of Female Genital Mutilation

IMMEDIATE RISKS Pain, shock (caused by pain or hemorrhage, or both), excessive bleeding, difficulty passing urine or feces, infection (including tetanus inoculation and the transmission of bloodborne viruses such as HIV, hepatitis B, and hepatitis C), psychologic consequences (as a result of pain, shock, or physical restraint), unintended labial fusion, death (caused by hemorrhage or infection).
LONG-TERM RISKS Pain (chronic neuropathic pain), keloid scarring, infections (including chronic pelvic infections, recurrent urinary tract infections, and an increased incidence of certain genital infections), birth complications (cesarean section, postpartum hemorrhage, and episiotomy), danger to the newborn (including death), decreased quality of sexual life, psychologic consequences (including posttraumatic stress disorder, depression, and anxiety)
LONG-TERM RISKS PARTICULAR TO TYPE 3 FEMALE GENITAL MUTILATION Need for later surgery (deinfibulation), urinary and menstrual problems, painful sexual intercourse, and infertility

From Simpson J, Robinson K, Creighton SM, Hodes D: Female genital mutilation: the role of health professionals in prevention, assessment, and management. BMJ *344:e1361, 2012, Box 3.*

The Endocrine System

Table 557-4 Proposed Classification of Growth Hormone Insensitivity

Primary GH insensitivity (hereditary defects)
- GH receptor defect (may be positive or negative for GH-binding protein)
  - Extracellular mutation (e.g., Laron syndrome)
  - Cytoplasmic mutation
  - Intracellular mutation
- GH signal transduction defects (distal to cytoplasmic domain of GH receptor)
  - Stat5b mutations
- Insulin-like growth factor-1 defects
  - IGF-1 gene deletion
  - IGF-1 transport defect (ALS mutation)
  - IGF-1 receptor defect
- Bioinactive GH molecule (responds to exogenous GH)

Secondary GH insensitivity (acquired defects)
- Circulating antibodies to GH that inhibit GH action
- Antibodies to the GH receptor
- GH insensitivity caused by malnutrition, liver disease, catabolic states, diabetes mellitus
- Other conditions that cause GH insensitivity

GH insensitivity: Clinical and biochemical features of IGF-1 deficiency and insensitivity to exogenous GH, associated with GH secretion that would not be considered abnormally low.

GH insensitivity syndrome: GH insensitivity associated with the recognizable dysmorphic features described by Laron.

Partial GH insensitivity: GH insensitivity in the absence of dysmorphic features described by Laron.

ALS, acid labile subunit; GH, growth hormone; IGF, insulin-like growth factor.

From Sperling MA: Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Box 10-4, p. 347.*

Table 557-5 Causes of Acquired Hypopituitarism

BRAIN DAMAGE*
Traumatic brain injury
Subarachnoid hemorrhage
Neurosurgery
Irradiation
Stroke

PITUITARY TUMORS*
Adenomas
Others

NONPITUITARY TUMORS
Craniopharyngiomas
Meningiomas
Gliomas
Chordomas
Ependymomas
Metastases

INFECTION
Abscess
Hypophysitis
Meningitis
Encephalitis

INFARCTION
Apoplexy
Sheehan syndrome

AUTOIMMUNE DISORDER
Lymphocytic hypophysitis

OTHER
Hemochromatosis, granulomatous diseases, histiocytosis
Empty sella
Perinatal insults

*Pituitary tumors are classically the most common cause of hypopituitarism. However, new findings imply that causes related to brain damage might outnumber pituitary adenomas in causing hypopituitarism.

From Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, et al: Hypopituitarism, Lancet *369:1461–1470, 2007.*

Table 556-1 Hormones of the Hypothalamus and Pituitary Gland

HORMONES	LOCATION	S/I	FUNCTION
ACTH	Anterior pituitary	S	Production and secretion of GCs, MCs, and androgens from adrenal gland
ADH	Posterior pituitary	S	Reabsorption of water into the bloodstream via renal collecting ducts
CRH	Hypothalamus	S	Secretion of ACTH
Dopamine	Hypothalamus	S	Secretion of PRL
FSH (females)	Anterior pituitary	I	Secretion of estrogen from ovary
FSH (males)	Anterior pituitary	S	Production of sperm from testis
GH	Anterior pituitary	S	Secretion of IGF-1
GHRH	Hypothalamus	S	Secretion of GH
Ghrelin	Hypothalamus	S	Secretion of GH
GnRH	Hypothalamus	S	Secretion of FSH and LH
LH (females)	Anterior pituitary	S	Ovulation and development of the corpus luteum
LH (males)	Anterior pituitary	S	Production and secretion of testosterone
Oxytocin	Posterior pituitary	S	Contractions of uterus at birth and release of milk from breast
PRL	Anterior pituitary	S	Promotion of milk synthesis
Somatostatin	Hypothalamus	I	Secretion of GH and TSH
TRH	Hypothalamus	S	Secretion of TSH and PRL
TSH	Anterior pituitary	S	Secretion of T_4 and T_3

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GC, glucocorticoids; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-derived growth factor 1; LH, luteinizing hormone; MC, mineralocorticoids; PRL, prolactin; S/I, stimulate/inhibit; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin).

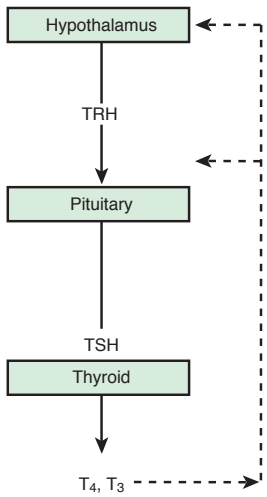

Figure 556-1 Hypothalamic–pituitary–thyroid (HPT) axis. Thyroid-releasing hormone (TRH) from the hypothalamus stimulates the pituitary gland to secrete thyroid-stimulating hormone (TSH). TSH stimulates the thyroid gland to produce and secrete thyroid hormones (T_4 and T_3). High circulating levels of T_3 and T_4 inhibit further TRH and TSH secretion and thyroid hormone production through a negative feedback mechanism *(dashed lines)*. T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin); <---, inhibits; ←, stimulates.

Table 557-7	Evaluation of Suspected Growth Hormone Deficiency
Growth-related history and patient physical exam	• Infants and children with GHD have growth failure • Short stature and growth failure may be the only clinical features present • GHD affects ~1 in 3,500 children
Imaging and other evaluations	• Diagnosis is based on clinical, auxologic, and biochemical parameters • Radiologic evaluation of bone age • Central nervous system MRI or CT scan to evaluate the hypothalamic-pituitary region and to exclude other conditions • Evaluation and management by a pediatric endocrinologist
Laboratory evaluation	• Measurements of GH, IGF-1, and IGF-1–binding protein levels • Determination of peak GH levels after stimulation test
Special testing (if applicable)	• Family history and genetic analyses (e.g., search for *PROP1* and *POU1F1* mutations)
Rationale for treatment and treatment modalities	• Replacement therapy with rhGH (GHT) • Predictors of greater benefit with GHT in GHD include early initiation of treatment, higher rhGH dose, and IGF-1–guided dosing • GHT should be started as soon as GHD is diagnosed

GH, growth hormone; GHD, growth hormone deficiency; GHT, growth hormone therapy; IGF, insulin-like growth factor; *POU1F1*, POU class 1 homeobox 1; *PROP1*, homeobox protein prophet of Pit1; rhGH, human recombinant growth hormone.

From Rogol AD, Hayden GF: Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Pediatr 164(5):S1–S14, 2014, Table XIII, p. S10.

Table 558-1	Differential Diagnosis of Polyuria and Polydipsia
Diabetes insipidus (DI)	
• Central DI	
Genetic (autosomal dominant)	
Acquired	
Trauma (surgical or accidental)	
Congenital malformations (holoprosencephaly, septooptic dysplasia, encephalocele)	
Neoplasms (craniopharyngioma, germinoma, metastasis)	
Infiltrative (Langerhans cell histiocytosis), autoimmune (lymphocytic infundibuloneurohypophysitis), and infectious diseases	
Drugs (chemotherapy)	
Idiopathic	
• Nephrogenic DI	
Genetic (X-linked, autosomal recessive, autosomal dominant)	
Acquired	
Hypercalcemia, hypokalemia	
Drugs (lithium, demeclocycline)	
Kidney disease	
Primary polydipsia	
Sickle cell anemia	
• Diabetes mellitus	

Figure 558-1 Regulation of vasopressin (VP) secretion and serum osmolality. Hyperosmolality, hypovolemia, and hypotension are sensed by osmosensors, volume sensors, and barosensors, respectively. These stimulate both VP secretion and thirst. VP, acting on the kidney, causes increased reabsorption of water (antidiuresis). Thirst causes increased water ingestion. The results of these dual negative feedback loops cause a reduction in hyperosmolality or in hypotension or hypovolemia. Additional stimuli for VP secretion include nausea, hypoglycemia, and pain. *(From Muglia LJ, Majzoub JA: Disorders of the posterior pituitary. In Sperling MA, editor:* Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Fig. 6.)*

Table 557-6	Clinical Features of Growth Hormone Insensitivity
Growth and development	
Birthweight: near-normal	
Birth length: may be slightly decreased	
Postnatal growth: severe growth failure	
Bone age: delayed, but may be advanced relative to height age	
Genitalia: micropenis in childhood; normal for body size in adults	
Puberty: delayed 3-7 yr	
Sexual function and fertility: normal	
Craniofacies	
Hair: sparse before the age of 7 yr	
Forehead: prominent; frontal bossing	
Skull: normal head circumference; craniofacial disproportion due to small facies	
Facies: small	
Nasal bridge: hypoplastic	
Orbits: shallow	
Dentition: delayed eruption	
Sclerae: blue	
Voice: high pitched	
Musculoskeletal/metabolic/miscellaneous	
Hypoglycemia: in infants and children; fasting symptoms in some adults	
Walking and motor milestones: delayed	
Hips: dysplasia; avascular necrosis of femoral head	
Elbow: limited extensibility	
Skin: thin, prematurely aged	
Osteopenia	

From Sperling MA: Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Table 10-5, p. 355.*

Table 559-1	Differential Diagnosis of Hyponatremia	
DISORDER	**INTRAVASCULAR VOLUME STATUS**	**URINE SODIUM**
Systemic dehydration	Low	Low
Decreased effective plasma volume	Low	Low
Primary salt loss (nonrenal)	Low	Low
Primary salt loss (renal)	Low	High
SIADH	High	High
Cerebral salt wasting	Low	Very high
Decreased free water clearance	Normal or high	Normal or high
Primary polydipsia	Normal or high	Normal
Runner's hyponatremia	Low	Low
NSIAD	High	High
Pseudohyponatremia	Normal	Normal
Factitious hyponatremia	Normal	Normal

NSIAD, nephrogenic syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

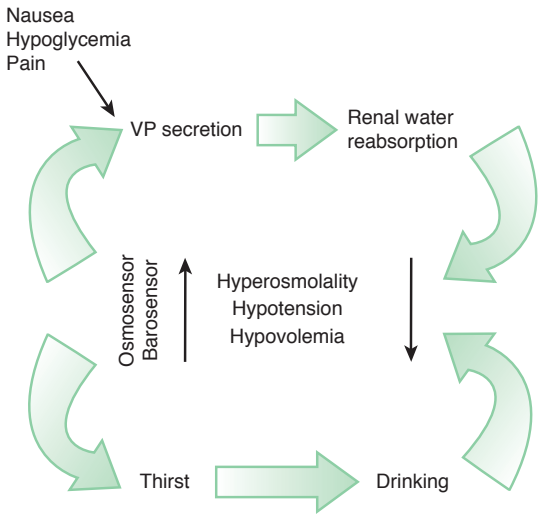

Table 559-2 Clinical Parameters to Distinguish Among SIADH, Cerebral Salt Wasting, and Central Diabetes Insipidus

CLINICAL PARAMETER	SIADH	CEREBRAL SALT WASTING	CENTRAL DI
Serum sodium	Low	Low	High
Urine output	Normal or low	High	High
Urine sodium	High	Very high	Low
Intravascular volume status	Normal or high	Low	Low
Vasopressin level	High	Low	Low

DI, diabetes insipidus; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 559-3 Genetic Mutations Associated with Hypoaldosteronism/Pseudohypoaldosteronism (Type IV Renal Tubular Acidosis)

GENE CHROMOSOME OMIM	PATHOPHYSIOLOGY	MUTATION–CLINICAL MANIFESTATIONS–OMIM–INHERITANCE
PRIMARY HYPOALDOSTERONISM		
CYP21A2—cytochrome P450, subfamily XXIA, polypeptide 2 6p21.3 613815	P450c21—steroid 21-hydroxylase that converts 17 α-hydroxyprogesterone to 11-deoxycortisol and progesterone to 11-deoxycorticosterone in the adrenal zona fasciculata	Loss-of-function mutations decrease synthesis of cortisol and aldosterone, the latter resulting in the salt-losing form of classical congenital adrenal hyperplasia, AR–201910
CYP11B2—cytochrome P450, subfamily XIB, polypeptide 2 8q21 124080	P450c11B2—aldosterone synthase/corticosterone methyoxidase types I and II expressed only in the zona glomerulosa; hydroxylates deoxycorticosterone at carbon-11 and corticosterone at carbon-18 and oxidizes 18-hydroxycorticosterone to aldosterone	Loss-of-function mutations associated with severe salt loss and volume depletion but not with abnormalities of genital formation or glucocorticoid synthesis AR (CMOI 203400; CMOII 610600)
PSEUDOHYPOALDOSTERONISM TYPE I		
NR3C2—nuclear receptor subfamily 3, group C, member 2 (MR-mineralocorticoid receptor), 4q31.1 600983	Ligand-activated nuclear transcription factor that transmits aldosterone-mediated control of gene expression by binding to the mineralocorticoid response element in the promoter region of the target gene	Loss-of-function mutations lead to mineralocorticoid resistance and pseudohypoaldosteronism type I, AD–177735
SCNN1A—sodium channel, non–voltage-gated, α-subunit 12p13.31 600228	Inactivating mutation of α-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
SCNN1B—sodium channel, non–voltage-gated, β-subunit 16p12.2 600760	Inactivating mutation of β-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
SCNN1G—sodium channel, non–voltage-gated, γ-subunit 16p12.2 600761	Inactivating mutation of γ-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
PSEUDOHYPOALDOSTERONISM TYPE II		
WNK4—protein kinase, lysine-deficient 4 17q21.31 601844	Multifunctional serine-threonine protein kinase whose substrate is SLC12A3, the thiazide-sensitive sodium/chloride cotransporter (NCCT)—OMIM 600968—that also regulates lysosomal degradation of NCCT and endocytosis of the KCNJ1 potassium channel	Pseudohypoaldosteronism type IIB, AD–614491
WNK1—protein kinase, lysine-deficient 1 12p13.33 605232	Serine-threonine protein kinase that inactivates WNK4 by phosphorylating its kinase domain	Pseudohypoaldosteronism type IIC, AD–614492
KLH3—Kelch-like 3 5q31.2 605775	Adaptor protein within the ubiquitination sequence that links WNK1 and WNK4 to CUL3	Pseudohypoaldosteronism type IID, AD/AR–614495
CUL3—Cullin 3 2q36.2 603136	Scaffold protein that links to RING-box E3 ligase facilitating WNK4 ubiquitination and proteasomal destruction of WNK4	Pseudohypoaldosteronism type IIE, AD–614496

AD, autosomal dominant; AR, autosomal recessive; CMO, corticosterone methyloxidase; OMIM, Online Mendelian Inheritance in Man.
From Root AW: Disorders of aldosterone synthesis, secretion, and cellular function. Curr Opin Pediatr *26:480–486, 2014, Table 1, p. 483.*

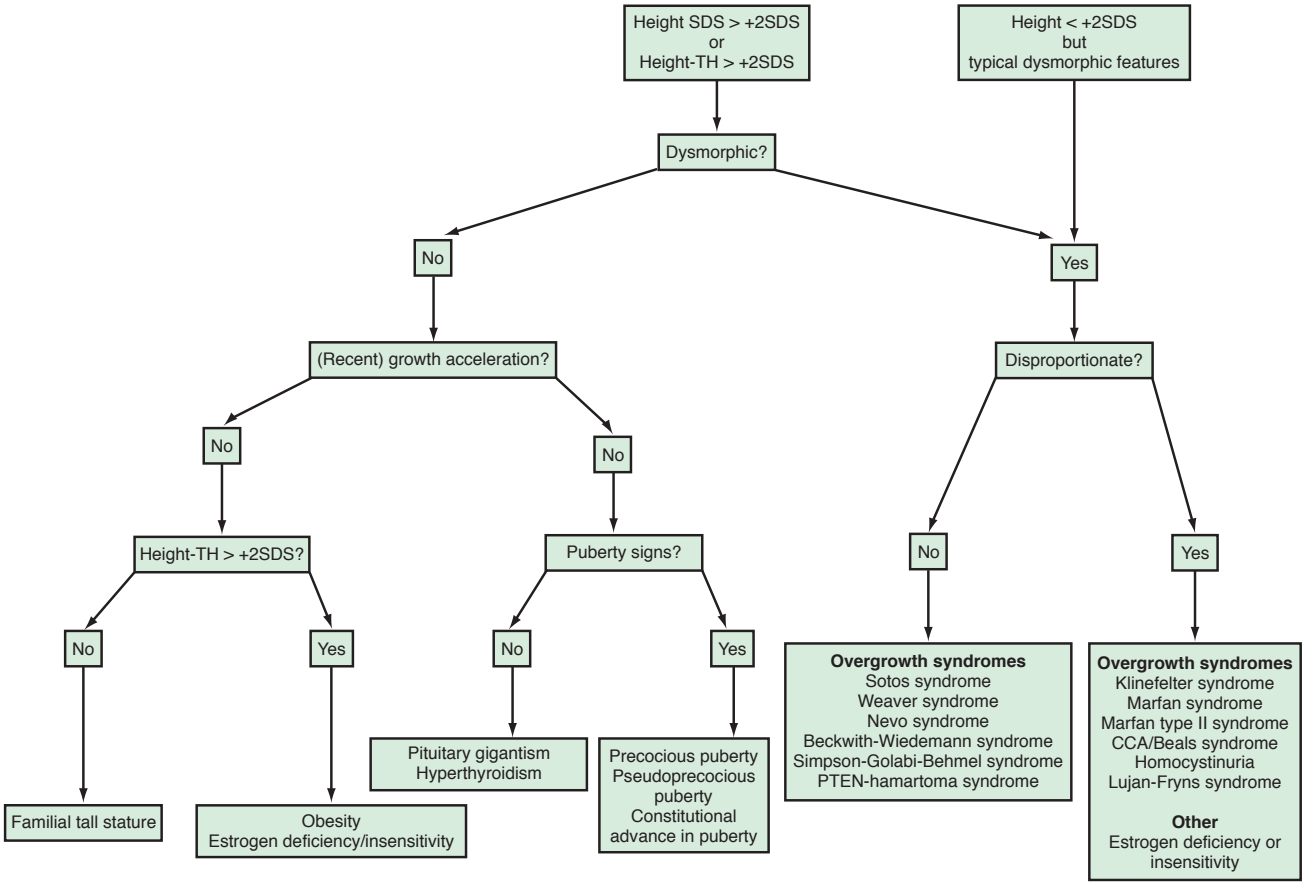

Figure 560-1 Diagnostic flow chart for the differential diagnosis of tall stature and overgrowth syndromes. Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; SDS, standard deviation score. *(From Neylon OM, Werther GA, Sabin MA: Overgrowth syndromes.* Curr Opin Pediatr *24:505–511, 2012, Fig. 1, p. 507.)*

Table 560-1 Differential Diagnosis of Tall Stature and Overgrowth Syndromes

FETAL OVERGROWTH
Maternal diabetes mellitus
Cerebral gigantism (Sotos syndrome)
Weaver syndrome
Beckwith-Wiedemann syndrome
Other IGF-2 excess syndromes
POSTNATAL OVERGROWTH LEADING TO CHILDHOOD TALL STATURE
Nonendocrine Causes
Familial (constitutional) tall stature
Exogenous obesity
Cerebral gigantism (Sotos syndrome)
Weaver syndrome
Marfan syndrome
Fragile X syndrome
Beckwith-Wiedemann syndrome
Klinefelter syndrome (XXY)
SHOX excess syndromes
Homocystinuria
XYY
Endocrine Causes
Excess GH secretion (pituitary gigantism)
McCune-Albright syndrome or MEN associated with excess GH secretion
Precocious puberty
Hyperthyroidism
POSTNATAL OVERGROWTH LEADING TO ADULT TALL STATURE
Familial (constitutional) tall stature
Marfan syndrome
Klinefelter syndrome (XXY)
XYY
Androgen or estrogen deficiency or estrogen resistance
Androgen insensitivity syndrome (testicular feminization)
ACTH or cortisol deficiency or resistance
Excess GH secretion (pituitary gigantism)

Table 564-1 Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

DECREASED TBG	INCREASED TBG
Androgens	Estrogens
Anabolic steroids	Selective estrogen receptor modulators
Glucocorticoids	Pregnancy
Hepatocellular disease	Hepatitis
Severe illness	Porphyria
Protein-losing nephropathies	Heroin, methadone
Protein-losing enteropathies	Mitotane
Nicotinic acid	5-Flurouracil
L-Asparaginase	Perphenazine

Table 560-2 Genetic Overgrowth Syndromes

GENETIC SYNDROMES	CLINICAL FEATURES	INCIDENCE OF MALIGNANCY (%)	ETIOLOGY	INVESTIGATIONS AND MANAGEMENT
Beckwith-Wiedemann syndrome*	Hypoglycemia, large tongue, ear pits, omphalocele or umbilical hernia, hemihyperplasia	~7.5		US heart, kidneys Chromosomes 11p FISH and/or MLPA, methylation studies Tumor surveillance justified
Perlman syndrome*	Macrosomia, unusual facies Nephroblastosis		Rare autosomal recessive	US brain (ACC), heart (coarctation), kidneys
Simpson-Golabi-Behmel syndrome*	Coarse facial features, macroglossia, central groove lower lip, supernumerary nipples	~7.5	X-linked recessive (glypican-3 mutations)	US heart, kidney X-ray spine (vertebral segmentation anomaly) Tumor surveillance justified
Sotos syndrome	Facial gestalt (long, thin face, broad forehead) Feeding difficulties Hypotonia	~4	Usually de novo dominant *NSD1* deletion or mutation Rare familial cases	US heart, kidneys Monitor development
PTEN-hamartoma syndrome (Bannayan-Ruvalcaba-Riley)	Macrocephaly (>97th percentile) often progressive from birth, hypotonia, pigmented skin, penile macules, lipomas	Uncertain	Sporadic or autosomal dominant *PTEN* mutation	US head, heart, and kidney Monitor development
Weaver syndrome	Broad forehead, hypertelorism, small chin, long philtrum, camptodactyly, fetal finger pads	~5-6	Rare, unknown	US heart, brain, kidney
Marfan syndrome type I	Facial gestalt, arachnodactyly, scoliosis, pectus carinatum or excavatum, aortic root dilation, lens dislocation		Autosomal dominant fibrillin-1 *(FBN1)*	Eye examination and follow-up Heart US and cardiology follow-up Monitor scoliosis
Marfan syndrome type II or Loeys-Dietz syndrome	Marfan-like habitus, aortic root dilation, aortic dissection, vasculopathy		Autosomal dominant, TGF-β pathway anomaly *TGFBR1* and *TGFBR2* genes	Eye examination usually normal Heart US and follow-up Monitor scoliosis
Beals syndrome	Congenital distal arthrogryposis Crumpled ears		Autosomal dominant fibrillin 2 *(FBN2)*	Eye examination and heart US usually normal
Homocystinuria	Marfan-like habitus Developmental delay Lens dislocation		Autosomal recessive Cystathionine β-synthase (CBS) mutation	Urine metabolic screen Eye examination Monitor development
Lujan syndrome	Marfanoid habitus plus intellectual disability		X-linked recessive *MED12* gene	Eye examination usually normal Heart US usually normal
Sex chromosome aneuploidy Klinefelter 47XXY, 47XYY, 47XXX	Tall stature, small testes, gynecomastia Tall stature, ± learning disability			Androgen replacement from puberty in Klinefelter syndrome Monitor development
Autosomal anomaly Tetrasomy 12p mosaicism,* pat 11pdup, 4pdub, 22q13del, 15q26-qter dup	Congenital overgrowth or childhood tall stature with intellectual disability			Monitor development

*Overgrowth often presenting at birth.

ACC, agenesis of the corpus callosum; FISH, fluorescence in situ hybridization; MLPA, multiple ligation probe amplification; PTEN, phosphatase and tensin homolog; TGF, transforming growth factor; TGFBR, transforming growth factor β receptor; US, ultrasound.

From Verge CF, Mowat D: Overgrowth, Arch Dis Child *95:458–463, 2010.*

Table 565-1 Etiologic Classification of Congenital Hypothyroidism

PRIMARY HYPOTHYROIDISM
Defect of fetal thyroid development (dysgenesis)
- Aplasia
- Hypoplasia
- Ectopia

Defect in thyroid hormone synthesis (dyshormonogenesis)
- Iodide transport defect from blood into follicular cell: mutation in sodium–iodide symporter gene
- Defective iodide transport from follicular cell into colloid: mutation in Pendrin transport protein
- Thyroid organification, or coupling defect: mutation in thyroid peroxidase gene
- Defects in H_2O_2 generation: mutations in DUOXA2 maturation factor or *DUOX2* gene
- Thyroglobulin synthesis defect: mutation in thyroglobulin gene
- Deiodination defect: mutation in *DEHAL1* gene

TSH unresponsiveness
- Mutation in TSH receptor
- Defective TSH signaling: $G_s\alpha$ mutation (e.g., type IA pseudohypoparathyroidism)

Defect in thyroid hormone transport: mutation in monocarboxylate transporter 8 *(MCT8)* gene
Resistance to thyroid hormone
Maternal antibodies: thyrotropin receptor–blocking antibody (TRBAb, measured as *thyrotropin-binding inhibitor immunoglobulin*)
Iodine deficiency (endemic goiter)
Maternal medications
- Iodides, amiodarone
- Propylthiouracil, methimazole
- Radioiodine

CENTRAL (HYPOPITUITARY) HYPOTHYROIDISM
Isolated TSH deficiency: mutation in TSH β-subunit gene (depending on mutation, TSH may be undetectable, measurable ["normal"], or elevated)
Isolated TRH deficiency: mutation in TRH gene
TRH unresponsiveness: mutation in TRH receptor gene
Multiple congenital pituitary hormone deficiencies (e.g., septooptic dysplasia)
PIT-1 mutations
- Deficiency of TSH
- Deficiency of growth hormone
- Deficiency of prolactin

PROP-1 mutations
- Deficiency of TSH
- Deficiency of growth hormone
- Deficiency of prolactin
- Deficiency of LH
- Deficiency of FSH
- ±Deficiency of ACTH

Table 562-1 Conditions Causing Precocious Puberty

CENTRAL (GONADOTROPIN-DEPENDENT, TRUE PRECOCIOUS) PUBERTY
Idiopathic
Organic brain lesions
Hypothalamic hamartoma
Brain tumors, hydrocephalus, severe head trauma, myelomeningocele
Hypothyroidism, prolonged and untreated*

COMBINED PERIPHERAL AND CENTRAL
Treated congenital adrenal hyperplasia
McCune-Albright syndrome, late
Familial male precocious puberty, late

PERIPHERAL (GONADOTROPIN-INDEPENDENT, PRECOCIOUS) PSEUDOPUBERTY
GIRLS
Isosexual (feminizing) conditions
McCune-Albright syndrome
Autonomous ovarian cysts
Ovarian tumors
Granulosa–theca cell tumor associated with Ollier disease
Teratoma, chorionepithelioma
SCTAT associated with Peutz-Jeghers syndrome
Feminizing adrenocortical tumor
Exogenous estrogens
Heterosexual (masculinizing) conditions
Congenital adrenal hyperplasia
Adrenal tumors
Ovarian tumors
Glucocorticoid receptor defect
Exogenous androgens
BOYS
Isosexual (masculinizing) conditions
Congenital adrenal hyperplasia
Adrenocortical tumor
Leydig cell tumor
Familial male precocious puberty
Isolated
Associated with pseudohypoparathyroidism
hCG-secreting tumors
- Central nervous system
- Hepatoblastoma

Mediastinal tumor associated with Klinefelter syndrome
Teratoma
Glucocorticoid receptor defect
Exogenous androgen
Heterosexual (feminizing) conditions
Feminizing adrenocortical tumor
SCTAT associated with Peutz-Jeghers syndrome
Exogenous estrogens

INCOMPLETE (PARTIAL) PRECOCIOUS PUBERTY
Premature thelarche
Premature adrenarche
Premature menarche

*Central puberty without true gonadotropin dependency (see text).
hCG, human chorionic gonadotropin; SCTAT, sex-cord tumor with annular tubules.

Table 566-1 Characteristics of Thyroiditis Syndromes

CHARACTERISTIC	HASHIMOTO THYROIDITIS	PAINLESS POSTPARTUM THYROIDITIS	PAINLESS SPORADIC THYROIDITIS	PAINFUL SUBACUTE THYROIDITIS	ACUTE SUPPURATIVE THYROIDITIS	RIEDEL THYROIDITIS
Sex ratio (F:M)	4-6:1	—	2:1	5:1	1:1	3-4:1
Cause	Autoimmune	Autoimmune	Autoimmune	Unknown (probably viral)	Infectious (bacterial)	Unknown
Pathologic findings	Lymphocytic infiltration, germinal centers, fibrosis	Lymphocytic infiltration	Lymphocytic infiltration	Giant cells, granulomas	Abscess formation	Dense fibrosis
Thyroid function	Usually euthyroidism; some hypothyroidism	Hyperthyroidism, hypothyroidism, or both	Hyperthyroidism, hypothyroidism, or both	Hyperthyroidism, hypothyroidism, or both	Usually euthyroidism	Usually euthyroidism
TPO antibodies	High titer, persistent	High titer, persistent	High titer, persistent	Low titer, or absent, or transient	Absent	Usually present
ESR	Normal	Normal	Normal	High	High	Normal
24 hr ^{123}I uptake	Variable	<5%	<5%	<5%	Normal	Low or normal

ESR, erythrocyte sedimentation rate; ^{123}I, iodine 123; TPO, thyroid peroxidase.
Data from Farwell AP, Braverman LE. Inflammatory thyroid disorders. Otolaryngol Clin North Am *4:541–556, 1996.*

Table 565-2 Thyroid Function Tests

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
THYROID THYROGLOBULIN, SERUM			
Cord blood	14.7-101.1 ng/mL	×1	14.7-101.1 µg/L
Birth to 35 mo	10.6-92.0 ng/mL	×1	10.6-92.0 µg/L
3-11 yr	5.6-41.9 ng/mL	×1	5.6-41.9 µg/L
12-17 yr	2.7-21.9 ng/mL	×1	2.7-21.9 µg/L
THYROID-STIMULATING HORMONE, SERUM			
Premature Infants (28-36 wk)			
1st wk of life	0.7-27.0 mIU/L	×1	0.7-27.0 mIU/L
Term Infants			
Birth to 4 days	1.0-17.6 mIU/L	×1	1.0-17.6 mIU/L
2-20 wk	0.6-5.6 mIU/L	×1	0.6-5.6 mIU/L
5 mo-20 yr	0.5-5.5 mIU/L	×1	0.5-5.5 mIU/L
THYROXINE-BINDING GLOBULIN, SERUM			
Cord blood	1.4-9.4 mg/dL	×10	14-94 mg/L
1-4 wk	1.0-9.0 mg/dL	×10	10-90 mg/L
1-12 mo	2.0-7.6 mg/dL	×10	20-76 mg/L
1-5 yr	2.9-5.4 mg/dL	×10	29-54 mg/L
5-10 yr	2.5-5.0 mg/dL	×10	25-50 mg/L
10-15 yr	2.1-4.6 mg/dL	×10	21-46 mg/L
Adult	1.5-3.4 mg/dL	×10	15-34 mg/L
THYROXINE, TOTAL, SERUM			
Full-Term Infants			
1-3 days	8.2-19.9 µg/dL	×12.9	106-256 nmol/L
1 wk	6.0-15.9 µg/dL	×12.9	77-205 nmol/L
1-12 mo	6.1-14.9 µg/dL	×12.9	79-192 nmol/L
Prepubertal Children			
1-3 yr	6.8-13.5 µg/dL	×12.9	88-174 nmol/L
3-10 yr	5.5-12.8 µg/dL	×12.9	71-165 nmol/L
Pubertal Children and Adults			
>10 yr	4.2-13.0 µg/dL	×12.9	54-167 nmol/L
THYROXINE, FREE, SERUM			
Full-term (3 days)	2.0-4.9 ng/dL	×12.9	26-63.1 pmol/L
Infants	0.9-2.6 ng/dL	×12.9	12-33 pmol/L
Prepubertal children	0.8-2.2 ng/dL	×12.9	10-28 pmol/L
Pubertal children and adults	0.8-2.3 ng/dL	×12.9	10-30 pmol/L
THYROXINE, TOTAL, WHOLE BLOOD			
Newborn screen (filter paper)	6.2-22 µg/dL	×12.9	80-283 nmol/L
TRIIODOTHYRONINE, FREE, SERUM			
Cord blood	20-240 pg/dL	×0.01536	0.3-0.7 pmol/L
1-3 days	180-760 pg/dL	×0.01536	2.8-11.7 pmol/L
1-5 yr	185-770 pg/dL	×0.01536	2.8-11.8 pmol/L
5-10 yr	215-700 pg/dL	×0.01536	3.3-10.7 pmol/L
10-15 yr	230-650 pg/dL	×0.01536	3.5-10.0 pmol/L
>15 yr	210-440 pg/dL	×0.01536	3.2-6.8 pmol/L
TRIIODOTHYRONINE RESIN UPTAKE TEST (RT_3U), SERUM			
Newborn	26-36%	×0.01	0.26-0.36 fractional uptake
Thereafter	26-35%	×0.01	0.26-0.35 fractional uptake
TRIIODOTHYRONINE, TOTAL, SERUM			
Cord blood	30-70 ng/dL	×0.0154	0.46-1.08 nmol/L
1-3 days	75-260 ng/dL	×0.0154	1.16-4.00 nmol/L
1-5 yr	100-260 ng/dL	×0.0154	1.54-4.00 nmol/L
5-10 yr	90-240 ng/dL	×0.0154	1.39-3.70 nmol/L
10-15 yr	80-210 ng/dL	×0.0154	1.23-3.23 nmol/L
>15 yr	115-190 ng/dL	×0.0154	1.77-2.93 nmol/L

Adapted from Nicholson JF, Pesce MA: Reference ranges for laboratory tests and procedures. In Behrman RE, Kliegman RM, Jenson HB, editors: Nelson textbook of pediatrics, *ed 17, Philadelphia, 2004, WB Saunders, pp. 2412–2413; TSH from Lem AJ, de Rijke YB, van toor H, et al: Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age.* J Clin Endocrinol Metab *97:3170–3178, 2012; free T_3 from Elmlinger MW, Kuhnel W, Lambrecht H-G, Ranke MB: Reference intervals from birth to adulthood for serum thyroxine (T_4), triiodothyronine (T_3), free T_3, free T_4, thyroxine binding globulin (TBG), and thyrotropin (TSH).* Clin Chem Lab Med *39:973–979, 2001.*

Table 565-6 Pathogenesis of General Complications in Management of Complicated Hypothyroidism

COMPLICATION	PATHOGENESIS
Heart failure	Impaired ventricular systolic and diastolic functions and increased peripheral vascular resistance
Ventilatory failure	Blunted hypercapnic and hypoxic ventilatory drives
Hyponatremia	Impaired renal free water excretion and syndrome of inappropriate antidiuretic hormone secretion
Ileus	Bowel hypomotility
Medication sensitivity	Reduced clearance rate and increased sensitivity to sedative, analgesic, and anesthetic agents
Hypothermia and lack of febrile response to sepsis	Decreased calorigenesis
Delirium, dementia, seizure, stupor, and coma	Decreased central nervous system thyroid hormone actions, and encephalopathy from hyponatremia and hypercapnia
Adrenal insufficiency	Associated intrinsic adrenal or pituitary disease, or reversible impairment of hypothalamic-pituitary-adrenal stress response
Coagulopathy	Acquired von Willebrand syndrome (type 1) and decreased factors VIII, VII, V, IX, and X

Table 565-4 Autoimmune Polyglandular Syndromes 1 and 2

	APS-1	APS-2
Incidence	<1 in 100,000 population/yr	1-2 in 10,000 population/yr
Onset	Infancy/early childhood	Late childhood/ adulthood
Male:female ratio	3:4	1:3
Inheritance	Monogenic (*AIRE* gene)	Polygenic (HLA-associated)
Mucocutaneous candidiasis	73-100%	None
Hypoparathyroidism	77-89%	None
Addison disease	60-86%	70-100%
Type 1 diabetes	4-18%	41-52%
Autoimmune thyroid disease	8-40%	70%
GONADAL FAILURE		
Male	7-17%	5%
Female	30-60%	3.5-10%
Ectodermal dysplasia	77%	None
Vitiligo	4-13%	4-5%
Pernicious anemia	12-15%	2-25%
Alopecia	27%	2%
Autoimmune hepatitis	10-15%	Rare
Malabsorption	10-18%	Rare

HLA, human leukocyte antigen.
From Nambam B, Winter WE, Schatz DA: IgG_4 antibodies in autoimmune polyglandular disease and IgG_4-related endocrinopathies: pathophysiology and clinical characteristics. Curr Opin Pediatr *26:493–499, 2014, Table 1, p. 494.*

Table 565-3 Etiologic Classification of Acquired Hypothyroidism

Autoimmune
- Hashimoto thyroiditis
- Autoimmune polyglandular syndromes types 1 and 2 (APS-1, APS-2)

Drug-induced
- Excess iodide: amiodarone, nutritional supplements, expectorants
- Anticonvulsants: phenytoin, phenobarbital, valproate
- Antithyroid drugs: methimazole, propylthiouracil
- Miscellaneous: lithium, tyrosine kinase inhibitors, interferon alfa, stavudine, thalidomide, aminoglutethimide

Postablative
- Irradiation
- Radioiodine
- Thyroidectomy

Systemic infiltrative disease
- Cystinosis
- Langerhans cell histiocytosis

Hemangiomas (large) of the liver (type 3 iodothyronine deiodinase)

Hypothalamic-pituitary disease with multiple pituitary hormone deficiencies
- Hypothalamic-pituitary tumors (e.g., craniopharyngioma)
- Meningoencephalitis
- Cranial radiation
- Head trauma
- Langerhans cell histiocytosis

Table 565-5

DISEASE	AUTOANTIGENS
Addison disease	P450c21, P450c17, P450scc
Hashimoto thyroiditis	Thyroid peroxidase, thyroglobulin
Graves disease	TSH receptor
Hypoparathyroidism	[redacted]
Type 1 diabetes	[redacted] IA-2A, Zn18
Hypogonadism	P450c17, P450scc
Immune gastritis	H+, K+-ATPase
Pernicious anemia	Intrinsic factor
Celiac disease	Transglutaminase, gliadin
Immune hepatitis	P450D6, P4502C9, P4501A2
Alopecia areata	Tyrosine hydroxylase
Vitiligo	Tyrosinase

ATPase, adenosine triphosphatase; TSH, thyroid-stimulating hormone.
From Nambam B, Winter WE, Schatz DA: IgG_4 antibodies in autoimmune polyglandular disease and IgG_4-related endocrinopathies: pathophysiology and clinical characteristics. Curr Opin Pediatr *26:493–499, 2014, Table 2, p. 495.*

Table 568-2 Major Symptoms and Signs of Hyperthyroidism and of Graves Disease and Conditions Associated with Graves Disease

MANIFESTATIONS OF HYPERTHYROIDISM
Symptoms
Hyperactivity, irritability, altered mood, insomnia, anxiety, poor concentration
Heat intolerance, increased sweating
Palpitations
Fatigue, weakness
Dyspnea
Weight loss with increased appetite (weight gain in 10% of patients)
Pruritus
Increased stool frequency
Thirst and polyuria
Oligomenorrhea or amenorrhea
Signs
Sinus tachycardia, atrial fibrillation (rare in children), supraventricular tachycardia
Fine tremor, hyperkinesis, hyperreflexia
Warm, moist skin
Palmar erythema, onycholysis
Hair loss or thinning
Osteoporosis
Muscle weakness and wasting
High-output heart failure
Chorea
Periodic (hypokalemic) paralysis (primarily in Asian men)
Psychosis (rare)
MANIFESTATIONS OF GRAVES DISEASE
Diffuse goiter
Ophthalmopathy
A feeling of grittiness and discomfort in the eye
Retrobulbar pressure or pain
Eyelid lag or retraction
Periorbital edema, chemosis, scleral or conjunctival injection
Exophthalmos (proptosis)
Extraocular muscle dysfunction
Exposure keratitis
Optic neuropathy
Localized dermopathy (rare in children)
Lymphoid hyperplasia
Thyroid acropachy (rare in children)
CONDITIONS ASSOCIATED WITH GRAVES DISEASE
Type 1 diabetes mellitus
Addison disease
Vitiligo
Pernicious anemia
Alopecia areata
Myasthenia gravis
Celiac disease

Table 567-1 Goitrogens and Their Mechanism

GOITROGEN	MECHANISM
FOODS	
Cassava, lima beans, linseed, sorghum, sweet potato	Contain cyanogenic glucosides that are metabolized to thiocyanates that compete with iodine for uptake by the thyroid
Cruciferous vegetables such as cabbage, kale, cauliflower, broccoli, turnips, rapeseed	Contain glucosinolates; metabolites compete with iodine for uptake by the thyroid
Soy, millet	Flavonoids impair thyroid peroxidase activity
INDUSTRIAL POLLUTANTS	
Perchlorate	Competitive inhibitor of the sodium–iodine symporter, decreasing iodine transport into the thyroid
Others (e.g., disulfides from coal processes)	Reduce thyroidal iodine uptake
Smoking	An important goitrogen; smoking during breastfeeding is associated with reduced iodine concentrations in breast milk; high serum concentration of thiocyanate from smoking might compete with iodine for active transport into the secretory epithelium of the lactating breast
NUTRIENTS	
Selenium deficiency	Accumulated peroxides can damage the thyroid, and deiodinase deficiency impairs thyroid hormone activation
Iron deficiency	Reduces heme-dependent thyroperoxidase activity in the thyroid and might blunt the efficacy of iodine prophylaxis
Vitamin A deficiency	Increases TSH stimulation and goiter through decreased vitamin A–mediated suppression of the pituitary TSH-β gene

Table 568-3 Treatments for Hyperthyroidism Caused by Graves Disease

TREATMENT	ADVANTAGE	DISADVANTAGE	COMMENT
Antithyroid drugs	Noninvasive Less initial cost Low risk of permanent hypothyroidism Possible remission	Cure rate 30-80% (average: 40-50%) Adverse drug reactions Drug compliance required	First-line treatment in children and adolescents and in pregnancy Initial treatment in severe cases or preoperative preparation
Radioactive iodine (^{131}I)	Cure of hyperthyroidism Most cost-effective	Permanent hypothyroidism is almost inevitable Might worsen ophthalmopathy Pregnancy must be deferred for 6-12 mo, mother cannot breastfeed; small potential risk of exacerbation of hyperthyroidism	No evidence for infertility, birth defects, cancer when currently recommended doses are applied
Surgery	Rapid, effective treatment especially in patients with large goiter	Most invasive therapy Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Most costly therapy Permanent hypothyroidism; pain; scarring	Potential use in pregnancy if major side effect from antithyroid drugs Useful when coexisting suspicious nodule is present or thyromegaly is massive Option for patients who refuse radioiodine

From Cooper DS: Hyperthyroidism, Lancet *362:459–468, 2003.*

Table 568-1 Causes of Hyperthyroidism

CAUSES OF HYPERTHYROIDISM	PATHOPHYSIOLOGIC FEATURES	INCIDENCE
CIRCULATING THYROID STIMULATORS		
Graves disease	Thyroid-stimulating immunoglobulins	Common
Neonatal Graves disease	Thyroid-stimulating immunoglobulins	Rare
Thyrotropin-secreting tumor	Pituitary adenoma	Very rare
Choriocarcinoma	Human chorionic gonadotropin secretion stimulating the thyroid-stimulating hormone receptor	Rare
THYROIDAL AUTONOMY		
Toxic multinodular goiter	Activating mutations in thyrotropin receptor or G-protein	Common
Toxic solitary adenoma	Activating mutations in thyrotropin receptor or G-protein	Common
Congenital hyperthyroidism	Activating mutations in thyrotropin receptor	Very rare
Iodine-induced hyperthyroidism (Jod-Basedow phenomenon)	Unknown; excess iodine results in unregulated thyroid hormone production	Uncommon in United States and other iodine-sufficient areas
DESTRUCTION OF THYROID FOLLICLES (THYROIDITIS)		
Subacute painful thyroiditis	Probable viral infection	Uncommon
Painless sporadic thyroiditis (or postpartum thyroiditis)	Autoimmune	Common
Amiodarone-induced thyroiditis	Direct toxic drug effects	Uncommon
Acute (infectious) thyroiditis	Thyroid infection (e.g., bacterial, fungal) and release of preformed hormone	Uncommon
EXOGENOUS THYROID HORMONE		
Iatrogenic	Overtreatment with thyroid hormone	Common
Factitious	Excess ingestion of thyroid hormone	Rare
Hamburger thyrotoxicosis	Thyroid gland included in ground beef	Probably rare
ECTOPIC THYROID TISSUE		
Struma ovarii	Ovarian teratoma containing thyroid tissue	Rare
Metastatic follicular thyroid cancer	Large tumor mass capable of secreting thyroid hormone autonomously	Rare
Pituitary resistance to thyroid hormone	Mutated thyroid hormone receptor-β	Rare

Table 568-4 Management of Thyroid Storm in Adolescents

GOAL	TREATMENT
Inhibition of thyroid hormone formation and secretion	Propylthiouracil, 400 mg every 8 hr PO or by nasogastric tube Saturated solution of potassium iodide, 3 drops every 8 hr
Sympathetic blockade	Propranolol, 20-40 mg every 4-6 hr or 1 mg IV slowly (repeat doses until heart rate slows); not indicated in patients with asthma or heart failure that is not rate related
Glucocorticoid therapy	Prednisone 20 mg bid
Supportive therapy	Intravenous fluids (depending on indication: glucose, electrolytes, multivitamins) Temperature control (cooling blankets, acetaminophen; avoid salicylates) O_2 if required Digitalis for heart failure and to slow ventricular response; pentobarbital for sedation Treatment of precipitating event (e.g., infection)

Table 569-1 Etiologic Classification of Solitary Thyroid Nodules

Lymphoid follicle, as part of chronic lymphocytic thyroiditis
Thyroid developmental anomalies
  Intrathyroidal thyroglossal duct cyst
Thyroid abscess (acute suppurative thyroiditis)
Simple cyst
  Neoplasms
    Benign
      Colloid (adenomatous) nodule
      Follicular adenoma
      Toxic adenoma
      Nonthyroidal (e.g., lymphohemangioma)
    Malignant
      Papillary carcinoma
      Follicular carcinoma
      Mixed papillary-follicular carcinoma
      Undifferentiated (anaplastic)
      Medullary carcinoma
    Nonthyroidal
      Lymphoma
      Teratoma

Table 571-1 Causes of Hypocalcemia

I. Neonatal
  A. Maternal Disorders
    Diabetes mellitus
    Toxemia of pregnancy
    Vitamin D deficiency
    High intake of alkali or magnesium sulfate
    Use of anticonvulsants
    Hyperparathyroidism
  B. Neonatal Disorders
    Low birthweight: prematurity, intrauterine growth restriction
    Peripartum asphyxia, sepsis, critical illness
    Hyperbilirubinemia, phototherapy, exchange transfusion
    Hypomagnesemia, hypermagnesemia
    Acute/chronic renal failure
    Nutrients/medications: high phosphate intake, fatty acids, phytates, bicarbonate infusion, citrated blood, anticonvulsants, aminoglycosides
    Hypoparathyroidism
    Vitamin D deficiency or resistance
    Osteopetrosis type II
II. Hypoparathyroidism
  A. Congenital
    1. Transient neonatal
    2. Congenital hypoparathyroidism
      a. Familial isolated hypoparathyroidism
        (1) Autosomal recessive hypoparathyroidism (GCMB, PTH)
        (2) Autosomal dominant hypoparathyroidism (CaSR)
        (3) X-linked hypoparathyroidism *(SOX3)*
      b. DiGeorge syndrome *(TBX1)*
      c. Sanjad-Sakati syndrome (short stature, retardation, dysmorphism; HRD); Kenny-Caffey syndrome 1 (short stature, medullary stenosis) *(TBCE)*
      d. Barakat syndrome (sensorineural deafness, renal dysplasia; HDR) *(GATA3)*
      e. Lymphedema-hypoparathyroidism-nephropathy, nerve deafness
      f. Mitochondrial fatty acid disorders (Kearns-Sayre, Pearson, MELAS)
    3. Insensitivity to PTH
      a. Blomstrand chondrodysplasia *(PTHR1)*
      b. Pseudohypoparathyroidism type IA *(GNAS)*
        Pseudohypoparathyroidism type IB
        Pseudohypoparathyroidism type IC
        Pseudohypoparathyroidism type II
        Pseudopseudohypoparathyroidism
      c. Acrodysostosis with hormone resistance *(PRKAR1A)*
      d. Hypomagnesemia
    4. CaSR-activating mutation
      a. Sporadic
      b. Autosomal dominant (G protein subunit α11 mutation)
  B. Acquired
    1. Autoimmune polyglandular syndrome type I *(AIRE* gene mutation*)*
    2. Activating antibodies to the CaSR
    3. Postsurgical, radiation destruction
    4. Infiltrative—excessive iron (hemochromatosis, thalassemia) or copper (Wilson disease) deposition; granulomatous inflammation, neoplastic invasion; amyloidosis, sarcoidosis
    5. Maternal hyperparathyroidism
    6. Hypomagnesemia/hypermagnesemia
III. Vitamin D Deficiency
IV. Other Causes of Hypocalcemia
  A. Calcium Deficiency
    1. Nutritional deprivation
    2. Hypercalciuria
  B. Disorders of Magnesium Homeostasis
    1. Congenital hypomagnesemia
    2. Acquired
      a. Acute renal failure
      b. Chronic inflammatory bowel disease, intestinal resection
      c. Diuretics
  C. Hyperphosphatemia
    1. Renal failure
    2. Phosphate administration (intravenous, oral, rectal)
    3. Tumor cell lysis
    4. Muscle injuries (crush, rhabdomyolysis)
  D. Miscellaneous
    1. Hypoproteinemia
    2. Hyperventilation
    3. Drugs: furosemide, aminoglycosides, bisphosphonates, calcitonin, anticonvulsants, ketoconazole, antineoplastic agents (plicamycin, asparaginase, cisplatinum, cytosine arabinoside, doxorubicin), citrated blood products
    4. Hungry bone syndrome
    5. Acute and critical illness: sepsis, acute pancreatitis, toxic shock
      a. Organic acidemia: propionic, methylmalonic, isovaleric

HDR, hypoparathyroidism, sensorineural deafness, and renal anomaly; HRD, hypoparathyroidism, retardation, dysmorphism; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episode; PTH, parathyroid hormone.

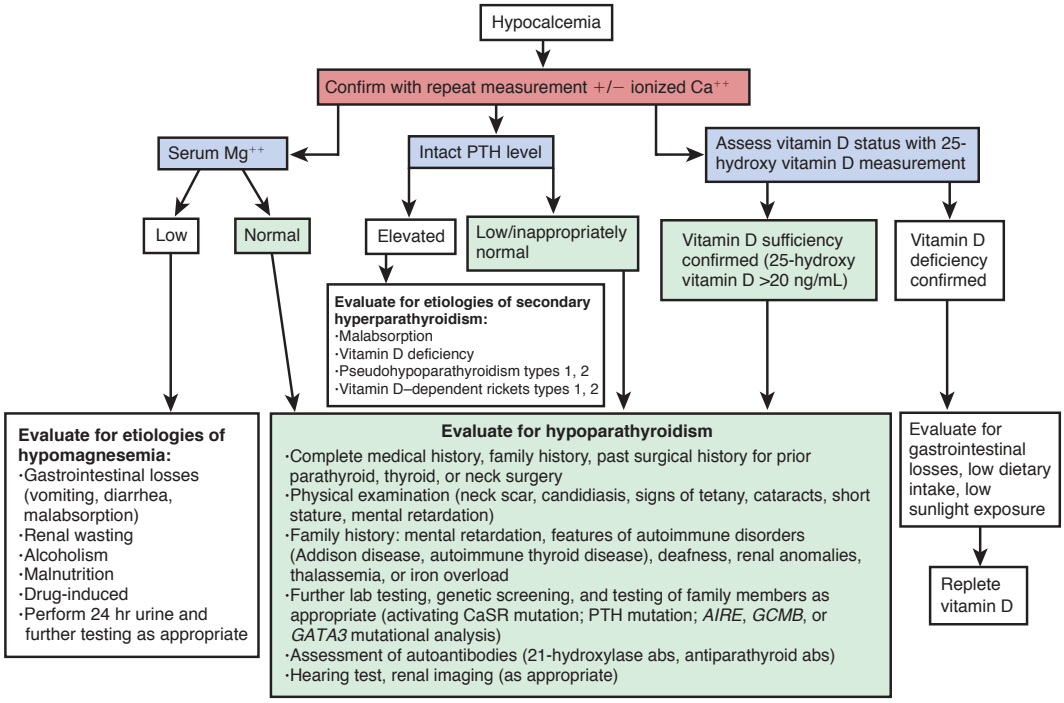

Figure 571-1 Evaluation of hypocalcemia. Abs, autoantibodies; CaSR, calcium-sensing receptor; PTH, parathyroid hormone. *(From Bilezikian JP, Khan A, Potts JT Jr, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research.* J Bone Miner Res *26:2317–2337, 2011, Fig. 1.)*

Table 573-1 Causes of Hypercalcemia

I. Neonate/Infant
  A. Maternal Disorders
    1. Excessive vitamin D ingestion, hypoparathyroidism, pseudohypoparathyroidism
  B. Neonate/Infant
    1. Iatrogenic: excessive intake of calcium, vitamin D, vitamin A
    2. Phosphate depletion
    3. Subcutaneous fat necrosis
    4. Williams-Beuren syndrome (del7q11.23/*BAZ1B*) (transient receptor potential; 3-channel defect)
    5. Neonatal severe hyperparathyroidism *(CaSR)*
    6. Metaphyseal chondrodysplasia, Murk-Jansen type *(PTH1R)*
    7. Idiopathic infantile hypercalcemia *(CYP24A1)* (25-hydroxyvitamin D 24-hydroxylase)
    8. Persistent parathyroid hormone–related protein
    9. Lactase/disaccharidase deficiency *(LCT)*
    10. Infantile hypophosphatasia *(TNSALP)*
    11. Mucolipidosis type II *(GNPTAB)*
    12. Blue diaper syndrome
    13. Antenatal Bartter syndrome types 1 and 2 *(SLC12A1, KCNJ1)*
    14. Distal renal tubular acidosis
    15. IMAGe syndrome *(CDKN1C)*
    16. Post bone marrow transplantation for osteopetrosis
    17. Endocrinopathies: primary adrenal insufficiency, severe congenital hypothyroidism, hyperthyroidism
II. Hyperparathyroidism
  A. Sporadic
    1. Parathyroid hyperplasia, adenoma, carcinoma
  B. Familial
    1. Neonatal severe hyperparathyroidism *(CaSR)*
    2. Multiple endocrine neoplasia, type I *(MEN1)*
    3. Multiple endocrine neoplasia, type IIA *(RET)*
    4. Multiple endocrine neoplasia, type IIB *(RET)*
    5. Multiple endocrine neoplasia, type IV *(CDKN1B)*
    6. McCune-Albright syndrome *(GNAS)*
    7. Familial isolated hyperparathyroidism 1 *(CDC73)*
    8. Familial isolated hyperparathyroidism 2 (jaw tumor syndrome) *(CDC73)*
    9. Familial isolated hyperparathyroidism 3
    10. Jansen metaphyseal dysplasia *(PTH1R)*
  C. Secondary/Tertiary
    1. Postrenal transplantation
    2. Chronic hyperphosphatemia
  D. Hypercalcemia of Malignancy
    1. Ectopic production of parathyroid hormone–related peptide
    2. Metastatic dissolution of bone
III. Familial Hypocalciuric Hypercalcemia
  A. Familial Hypocalciuric Hypercalcemia I *(CaSR)*
    1. Loss-of-function mutations in *CaSR*
      a. Monoallelic: familial benign hypercalcemia
      b. Biallelic: neonatal severe hyperparathyroidism
  B. Familial Hypocalciuric Hypercalcemia II *(GNA11)*
  C. Familial Hypocalciuric Hypercalcemia III, Oklahoma Variant *(AP2S1)*
  D. *CaSR*-blocking autoantibodies
IV. Excessive Calcium or Vitamin D
  A. Milk-Alkali Syndrome
  B. Exogenous Ingestion of Calcium or Vitamin D or Topical Application of Vitamin D (calcitriol or analog)
  C. Ectopic Production of Calcitriol Associated with Granulomatous Diseases (sarcoidosis, cat-scratch fever; tuberculosis, histoplasmosis, coccidioidomycosis, leprosy; human immunodeficiency virus; cytomegalovirus; chronic inflammatory bowel disease)
  D. Neoplasia
    1. Primary bone tumors
    2. Metastatic tumors with osteolysis
    3. Lymphoma, leukemia
    4. Dysgerminoma
    5. Pheochromocytoma
    6. Tumors secreting parathyroid hormone–related peptide, growth factors, cytokines, prostaglandins, osteoclast-activating factors
  E. Williams-Beuren Syndrome (del7q11.23)
V. Immobilization
VI. Other Causes
  A. Drugs: Thiazides, Lithium, Vitamin A and Analogs, Calcium, Alkali, Antiestrogens, Aminophylline
  B. Total Parenteral Nutrition
  C. Endocrinopathies: Hyperthyroidism, Addison disease, Pheochromocytoma
  D. Vasoactive Intestinal Polypeptide–Secreting Tumor
  E. Acute or Chronic Renal Failure/Administration of Aluminum
  F. Hypophosphatasia
  G. Juvenile Rheumatoid Arthritis: Cytokine Mediated

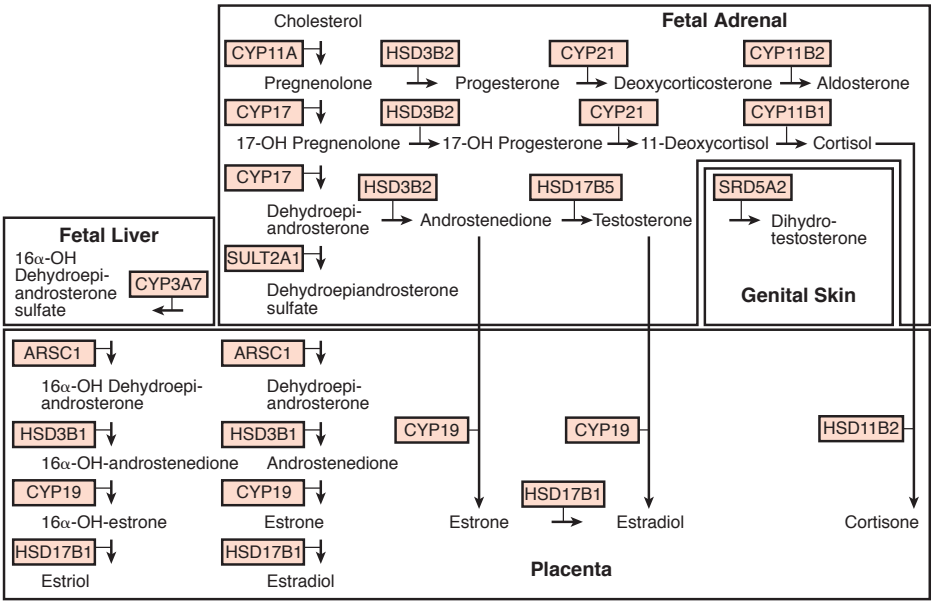

Figure 574-1 **Steroid biosynthesis and metabolism during gestation.** Conversions within the fetal adrenal cortex, fetal liver, male (i.e., testosterone-exposed) genital skin, and placenta are denoted by *arrows;* the enzyme mediating each conversion is also shown. Enzymatic conversions in the adrenal cortex are the same postnatally as prenatally, but cortisol and aldosterone biosynthesis are more prominent, and normally little testosterone is synthesized. Many of the involved enzymes are cytochromes P450 (CYPs). Adrenal enzymes include CYP 11A, cholesterol side-chain cleavage enzyme (P450scc in older terminology); HSD3B2, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 2; CYP 17, 17β-hydroxylase/17,20-lyase (P450c17); CYP 21, 21-hydroxylase (P450c21); CYP 11B1, 11β-hydroxylase (P450c11); CYP 11B2, aldosterone synthase (P450aldo; this enzyme mediates successive 11β-hydroxylase, 18-hydroxylase, and 18-oxidase reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone). Other enzymes important in the fetoplacental unit include ARSC1, arylsulfatase; CYP 19, aromatase (P450arom); HSD3B1, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; HSD17B1 and HSD17B5 are 2 different 17-hydroxysteroid dehydrogenase enzymes; SRD5A2, steroid 5α-reductase type 2; SULT2A1, steroid sulfotransferase.

Table 575-3 Frequencies of Etiologies of Primary Adrenal Insufficiency

ETIOLOGY		AGE AT DIAGNOSIS
Congenital adrenal hyperplasia	59%	Infancy
Autoimmune	16%	Childhood-adolescence
APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)	6%	Childhood-adolescence
Adrenoleukodystrophy	4%	Childhood-adolescence
Isolated glucocorticoid deficiency	4%	Infancy
Idiopathic	4%	Childhood
Syndromes	3%	Infancy
X-linked adrenal hypoplasia congenita	2%	Infancy-childhood
Hemorrhage	1%	Infancy

Data from Perry R, Kecha O, Paquette J, et al. Primary adrenal insufficiency in children: twenty years' experience at the Sainte-Justine Hospital, Montreal. J Clin Endocrinol Metab *90:3243–3250, 2005; Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood.* J Clin Endocrinol Metab *96:E925–E928, 2011.*

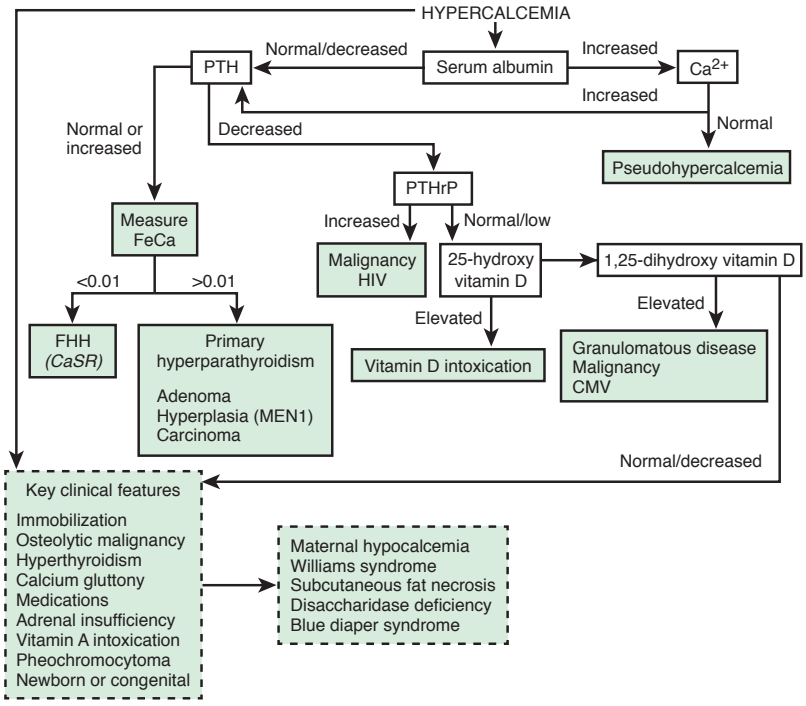

Figure 573-1 **Evaluation of hypercalcemia.** Ca^{2+}, calcium ions; CaSR, calcium-sensing receptor; CMV, cytomegalovirus; FeCa, fractional excretion of urinary calcium. *(From Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents.* Curr Opin Pediatr *22:508–515, 2010.)*

Table 575-1 Causes of Primary Adrenal Insufficiency

	PATHOGENESIS OR GENETICS	CLINICAL FEATURES IN ADDITION TO ADRENAL INSUFFICIENCY
CONGENITAL ADRENAL HYPERPLASIA		
21-Hydroxylase deficiency	*CYP21A2* mutations	Hyperandrogenism
11β-Hydroxylase deficiency	*CYP11B1* mutations	Hyperandrogenism, hypertension
3β-Hydroxysteroid dehydrogenase type 2 deficiency	*HSD3B2* mutations	Ambiguous genitalia in boys, postnatal virilization in girls
17α-Hydroxylase deficiency	*CYP17A1* mutations	XY sex reversal, pubertal delay in both sexes, hypertension
P450 oxidoreductase deficiency	*POR* mutations	Skeletal malformation (Antley-Bixler syndrome), abnormal genitalia
P450 side-chain cleavage deficiency	*CYP11A1* mutations	XY sex reversal
Congenital lipoid adrenal hyperplasia	*STAR* mutations	XY sex reversal
OTHER GENETIC DISORDERS		
Adrenoleukodystrophy or adrenomyeloneuropathy	*ABCD1* mutations	Weakness, spasticity, dementia, blindness, quadriparesis. Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy with slower progression
Triple A syndrome (Allgrove syndrome)	*AAAS* mutations	Achalasia, alacrima, cognitive deficits, neuromuscular deficits, hyperkeratosis
Smith-Lemli-Opitz syndrome	*DHCR7* mutations	Craniofacial malformations, developmental delay growth failure, cholesterol deficiency
Wolman disease	*LIPA* mutations	Bilateral adrenal calcification, hepatosplenomegaly
Kearns-Sayre syndrome	Mitochondrial DNA deletions	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrine disorders
Pallister-Hall syndrome	*GLI3* mutations	hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly
IMAGe syndrome	*CDKN1C* mutations	Intrauterine growth retardation, metaphyseal dysplasia, genital abnormalities
Adrenal Hypoplasia Congenita		
X-linked	*NR0B1* mutations	Hypogonadotropic hypogonadism in boys
Xp21 contiguous gene syndrome	Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and *NR0B1*	Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation
SF-1 linked	*NR5A1* mutations	XY sex reversal
Familial Glucocorticoid Deficiency or Corticotropin Insensitivity Syndromes		
Type 1	*MC2R* mutations	Tall stature, characteristic facial features, such as hypertelorism and frontal bossing
Type 2	*MRAP* mutations	
Variant of familial glucocorticoid deficiency	*MCM4* mutations	Growth failure, increased chromosomal breakage, natural killer cell deficiency
Variant of familial glucocorticoid deficiency	*NNT* mutations	
AUTOIMMUNE		
Isolated	Sporadic; associations with *HLA-DR3-DQ2, HLA-DR4-DQ8, MICA, CTLA4, PTPN22, CIITA, CLEC16A*	None
APS type 1 (APECED)	*AIRE* mutations	Chronic mucocutaneous candidosis, hypoparathyroidism, other autoimmune diseases
APS type 2	Sporadic; associations with *HLA-DR3, HLA-DR4, CTLA4*	Thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases
APS type 4	Sporadic; associations with *HLA-DR3, CTLA4*	Other autoimmune diseases (autoimmune gastritis, vitiligo, coeliac disease, alopecia), excluding thyroid disease and type 1 diabetes
INFECTIOUS		
Tuberculous adrenalitis	Tuberculosis	Tuberculosis-associated manifestations in other organs
AIDS	HIV-1	Other AIDS-associated diseases
Fungal adrenalitis	Histoplasmosis, cryptococcosis, coccidioidomycosis	Opportunistic infections
Meningococcal sepsis (Waterhouse-Friderichsen syndrome),	*Neisseria meningitidis*	
African trypanosomiasis	*Trypanosoma brucei*	Other trypanosomiasis-associated organ involvement
OTHER ACQUIRED CAUSES		
Bilateral adrenal hemorrhage	Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome, traumatic birth, anticoagulation	Symptoms and signs of underlying disease
Bilateral adrenal metastases	Mainly cancers of the lung, stomach, breast, and colon	Symptoms and signs of underlying disease
Bilateral adrenal infiltration	Primary adrenal lymphoma, amyloidosis, hemochromatosis, sarcoidosis (rare)	Symptoms and signs of underlying disease
Bilateral adrenalectomy		Symptoms and signs of underlying disease

Table 575-1 Causes of Primary Adrenal Insufficiency—cont'd

	PATHOGENESIS OR GENETICS	CLINICAL FEATURES IN ADDITION TO ADRENAL INSUFFICIENCY
DRUG-INDUCED		
Mitotane (o,p-DDD)	Cytotoxicity	None, unless related to drug
Aminoglutethimide	Inhibition of cholesterol side chain cleavage enzyme (CYP11A1)	None, unless related to drug
Trilostane	Inhibition of 3β-hydroxysteroid dehydrogenase type 2	None, unless related to drug
Etomidate	Inhibition of 11β-hydroxylase (CYP11B1)	None, unless related to drug
Ketoconazole, fluconazole	Inhibition of mitochondrial cytochrome P450 enzymes (e.g., CYP11A1, CYP11B1)	None, unless related to drug

AAAS, achalasia, adrenocortical insufficiency, alacrima syndrome; ABCD, ATP-binding cassette, subfamily D; ABCG5, ATP-binding cassette, subfamily G, member 5; ABCG8, ATP-binding cassette, subfamily G, member 8; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS, autoimmune polyendocrinopathy syndrome; CIITA, class II transactivator; CTLA-4, cytotoxic T-lymphocyte antigen 4; DHCR7, 7-dehydrocholesterol reductase; HLA, human leukocyte antigen; IMAGe, intrauterine growth restriction (IUGR), metaphyseal dysplasia, adrenal hypoplasia congenita (AHC), and genitourinary abnormalities; LIPA, lipase A; MC2R, melanocortin 2 receptor; MCM4, minichromosome maintenance complex component 4; MICA, major histocompatibility complex class I chain-related gene A; MRAP, melanocortin 2 receptor accessory protein; PTPN22, protein tyrosine phosphatase, non-receptor type 22; StAR, steroidogenic acute regulatory protein.

Adapted from: Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet *383:2152–2164, 2014, Table 1, pp. 2153–2154.*

Table 575-2 Causes of Secondary Adrenal Insufficiency

	ETIOLOGIES	CLINICAL MANIFESTATIONS IN ADDITION TO ADRENAL INSUFFICIENCY
DRUG-INDUCED		
Abrupt cessation of glucocorticoid therapy (systemic or topical)	Suppression of CRH and ACTH secretion leading to atrophy of the adrenal cortex	Primary disease-associated symptoms
OTHER ACQUIRED CAUSES		
Hypothalamic or pituitary tumors	Adenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, rarely carcinomas, metastasis	Panhypopituitarism*; primary disease-associated symptoms
Traumatic brain injury		Panhypopituitarism*; primary disease-associated symptoms
Hypothalamic or pituitary surgery or irradiation		Panhypopituitarism*; primary disease-associated symptoms
Infections or infiltrative processes	Lymphocytic hypophysitis, hemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener granulomatosis	Panhypopituitarism*; primary disease-associated symptoms
Pituitary apoplexy (when occurring in a peripartum mother, termed Sheehan syndrome)	High blood loss or hypotension	Abrupt onset of severe headache, visual disturbance, nausea, vomiting; panhypopituitarism*; primary disease-associated symptoms
CONGENITAL OR GENETIC CAUSES		
Abnormal Central Nervous System Development		
Anencephaly	Multiple	Primary disease-associated symptoms
Holoprosencephaly	Multiple	Primary disease-associated symptoms
Combined Pituitary Hormone Deficiency (CPHD)†		
CPHD2	Mutations in *PROP1* (paired-like homeobox 1)	Panhypopituitarism; corticotropin deficiency occurs in adolescence
CPHD3	Mutations in *LHX3* (LIM homeobox 3)	Panhypopituitarism; deafness, short neck
CPHD4	Mutations in *LHX4* (LIM homeobox 4)	Panhypopituitarism; small sella, cerebellar defects
Septooptic dysplasia, CPHD5	Mutations in *HESX1* (HESX homeobox 1)	Panhypopituitarism; septooptic dysplasia (blindness owing to hypoplasic optic nerves, absence of the septum pellucidum); developmental delay
CPHD6	Mutations in *OTX2* (orthodenticle homeobox 2)	Panhypopituitarism; ectopic posterior pituitary gland
X-linked panhypopituitarism	Mutations in *SOX3* (SRY(sex-determining region Y) box 3)	Panhypopituitarism; infundibular hypoplasia, developmental delay
Other Genetic Syndromes Affecting Corticotropin Secretion		
Congenital proopiomelanocortin deficiency	Mutations in *POMC* (proopiomelanocortin)	Early-onset severe obesity, hyperphagia, red hair
Prohormone convertase 1/3 deficiency	Mutations in *PC1* (prohormone convertase 1/3)	Obesity, malabsorption or diarrhea, hypogonadotropic hypogonadism
Isolated ACTH (corticotropin) deficiency	Mutations in *TBX19* (T-box 19)	
Prader-Willi syndrome	Deletion or silencing of genes on the parental copy of genes within the imprinted chromosome region 15q11-q13 including *SNRPN* (small nuclear ribonucleoprotein polypeptide N) and *NDN* (necdin, melanoma antigen (MAGE) family member)	Dysmorphic features, hypotonia, developmental delay, obesity, growth hormone deficiency, hypogonadotropic hypogonadism

*The associated anterior and/or posterior hormone deficiencies may vary.

†CPHD1 (mutations in *POUF1*) is not associated with corticotropin deficiency.

Table 576-1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
21-Hydroxylase deficiency, classic form	*CYP21* 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ACTH ↑↑ Baseline and ACTH-stimulated 17-hydroxy-progesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	*CYP21* 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	*CYP11B1* 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency, classic form	*HSD3B2* 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxy-pregnenolone, DHEA)	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/ 17,20-lyase deficiency	*CYP17* 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH ↑ DOC, corticosterone Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids
Congenital lipoid adrenal hyperplasia	*STAR* 8p11.2	Glucocorticoid deficiency	↑ ACTH Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑ LH, ↓ estradiol (after puberty)	Estrogen replacement

Table 576-1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia—cont'd

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
P450 oxidoreductase deficiency	*POR* 7q11.3	Glucocorticoid deficiency Ambiguous genitalia in males and females Maternal virilization Antley-Bixler syndrome	↓ Cortisol, ↑ ACTH ↑ Pregnenolone, ↑ progesterone ↑ Serum androgens prenatally, ↓ androgens and estrogens at puberty Decreased ratio of estrogens to androgens	Glucocorticoid (hydrocortisone) replacement Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing

↓, Decreased; ↑, increased; ↑↑, markedly increased; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

Table 576-2 Genotype-Phenotype Correlations in Congenital Adrenal Hyperplasia Owing to 21-Hydroxylase Deficiency

MUTATION GROUP	A	B	C
Enzymatic activity, % normal	Nil	1-2%	20-50%
CYP21 mutations (phenotype generally corresponds to the least affected allele)	Gene deletion Exon 3 del 8 bp Exon 6 cluster Q318X R356W Intron 2 splice	I172N	P30L V281L P453S
Severity	Salt wasting	Simple virilizing	Nonclassic
Aldosterone synthesis	Low	Normal	Normal
Age at diagnosis (without newborn screening)	Infancy	Infancy (females) Childhood (males)	Childhood to adulthood, or asymptomatic
Virilization	Severe	Moderate to severe	None to Mild
Incidence	1/20,000	1/50,000	1/500

Table 575-4 Clinical Manifestations and Biochemical Findings in Adrenal Insufficiency

	PATHOPHYSIOLOGIC MECHANISM	PREVALENCE (%)*
SYMPTOMS		
Fatigue	Glucocorticoid deficiency	90
Anorexia, weight loss	Glucocorticoid deficiency	90
Nausea, vomiting	Glucocorticoid deficiency, mineralocorticoid deficiency	90
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency	20
Myalgia or joint pain	Glucocorticoid deficiency	
SIGNS		
Low blood pressure, orthostatic hypotension	Mineralocorticoid deficiency, glucocorticoid deficiency	70-100%
Skin or mucosal hyperpigmentation (primary adrenal insufficiency only)	Excess of proopiomelanocortin-derived peptides	70
LABORATORY FINDINGS		
Hyponatremia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to decreased free water excretion)	90
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency	50
Hypoglycemia	Glucocorticoid deficiency	30
Ketosis	Glucocorticoid deficiency	30
Low random cortisol level	Glucocorticoid deficiency	80
Eosinophilia, lymphocytosis	Glucocorticoid deficiency	
High ACTH level (primary adrenal insufficiency only)	Glucocorticoid deficiency	100
High plasma renin activity (primary adrenal insufficiency only)	Mineralocorticoid deficiency	100

*Prevalence data are for primary insufficiency only. Blanks indicate that no pediatric prevalence data are available.
Data from Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. J Clin Endocrinol Metab *96:E925–E928, 2011*

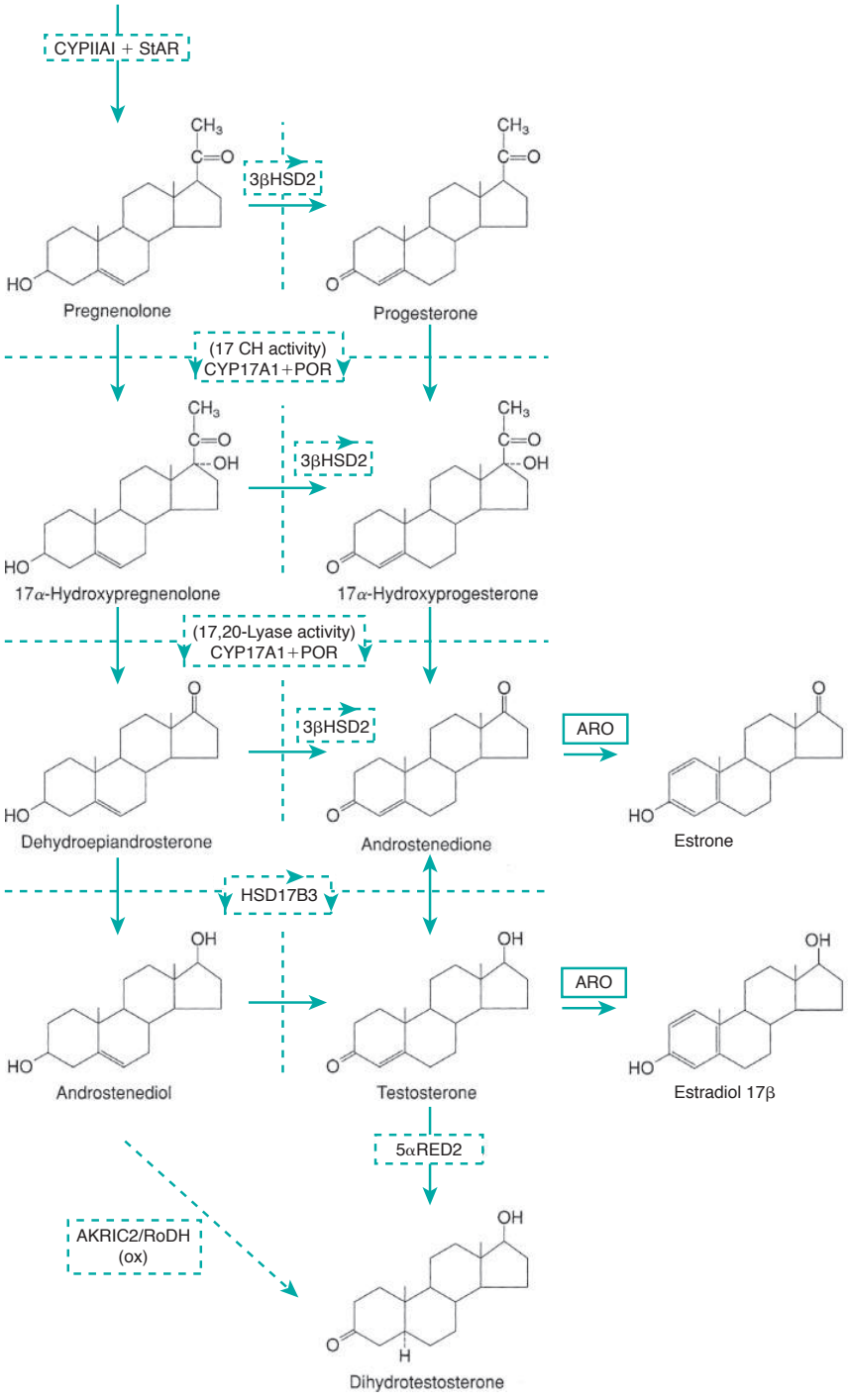

Figure 582-1 Biosynthesis of sex steroids. *Dashed lines* indicate enzymatic defects associated with 46,XY disorder of sex differentiation. *3β-HSD2*, 3β-hydroxysteroid dehydrogenase type 2; *AKR1C2/RoDH (Ox)*, one of the enzymes in the recently described alternative androgen biosynthetic pathway; *ARO*, aromatase; *CYP17A1*, the enzyme that catalyzes both 17α-hydroxylase (17-OH) and 17,20-lyase activities; *HSD17B3*, enzyme that catalyzes the 17-ketoreductase reaction; *POR*, P450 oxidoreductase; *StAR*, steroidogenic acute regulatory protein.

Table 585-1 Causes of Gynecomastia

SYMPTOMS	SIGNS
FETAL ANDROGEN DEFICIENCY	
Ambiguous genitalia	Ambiguous genitalia (47,XY disorders of sex development) Normal female genitalia Microphallus (resembling clitoromegaly) Pseudovaginal perineoscrotal hypospadias Bifid scrotum Cryptorchidism
PREPUBERTAL ANDROGEN DEFICIENCY	
Delayed puberty Lack of sexual interest or desire (libido) Reduced nighttime or morning spontaneous erections Breast enlargement and tenderness Reduced motivation and initiative Diminished strength and physical performance No ejaculate or ejaculation (spermarche) Inability to father children (infertility)	Eunuchoidism Infantile genitalia Small testes Lack of male hair pattern growth, no acne Disproportionately long arms and legs relative to height Pubertal fat distribution Poorly developed muscle mass High-pitched voice Reduced peak bone mass, osteopenia, or osteoporosis Gynecomastia Small prostate gland Aspermia, severe oligozoospermia, or azoospermia
ADULT ANDROGEN DEFICIENCY	
Incomplete sexual development Lack of sexual interest or desire (libido) Reduced nighttime or morning spontaneous erections Breast enlargement and tenderness Inability to father children (infertility) Height loss, history of minimal-trauma fracture Hot flushes, sweats Reduced shaving frequency	Eunuchoidism Small or shrinking testes Loss of male hair (axillary and pubic hair) Gynecomastia Aspermia or azoospermia or severe oligozoospermia Low bone mineral density (osteopenia or osteoporosis) Height loss, minimal-trauma or vertebral compression fracture Unexplained reduction in prostate size or prostate-specific antigen
Less-Specific Symptoms	**Less-Specific Signs**
Decreased energy, vitality	Mild normocytic, normochromic anemia (normal female range)
Decreased motivation, self-confidence	Depressed mood, mild depression or dysthymia
Feeling sad or blue, irritability	Reduced muscle bulk and strength
Weakness, decreased physical or work performance	Increased body fat or body mass index
Poor concentration and memory	Fine facial skin wrinkling (lateral to orbits and mouth)
Increased sleepiness	

Table 589-2 Diagnostic Criteria for Impaired Glucose Tolerance and Diabetes Mellitus

IMPAIRED GLUCOSE TOLERANCE	DIABETES MELLITUS
Fasting glucose 100-125 mg/dL (5.6-7.0 mmol/L)	Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L)
	or
2-hr plasma glucose during the OGTT ≥140 mg/dL, but <200 mg/dL (11.1 mmol/L)	Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) *or* 2 hr plasma glucose during the OGTT ≥200 mg/dL *or* Hemoglobin A_{1C} ≥6.5%†

*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.

†Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia.

OGTT, oral glucose tolerance test.

Table 583-1 Etiologic Classification of Male Hypogonadism

HYPERGONADOTROPIC HYPOGONADISM (PRIMARY HYPOGONADISM; TESTES)

Congenital

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) resistance
Mutations in steroid synthetic pathways
Gonadal dysgenesis
Klinefelter syndrome (47,XXY)
Noonan syndrome (*PTPN-11* gene mutation in many cases)
Cystic fibrosis (infertility)

Acquired

Cryptorchidism (some cases)
Vanishing testes
Chemotherapy
Radiation
Infection (e.g., mumps)
Infarction (testicular torsion)
Trauma

HYPOGONADOTROPIC HYPOGONADISM (SECONDARY HYPOGONADISM; HYPOTHALAMIC-PITUITARY)

Congenital

Genetic defects causing Kallmann syndrome and/or normosmic hypogonadotropic hypogonadism (HH)
Other genetic disorders associated with HH: leptin gene, leptin receptor, DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), SF-1 (steroidogenic factor-1)
Inherited syndromes: Prader-Willi, Bardet-Biedl, Laurence-Moon-Biedl, Alström
Isolated HH at pituitary level (gonadotropin-releasing hormone receptor, FSH and LH β-subunit)
Multiple pituitary hormone deficiencies: septooptic dysplasia (*HESX-1* in some cases) and other disorders of pituitary organogenesis (e.g., *PROP1, LHX3, LHX4, SOX-3*)
Idiopathic

Acquired

Anorexia nervosa
Drug use
Malnutrition
Chronic illness, especially Crohn disease
Hyperprolactinemia
Pituitary tumors
Pituitary infarction
Infiltrative disorders (e.g., histiocytosis, sarcoidosis)
Hemosiderosis and hemochromatosis
Radiation

Table 577-1 Etiologic Classification of Adrenocortical Hyperfunction

EXCESS ANDROGEN

Congenital adrenal hyperplasia
21-Hydroxylase (P450c21) deficiency
11β-Hydroxylase (P450c11) deficiency
3β-Hydroxysteroid dehydrogenase defect (deficiency or dysregulation)
Tumor

EXCESS CORTISOL (CUSHING SYNDROME)

Bilateral adrenal hyperplasia
Adenoma
Hypersecretion of corticotropin (Cushing disease)
Ectopic secretion of corticotropin
Exogenous corticotropin
Adrenocortical nodular dysplasia
Pigmented nodular adrenocortical disease (Carney complex)
Tumor
McCune-Albright syndrome

EXCESS MINERALOCORTICOID

Primary hyperaldosteronism
Aldosterone-secreting adenoma
Bilateral micronodular adrenocortical hyperplasia
Glucocorticoid-suppressible aldosteronism
Tumor
Deoxycorticosterone excess
Congenital adrenal hyperplasia
11β-Hydroxylase (P450c11)
17α-Hydroxylase (P450c17)
Tumor
Apparent mineralocorticoid excess (deficiency of 11β-hydroxysteroid dehydrogenase type 2)

EXCESS ESTROGEN

Tumor

Table 588-1 Revised Nomenclature

PREVIOUS	CURRENTLY ACCEPTED
Intersex	Disorders of sex development (DSD)
Male pseudohermaphrodite	46,XY DSD
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	46,XY DSD
46,XY intersex	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	46,XX DSD
46,XX intersex	46,XX DSD
True hermaphrodite	Ovotesticular DSD
Gonadal intersex	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

Table 588-4 Sources of Maternal-Derived Androgens

ENDOGENOUS	EXOGENOUS
BENIGN	SYNTHETIC ANDROGENS
Luteoma of pregnancy	Danazol
Adrenal adenoma	Progestins (medroxyprogesterone acetate)
Hyperreactio luteinalis	Potassium-sparing diuretics
Thecoma/fibroma	
Stromal hyperthecosis	
Brenner tumor	
Serous cystadenoma	
Mature cystic teratoma (dermoid cyst)	
MALIGNANT	
Metastatic carcinomas (Krukenberg tumor)	
Sex-cord stromal tumors—granulosa cell and Sertoli-Leydig tumors	
Adrenal cortical carcinoma	
Cystadenocarcinoma	
Hilar cell tumor	

From Auchus RJ, Chang AY: 46,XX DSD: the masculinised female. Best Pract Res Clin Endocrinol Metab *24:219–242, 2010, Table 2, p. 237.*

Table 588-5 Causes of a PAIS-Like Phenotype

DEFECTS IN ANDROGEN PRODUCTION
- Partial gonadal dysgenesis
  - Mutations in *SRY, NR5A1, WT1*
- Mutations of the luteinizing hormone receptor
- Biosynthetic enzyme deficiencies
- 17,20-Lyase deficiency
- P450 oxidoreductase deficiency
- 17β-hydroxysteroid dehydrogenase deficiency type 3
- 5α-Reductase deficiency type 2

GENETIC
- Klinefelter syndrome
- Smith-Lemli-Opitz syndrome
- Denys-Drash syndrome
- Frasier syndrome

PAIS
- Mutations of the androgen receptor gene
- Normal androgen receptor gene with fetal growth restriction

NR5A1, nuclear receptor subfamily 5 A1; PAIS, partial androgen insensitivity syndrome; SRY, sex-determining region Y; WT1, Wilms tumor 1.

From Hughes IA, Davies JD, Bunch TI, et al: Androgen insensitivity syndrome. Lancet *380:1419–1428, 2012, Panel 1, p. 1421.*

Table 588-2 Etiologic Classification of Disorders of Sex Development (DSD)

46,XX DSD
Androgen Exposure
Fetal/Fetoplacental Source
21-Hydroxylase (P450c21 or CYP21) deficiency
11β-Hydroxylase (P450c11 or CYP11B1) deficiency
3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency
Cytochrome P450 oxidoreductase (POR)
Aromatase (P450arom or CYP19) deficiency
Glucocorticoid receptor gene mutation
Maternal Source
Virilizing ovarian tumor
Virilizing adrenal tumor
Androgenic drugs
Disorder of Ovarian Development
XX gonadal dysgenesis
Testicular DSD (SRY+, SOX9 duplication)
Undetermined Origin
Associated with genitourinary and gastrointestinal tract defects

46,XY DSD
Defects in Testicular Development
Denys-Drash syndrome (mutation in *WT1* gene)
WAGR syndrome (Wilms tumor, aniridia, genitourinary malformation, retardation)
Deletion of 11p13
Campomelic syndrome (autosomal gene at 17q24.3-q25.1) and *SOX9* mutation
XY pure gonadal dysgenesis (Swyer syndrome)
Mutation in *SRY* gene
XY gonadal agenesis
Unknown cause
Deficiency of Testicular Hormones
Leydig cell aplasia
Mutation in LH receptor
Lipoid adrenal hyperplasia (P450scc or CYP11A1) deficiency; mutation in StAR (steroidogenic acute regulatory protein)
3β-HSD II deficiency
17-Hydroxylase/17,20-lyase (P450c17 or CYP17) deficiency
Persistent müllerian duct syndrome because of antimüllerian hormone gene mutations or receptor defects for antimüllerian hormone
Defect in Androgen Action
Dihydrotestosterone deficiency because of 5α-reductase II mutations or *AKR1C2/AKR1C4* mutations
Androgen receptor defects:
Complete androgen insensitivity syndrome
Partial androgen insensitivity syndrome (Reifenstein and other syndromes)
Smith-Lemli-Opitz syndrome (defect in conversion of 7-dehydrocholesterol to cholesterol, DHCR7)
Ovotesticular DSD
XX
XY
XX/XY chimeras
Sex Chromosome DSD
45,X (Turner syndrome and variants)
47,XXY (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis, sometimes a cause of ovotesticular DSD)
46,XX/46,XY (chimeric, sometimes a cause of ovotesticular DSD)

Table 589-1 Etiologic Classifications of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction ultimately leading to complete insulin deficiency)
  A. Immune mediated
  B. Idiopathic
II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
  A. Typical
  B. Atypical
III. Genetic defects of β-cell function
  A. MODY (maturity-onset diabetes of the young) syndromes
    1. MODY 1 chromosome 20, HNF4α
    2. MODY 2 chromosome 7, glucokinase
    3. MODY 3 chromosome 12, HNF1α, TCF-1
    4. MODY 4 chromosome 13, IPF-1
    5. MODY 5 chromosome 17, HNF1β, TCF-2
    6. MODY 6 chromosome 2q32, neuro-D_1/β_2
  B. Mitochondrial DNA mutations (includes 1 form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, diabetes mellitus, deafness)
  C. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness): WFS1-Wolframin—chromosome 4p
    1. Wolfram locus 2—chromosome 4q22-24
    2. Wolfram mitochondrial
  D. Thiamine responsive megaloblastic anemia and diabetes
IV. Drug or chemical induced
  A. Antirejection—cyclosporine, sirolimus
  B. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)
  C. L-Asparaginase
  D. β-Adrenergic blockers
  E. Vacor (rodenticide)
  F. Phenytoin (Dilantin)
  G. α-Interferon
  H. Diazoxide
  I. Nicotinic acid
  J. Pentamidine
V. Diseases of exocrine pancreas
  A. Cystic fibrosis–related diabetes
  B. Trauma—pancreatectomy
  C. Pancreatitis—ionizing radiation
  D. Others
VI. Infections
  A. Congenital rubella
  B. Cytomegalovirus
  C. Hemolytic-uremic syndrome
VII. Variants of type 2 diabetes
  A. Genetic defects of insulin action
    1. Rabson-Mendenhall syndrome
    2. Leprechaunism
    3. Lipoatrophic diabetes syndromes
    4. Type A insulin resistance—acanthosis
  B. Acquired defects of insulin action
    1. Endocrine tumors—rare in childhood
  C. Pheochromocytoma
  D. Cushing
  E. Others
    1. Antiinsulin receptor antibodies
VIII. Genetic syndromes with diabetes and insulin resistance/insulin deficiency
  A. Prader-Willi syndrome, chromosome 15
  B. Down syndrome, chromosome 21
  C. Turner syndrome
  D. Klinefelter syndrome
  E. Others
    1. Bardet-Biedel
    2. Alström
    3. Werner
  F. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)
  G. Celiac disease
  H. Autoimmune polyendocrinopathy
IX. Gestational diabetes
X. Neonatal diabetes
  A. Transient—chromosome 6q24, KCNJ11, ABCC8, INS, HNF1β, others
  B. Permanent—agenesis of pancreas—glucokinase deficiency, homozygous, KCNJ11, ABCC8, others

Table 588-3 Ambiguous Genitalia: Steps in Establishing the Diagnosis

	21-OH DEFICIENCY	GONADAL DYSGENESIS WITH Y CHROMOSOME	OVOTESTICULAR DSD	PARTIAL ANDROGEN INSENSITIVITY	BLOCK IN TESTOSTERONE SYNTHESIS
CLINICAL FEATURE					
Palpable gonad(s)	–	±	±	+	+
Uterus present*	+	+	Usually	–	–
Increased skin pigmentation	±	–	–	–	–
Sick baby	±	–	–	–	±
Dysmorphic features	–	±	–	–	–
DIAGNOSTIC CONSIDERATIONS					
Serum 17-OHP	Elevated	Normal	Normal	Normal	Normal
Electrolytes	Possibly abnormal	Normal	Normal	Normal	Possibly abnormal
Karyotype	46,XX	45,X/46,XY or others	46,XX	46,XY	46,XY
Testosterone response to hCG	NA	Positive	Normal or reduced	Positive response	Reduced or absent
Gonadal biopsy	NA	Dysgenetic gonad	Ovotestis	Normal testis with ± Leydig cell hyperplasia	Normal testis
Other testing				Genital skin fibroblast culture	Measure
				For AR assay	Testosterone
				Or DNA screening for AR mutations in blood cells	Precursors

*As determined by ultrasound or rectal examination.
AR, androgen receptor; DSD, disorders of sex development; hCG, human chorionic gonadotropin; 21-OH, 21-hydroxylase; 17-OHP, 17-hydroxyprogesterone; NA, not applicable.
Adapted from Donohoue PA, Saenger PH: Ambiguous genitalia. In Finberg L, Kleinman RE, editors: Saunders manual of pediatric practice, *Philadelphia, 2002, WB Saunders, p. 874.*

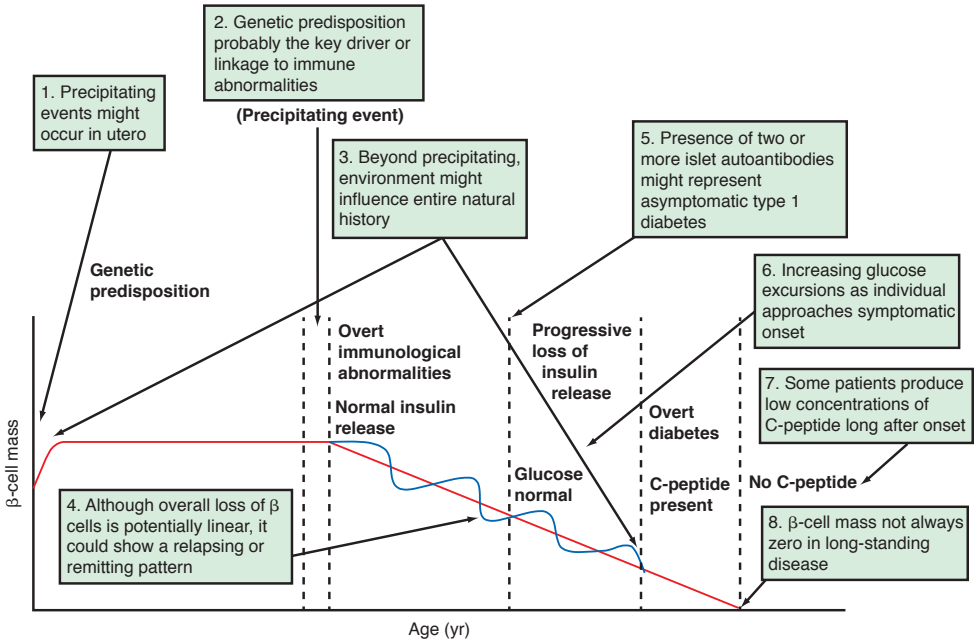

Figure 589-3 The natural history of type 1 diabetes—a 25 yr old concept revisited. A recreation of the model of type 1 diabetes, originally proposed in 1986, is shown in *black*. Additions and conjectures based on recent knowledge gains are shown in *green*. *(From Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes.* Lancet *383:69–78, 2014, Fig. 4, p. 73.)*

Table 589-3 Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue*

	HIGH PLASMA INSULIN (POSTPRANDIAL STATE)	LOW PLASMA INSULIN (FASTED STATE)
Liver	Glucose uptake	Glucose production
	Glycogen synthesis	Glycogenolysis
	Absence of gluconeogenesis	Gluconeogenesis
	Lipogenesis	Absence of lipogenesis
	Absence of ketogenesis	Ketogenesis
Muscle	Glucose uptake	Absence of glucose uptake
	Glucose oxidation	Fatty acid and ketone oxidation
	Glycogen synthesis	Glycogenolysis
	Protein synthesis	Proteolysis and amino acid release
Adipose tissue	Glucose uptake	Absence of glucose uptake
	Lipid synthesis	Lipolysis and fatty acid release
	Triglyceride uptake	Absence of triglyceride uptake

*Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, untreated, results in exaggerated fasting.

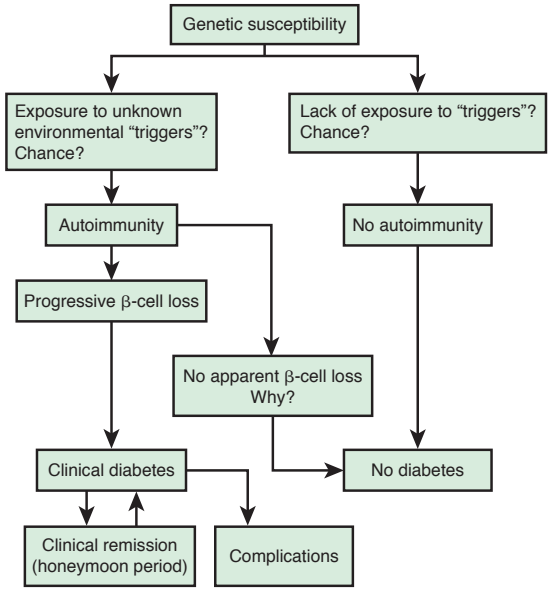

Figure 589-4 Schematic of the natural history of type 1 diabetes mellitus. Unknown triggers act upon a genetically susceptible host to trigger autoimmunity. Some proportion of those with autoimmunity develop progressive β-cell loss that eventually leads to clinical diabetes. This is followed by temporary clinical remission (honeymoon period) in most patients. Over time, insulin secretion is almost completely lost and complications may develop in some patients (in direct proportion to the occurrence of hyperglycemia).

Table 589-15 Monitoring for Complications and Comorbidities

CONDITION	SCREENING TEST	COMMENT
Hypertension	Blood pressure	
Fatty liver	Aspartate aminotransferase, alanine aminotransferase, possibly liver ultrasound	
Polycystic ovary syndrome	Menstrual history, assessment for androgen excess with free/total testosterone, dehydroepiandrosterone	
Microalbuminuria	Urine albumin concentration and albumin : creatinine ratios	
Dyslipidemia	Fasting lipid profile (total, low-density lipoprotein, high-density lipoprotein cholesterol, triglycerides)	Obtain at diagnosis and every 2 yr
Sleep apnea	Sleep study to assess overnight oxygen saturation	

Table 589-4 Classification of Diabetic Ketoacidosis

	NORMAL	MILD	MODERATE	SEVERE*
CO_2 (mEq/L, venous)†	20-28	16-20	10-15	<10
pH (venous)†	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

*Severe hypernatremia (corrected Na >150 mEq/L) would also be classified as severe diabetic ketoacidosis.
†CO_2 and pH measurement are method dependent; normal ranges may vary.

Table 589-5 Starting Doses of Insulin (units/kg/day)

	NO DIABETIC KETOACIDOSIS	DIABETIC KETOACIDOSIS
Prepubertal	0.25-0.50	0.75-1.0
Pubertal	0.50-0.75	1.0-1.2
Postpubertal	0.25-0.50	0.8-1.0

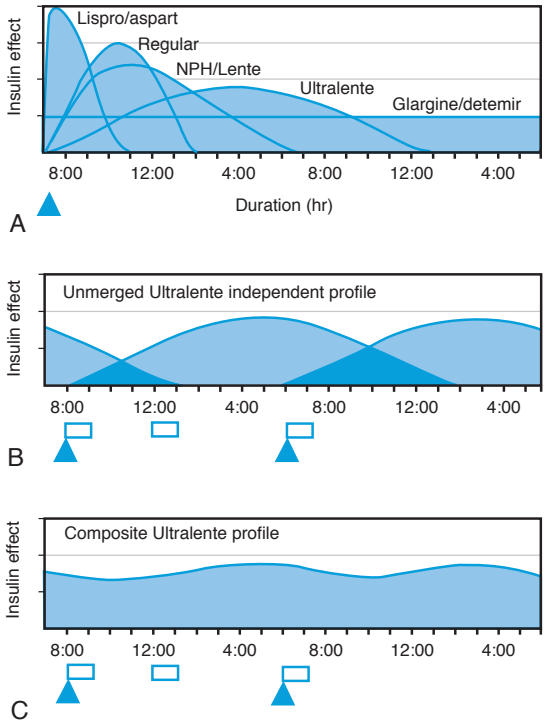

Figure 589-6 Approximate insulin effect profiles. Meals are shown as rectangles below time axis. **A,** The following relative peak effect and duration units are used: lispro/aspart, peak 20 for 4 hr; regular, peak 15 for 7 hr; neutral protamine Hagedorn/Lente, peak 12 for 12 hr; Ultralente, peak 9 for 18 hr; glargine, peak 5 for 24 hr. Although Lente and Ultralente are no longer manufactured, they are shown to give historical comparison to newer insulin analogs. ▲, Injection time. **B,** Two Ultralente injections given at breakfast and supper. Note overlap of profiles. **C,** Composite curve showing approximate cumulative insulin effect for the 2 Ultralente injections. This composite view is much more useful to the patient, parents, and medical personnel because it shows important combined effects of multiple insulin injections with variable absorption characteristics and overlapping durations.

Table 589-6 Diabetic Ketoacidosis Treatment Protocol

TIME	THERAPY	COMMENTS
1st hr	10-20 mL/kg IV bolus 0.9% NaCl or LR Insulin drip at 0.05 to 0.10 units/kg/hr	Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral edema
2nd hr until DKA resolution	0.45% NaCl: plus continue insulin drip 20 mEq/L KPhos and 20 mEq/L KAc 5% glucose if blood sugar >250 mg/dL (14 mmol/L)	$\text{IV rate} = \frac{85\,\text{mL/kg} + \text{maintenance} - \text{bolus}}{23\,\text{hr}}$ If K <3 mEq/L, give 0.5-1.0 mEq/kg as oral K solution *or* increase IV K to 80 mEq/L
Variable	Oral intake with subcutaneous insulin	No emesis; CO_2 ≥16 mEq/L; normal electrolytes
Note that the initial IV bolus is considered part of the total fluid allowed in the 1st 24 hr and is subtracted before calculating the IV rate.		
Maintenance (24 hr) = 100 mL/kg (for the first 10 kg) + 50 mL/kg (for the second 10 kg) + 25 mL/kg (for all remaining kg)		
Sample calculation for a 30-kg child: 1st hr = 300 mL IV bolus 0.9% NaCl or LR $\text{2nd and subsequent hr} = \frac{(85\,\text{mL} \times 30) + 1750\,\text{mL} - 300\,\text{mL}}{23\,\text{hr}} = \frac{175\,\text{mL}}{\text{hr}}$ (0.45% NaCl with 20 mEq/L Kphos and 20 mEq/L KAc)		

DKA, diabetic ketoacidosis; I/O, input and output (urine, emesis); K, potassium; KAc, potassium acetate; KPhos, potassium phosphate; LR, lactated Ringer solution; NaCl, sodium chloride; NPO, nothing by mouth.

Table 589-8 Summary of Nutrition Guidelines for Children and/or Adolescents with Type 1 Diabetes Mellitus

NUTRITION CARE PLAN

Promotes optimal compliance.

Incorporates goals of management: normal growth and development, control of blood glucose, maintenance of optimal nutritional status, and prevention of complications. Uses staged approach.

NUTRIENT RECOMMENDATIONS AND DISTRIBUTION

NUTRIENT	(%) OF CALORIES	RECOMMENDED DAILY INTAKE
Carbohydrate	Will vary	High fiber, especially soluble fiber; optimal amount unknown
Fiber	>20 g/day	
Protein	12-20	
Fat	<30	
Saturated	<10	
Polyunsaturated	6-8	
Monounsaturated	Remainder of fat allowance	
Cholesterol		300 mg
Sodium		Avoid excessive; limit to 3,000-4,000 mg if hypertensive

ADDITIONAL RECOMMENDATIONS

Energy: If using measured diet, reevaluate prescribed energy level at least every 3 mo.

Protein: High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore, 12-20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful.

Alcohol: Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school.

Snacks: Snacks vary according to individual needs (generally 3 snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).

Alternative sweeteners: Use of a variety of sweeteners is suggested.

Educational techniques: No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required.

Eating disorders: Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.

Exercise: Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.

Table 589-7 Calorie Needs for Children and Young Adults

AGE	KCAL REQUIRED/KG BODY WEIGHT*
CHILDREN	
0-12 mo	120
1-10 yr	100-75
YOUNG WOMEN	
11-15 yr	35
≥16 yr	30
YOUNG MEN	
11-15 yr	80-55 (65)
16-20 yr	
Average activity	40
Very physically active	50
Sedentary	30

Numbers in parentheses are means.

*Gradual decline in calories per unit weight as age increases.

From Nutrition guide for professionals: diabetes education and meal planning, *Alexandria, VA, and Chicago, IL, 1988, The American Diabetes Association and The American Dietetic Association.*

Table 589-11 Guidelines for Intravenous Insulin Coverage During Surgery

BLOOD GLUCOSE LEVEL (mg/dL)	INSULIN INFUSION (units/kg/hr)	BLOOD GLUCOSE MONITORING
<120	0.00	1 hr
121-200	0.03	2 hr
200-300	0.06	2 hr
300-400	0.08	1 hr*
400	0.10	1 hr*

An infusion of 5% glucose and 0.45% saline solution with 20 mEq/L of potassium acetate is given at 1.5 times maintenance rate.

*Check urine ketones.

Table 589-9 Target Premeal and 30-Day Average Blood Glucose Ranges and the Corresponding Hemoglobin A_{1c} for Each Age Group

AGE GROUP (yr)	TARGET PREMEAL BG RANGE (mg/dL)	30-DAY AVERAGE BG RANGE (mg/dL)	TARGET HbA_{1c} (%)
<5	100-200	180-250	7.5-9.0
5-11	80-150	150-200	6.5-8.0
12-15	80-130	120-180	6.0-7.5
16-18	70-120	100-150	5.5-7.0

In our laboratory, the nondiabetic reference range for HbA_{1c} is 4.5-5.7% (95% confidence interval).

BG, blood glucose; HbA_{1c}, hemoglobin A_{1c}.

Table 589-13 Testing for Type 2 Diabetes in Children

- Criteria*
  - Overweight (body mass index >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
  - *Plus*
  - Any 2 of the following risk factors:
    - Family history of type 2 diabetes in 1st- or 2nd-degree relative
    - Race/ethnicity (Native American, African-American, Hispanic, Asian/Pacific Islander)
    - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)
- Age of initiation: age 10 yr or at onset of puberty if puberty occurs at a younger age
- Frequency: every 2 yr
- Test: fasting plasma glucose preferred

*Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

Table 589-10 Guidelines for Sick Day Management

	GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN		
URINE KETONE STATUS	Insulin	Correction Doses*	COMMENT
Negative or small†	q2hr	q2hr for glucose >250 mg/dL	Check ketones every other void
Moderate to large‡	q1hr	q1hr for glucose >250 mg/dL	Check ketones each void; go to hospital if emesis occurs

Basal insulin: glargine or detemir basal insulin should be given at the usual dose and time. NPH and Lente should be reduced by half if blood glucose <150 mg/dL and the oral intake is limited.
Oral fluids: sugar-free if blood glucose >250 mg/dL (14 mmol/L); sugar-containing if blood glucose <250 mg/dL.
Call physician or nurse if blood glucose remains elevated after 3 extra doses; if blood glucose remains less than 70 mg/dL and child cannot take oral supplement; if dehydration occurs.
*Give insulin based on individualized dosing schedule. Also give usual dose for carbohydrate intake if glucose >150 mg/dL.
†For home serum ketones <1.5 mmol/L per commercial kit.
‡For home serum ketones >1.5 mmol/L.

Table 589-14 Oral Hypoglycemic Agents

DRUG	MECHANISM OF ACTION	DURATION OF BIOLOGIC EFFECT (hr)	USUAL DAILY DOSE (mg)	DOSES/DAY	SIDE EFFECTS	CAUTION
Biguanide	Insulin sensitizer				Gastrointestinal disturbance, lactic acidosis	Avoid in hepatic or renal impairment
Metformin			1500-2500	2-3		
Sulfonylureas						
1st generation						
Acetohexamide		12-18	500-750	1 or divided		
Chlorpropamide		27-72	250-500	1		
Tolbutamide		14-16	1000-2000	1 or divided		
2nd generation						
Glipizide		14-16	2.5-10 XL: 5-10	1 or divided 1		
Glyburide		20-24+	2.5-10	1 or divided		
Glimepiride		24+	2-4	1		
Glitinides	Promote insulin secretion					Titrate carefully in renal or hepatic dysfunction
Repaglinide		≤24	2-16	3		
Nateglinide		4	360	3		
α-Glucosidase inhibitors	Slow hydrolysis and absorption of complex carbohydrates		150-300	3 (with meals)	Transient gastrointestinal disturbances	
Acarbose Miglitol			150-300	3 (with meals)		
Thiazolidinedione	Peripheral insulin sensitizer				Upper respiratory tract infection, headache, edema, weight gain	
Rosiglitazone			4-8	1 or divided		
Pioglitazone			15-45	1		
Sitagliptin	GLP-1 receptor agonist	24	50-100	1	Upper respiratory tract infection, sore throat, diarrhea	No data in children or adolescents

Table 589-16 Summary of MODY Types and Special Clinical Characteristics

	GENE MUTATED	FUNCTION	SPECIAL FEATURE
MODY1	*HNF4α*	Transcription factor	Decreased levels of triglycerides, apolipoproteins AII and CIII (5-10% of MODY), neonatal hypoglycemia, very sensitive to sulfonylureas
MODY2	Glucokinase *(GCK)*	Enzyme, glucose sensor	Hyperglycemia of early onset but mild and nonprogressive; common (30-70% MODY)
MODY3	*HNF1α*	Transcription factor	Decreased renal absorption of glucose and consequent glycosuria; common (30-70% of cases of MODY); very sensitive to sulfonylureas
MODY4	*IPF-1*	Necessary for pancreatic development	Homozygous mutation causes pancreatic agenesis
MODY5	*HNF1β*	Transcription factor	Renal malformations; associated with uterine abnormalities, hypospadias, joint laxity, and learning difficulties, pancreatic atrophy, pancreatic exocrine insufficiency; 5-10% of MODY
MODY6	*NEUROD1*	Differentiation factor in the development of pancreatic islets	Extremely rare
MODY7	*KFL11*	Zinc finger transcription factor	Early-onset type II diabetes mellitus
MODY8	*CEL*	Bile salt–dependent lipase	Hyperglycemia; fecal elastase deficiency; exocrine pancreatic atrophy
MODY9	*PAX4*	Transcription factor	
MODY10	*INS*	Insulin gene	Usually associated with neonatal diabetes
MODY11	*BLK*	B-lymphocyte tyrosine kinase	Early-onset T1DM without autoantibodies

MODY, maturity-onset diabetes of the young.
From Nakhla M, Polychronakos C: Monogenic and other unusual causes of diabetes mellitus, Pediatr Clin North Am *52:1637–1650, 2005.*

Table 589-17 Clinical and Biochemical Features Associated with Type 1 Diabetes, Type 2 Diabetes and the Common Subtypes of Maturity-Onset Diabetes of the Young

FEATURES	TYPE 1 DIABETES	TYPE 2 DIABETES	GCK-MODY	HNF1A/4A-MODY
Typical age of diagnosis (yr)	10-30	>25	Present from birth; presents at any age	15-45
Diabetic ketoacidosis	Common	Rare	Rare	Rare
Insulin dependent	Yes	No	No	No
Parental history of diabetes	<15%	>50% in young onset type 2 diabetes	If tested, 1 parent usually has impaired fasting glycemia (may not be previously known)	60-90%*
Obesity	Uncommon	Common	Uncommon	Uncommon
Insulin resistance	Uncommon	Common	Uncommon	Uncommon
Presence of β-cell antibodies	>90%	Negative	Rare	Rare
C-peptide concentrations	Undetectable/low	Normal/high	Normal	Normal
Optimal first-line treatment	Insulin	Metformin	None	Sulfonylurea

*Family history is often part of the criteria for testing. Some reports cite a parental history of 60-70%.
GCK, glucokinase; HNF1A/4A, hepatocyte nuclear factor 1α/4α; MODY, maturity-onset diabetes of the young.
From Thanabalasingham G, Owen KR: Diagnosis and management of maturity onset diabetes of the young (MODY), BMJ *343:d6044, 2011, Table 2, p. 838.*

Table 589-18 Clinical and Biochemical Features of Inherited Lipodystrophies

	CONGENITAL GENERALIZED LIPODYSTROPHY		FAMILIAL PARTIAL LIPODYSTROPHY	
Subtype	**BSCL1**	**BSCL2**	**FPLD2**	**FPLD3**
Defective gene	*AGPAT2*	*BSCL2*	*LMNA*	*PPARG*
Clinical onset	Soon after birth	Soon after birth	Puberty	Usually puberty, but may present in younger children
Fat distribution	Generalized absence	Generalized absence	Loss of limb and gluteal fat; typically excess facial and nuchal fat; trunk fat often lost	Loss of limb and gluteal fat; preserved facial and trunk fat
Cutaneous features	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women
Musculoskeletal	Acromegaloid features common	Acromegaloid features common	Frequent muscle hypertrophy; some have overlap features of muscular dystrophy	Nil specific
Nonalcoholic fatty liver disease	Severe	Severe	Yes	Yes
Dyslipidemia	Severe associated with pancreatitis	Severe associated with pancreatitis	Yes, may be severe	Yes, may be severe
Insulin resistance	Severe early onset	Severe early onset	Severe	Severe; early onset in some
Diabetes onset	<20 yr	<20 yr	Variable; generally later in men than women	Variable; generally later in men than women
Hypertension	Common	Common	Common	Very common
Other		Mild mental retardation possible		

Table 590-1 Screening Scheme for Developmental Delay: Upper Range

AGE (mo)	GROSS MOTOR	FINE MOTOR	SOCIAL SKILLS	LANGUAGE
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with 1 hand held	Releases an object on command	Comes when called	1-2 meaningful words
18	Walks upstairs with assistance	Feeds from a spoon	Mimics actions of others	At least 6 words
24	Runs	Builds a tower of 6 blocks	Plays with others	2-3–word sentences

Table 590-2 Timing of Selected Primitive Reflexes

REFLEX	ONSET	FULLY DEVELOPED	DURATION
Palmar grasp	28 wk gestation	32 wk gestation	2-3 mo postnatal
Rooting	32 wk gestation	36 wk gestation	Less prominent after 1 mo postnatal
Moro	28-32 wk gestation	37 wk gestation	5-6 mo postnatal
Tonic neck	35 wk gestation	1 mo postnatal	6-7 mo postnatal
Parachute	7-8 mo postnatal	10-11 mo postnatal	Remains throughout life

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The Nervous System

Table 590-3 Preferred Imaging Procedures in Neurologic Diseases

ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK
CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions
Otherwise, MRI/MRA (head and neck) with and without gadolinium and with diffusion-weighted images
If the examination findings localize to the anterior circulation, carotid ultrasound should be performed rather than neck CTA or MRA
Obtain an MRV if the infarct does not follow an arterial distribution
CT or MRI can detect infarcts more than 24 hr old, although MRI is generally preferred to avoid exposure to ionizing radiation

INTRAPARENCHYMAL HEMORRHAGE
CT if <24 hr; MRI if >24 hr
MRI and MRA to assess for underlying vascular malformation, tumor, etc.
Catheter angiography if MRA is nondiagnostic

ARTERIOVENOUS MALFORMATION
CT for acute hemorrhage; MRI and MRA with and without gadolinium as early as possible
Catheter angiography if noninvasive imaging is nondiagnostic

CEREBRAL ANEURYSM
CT without contrast for acute subarachnoid hemorrhage
MRA or CTA to identify the aneurysm
Catheter angiography may be necessary in some cases
TCD to detect vasospasm

HYPOXIC–ISCHEMIC BRAIN INJURY
Ultrasound in infants
If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI
In older children, CT if unstable; otherwise, MRI
MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes

METABOLIC DISORDERS
MRI, particularly T2-weighted and FLAIR images
Diffusion-weighted images may be useful in distinguishing acute and chronic changes
MRS, SPECT, and PET may be useful in certain disorders

HYDROCEPHALUS
Ultrasound (in infants), CT with and without contrast, or MR with and without gadolinium for diagnosis of communicating hydrocephalus
MR with and without gadolinium for diagnosis of noncommunicating hydrocephalus
Ultrasound (in infants) or CT to follow ventricular size in response to treatment

HEADACHE
CT with and without contrast or MRI with and without gadolinium if a structural disorder is suspected (MRI is preferred in nonemergent situations as it does not involve ionizing radiation and provides a better view of the parenchyma)

HEAD TRAUMA
CT without contrast initially
MRI after initial assessment and treatment if clinically indicated. Diffusion tensor imaging and/or diffusion kurtosis sequences may be useful to detect subtle white matter abnormalities

EPILEPSY
MRI with and without gadolinium. Thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected
PET
Interictal SPECT

BRAIN TUMOR
MRI with and without gadolinium
MRS
PET

MULTIPLE SCLEROSIS
MRI with and without gadolinium
Obtain sagittal FLAIR images

MENINGITIS OR ENCEPHALITIS
CT without and with contrast before lumbar puncture if there are signs of increased ICP on examination
MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis

BRAIN ABSCESS
MRI with and without gadolinium
Diffusion-weighted images and MRS can help to differentiate abscess from necrotic tumor
If the patient is unstable, CT with and without contrast followed by MRI with and without contrast when feasible

MOVEMENT DISORDERS
MRI with and without gadolinium
PET
DaTscan (SPECT scan using ioflupane iodine-123 as the contrast agent for detecting dopamine transporters in suspected parkinsonian syndromes)

CTA, computed tomographic angiography; FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; MRA, magnetic resonance angiography; MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler ultrasonography.

Table 591-5 Commonly Used Clinical Genetic Classifications of Craniosynostoses

DISORDER	CAUSE
ISOLATED CRANIOSYNOSTOSIS	
Morphologically described	Unknown, uterine constraint, or *FGFR3* mutation
SYNDROMIC CRANIOSYNOSTOSIS	
Antler-Bixler syndrome	Unknown
Apert syndrome	Usually 1 of 2 mutations in *FGFR2*
Beare-Stevenson syndrome	Mutation in *GFGR2* or *FGFR3*
Baller-Gerold syndrome	Mutation in *TWIST* heterogenous
Carpenter syndrome	Unknown
Craniofrontonasal dysplasia	Unknown gene at *Xp22*
Crouzon syndrome	Numerous different mutations at *FGFR2*
Crouzonomesodermoskeletal syndrome	Mutation in *FGFR3*
Jackson-Weiss syndrome	Mutation in *FGFR2*
Muenke syndrome	Mutation in *FGFR3*
Pfeiffer syndrome	Mutation in *FGFR1* or numerous mutation in *FGFR2*
Saethre-Chotzen syndrome	Mutation in *TWIST*
Shprintzen-Goldberg syndrome	Mutation in *FBEN1*

From Ridgway EB, Weiner HL: Skull deformities, Pediatr Clin North Am *51:359–387, 2004.*

Table 591-1 Cutaneous Lesions Associated with Occult Spinal Dysraphism

IMAGING INDICATED
Subcutaneous mass or lipoma
Hairy patch
Dermal sinus
Atypical dimples (deep, >5 mm, >25 mm from anal verge)
Vascular lesion, e.g., hemangioma or telangiectasia
Skin appendages or polypoid lesions, e.g., skin tags, tail-like appendages
Scar-like lesions

IMAGING UNCERTAIN
Hyperpigmented patches
Deviation of the gluteal fold

IMAGING NOT REQUIRED
Simple dimples (<5 mm, <25 mm from anal verge)
Coccygeal pits

Table 591-2 Disorders Associated with Agenesis of the Corpus Callosum*

DISORDER	SALIENT FEATURES
WITH IDENTIFIED GENES†	
Andermann syndrome *(KCC3)*	ACC, progressive neuropathy, and dementia
Donnai-Barrow syndrome *(LRP2)*	Diaphragmatic hernia, exomphalos, ACC, deafness
Frontonasal dysplasia *(ALX1)*	ACC, bilateral extreme microphthalmia, bilateral oblique facial cleft
XLAG *(ARX)*	Lissencephaly, ACC, intractable epilepsy
Microcephaly *(TBR2)*	ACC, polymicrogyria
Microcephaly with simplified gyral pattern and ACC *(WDR62)*	
Mowat-Wilson syndrome *(ZFHX1B)*	Hirschsprung disease, ACC
Pyridoxine-dependent epilepsy *(ALDH7A1)*	ACC, seizures, other brain malformations
Pyruvate dehydrogenase deficiency *(PDHA1, PDHB, PDHX)*	ACC with other brain changes
ACC with fatal lactic acidosis *(MRPS16)*	Complexes I and IV deficiency, ACC, brain malformations
HSAS/MASA syndromes *(L1CAM)*	Hydrocephalus, adducted thumbs, ACC, MR
ACC SEEN CONSISTENTLY (NO GENE YET IDENTIFIED)	
Acrocallosal syndrome	ACC, polydactyly, craniofacial changes, MR
Aicardi syndrome	ACC, chorioretinal lacunae, infantile spasms, MR
Chudley-McCullough syndrome	Hearing loss, hydrocephalus, ACC, colpocephaly
FG syndrome	MR, ACC, craniofacial changes, macrocephaly
Genitopatellar syndrome	Absent patellae, urogenital malformations, ACC
Temtamy syndrome	ACC, optic coloboma, craniofacial changes, MR
Toriello-Carey syndrome	ACC, craniofacial changes, cardiac defects, MR
Vici syndrome	ACC, albinism, recurrent infections, MR
ACC SEEN OCCASIONALLY (PARTIAL LIST)‡	
ACC with spastic paraparesis *(SPG11; SPG15)*	Progressive spasticity and neuropathy, thin corpus callosum
Craniofrontonasal syndrome	Coronal craniosynostosis, facial asymmetry, bifid nose
Fryns syndrome	CDH, pulmonary hypoplasia, craniofacial changes
Marden-Walker syndrome	Blepharophimosis, micrognathia, contractures, ACC
Meckel-Gruber syndrome	Encephalocele, polydactyly, polycystic kidneys
Nonketotic hyperglycinemia *(GLDC, GCST, GCSH)*	ACC, cerebral and cerebellar atrophy, myoclonus, progressive encephalopathy
Microphthalmia with linear skin defects	Microphthalmia, linear skin markings, seizures
Opitz G syndrome	Pharyngeal cleft, craniofacial changes, ACC, MR
Orofaciodigital syndrome	Tongue hamartoma, microretrognathia, clinodactyly
Pyruvate decarboxylase deficiency	Lactic acidosis, seizures, severe MR and spasticity
Rubinstein-Taybi syndrome	Broad thumbs and great toes, MR, microcephaly
Septooptic dysplasia (de Morsier syndrome)	Hypoplasia of septum pellucidum and optic chiasm
Sotos syndrome	Physical overgrowth, MR, craniofacial changes
Warburg micro syndrome	Microcephaly, microphthalmia, microgenitalia, MR
Wolf-Hirschhorn syndrome	Microcephaly, seizures, cardiac defects, 4p–

*Reliable incidence data are unavailable for these very rare syndromes.

†Gene symbols in parentheses.

‡Many of these also may consistently have a thin of dysplastic corpus callosum, such as Sotos' syndrome or agenesis of the corpus callosum (ACC) with spastic paraparesis (SPG11). The overlap between ACC and these conditions is still under investigation. Other gene symbols are omitted from this section.

4p–, deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf-Hirschhorn patients; ACC, agenesis of the corpus callosum; ARX, Aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; HSAS/MASA, X-linked hydrocephalus/mental retardation, aphasia, shuffling gait, and adducted thumbs; KCC3, KCl cotransporter 3; L1CAM, L1 cell adhesion molecule; MR, mental retardation; MRPS16, mitochondrial ribosomal protein S16; SPG11, spastic paraplegia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFHX1B, zinc finger homeobox 1b.

From Sherr EH, Hahn JS: Disorders of forebrain development. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *5th ed. Philadelphia, 2012, WB Saunders, Table 23-2.*

Table 591-3 Causes of Microcephaly

CAUSES	CHARACTERISTIC FINDINGS
PRIMARY (GENETIC)	
Familial (autosomal recessive)	Incidence 1 in 40,000 live births Typical appearance with slanted forehead, prominent nose and ears; severe mental retardation and prominent seizures; surface convolutional markings of the brain, poorly differentiated and disorganized cytoarchitecture
Autosomal dominant	Nondistinctive facies, upslanting palpebral fissures, mild forehead slanting, and prominent ears Normal linear growth, seizures readily controlled, and mild or borderline mental retardation
Syndromes	
Down (trisomy 21)	Incidence 1 in 800 live births Abnormal rounding of occipital and frontal lobes and a small cerebellum; narrow superior temporal gyrus, propensity for Alzheimer neurofibrillary alterations, ultrastructure abnormalities of cerebral cortex
Edward (trisomy 18)	Incidence 1 in 6,500 live births Low birthweight, microstomia, micrognathia, low-set malformed ears, prominent occiput, rocker-bottom feet, flexion deformities of fingers, congenital heart disease, increased gyri, heterotopias of neurons
Cri-du-chat (5 p-)	Incidence 1 in 50,000 live births Round facies, prominent epicanthic folds, low-set ears, hypertelorism, characteristic cry No specific neuropathology
Cornelia de Lange	Prenatal and postnatal growth delay; synophrys; thin, downturning upper lip Proximally placed thumb
Rubinstein-Taybi	Beaked nose, downward slanting of palpebral fissures, epicanthic folds, short stature, broad thumbs and toes
Smith-Lemli-Opitz	Ptosis, scaphocephaly, inner epicanthic folds, anteverted nostrils Low birthweight, marked feeding problems
SECONDARY (NONGENETIC)	
Congenital Infections	
Cytomegalovirus	Small for dates, petechial rash, hepatosplenomegaly, chorioretinitis, deafness, mental retardation, seizures Central nervous system calcification and microgyria
Rubella	Growth retardation, purpura, thrombocytopenia, hepatosplenomegaly, congenital heart disease, chorioretinitis, cataracts, deafness Perivascular necrotic areas, polymicrogyria, heterotopias, subependymal cavitations
Toxoplasmosis	Purpura, hepatosplenomegaly, jaundice, convulsions, hydrocephalus, chorioretinitis, cerebral calcification
Drugs	
Fetal alcohol	Growth retardation, ptosis, absent philtrum and hypoplastic upper lip, congenital heart disease, feeding problems, neuroglial heterotopia, disorganization of neurons
Fetal hydantoin	Growth delay, hypoplasia of distal phalanges, inner epicanthic folds, broad nasal ridge, anteverted nostrils
Other Causes	
Radiation	Microcephaly and mental retardation most severe with exposure before 15th wk of gestation
Meningitis/encephalitis	Cerebral infarcts, cystic cavitation, diffuse loss of neurons
Malnutrition	Controversial cause of microcephaly
Metabolic	Maternal diabetes mellitus and maternal hyperphenylalaninemia
Hyperthermia	Significant fever during 1st 4-6 wk has been reported to cause microcephaly, seizures, and facial anomalies Pathologic studies show neuronal heterotopias Further studies show no abnormalities with maternal fever
Hypoxic–ischemic encephalopathy	Initially diffuse cerebral edema; late stages characterized by cerebral atrophy and abnormal signals on MRI

Table 591-6 Epidemiology and Clinical Characteristics of the Common Craniosynostoses

TYPE	EPIDEMIOLOGY	SKULL DEFORMITY	CLINICAL PRESENTATION
Sagittal	Most common CSO affecting a single suture, 80% male	Dolicocephaly or scaphocephaly (boat-shaped)	Frontal bossing, prominent occiput, palpable keel ridge. OFC normal and reduced biparietal diameter
Coronal	18% of CSO, more common in girls Associated with Apert syndrome (with syndactyly) and Crouzon disease, which includes abnormal sphenoid, orbital, and facial bones (hypoplasia of the midface)	Unilateral: plagiocephaly Bilateral: brachycephaly, acrocephaly	Unilateral: flattened forehead on affected side, flat checks, nose deviation on normal side; higher supraorbital margin leading to harlequin sign on radiograph and outward rotation of orbit can result in amblyopia Bilateral: broad, flattened forehead. In Apert syndrome accompanied by syndactyly and in Crouzon disease by hypoplasia of the midface and progressive proptosis
Lambdoid	10-20% of CSO, M:F ratio 4:1	Lambdoid/occipital plagiocephaly; right side affected in 70% of cases	Unilateral: flattening of occiput, indentation along synostotic suture, bulging of ipsilateral forehead leading to rhomboid skull, ipsilateral ear is anterior and inferior Bilateral: brachycephaly with bilateral anteriorly and inferiorly displaced ears
Metopic	Association with 19p chromosome abnormality	Trigonocephaly	Pointed forehead and midline ridge, hypotelorism
Multiple		Oxycephaly	Tower skull with undeveloped sinuses and shallow orbits, and elevated intercranial pressure

CSO, craniosynostosis; OFC, occipital-frontal circumference.
From Ridgway EB, Weiner HL: Skull deformities, Pediatr Clin North Am *51:359–387, 2004.*

Table 592-2 Important Historical and Physical Factors in the Evaluation of a Patient with Plagiocephaly

	DEFORMATIONAL	SYNOSTOTIC
Birth history	• Intrauterine compression • Firstborn child	• Typically no complications
Head shape at birth	• Typically normal	• Can be irregular
Age first noticed shape irregularity	• Usually in 1st few mo of life	• Can be at birth
How patient prefers to sleep	• Same side, same position • Same even during naps	• Variable
Bald spot	• Yes	• No
Motor development for age	• If age atypical for deformational plagiocephaly, typically slow motor development for age • Torticollis present • History of limited activity or mobility	• Varies depending on presence of concomitant syndrome
Tummy time	• Decreased	• Suggested time
Signs/symptoms of increasing intracranial pressure	• No	• Possible

Table 592-3 Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly

	DEFORMATIONAL PLAGIOCEPHALY	CRANIOSYNOSTOSIS
Causes	External forces applied to the skull • Prenatal: uterine compression, intrauterine constrained • Postnatal: congenital torticollis, sleeping position	Premature fusion of 1 or more cranial sutures
Common types	• Lateral • Posterior	• Bilateral coronal • Sagittal • Metopic
Common distinguishing features	• Normal round head shape at birth • Parallelogram shape to head • Ipsilateral ear anteriorly displaced • No palpable bony ridges	• Can have abnormal head shape at birth • Trapezoid shape to head • Ipsilateral ear posteriorly displaced • Palpable bony ridges
Management	• Repositioning • Physical therapy • Helmet in some cases	• Surgery • Helmet in some cases

Adapted from Nield LS, Brunner MD, Kamat D: The infant with a misshapen head. Clin Pediatr (Phila) *46:292–298, 2007, Tables 1 and 2.*

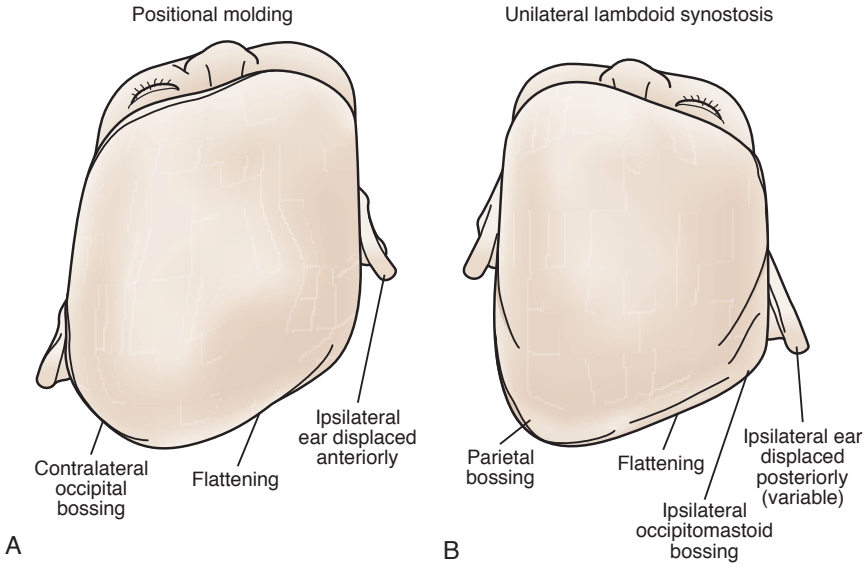

Figure 592-1 Differentiating physical find-ings between deformational plagiocephaly and craniosynostosis. Vertex views. **A,** Right-sided deformational plagiocephaly exhibit-ing a parallelogram head shape. **B,** Right-sided lambdoid craniosynostosis exhibiting a trapezoid-like head shape.

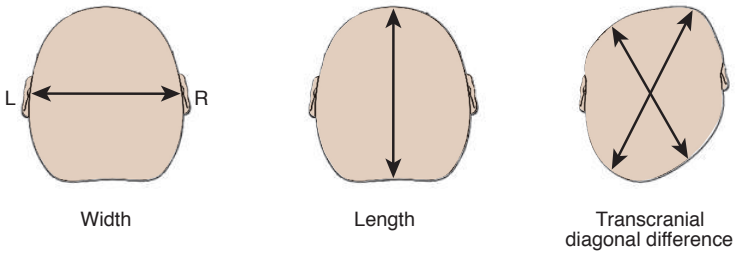

Figure 592-2 Cranial measurements.

Table 591-4 Causes of Hydrocephalus

COMMUNICATING
Achondroplasia
Basilar impression
Benign enlargement of subarachnoid space
Choroid plexus papilloma
Meningeal malignancy
Meningitis
Posthemorrhagic
NONCOMMUNICATING
Aqueductal stenosis
Infectious*
X-linked
Mitochondrial
Autosomal recessive
Autosomal dominant
L1CAM mutations
Chiari malformation
Dandy-Walker malformation
Klippel-Feil syndrome
Mass lesions
Abscess
Hematoma
Tumors and neurocutaneous disorders
Vein of Galen malformation
Walker-Warburg syndrome
HYDRANENCEPHALY
Holoprosencephaly
Massive hydrocephalus
Porencephaly

*Toxoplasmosis, neurocysticercosis mumps.

Table 592-4 Diagnostic Guide for Determining Type and Severity of Lateral and Posterior Deformational Plagiocephaly

TYPE CLINICAL FINDINGS	LATERAL DEFORMATIONAL PLAGIOCEPHALY	POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)
Occiput (vertex view)	Ipsilateral occipital flattening; contralateral occipital bossing	Uniform occipital flattening
Ear position (vertex view)	Ipsilateral ear may be anteriorly displaced	Normal
Face, forehead (anterior, lateral, and vertex views)	May be normal; more-severe cases may present with the following: mandibular asymmetry, ipsilateral frontal bossing, contralateral forehead flattening, ipsilateral cheek anteriorly displaced	Temporal bossing, increase in vertical height in severe cases
Other	Torticollis, head position preference	Large size, history of limited activity or limited mobility

SEVERITY	LATERAL DEFORMATIONAL PLAGIOCEPHALY			POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)	
Mild	TDD 3-10 mm	Type I	Flattening restricted to the back of the skull	CI: 0.82-0.9	Central posterior deformity ("ping-pong ball depression")
Moderate	TDD 10-12 mm	Type II Type III	Malposition of ear Forehead deformity	CI: 0.9-1.0	Central posterior deformity and widening of posterior skull
Severe	TDD >12 mm	Type IV Type V	Malar deformity Vertical or temporal skull growth	CI: >1.0	Vertical head, head growth, or temporal bossing

CI, cephalic index (cranial index); TDD, transcranial diameter difference.

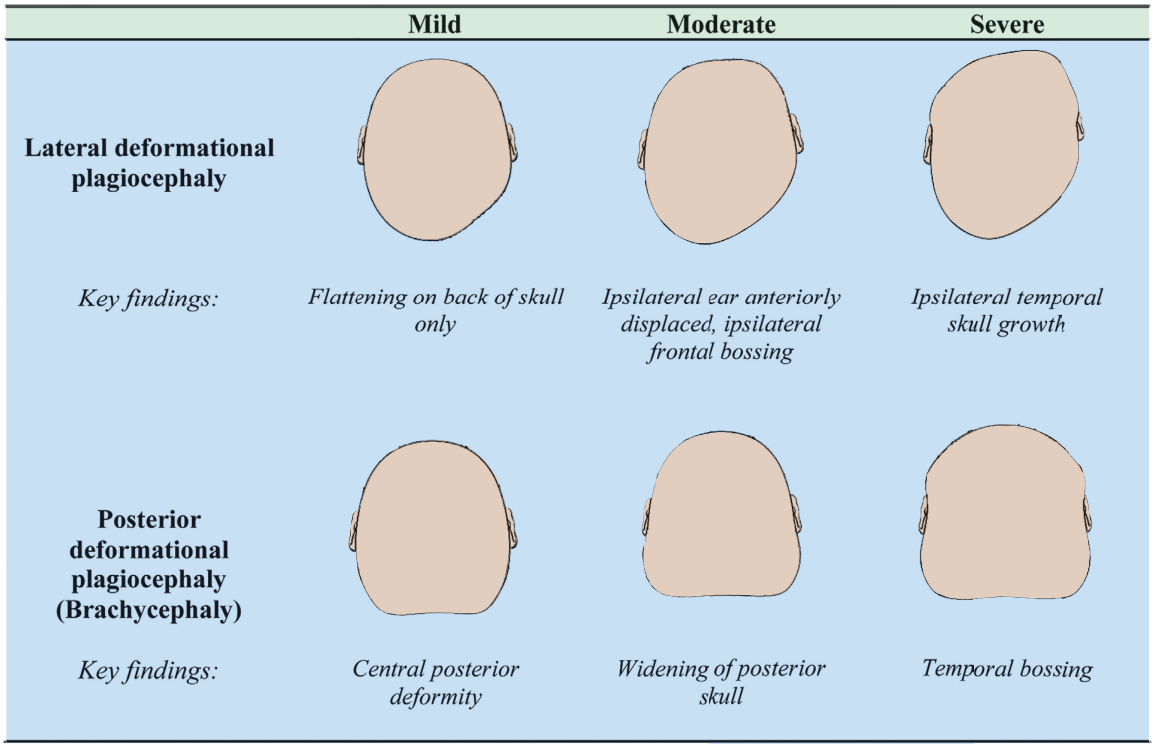

Figure 592-3 Types of deformational plagiocephaly.

Table 593-1 Types of Epileptic Seizures

SELF-LIMITED SEIZURE TYPES	CONTINUOUS SEIZURE TYPES
Focal Seizures	***Generalized Status Epilepticus***
Focal sensory seizures	Generalized tonic-clonic status epilepticus
• With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)	Clonic status epilepticus
• With experiential sensory symptoms (e.g., temporoparietooccipital junction seizures)	Absence status epilepticus
Focal motor seizures	Tonic status epilepticus
• With elementary clonic motor signs	Myoclonic status epilepticus
• With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)	***Focal Status Epilepticus***
• With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)	Epilepsia partialis continua of Kojevnikov
• With hyperkinetic automatisms	Aura continua
• With focal negative myoclonus	Limbic status epilepticus (psychomotor status)
• With inhibitory motor seizures	Hemiconvulsive status with hemiparesis
Gelastic seizures	
Hemiclonic seizures	PRECIPITATING STIMULI FOR REFLEX SEIZURES
Secondarily generalized seizures	Visual stimuli
Reflex seizures in focal epilepsy syndromes	• Flickering light—color to be specified when possible
Generalized Seizures	• Patterns
Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)	• Other visual stimuli
Clonic seizures	Thinking
• Without tonic features	Music
• With tonic features	Eating
Typical absence seizures	Praxis
Atypical absence seizures	Somatosensory
Absence with special features:	Proprioceptive
• Eyelid myoclonia	Reading
• Myoclonic absence	Hot water
Tonic seizures	Startle
Myoclonic seizures	
Myoclonic atonic seizures	
Negative myoclonus	
Atonic seizures	
Reflex seizures in generalized epilepsy syndromes	
Unknown	
Epileptic Spasms	

Table 593-1 Types of Epileptic Seizures

SELF-LIMITED SEIZURE TYPES	CONTINUOUS SEIZURE TYPES
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Focal motor seizures	Tonic status epilepticus
• With elementary clonic motor signs	Myoclonic status epilepticus
• With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)	***Focal Status Epilepticus***
• With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)	Epilepsia partialis continua of Kojevnikov
• With hyperkinetic automatisms	Aura continua
• With focal negative myoclonus	Limbic status epilepticus (psychomotor status)
• With inhibitory motor seizures	Hemiconvulsive status with hemiparesis
Gelastic seizures	
Hemiclonic seizures	PRECIPITATING STIMULI FOR REFLEX SEIZURES
Secondarily generalized seizures	Visual stimuli
Reflex seizures in focal epilepsy syndromes	• Flickering light—color to be specified when possible
Generalized Seizures	• Patterns
Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)	• Other visual stimuli
Clonic seizures	Thinking
• Without tonic features	Music
• With tonic features	Eating
Typical absence seizures	Praxis
Atypical absence seizures	Somatosensory
Absence with special features:	Proprioceptive
• Eyelid myoclonia	Reading
• Myoclonic absence	Hot water
Tonic seizures	Startle
Myoclonic seizures	
Myoclonic atonic seizures	
Negative myoclonus	
Atonic seizures	
Reflex seizures in generalized epilepsy syndromes	
Unknown	
Epileptic Spasms	

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

SPECIFIC SYNDROMES	AGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
EPILEPSIES OF UNKNOWN CAUSE OF INFANCY AND CHILDHOOD						
Benign infantile seizures (nonfamilial)	Infant	Infant	Good	PB	—	No
Benign childhood epilepsy with centrotemporal spikes	3-13 yr	16 yr	Good	CBZ, LEV, OXC, VPA	—	No
Early and late-onset idiopathic occipital epilepsy	2-8 yr; 6-17 yr	12 yr or younger; 18 yr	Good	CBZ, LEV, OXC, VPA	—	No
FAMILIAL (AUTOSOMAL DOMINANT) EPILEPSIES						
Benign familial neonatal convulsions	Newborn to young infant	Newborn to young infant	Good	PB	—	No
Benign familial infantile convulsions	Infant	Infant	Good	CBZ, PB	—	No
Autosomal dominant nocturnal frontal lobe epilepsy	Childhood		Variable	CBZ, GBP, OXC, PHT, TPM	CLB, LEV, PB, PHT	No
Familial lateral temporal lobe epilepsy	Childhood to adolescence		Variable	CBZ, GBP, OXC, PHT, TPM, VPA	CLB, LEV, PB, PHT	No
Generalized epilepsies with febrile seizures plus	Childhood to adolescence		Variable	ESM, LTG, TPM, VPA	CLB, LEV	No
STRUCTURAL–METABOLIC FOCAL EPILEPSIES						
Limbic Epilepsy						
Mesial temporal lobe epilepsy with hippocampal sclerosis	School-age or earlier	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Temporal resection
Mesial temporal lobe epilepsy defined by specific causes	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Temporal resection
Other types defined by location and causes	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, FBM, GBP, LAC, PB, PHT, ZON	Lesionectomy ± temporal resection
Neocortical Epilepsies						
Rasmussen syndrome	6-12 yr	Progressive	Ominous	Plasmapheresis, immunoglobulins	CBZ, LAC, PB, PHT, TPM	Functional hemispherectomy
Hemiconvulsion-hemiplegia syndrome	1-5 yr	Chronic	Severe	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Functional hemispherectomy
Other types defined by location and cause	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	PHT, PB, CLB, GBP, LAC, ZON	Lesionectomy ± cortical resection
Migrating partial seizures of early infancy	Infant	No remission	Ominous	Bromides, CBZ, LEV, PB, PHT, TPM, VPA	BDZ, LAC, ZON	No
GENERALIZED EPILEPSIES OF UNKNOWN CAUSE						
Benign myoclonic epilepsy in infancy	3 mo-3 yr	3-5 yr	Variable	LEV, TPM, VPA	BDZ, ZON	No
Epilepsy with myoclonic astatic seizures	3-5 yr	Variable	Variable	ESM, TPM, VPA	BDZ, ketogenic diet, LEV, LTG, steroids, ZON	No
Childhood absence epilepsy	5-6 yr	10-12 yr	Good	ESM, LTG, VPA	Acetazolamide, ketogenic diet, ZON	No
Epilepsy with myoclonic absences	1-12 yr	Variable	Guarded	ESM, VPA	BDZ, ZON	No

*Reflects current trends in practice, which may be off-label and may not be FDA approved for that indication. See Table 593-10 for FDA indications.

†May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types.

ACTH, adrenocorticotropic hormone; BDZ, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP: diazepam; ESM, ethosuximide; FBM: felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC: oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; RFD, rufinamide; TPM, topiramate; VGB: vigabatrin; VPA, valproic acid; ZON, zonisamide.

Continued

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options—cont'd

SPECIFIC SYNDROMES	AGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
GENERALIZED EPILEPSIES OF UNKNOWN CAUSE WITH VARIABLE PHENOTYPES						
Juvenile absence epilepsy	10-12 yr	Usually lifelong	Good	ESM, LTG, VPA	BDZ	No
Juvenile myoclonic epilepsy	12-18 yr	Usually lifelong	Good	LEV, TPM, VPA	BDZ, LTG, PB, PRM, ZON	No
Epilepsy with generalized tonic-clonic seizures only	12-18 yr	Usually lifelong	Good	LEV, LTG, TPM, VPA	BDZ, CBZ, ZON	No
REFLEX EPILEPSIES						
Idiopathic photosensitive occipital lobe epilepsy	10-12 yr	Unclear	Variable	VPA	BDZ, LEV, LTG, ZON	No
Other visual sensitive epilepsies	2-5 yr	Unclear	Variable	VPA	BDZ, LEV, LTG, ZON	No
Startle epilepsy	Variable	Long lasting	Guarded	CBZ, GBP, OXC, PHT, TPM, VPA	CLB, LEV, PB, PHT, ZON	Lesionectomy ± cortical resection in some
EPILEPTIC ENCEPHALOPATHIES						
Early myoclonic encephalopathy and Ohtahara syndrome	Newborn-infant	Poor, Ohtahara syndrome evolves into West syndrome	Ominous	PB, steroids, VGB	BDZ, ZON	No
West syndrome	Infant	Variable	Variable	ACTH, steroids, VGB	BDZ, FBM, IVIG, TPM, ZON	Lesionectomy ± cortical resection
Dravet syndrome (severe myoclonic epilepsy in infancy)	Infant	No remission	Severe	CLB, stiripentol, TPM, VPA	BDZ, ZON	No
Lennox-Gastaut syndrome	3-10 yr	No remission	Severe	CLB, LTG, RFD, TPM, VPA	BDZ, FBM, IVIG, steroids, ZON	Callosotomy
Landau-Kleffner syndrome	3-6 yr	8-12 yr	Guarded	LEV, nocturnal DZP, steroids, VPA	BDZ, ESM, IVIG, LTG	Multiple subpial transections, rarely lesionectomy
Epilepsy with continuous spike waves during slow-wave sleep	4-7 yr	8-12 yr	Guarded	LEV, nocturnal DZP, steroids, VPA	BDZ, ESM, IVIG, LTG	No
PROGRESSIVE MYOCLONUS EPILEPSIES						
Unverricht-Lundborg, Lafora, ceroid lipofuscinoses, etc.	Late infant to adolescent	Progressive	Ominous	TPM, VPA, ZON	BDZ, PB	No
OTHER EPILEPSIES AND SEIZURE DISORDERS OF UNKNOWN OR OTHER CAUSES						
Benign neonatal seizures	Newborn	Newborn	Good	LEV, PB	—	No
Febrile seizures	3-5 yr	3-6 yr	Good	PB or VPA if repeated and prolonged	—	No
Reflex seizures	Variable	n/a		LEV, VPA	LTG, ZON	No
Drug or other chemically induced seizures	Variable	n/a		Withdraw offending agent	—	No
Immediate and early posttraumatic seizures	Variable	n/a		LEV, PHT	—	No

Table 593-4 Identified Genes for Syndromic Epilepsy Syndromes*

SYNDROME	GENE	PROTEIN
Rett/atypical Rett syndromes	*MECP2* *CDKL5* *FOXG1* *MBD5* *MEF2C*	Methyl CpG binding protein 2 Cyclin-dependent kinase-like 5 Forkhead box protein G1 Methyl-CpG-binding domain protein 5 Myocyte-specific enhancer factor 2C
Angelman/Angelman-like/Pitt-Hopkins syndromes	*UBE3A* *SLC9A6* *MBD5* *TCF4* *NRXN1* *CNTNAP2*	Ubiquitin protein ligase E3A Sodium/hydrogen exchanger 6 Methyl-CpG-binding domain protein 5 Transcription factor 4 Neurexin-1 Contactin-associated protein-like 2
Mowat-Wilson syndrome	*ZEB2*	Zinc finger E-box-binding homeobox 2
Creatine deficiency syndromes	*GAMT* *GATM*	Guanidinoacetate *N*-methyltransferase Glycine amidinotransferase, mitochondrial
Neuronal ceroid lipofuscinosis (NCL)	*PPT1 (CLN1)* *TPP1 (CLN2)* *CLN3* *CLN5* *CLN6* *MFSD8 (CLN7)* *CLN8* *CTSD (CLN10)* *KCTD7 (CLN14)*	Palmitoyl-protein thioesterase 1 Tripeptidyl-peptidase 1 Battenin Ceroid-lipofuscinosis neuronal protein 5 Ceroid-lipofuscinosis neuronal protein 6 Major facilitator superfamily domain-containing protein 8 Ceroid-lipofuscinosis neuronal protein 8 Cathepsin D BTB/POZ domain-containing protein KCTD7
Adenosuccinate lyase deficiency	*ADSL*	Adenylosuccinate lyase
Cerebral folate deficiency	*FOLR1*	Folate receptor alpha
Epilepsy with variable learning and behavioral disorders	*GRIN2A* *SYN1*	Glutamate receptor ionotropic, *N*-methyl-D-aspartate (NMDA) 2A Synapsin-1
17q21.31 microdeletion syndrome	*KANSL1*	KAT8 regulatory nonspecific lethal (NSL) complex subunit 1
Microcephaly with early-onset intractable seizures and developmental delay (MCSZ)	*PNKP*	Bifunctional polynucleotide phosphatase/kinase

*Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing.

Table 593-5 Childhood Epileptic Syndromes with Generally Good Prognosis

SYNDROME	COMMENT
Benign neonatal familial convulsions	Dominant, may be severe and resistant for a few days Febrile or afebrile seizures (benign) occur later in a minority
Infantile familial convulsions	Dominant; seizures often in clusters
Febrile convulsions plus syndromes (see Table 593-2)	Febrile and afebrile generalized convulsions, absence and myoclonic seizures occur in different members. Seizures usually generalized (GEFS+) but in some families may be focal
Benign myoclonic epilepsy of infancy	Often seizures during sleep; 1 rare variety with reflex myoclonic seizures (touch, noise)
Partial idiopathic epilepsy with rolandic spikes (benign epilepsy with centrotemporal spikes)	Seizures with falling asleep or on awakening; focal sharp waves with centrotemporal location on EEG
Idiopathic occipital partial epilepsy	Early childhood form with seizures during sleep and ictal vomiting; can occur as status epilepticus Later form with occipital spikes that block on eye opening; migrainous symptoms and seizures; not always benign
Petit mal absence epilepsy	Cases with absences only; some have generalized seizures In most cases, absences disappear on therapy but there are resistant cases (unpredictable); 60-80% full remission
Juvenile myoclonic epilepsy	Adolescence onset, with early morning myoclonic seizures and generalized seizures during sleep or upon awakening; often history of absences in childhood

EEG, electroencephalogram; GEFS+, generalized epilepsy with febrile seizures plus.

Table 593-8 Selected Epilepsy Syndromes by Age of Onset

NEONATAL PERIOD
Benign familial neonatal seizures (BFNS)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
INFANCY
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile seizures
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
CHILDHOOD
Febrile seizures plus (FS+) (can start in infancy; this can be with generalized [GEFS+] or with focal seizures)
Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BCECTS)
Late-onset childhood occipital epilepsy (Gastaut type)
Autosomal dominant nocturnal frontal lobe epilepsy (AD-NFLE)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
Landau-Kleffner syndrome
Childhood absence epilepsy (CAE)
ADOLESCENCE–ADULT
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies
AGE-RELATED (AGE OF ONSET LESS SPECIFIC)
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
SEIZURE DISORDERS THAT ARE NOT TRADITIONALLY GIVEN THE DIAGNOSIS OF EPILEPSY
Benign neonatal seizures (BNS)
Febrile seizures (FS)
EPILEPTIC ENCEPHALOPATHIES
EME
Ohtahara syndrome
Migrating partial seizures of infancy
West syndrome
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Epilepsy with myoclonic astatic seizures
Lennox-Gastaut syndrome
Epileptic encephalopathy with CSWS
Landau-Kleffner syndrome
OTHER SECONDARY GENERALIZED EPILEPSIES
Generalized epilepsy secondary to neurodegenerative disease
Progressive myoclonus epilepsies

Table 593-9 Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy

Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that uses standardized terminology and that is sufficiently flexible to take into account the practical and dynamic aspects of epilepsy diagnosis:

- Axis 1: Ictal phenomenology, used to describe ictal events with any degree of detail needed.
- Axis 2: Seizure type, from the List of types of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
- Axis 3: Syndrome, from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
- Axis 4: Etiology, from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.
- Axis 5: Impairment; this is often useful to make sure one does not overlook the consequences of epilepsy, such as medication side effects, and learning and socialization difficulties.

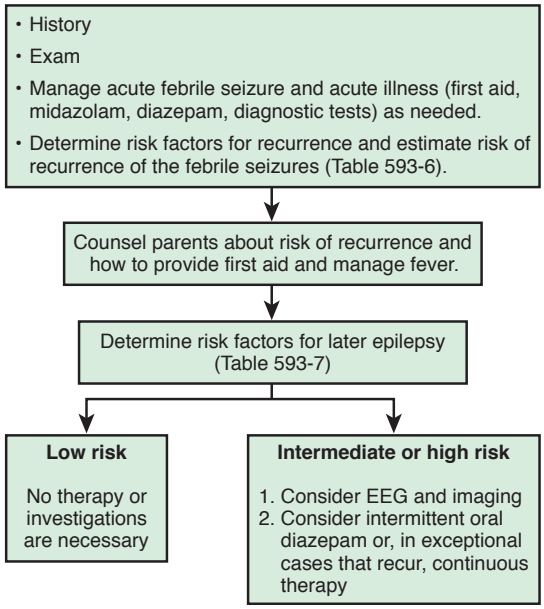

Figure 593-1 Management of febrile seizures.

Table 593-6 Risk Factors for Recurrence of Febrile Seizures

MAJOR
Age <1 yr
Duration of fever <24 hr
Fever 38-39°C (100.4-102.2°F)
MINOR
Family history of febrile seizures
Family history of epilepsy
Complex febrile seizure
Daycare
Male gender
Lower serum sodium at time of presentation

Having no risk factors carries a recurrence risk of approximately 12%; 1 risk factor, 25-50%; 2 risk factors, 50-59%; 3 or more risk factors, 73-100%.

Table 593-7 Risk Factors for Occurrence of Subsequent Epilepsy After a Febrile Seizure

RISK FACTOR	RISK FOR SUBSEQUENT EPILEPSY
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures (more than 15 min duration or recurrent within 24 hr)	6%
Fever <1 hr before febrile seizure	11%
Family history of epilepsy	18%
Complex febrile seizures (focal)	29%
Neurodevelopmental abnormalities	33%

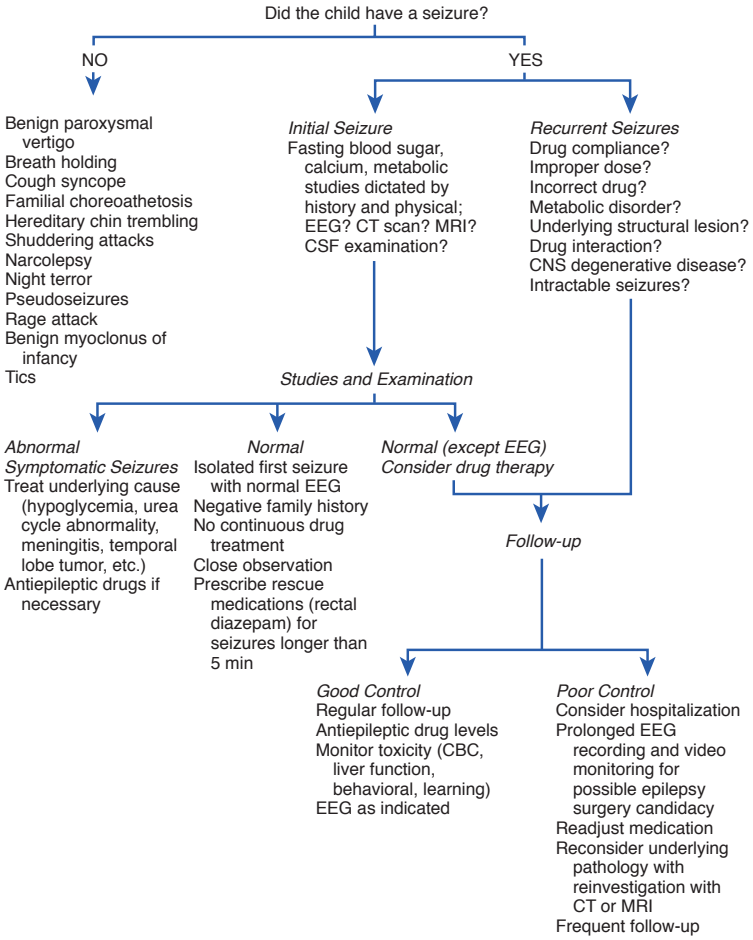

Figure 593-4 Approach to the child with a suspected convulsive disorder.

Table 593-10 Sports and Special Considerations for the Child with Epilepsy*

SPORTS TYPE	SPECIAL CONSIDERATIONS
Body contact sports	If there are more than occasional seizures, physician evaluation of benefits and risks of participation should be made based on the child's condition. No contraindications in general except for boxing.
Noncontact sports	Generally recommended. Anxiety and fatigue can cause a problem in some children. Individualization based on clinical history must be the rule.
Gymnastics	A fall can result if the child experiences a sudden seizure, especially with trampolines, parallel bars, and rope climbing, which should be avoided. Individual consideration remains the basic determinant.
Swimming	The child should always be under supervision, and scuba diving should be discouraged in poorly controlled epileptics.

*Specific advice should be individualized depending on the patient's clinical condition. Many patients actually have fewer seizures when they are active than when they are idle.

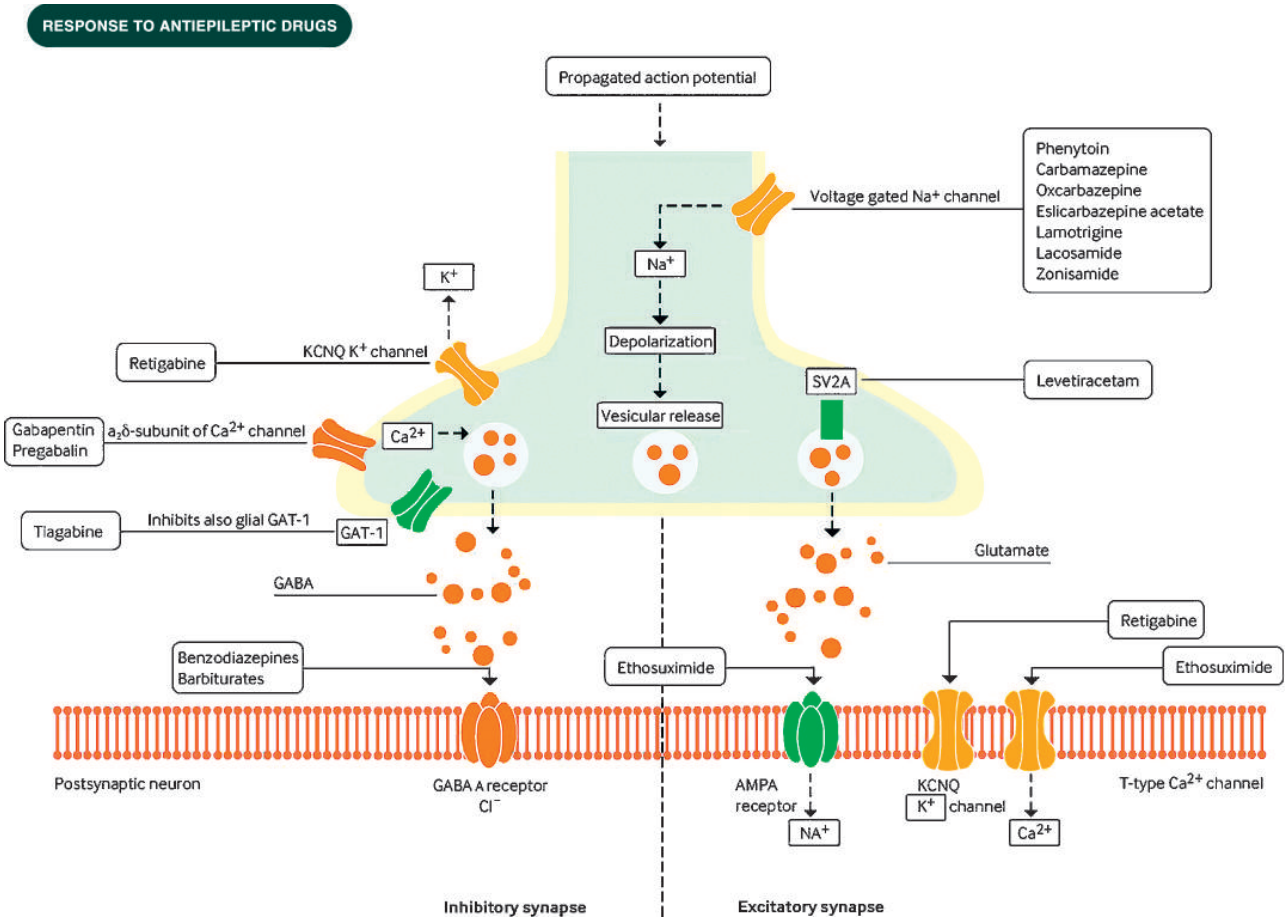

Figure 593-5 Mechanisms of action of antiepileptic drugs, which act by diverse mechanisms, mainly involving modulation of voltage activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved antiepileptic drugs have effects on inhibitory *(left hand side)* and excitatory *(right hand side)* nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-on does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism driven drug discovery has been largely ignored. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium-dependent and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. *(From Schmidt D, Schachter SC: Drug treatment of epilepsy in adults.* BMJ, *348:bmj.g254, 2014.)*

Table 593-11 Comparison of Recommendations for the Treatment of Pediatric Epilepsy

SEIZURE TYPE OR EPILEPSY SYNDROME	FDA APPROVED	SIGN (2005)	NICE (2012)	AAN (2004)	ILAE (2013)*	PEDIATRIC EXPERT CONSENSUS SURVEY (NORTH AMERICA–2005)	PEDIATRIC EXPERT CONSENSUS SURVEY (EUROPE–2007)
Partial-onset	CBZ, ezogabine, lacosamide, LEV, LTG, OXC, PB, perampanel, PHT, TPM, VGB	CBZ, CLB, LTG, OXC, PHT, TPM, VGB, VPA	CBZ, LEV, LTG, OXC, VPA	CBZ, GBP, LTG, OXC, PB, PHT, TPM	A: OXC B: None C: CBZ, PB, PHT, TPM, VGB, VPA D: CLB, CZP, LTG, ZNS	CBZ, OXC	CBZ, OXC
BCECT	None	Not specifically mentioned	CBZ, LEV, LTG, OXC, VPA	Not surveyed	A, B: None C: CBZ, VPA D: GBP, LEV, OXC, STM	CBZ, OXC	VPA
Childhood absence epilepsy	ESM, VPA	ESM, LTG, VPA	ESM, LTG, VPA	LTG	A: ESM, VPA B: None C: LTG D: None	ESM	VPA
Juvenile myoclonic epilepsy	LEV, LTG, TPM	VPA	LEV, LTG, TPM, VPA	Not surveyed	A, B, C: None D: TPM, VPA	LTG, VPA	VPA
Lennox-Gastaut syndrome	CLB, FLB, LTG, rufinamide (atonic), TPM	CLB, LTG, VPA	VPA	Not surveyed	Not reviewed	LTG, VPA	VPA
Infantile spasms	VGB	Nitrazepam, TPM, VGB, VPA	Corticosteroids, VGB	ACTH, VGB (updated IS guidelines 2012)	Not reviewed	ACTH, VGB	VGB
Primary generalized tonic-clonic seizures	LEV, LTG, TPM	TPM, VPA	LTG, TPM, VPA	No evidence given	A: None B: None C: CBZ, PB, PHT, TPM, VPA D: OXC		

*ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: ≥1 class I randomized controlled trial (RCT) or ≥2 class II RCTs; Level B: 1 class II RCT or ≥2 class III RCTs; Level C: ≥2 class III RCTs; Level D: 1 class III double-blind or open-label study *or* 1 class IV clinical study *or* data from expert committee reports, opinions from experienced clinicians.

AAN, American Academy of Neurology; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Modified and updated from Wheless JW, Clarke DF, Arzimanoglou A, et al: Treatment of pediatric epilepsy: European expert opinion, Epileptic Disord *9:353–412, 2007; and Perucca E, Tomson T; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes.* Epilepsia *54(3):551–563, 2013.*

Table 593-12 Teratogenesis and Perinatal Outcomes of Antiepileptic Drugs

FINDING	RECOMMENDATION	LEVEL OF RECOMMENDATION
VPA as part of polytherapy and possibly monotherapy probably contributes to the development of major congenital malformations and adverse cognitive outcome	If possible, avoidance of valproate polytherapy during the 1st trimester of pregnancy should be considered so as to decrease the risk of major congenital malformations and adverse cognitive outcome	B
AED polytherapy, as compared to monotherapy, regimens probably contribute to the development of major congenital malformations and to adverse cognitive outcomes	If possible, avoidance of AED polytherapy during the 1st trimester of pregnancy should be considered to decrease the risk of major congenital malformations and adverse cognitive outcome	B
Monotherapy exposure to phenytoin or phenobarbital possibly increases the likelihood of adverse cognitive outcomes	If possible, avoidance of phenytoin and phenobarbital during pregnancy may be considered to prevent adverse cognitive outcomes	C
Neonates of women with epilepsy taking AEDs probably have an increased risk of being small for gestational age and possibly have an increased risk of a 1 min Apgar score of <7	Pregnancy risk stratification should reflect that the offspring of women with epilepsy taking AEDs are probably at increased risk for being small for gestational age (level B) and possibly at increased risk of 1 min Apgar scores of <7	C

Levels of recommendation: A: strongest recommendation; based on class 1 evidence; B and C: lower levels of recommendations.

Types of malformations: Prior studies had reported the occurrence of spina bifida with valproate and carbamazepine therapy, and of cardiac malformation and cleft palate after carbamazepine, phenytoin, and phenobarbital exposure. There is variability from study to study. However, in general the relative incidence of major malformations of approximately 10% for valproate monotherapy, higher with valproate polytherapy, and in the range of 5% for monotherapy with the other above 3 AEDs and higher with polytherapy.

FDA categories: Valproate, phenobarbital, carbamazepine, and phenytoin are classified by the FDA as category D. Ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are category C. Category C: Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Category D: Studies, adequate, well-controlled, or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy might outweigh the potential risk.

AED, antiepileptic drug; VPA, valproate.

Table 593-13 Dosages of Selected Antiepileptic Drugs

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Acetazolamide	Absence seizures (adults)	1-12 mo; 10 <1 yr: 20-30	bid or tid	10-15 mg/L	125, 250, 500 mg tabs
Bromide		50-100	bid or qd	10-15 mEq/L	Supplied as triple bromide soln (240 mg/mL of bromide salt)
Carbamazepine*	Partial and GTC (all ages)	10-20	tid or qid SR usually bid	3-12 mg/L	150, 300 mg ER caps 100, 200, 400 mg ER tabs 100 mg chewable tabs 200 mg tabs 100 mg/5 mL susp
Clobazam†	LGS (all ages above 2 yr)	10-20 mg/day	bid or tid	60-200 μg/L	5 mg, 10 mg, 20 mg tabs 2.5 mg/mL soln
Clonazepam†	Absence sz, LGS, myoclonic sz (all ages)	0.05-0.2	bid or tid	25-85 μg/L	0.5, 1, 2 mg tabs 0.125, 0.25, 0.5 mg orally disintegrating tabs
Diazepam	Partial sz (all ages >6 mo)	0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal (according to age; see Table 593-15)	bid or tid	100-700 μg/L	2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln Rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg
Ethosuximide	Absence sz (>3 yr)	20-30	bid or tid	40-100 mg/L	250 mg caps 250 mg/5 mL syrup, soln
Ezogabine	Partial sz (adults)	No pediatric dose approved	tid	—	50, 200, 300, 400 mg tabs
Felbamate	LGS (>2 yr) Partial sz (>14 yr)	15-45	bid or tid	50-110 mg/L	400, 600 mg tabs 600 mg/5 mL susp
Gabapentin‡	Partial sz (>3 yr)	30-60	tid	2-20 mg/L	100, 300, 400 mg caps, 600, 800 mg tabs
Lacosamide	Partial sz (>17 yr)	No FDA approved dose. 4-12	bid	<= 15 μg/L	50, 100, 150, 200 mg tabs 10 mg/mL oral soln

Table 593-13 Dosages of Selected Antiepileptic Drugs—cont'd

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Lamotrigine	LGS, partial and tonic–clonic sz (age >2 yr)	5-15[§] 1-5[¶]	tid bid	1-15 mg/L	25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs
Levetiracetam[†]	Myoclonic, partial and tonic–clonic sz (age >4-6 yr)	20-40	bid or tid	6-20 mg/L	250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs
Lorazepam	Status epilepticus (all ages)	0.05-0.1	bid or tid	20-30 µg/L	0.5, 1, 2 mg tabs 2 mg/mL soln
Methsuximide (or methsuximide)	Absence sz (children and older)	10-30	bid or tid	10-50 mg/L	150, 300 mg caps
Nitrazepam	–	0.25-1	bid or tid	<200 µg/L	5 mg tabs
Oxcarbazepine*	Partial sz (>2 yr)	20-40	bid	13-28 mg/L	150, 300, 600 mg tabs 300 mg/5 mL susp
Perampanel	Partial sz (>12 yr)	2-12 mg per day (older than 12 yr)	qhs	-	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg tabs
Phenobarbital	Myoclonic, partial, and tonic–clonic sz and status (all ages)	<5 yr, 3-5 >5 yr, 2-3	bid or qd	10-40 mg/L	15, 30, 60, 90, 100 mg tabs 4 mg/mL soln
Phenytoin	Partial, tonic–clonic sz and status (all ages)	<3 yr, 8-10 >3 yr, 4-7	tabs, susp: tid caps: qd	5-20 mg/L	50 mg tabs 30,100 mg caps 125 mg/5 mL susp
Pregabalin	Partial sz (adults)	2-14	bid	Up to 10 µg/mL	25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln
Primidone	Partial and tonic–clonic sz (all ages)	10-20	bid or tid	4-13 mg/L	50, 250 mg tabs, susp
Rufinamide[†]	LGS (age >4 yr)	30-45	bid	<60 µg/mL	200, 400 mg tabs
Sulthiame[‖]		5-15	bid or tid	1.5-20 µg/mL	50, 200 mg caps Not available in all countries
Tiagabine	Partial sz (age >2 yr)	0.5-2	bid, tid, qid	80-450 µg/L	2, 4, 12, 16 mg tabs
Topiramate[†]	LGS, partial and tonic–clonic sz (all ages)	3-9, slow titration	bid or tid	2-25 mg/L	25, 100, 200 mg tabs 15, 25 mg sprinkle caps
Valproate	Absence, myoclonic, partial and tonic–clonic sz (age >2 yr)	15-40. Higher doses are used if the patient is on enzyme inducers (up to 60 kg/day)	Sprinkle caps: bid Soln: tid	50-100 mg/L	250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln
Vigabatrin	Infantile spasms and partial sz (age >1 mo)	50-150	bid	20-160 µg/mL	500 mg tabs 500 mg powder for soln
Zonisamide	Partial sz (age >16 yr)	4-8	bid or qd	10-40 mg/L	100 mg caps

Unless specified otherwise, as above, one would usually target the lower range of therapeutic dose then adjust as needed depending on response and/or levels. Dosing schedule (e.g., bid or tid) can depend on if a sustained release preparation is available and if the patient is on enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect that drug (as indicated in the dosing in the table and in the text).

*Usually start by one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.

[†]Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.

[‡]Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.

[§]Child on enzyme inducers.

[‖]Available in some European countries.

[¶]Child on valproate.

cap, capsule; ER, extended release; GTC, generalized tonic–clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.

Table 593-14 Some Common Adverse Effects of Antiepileptic Drugs*

ANTIEPILEPTIC DRUG	SIDE EFFECT(S)
Acetazolamide	Nuisance: dizziness, polyuria, electrolyte imbalance Serious: Stevens-Johnson syndrome
Benzodiazepines	Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions Serious: apnea
Bromide	Nuisance: irritability, spurious hyperchloremia (falsely high chloride owing to bromide) Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life
Carbamazepine	Nuisance: tics, transient leukopenia; hyponatremia, weight gain, nausea; dizziness Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity
Ezogabine	Nuisance: dizziness, somnolence tremor, abnormal coordination, disturbance in attention, memory impairment, blurred vision, gait disturbance, and dysarthria Serious: blue discoloration of the skin and retinal pigmentation that requires close ophthalmologic monitoring in follow up, urinary retention
Felbamate	Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children >2 yr with complex neurological disorders)
Gabapentin	In children: acute onset of aggression, hyperactivity In adults: euphoria and behavioral disinhibition, weight gain
Lacosamide	Nuisance: diplopia, headache, dizziness, nausea Serious: possibly cardiac arrhythmias (if predisposed)
Lamotrigine	Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs Serious: Stevens-Johnson syndrome, rarely liver toxicity
Levetiracetam	CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs In children: behavioral symptoms are common In adults: depressive mood
Oxcarbazepine	Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia
Perampanel	Dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder
Phenobarbital and other barbiturates	Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts Serious: liver toxicity, Stevens-Johnson syndrome
Phenytoin and other hydantoins	Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism, cerebellovestibular symptoms (nystagmus and ataxia) Serious: Stevens-Johnson syndrome, liver toxicity
Pregabalin	Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia Serious: hypersensitivity reactions, rhabdomyolysis
Primidone	Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression) Serious: liver toxicity, Stevens-Johnson syndrome
Rufinamide	Nuisance: somnolence, vomiting Serious: contraindicated in familial short QT interval
Succinimides	Nuisance: nausea, abdominal discomfort, anorexia, hiccups Serious: Stevens-Johnson syndrome, drug-induced lupus
Tiagabine	Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures Serious: precipitation of nonconvulsive status epilepticus
Topiramate	Nuisance: cognitive dysfunction, weight loss, renal calculi, hypohidrosis, fever Serious: precipitation of glaucoma
Valproic acid	Nuisance: weight gain; hyperammonemia tremor, alopecia, menstrual irregularities Serious: hepatic and pancreatic toxicity
Vigabatrin	Nuisance: hyperactivity Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow up
Zonisamide	Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever

*Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions.
AED, antiepileptic drug; CNS, central nervous system.

Table 593-16 Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures

CLASSIFICATION	CHARACTERIZATION
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on 1 side of the body May occur simultaneously but asynchronously on both sides Cannot be suppressed by restraint Pathophysiology: epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetrical posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Generalized tonic	Sustained symmetrical posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation Presumed pathophysiology: may be epileptic or nonepileptic
Spasms	May be flexor, extensor, or mixed extensor/flexor May occur in clusters Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Motor automatisms	
Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation Presumed pathophysiology: nonepileptic
Oral-buccal-lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic
Progression movements	Rowing or swimming movements Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Complex purposeless movements	Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic

From Mizrahi EM, Kellaway P. Diagnosis and management of neonatal seizures. *Philadelphia, 1998, Lippincott-Raven. Tab 4, p. 21.*

Table 593-17 Causes of Neonatal Seizures According to Common Age of Presentation

AGES 1-4 DAYS
Hypoxic–ischemic encephalopathy
Drug withdrawal, maternal drug use of narcotic or barbiturates
Drug toxicity: lidocaine, penicillin
Intraventricular hemorrhage
Acute metabolic disorders
• Hypocalcemia
• Sepsis
• Maternal hyperthyroidism, or hypoparathyroidism
• Hypoglycemia
• Perinatal insults, prematurity, small for gestational age
• Maternal diabetes
• Hyperinsulinemic hypoglycemia
• Hypomagnesemia
• Hyponatremia or hypernatremia
• Iatrogenic or inappropriate antidiuretic hormone secretion
Inborn errors of metabolism
• Galactosemia
• Hyperglycinemia
• Urea cycle disorders
Pyridoxine deficiency and pyridoxal-5-phosphate deficiency (must be considered at any age)
AGES 4-14 DAYS
Infection
• Meningitis (bacterial)
• Encephalitis (enteroviral, herpes simplex)
Metabolic disorders
• Hypocalcemia
• Diet, milk formula
• Hypoglycemia, persistent
• Inherited disorders of metabolism
• Galactosemia
• Fructosemia
• Leucine sensitivity
• Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome
• Anterior pituitary hypoplasia, pancreatic islet cell tumor
• Beckwith syndrome
Drug withdrawal, maternal drug use of narcotics or barbiturates
Benign neonatal convulsions, familial and nonfamilial
Kernicterus, hyperbilirubinemia
Developmental delay, epilepsy, neonatal diabetes syndrome
AGES 2-8 WK
Infection
• Herpes simplex or enteroviral encephalitis
• Bacterial meningitis
Head injury
• Subdural hematoma
• Child abuse
Inherited disorders of metabolism
• Aminoacidurias
• Urea cycle defects
• Organic acidurias
• Neonatal adrenoleukodystrophy
Malformations of cortical development
• Lissencephaly
• Focal cortical dysplasia
Tuberous sclerosis
Sturge-Weber syndrome

Table 597-9 Selected Causes of Tremor in Children

BENIGN
Enhanced physiologic tremor
Shuddering attacks
Jitteriness
Spasmus nutans
STATIC INJURY/STRUCTURAL
Cerebellar malformation
Stroke (particularly in the midbrain or cerebellum)
Multiple sclerosis
HEREDITARY/DEGENERATIVE
Familial essential tremor
Fragile X premutation
Wilson disease
Huntington disease
Juvenile parkinsonism (tremor is rare)
Pallidonigral degeneration
METABOLIC
Hyperthyroidism
Hyperadrenergic state (including pheochromocytoma and neuroblastoma)
Hypomagnesemia
Hypocalcemia
Hypoglycemia
Hepatic encephalopathy
Vitamin B_{12} deficiency
Inborn errors of metabolism
Mitochondrial disorders
DRUGS/TOXINS
Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, bronchodilators), neuroleptics, cyclosporine, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors
PERIPHERAL NEUROPATHIES
PSYCHOGENIC

Table 593-19 Consensus Case Definition and Modified Consensus Case Definition for Nodding Syndrome—Uganda, 2012-2013*

TYPE OF CASE	CONSENSUS CASE DEFINITION	MODIFIED CONSENSUS CASE DEFINITION
Suspected case	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person
Probable case	Suspected case of head nodding, with both major criteria: • Age of onset of nodding ranging from 3-18 yr • Frequency of nodding 5-20 per minute Plus at least 1 of the following minor criteria: • Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) • Clustering in space or time with similar cases • Triggering by food or cold weather • Stunting or wasting • Delayed sexual or physical development • Psychiatric symptoms	Suspected case of head nodding, with 1 major criterion: • Age of onset of nodding ranging from 3-18 yr Plus at least 1 of the following minor criteria: • Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) • Clustering in space or time with similar cases • Triggering by food or cold weather • Stunting or wasting • Psychiatric symptoms
Confirmed case	Probable case, with documented nodding episode • Observed and recorded by a trained healthcare worker, *or* • Videotaped nodding episode, *or* • Video/EEG/EMG documenting head nodding as atonic seizures	Probable case, with documented nodding episode • Observed and recorded by a trained healthcare worker, *or* • Videotaped nodding episode, *or* • Video/EEG/EMG documenting head nodding as atonic seizures

*The consensus case definition was drafted at the first International Scientific Meeting on Nodding Syndrome, held July 30–August 1, 2012, in Kampala, Uganda. Meeting report available at http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf. The modified consensus case definition was developed during the March 2013 single-stage cluster survey conducted by Centers for Disease Control and Prevention (CDC) and the Ugandan Ministry of Health to assess prevalence of nodding syndrome in Uganda.

EEG, electroencephalographic; EMG, electromyographic.

From Iyengar PJ, Wamala J, Ratto J, et al: Prevalence of nodding syndrome–Uganda, 2012-2013. MMWR Morb Mortal Wkly Rep *63:603–606, 2014, Table 1.*

Table 593-18 Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus

DRUG*	ROUTE	DOSAGE
Lorazepam	Intravenous Intranasal	0.1 mg/kg up to 4 mg total, may repeat in 5-10 min 0.1 mg/kg
Midazolam	Intravenous Intramuscular Intranasal Buccal	0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min 0.08-0.23 mg/kg/hr maintenance 0.2 mg/kg 0.2 mg/kg 0.5 mg/kg
Diazepam	Intravenous Rectal	0.15 mg/kg up to a max total dose of 10 mg, may repeat in 5-10 min 2-5 yr: 0.5 mg/kg 6-11 yr: 0.3 mg/kg ≥12 yr: 0.2 mg/kg
Fosphenytoin	Intravenous	20 mg/kg PE, then 3-6 mg/kg/24 hr, loading rate up to 50 mg PE per min
Phenobarbital†	Intravenous	5-20 mg/kg
Pentobarbital coma†	Intravenous	13.0 mg/kg, then 1-5 mg/kg/hr
Propofol†	Intravenous	1 mg/kg (bolus), then 1-15 mg/kg/hr (infusion)
Thiopental†	Intravenous	5 mg/kg/1st hr, then 1-2 mg/kg/hr
Valproate†	Intravenous	Loading: 25 mg/kg, then 30-60 mg/kg/24 hr
Lacosamide†	Intravenous	Loading: 4 mg/kg then 4-12 mg/kg/24 hr
Levetiracetam	Intravenous	20-60 mg/kg
Topiramate	Enterally	5-10 mg/kg/24 hr (loading dose) then same or lower for maintenance

*Reflects current trends in use which may not be FDA approved. For FDA indications, see Table 593-13.

†May cause PR prolongation.

PE, phenytoin sodium equivalents.

Table 593-3 Identified Genes for Epilepsy Syndromes*†

EPILEPSY TYPE	GENE	PROTEIN
INFANTILE ONSET		
Benign familial neonatal seizures	*KCNQ2*	Potassium voltage-gated channel
	KCNQ3	Potassium voltage-gated channel
Benign familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early infantile epileptic encephalopathy (EIEE)	*CDKL5 (EIEE2)*	Cyclin-dependent kinase-like 5
	ARX (EIEE1)	Aristaless-related homeobox
	TSC1	Hamartin
	TSC2	Tuberin
	SCN1A (EIEE6)	Sodium channel protein type 1α
	PCDH19(EIEE9)	Protocadherin-19
	KCNQ2 (EIEE7)	Potassium voltage-gated channel
	STXBP1 (EIEE4)	Syntaxin binding protein 1
	SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1
	ALDH7A1	α-Aminoadipic semialdehyde dehydrogenase (antiquitin)
	POLG	DNA polymerase subunit gamma-1
	SCN2A (EIEE11)	Sodium channel protein type 2α
	PLCβ1 (EIEE12)	Phospholipase C β1
	ATP6AP2	Renin receptor
	SPTAN1 (EIEE5)	α_2-Spectrin
	SLC25A22 (EIEE3)	Mitochondrial glutamate carrier 1
	PNPO	Pyridoxine-5′-phosphate oxidase
Generalized epilepsy with febrile seizures plus (early onset)	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
CHILDHOOD ONSET		
Childhood onset epileptic encephalopathies	*SCN1A*	Sodium channel protein type 1α
	PCDH19	Protocadherin-19
	SLC2A1	Solute carrier family 2, facilitated GTM1
	POLG	DNA polymerase subunit γ1
	SCN2A	Sodium channel protein type 2α
Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder	*GLUT-1* deficiency syndrome, *SLC2A1*gene	Solute carrier family 2, facilitated GTM1
Generalized epilepsy with febrile seizure plus	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
Juvenile myoclonic epilepsy (more commonly presents in adolescence)	*EFHC1*	EF-hand domain-containing protein 1
	CACNB4	Voltage-dependent L-type calcium channel
	GABRA1	γ-Aminobutyric acid receptor subunit α1
Progressive myoclonic epilepsy (different forms present from infancy through adulthood)	*EPM2A*	Laforin
	NHLRC1	NHL repeat-containing protein 1 (Malin)
	CSTB	Cystatin-B
	PRICKLE1	Prickle-like protein 1
	PPT1, TPP1,CLN3, CLN5, CLN6, CLN8, CTSD, DNAJC5, MFSD8	Multiple proteins causing neuronal ceroid lipofuscinosis
Autosomal dominant nocturnal frontal lobe epilepsies (presents in childhood through adulthood)	*CHRNA4*	Neuronal acetylcholine receptor α4
	CHRNB2	Neuronal acetylcholine receptor β2
	CHRNA2	Neuronal acetylcholine receptor α2
ADOLESCENT ONSET		
Juvenile myoclonic epilepsy (JME)	See Childhood Onset JME	
Progressive myoclonic epilepsy (PME)	See Childhood Onset PME	
Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)	See Childhood Onset AD-NFLE	
Autosomal dominant lateral temporal lobe epilepsy (AD-LTLE)	See Childhood Onset AD-LTLE	
Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood)	*LGI1*	Leucine-rich glioma-inactivated protein 1

*Note that the same gene (different mutations) often appears as causing different epilepsy syndromes.

†Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests).

Table 594-2 Comparison of Generalized Seizures and Some Disorders That Can Mimic Them

CONDITION	PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)	PRODROME	ICTAL SYMPTOMS	POSTICTAL SYMPTOMS
Generalized seizures	Sleep deprivation, television, video games, visual patterns, and photic stimulation	Rarely irritability or nonspecific behavioral changes	Usually 2-3 min Consciousness might be preserved if atonic, or in some, tonic seizures Synchronous bilateral movements Tongue biting	Delayed recovery with postictal depression, incontinence (may be ictal also)
Syncope: vasovagal Syncope with reflex anoxic seizures Syncope: trigeminal vagal Syncope: orthostatic	Fatigue, emotional stress, dehydration, vomiting, choking, swallowing Minor bump to head, upsetting surprises Cold water on face Standing up, bathing, awakening	Blurring of vision, tinnitus, dizziness Crying in breath-holding spells	Loss of consciousness for seconds, pallor and rarely reflex anoxic seizures	Rapid recovery with no postictal depression
Hyperekplexia	Auditory and tactile stimuli	None	Tonic stiffening, cyanosis if severe, nonfatigable nose-tap–induced startles	Depending on severity, may have postictal depression
Cardiac	Exercise	None	Loss of consciousness, often only few seconds, pallor	Rarely
Psychogenic	Suggestion, stress	None	Eyes closed Asynchronous flailing limb movements that vary between attacks No injury, closed eyelids May respond to suggestion during "loss of consciousness" Usually longer than 2-3 min	No postictal depression

Adapted from Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy, Pediatr Neurol *37(5):309–316, 2007.*

Table 594-3 Differential Diagnoses of Various Types of Paroxysmal Dyskinesia

Features	PKD	PNKD MR1+	PNKD MR1–	PED	PHD
Nomenclature	PKC	PDC, FPC	PDC, FPC	PEDt	ADNFLE
Inheritance	AD–16q	AD–2q35	AD–2q13	AD/AR	AD–20q13, 15q24, 1q21, 8p21
Age at onset (yr)	1-20	<1-12	1-23	Usually childhood	Usually childhood
Triggers	Sudden whole-body movement	Coffee, alcohol, stress	Exercise	After 10-15 minutes of exercise	Sleep
Clinical features	Chorea, athetosis, ballismus, dystonia	Chorea, athetosis, dystonia, ballismus	Chorea, athetosis, dystonia, ballismus	Mainly leg dystonia	Wakes up with dystonic posture
Usual duration	<1-5 min	10 min to 1 hr	10 min to 2-3 hr	10-15 min	<1 min
Frequency	1-20/day	1/week	1/week	Unclear	Several/night
Associations	Infantile seizures, migraine, writer's cramp, essential tremor	Migraine	Epilepsy	RE-PED-WC	
Medication	Carbamazepine Phenytoin Oxcarbazepine	Clonazepam Benzodiazepine	Clonazepam Benzodiazepine	Acetazolamide L-DOPA	Carbamazepine Oxcarbazepine
Prognosis	Excellent	Excellent, worse than PKD	Minimally worse than PNKD MR1+	Poor medication response	Excellent

AD, autosomal-dominant; ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; AR, autosomal-recessive; FPC, familial paroxysmal choreoathetosis; MR1+, myofibrillogenesis regulator 1-positive; MR1–, myofibrillogenesis regulator 1-negative; PDC, paroxysmal dystonic choreoathetosis; PED, paroxysmal exercise-induced dyskinesia; PEDt, paroxysmal exercise-induced dystonia; PHD, paroxysmal hypnogenic dyskinesia; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; RE-PED-WC, rolandic epilepsy–paroxysmal exercise-induced dystonia–writer's cramp.

From Friedman NR, Ghosh D, Moodley M: Syncope and paroxysmal disorders other than epilepsy. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 65-1.*

Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)

MIGRAINE
Migraine with or without aura
Migraine with typical aura (with or without headache)
Migraine with brainstem aura
Hemiplegic migraine (sporadic or familial types 1, 2, 3, or other genetic loci)
Retinal migraine
Chronic migraine
Complications of Migraine
Status migrainosus
Persistent aura without infarction
Migrainous infarction
Migraine aura-triggered seizure
Episodic Syndromes That May Be Associated with Migraine
Recurrent gastrointestinal disturbance
Cyclical vomiting syndrome
Abdominal migraine
Benign paroxysmal vertigo
Benign paroxysmal torticollis

TENSION-TYPE HEADACHE (TTH)
Infrequent episodic tension-type headache associated with or without pericranial tenderness
Frequent episodic tension-type headache associated with or without pericranial tenderness
Chronic tension-type headache associated with or without pericranial tenderness
Probable tension-type headaches

TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS)
Cluster headache (episodic or cluster)
Paroxysmal hemicrania (episodic or cluster)
Short-lasting unilateral neuralgiform headache attacks with or without conjunctival injection and tearing (SUNCT)
Episodic SUNCT
Chronic SUNCT
Short-lasting unilateral neuralgiform headache attacks with or without cranial autonomic symptoms (SUNA)
Episodic SUNA
Chronic SUNA
Hemicrania continua
Probable trigeminal autonomic cephalalgias

OTHER PRIMARY HEADACHE DISORDERS
Primary cough headache
Primary exercise headache
Primary headache associated with sexual activity
Primary thunderclap headache
Cold-stimulus headache (external application, ingestion, or inhalation)
External-pressure headache
External-compression headache
External-traction headache
Primary stabbing headache
Nummular headache
Hypnic headache
New daily persistent headache (NDPH)

HEADACHE ATTRIBUTED TO TRAUMA OR INJURY TO THE HEAD AND/OR NECK
Acute headache attributed to traumatic (mild, moderate, or severe) injury to the head
Persistent headache attributed to traumatic (mild, moderate, or severe) injury to the head
Acute or persistent headache attributed to whiplash
Acute or persistent headache attributed to craniotomy

HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDER
Headache attributed to ischemic stroke or transient ischemic attack
Headache attributed to nontraumatic intracerebral hemorrhage
Headache attributed to nontraumatic subarachnoid hemorrhage (SAH)
Headache attributed to nontraumatic acute subdural hemorrhage (ASDH)
Headache attributed to unruptured vascular malformation
Headache attributed to unruptured saccular aneurysm
Headache attributed to arteriovenous malformation (AVM)
Headache attributed to dural arteriovenous fistula (DAVF)
Headache attributed to cavernous angioma
Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge-Weber syndrome)
Headache attributed to arteritis
Headache attributed to giant cell arteritis (GCA)
Headache attributed to primary angiitis of the central nervous system (PACNS)
Headache attributed to secondary angiitis of the central nervous system (SACNS)
Headache attributed to cervical carotid or vertebral artery disorder
Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection
Post-endarterectomy headache
Headache attributed to carotid or vertebral angioplasty
Headache attributed to cerebral venous thrombosis (CVT)
Headache attributed to other acute intracranial arterial disorder
Headache attributed to an intracranial endovascular procedure
Angiography headache
Headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)
Headache attributed to intracranial arterial dissection
Headache attributed to genetic vasculopathy
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
Headache attributed to another genetic vasculopathy
Headache attributed to pituitary apoplexy

HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDER
Headache attributed to increased cerebrospinal fluid pressure
Headache attributed to idiopathic intracranial hypertension (IIH)
Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes
Headache attributed to intracranial hypertension secondary to hydrocephalus
Headache attributed to low cerebrospinal fluid pressure
Postdural puncture headache
Cerebrospinal fluid fistula headache
Headache attributed to spontaneous intracranial hypotension
Headache attributed to noninfectious inflammatory disease
Headache attributed to neurosarcoidosis
Headache attributed to aseptic (noninfectious) meningitis
Headache attributed to other noninfectious inflammatory disease
Headache attributed to lymphocytic hypophysitis
Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)
Headache attributed to intracranial neoplasm
Headache attributed to colloid cyst of the third ventricle
Headache attributed to carcinomatous meningitis
Headache attributed to hypothalamic or pituitary hyper- or hyposecretion
Headache attributed to intrathecal injection
Headache attributed to epileptic seizure
Hemicrania epileptica
Postictal headache
Headache attributed to Chiari malformation type I (CM1)
Headache attributed to other nonvascular intracranial disorder

Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)—cont'd

HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL
Headache attributed to use of or exposure to a substance
Nitric oxide (NO) donor-induced headache
Phosphodiesterase (PDE) inhibitor-induced headache
Carbon monoxide (CO)-induced headache
Alcohol-induced headache
Monosodium glutamate (MSG)-induced headache
Cocaine-induced headache
Histamine-induced headache
Calcitonin gene-related peptide (CGRP)-induced headache
Headache attributed to exogenous acute pressor agent
Headache attributed to occasional or long-term use of nonheadache medication
Headache attributed to exogenous hormone
Medication-Overuse Headache (MOH)
Ergotamine-overuse headache
Triptan-overuse headache
Simple analgesic-overuse headache
Paracetamol (acetaminophen)-overuse headache
Acetylsalicylic acid-overuse headache
Other non-steroidal antiinflammatory drug (NSAID)-overuse headache
Opioid-overuse headache
Combination analgesic-overuse headache
Headache Attributed to Substance Withdrawal
Caffeine-withdrawal headache
Opioid-withdrawal headache
Estrogen-withdrawal headache

HEADACHE ATTRIBUTED TO INFECTION
Acute or chronic headache attributed to bacterial meningitis or meningoencephalitis
Persistent headache attributed to past bacterial meningitis or meningoencephalitis
Acute or chronic headache attributed to intracranial fungal or other parasitic infection
Headache attributed to brain abscess
Headache attributed to subdural empyema
Headache attributed to systemic infection (acute or chronic)

HEADACHE ATTRIBUTED TO DISORDER OF HOMEOSTASIS
Headache attributed to hypoxia and/or hypercapnia
High-altitude headache
Headache attributed to airplane travel
Diving headache
Sleep apnea headache
Dialysis headache
Headache attributed to arterial hypertension
Headache attributed to pheochromocytoma
Headache attributed to hypertensive crisis with or without hypertensive encephalopathy
Headache attributed to preeclampsia or eclampsia
Headache attributed to autonomic dysreflexia
Headache attributed to hypothyroidism
Headache attributed to fasting
Cardiac cephalalgia
Headache attributed to other disorder of homoeostasis

HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE
Headache attributed to disorder of cranial bone
Headache attributed to retropharyngeal tendonitis
Headache attributed to craniocervical dystonia
Headache attributed to acute glaucoma
Headache attributed to refractive error
Headache attributed to heterophoria or heterotropia (latent or persistent squint)
Headache attributed to ocular inflammatory disorder
Headache attributed to trachelitis
Headache attributed to disorder of the ears
Headache attributed to acute or chronic or recurring rhinosinusitis
Headache attributed to temporomandibular disorder (TMD)
Head or facial pain attributed to inflammation of the stylohyoid ligament
Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure

HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDER
Headache attributed to somatization disorder
Headache attributed to psychotic disorder

PAINFUL CRANIAL NEUROPATHIES AND OTHER FACIAL PAINS
Classical trigeminal neuralgia
Classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent facial pain
Painful trigeminal neuropathy
Painful trigeminal neuropathy attributed to acute herpes zoster
Postherpetic trigeminal neuropathy
Painful posttraumatic trigeminal neuropathy
Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque
Painful trigeminal neuropathy attributed to space-occupying lesion
Painful trigeminal neuropathy attributed to other disorder
Glossopharyngeal neuralgia
Classical nervus intermedius (facial nerve) neuralgia
Nervus intermedius neuropathy attributed to herpes zoster
Occipital neuralgia
Optic neuritis
Headache attributed to ischemic ocular motor nerve palsy
Tolosa-Hunt syndrome
Paratrigeminal oculosympathetic (Raeder) syndrome
Recurrent painful ophthalmoplegic neuropathy
Burning mouth syndrome (BMS)
Persistent idiopathic facial pain (PIFP)
Central neuropathic pain
Central neuropathic pain attributed to multiple sclerosis (MS)
Central post-stroke pain (CPSP)

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013.*

595.1 Migraine

Andrew D. Hershey, Marielle A. Kabbouche, and Hope L. O'Brien

Migraine is the most frequent type of recurrent headache that is brought to the attention of parents and primary care providers, but it remains underrecognized and undertreated, particularly in children. Migraine is characterized by episodic attacks that may be moderate to severe in intensity, focal in location on the head, have a throbbing quality, and may be associated with nausea, vomiting, light sensitivity, and sound sensitivity. Compared to adults, pediatric migraine is shorter in duration and has a bilateral, often bifrontal, location. Migraine can also be associated with an aura that may be typical (visual, sensory, or dysphasic) or atypical (i.e., hemiplegic, "Alice in Wonderland" syndrome) (Tables 595-2 to 595-6). In addition, a number of migraine variants have been described and, in children, include abdominal related symptoms without headache, and components of the painless periodic syndromes of childhood (see Table 595-1). Treatment of migraine requires the incorporation of an acute treatment plan, a preventive treatment plan if the migraine occurs frequently or is disabling, and a biobehavioral plan to help cope with both the acute attacks and frequent or persistent attacks if present.

EPIDEMIOLOGY

Up to 75% of children report having a significant headache by the time they are 15 yr old. Recurrent headaches are less common, but remain highly frequent. Migraine has been reported to occur in up to 10.6% of children between the ages of 5 and 15 yr, and up to 28% of older

Table 595-2 Migraine Without Aura

A. At least 5 attacks fulfilling criteria B to D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 4.*

Table 595-3 Migraine with Typical Aura

A. At least 2 attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
C. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 6.*

Table 595-4 Migraine with Brainstem Aura

A. At least 2 attacks fulfilling criteria B to D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
C. At least 2 of the following brainstem symptoms:
   1. Dysarthria
   2. Vertigo
   3. Tinnitus
   4. Hypacusis
   5. Diplopia
   6. Ataxia
   7. Decreased level of consciousness
D. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 7.*

Table 595-5 Vestibular Migraine with Vertigo

A. At least 5 episodes fulfilling criteria C and D
B. A current or past history of 1.1 *Migraine without aura* or 1.2 *Migraine with aura*
C. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
D. At least 50% of episodes are associated with at least 1 of the following 3 migrainous features:
   1. Headache with at least 2 of the following 4 characteristics:
      a. Unilateral location
      b. Pulsating quality
      c. Moderate or severe intensity
      d. Aggravation by routine physical activity
   2. Photophobia and phonophobia
   3. Visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013 (Table 8).*

Table 595-6 Chronic Migraine

A. Headache (tension-type-like and/or migraine-like) on 15 or more days per month for more than 3 mo and fulfilling criteria B and C
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B to D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On 8 or more days per month for more than 3 mo, fulfilling any of the following:
   1. Criteria C and D for 1.1 *Migraine without aura*
   2. Criteria B and C for 1.2 *Migraine with aura*
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 9.*

Table 595-9 Infrequent Episodic Tension-Type Headache

A. At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B to D
B. Lasting from 30 min to 7 days
C. At least 2 of the following 4 characteristics:
   1. Bilateral location
   2. Pressing or tightening (nonpulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. No nausea or vomiting
   2. No more than 1 of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 beta diagnosis

Table 595-7 Indications for Neuroimaging in a Child with Headaches

Abnormal neurologic examination
Abnormal or focal neurologic signs or symptoms
- Focal neurologic symptoms or signs developing during a headache (i.e., complicated migraine)
- Focal neurologic symptoms or signs (except classic visual symptoms of migraine) develop during the aura, with fixed laterality; focal signs of the aura persisting or recurring in the headache phase

Seizures or very brief auras (<5 min)
Unusual headaches in children
- Atypical auras including basilar-type, hemiplegic
- Trigeminal autonomic cephalalgia including cluster headaches in child or adolescent
- An acute secondary headache (i.e., headache with known underlying illness or insult)

Headache in children younger than 6 yr old or any child who cannot adequately describe his or her headache
Brief cough headache in a child or adolescent
Headache worst on first awakening or that awakens the child from sleep
Migrainous headache in the child with no family history of migraine or its equivalent

Table 595-8 Drugs Used in the Management of Migraine Headaches in Children

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
ACUTE MIGRAINE				
Analgesics				
Acetaminophen	15 mg/kg/dose	Analgesic effects	Overdose, fatal hepatic necrosis	Effectiveness limited in migraine
Ibuprofen	7.5-10 mg/kg/dose	Antiinflammatory and analgesic	GI bleeding stomach upset, kidney injury	Avoid overuse (2-3 times per wk)
Triptans				
Almotriptan* (ages 12-17 yr)	12.5 mg	5-$HT_{1b/1d}$ agonist	Vascular constriction, serotonin symptoms such as flushing, paresthesias, somnolence, GI discomfort	Avoid overuse (more than 4-6 times per mo)
Eletriptan	40 mg	Same	Same	Avoid overuse (more than 4-6 times per mo)
Frovatriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (more than 4-6 times per mo)
Naratriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (more than 4-6 times per mo)
Rizatriptan* (ages 6-17 yr)	5 mg for child weighing <40 kg, 10 mg	Same	Same	Available in tablets and melts Avoid overuse (more than 4-6 times per mo)
Sumatriptan	Oral: 25 mg, 50 mg, 100 mg Nasal: 10 mg SC: 6 mg	Same	Same	Avoid overuse (more than 4-6 times per mo)
Zolmitriptan	Oral: 2.5 mg, 5 mg Nasal: 5 mg	Same	Same	Available in tablets and melts Avoid overuse (more than 4-6 times per mo)

Continued

Table 595-8 Drugs Used in the Management of Migraine Headaches in Children—cont'd

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
PROPHYLAXIS (NONE APPROVED BY FDA FOR CHILDREN)				
Calcium Channel Blockers				
Flunarizine†	5 mg hs	Calcium channel blocking agent	Headache, lethargy, dizziness	May ↑ to 10 mg hs
Anticonvulsants				
Valproic acid	20 mg/kg/24 hr (begin 5 mg/kg/24 hr)	↑ Brain GABA	Nausea, pancreatitis, fatal hepatotoxicity	↑ 5 mg/kg every 2 wk
Topiramate	100-200 mg divided bid	↑ Activity of GABA	Fatigue, nervousness	Increase slowly over 12-16 wk
Levetiracetam	20-60 mg/kg divided bid	Unknown	Irritability, fatigue	Increase every 2 wk starting at 20 mg/kg divided bid
Gabapentin	900-1800 mg divided bid	Unknown	Somnolence, fatigue aggression, weight gain	Begin 300 mg, ↑ 300 mg/wk
Antidepressants				
Amitriptyline	1 mg/kg/day	↑ CNS serotonin and norepinephrine	Cardiac conduction, abnormalities and dry mouth, constipation, drowsiness, confusion	Increase by 0.25 mg/kg every 2 wk Morning sleepiness reduced by administration at dinnertime
Antihistamines				
Cyproheptadine	0.2-0.4 mg/kg divided bid; max: 0.5 mg/kg/24 hr	H_1-receptor and serotonin agonist	Drowsiness, thick bronchial secretions	Preferred in children who cannot swallow pills; not well tolerated in adolescents
Antihypertensive				
Propranolol	10-20 mg tid	Nonselective β-adrenergic blocking agent	Dizziness, lethargy	Begin 10 mg/24 hr ↑ 10 mg/wk (contraindicated in asthma and depression)
Others				
Coenzyme Q10	1-3 mg/kg/day	Increases fatty acid oxidation in mitochondria	No adverse effects reported	Fat soluble; ensure brand contains small amount of vitamin E to help absorption
Riboflavin	50-400 mg daily	Cofactor in energy metabolism	Bright yellow urine, polyuria and diarrhea	
Magnesium	9 mg/kg divided tid	Cofactor in energy metabolism	Diarrhea or soft stool	
Butterbur	50-150 mg daily	May act similar to a calcium channel blocker	Burping	
OnabotulinumtoxinA	100 units (age 11-17 yr)	Inhibits acetylcholine release from nerve endings	Ptosis, blurred vision, hematoma at injection site	Used off label in children
SEVERE INTRACTABLE				
Prochlorperazine	0.15 mg/kg/IV; max dose 10 mg	Dopamine antagonist	Agitation, drowsiness, muscle stiffness, akinesia and akathisia	May have increased effectiveness when combined with ketorolac and fluid hydration
Metoclopramide	0.2 mg/kg IV; 10 mg max dose	Dopamine antagonist	Drowsiness, urticaria, agitation, akinesia and akathisia	Caution in asthma patients
Ketorolac	0.5 mg/kg IV; 15 mg max dose	Antiinflammatory and analgesic	GI upset, bleeding	
Valproate sodium injection	15 mg/kg IV: 1,000 mg max dose	↑ Brain GABA	Nausea, vomiting, somnolence, thrombocytopenia	Would avoid in hepatic disease
Dihydroergotamine IV	0.5 mg/dose every 8 hr (<40 kg) 1.0 mg/dose every 8 hr (>40 kg)		Nausea, vomiting, vascular constriction, phlebitis	Dose may need to be adjusted for side effects (decrease) or limited effectiveness (increase).
Nasal spray	0.5-1.0 mg/dose 0.5 mg/spray			

*FDA approved in the pediatric population.
†Available in Europe.
↑, Increase; CNS, central nervous system; GABA, γ-aminobutyric acid; GI, gastrointestinal; hs, at night; SC, subcutaneous.

Table 596-2 Frequency of Lesions Associated with Neurofibromatosis Type 2

	FREQUENCY OF ASSOCIATION WITH NF-2
NEUROLOGIC LESIONS	
Bilateral vestibular schwannomas	90-95%
Other cranial nerve schwannomas	24-51%
Intracranial meningiomas	45-58%
Spinal tumors	63-90%
Extramedullary	55-90%
Intramedullary	18-53%
Peripheral neuropathy	Up to 66%
OPHTHALMOLOGIC LESIONS	
Cataracts	60-81%
Epiretinal membranes	12-40%
Retinal hamartomas	6-22%
CUTANEOUS LESIONS	
Skin tumors	59-68%
Skin plaques	41-48%
Subcutaneous tumors	43-48%
Intradermal tumors	Rare

Table 596-3 Major Features of TSC

Cortical tuber
Subependymal nodule
Subependymal giant cell astrocytoma
Facial angiofibroma or forehead plaque
Ungual or periungual fibroma (non-traumatic)
Hypomelanotic macules (>3)
Shagreen patch
Multiple retinal hamartomas
Cardiac rhabdomyoma
Renal angiomyolipoma
Pulmonary lymphangioleiomyomatosis

Table 596-4 Minor Features of TSC

Cerebral white matter migration lines
Multiple dental pits
Gingival fibromas
Bone cysts
Retinal achromatic patch
Confetti skin lesions
Nonrenal hamartomas
Multiple renal cysts
Hamartomatous rectal polyps

Table 596-1 Diseases Associated with Multiple Café-Au-Lait Spots

DISEASE	MAJOR FEATURES
Ataxia telangiectasia	Progressive ataxia, lymphoreticular malignancy
Bannayan-Riley-Ruvalcaba syndrome	Macrosomia, megalencephaly, lipomas, intestinal polyps
Basal cell nevus syndrome	Multiple basal cell epitheliomas, jaw cysts, skeletal anomalies
Bloom syndrome	Short stature, photosensitivity, chromosome breaks, malignancy
Fanconi anemia	Limb anomalies, renal anomalies, pancytopenia
Gaucher disease	Jewish predilection, ataxia, mental retardation
Hunter syndrome	Thickened skin, coarse facies, skin papules, joint contractures
Jaffe-Campanacci syndrome	Fibromas of long bones, hypogonadism, mental retardation, ocular/cardiac anomalies
Maffucci syndrome	Venous malformations, enchondromas
McCune-Albright syndrome	Polyostotic fibrous dysplasia, precocious puberty
Multiple lentigines syndrome	Multiple lentigines, hypertelorism, pulmonic stenosis
Multiple mucosal neuroma syndrome	Mucosal neuromas, thyroid carcinoma, pheochromocytoma, parathyroid adenoma, dysautonomia
Neurofibromatosis	Neurofibromas, central nervous system tumors, iris hamartomas, axillary freckles, skeletal anomalies
Russell-Silver syndrome	Short stature, asymmetry, limb anomalies
Tuberous sclerosis	White macules, multiple hamartomas, central nervous system anomalies
Watson syndrome	Pulmonic stenosis, axillary freckles, low intelligence
Legius syndrome	Axillary freckling macrocephaly, a Noonan-like facial dysmorphism, lipomas

Table 597-2 Selected Causes of Ataxia in Childhood

CONGENITAL
- Agenesis of vermis of the cerebellum
- Aplasia or dysplasia of the cerebellum
- Basilar impression
- Cerebellar dysplasia with microgyria, macrogyria, or agyria
- Cervical spinal bifida with herniation of the cerebellum (Chiari malformation type 3)
- Chiari malformation
- Dandy-Walker syndrome
- Encephalocele
- Hydrocephalus (progressive)
- Hypoplasia of the cerebellum

DEGENERATIVE AND/OR GENETIC
- Acute intermittent cerebellar ataxia
- Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration
- Ataxia-telangiectasia
- Biemond posterior column ataxia
- Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia
- Cockayne syndrome
- Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva)
- Familial ataxia with macular degeneration
- Friedreich ataxia
- Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism
- Hereditary cerebellar ataxia with myotonia and cataracts
- Hypertrophic interstitial neuritis
- Marie ataxia
- Marinesco-Sjögren syndrome
- Multiple-system atrophy
- Pelizaeus-Merzbacher disease
- Periodic attacks of vertigo, diplopia, and ataxia–autosomal-dominant inheritance
- Posterior and lateral column difficulties, nystagmus, and muscle atrophy
- Progressive cerebellar ataxia and epilepsy
- Ramsay Hunt syndrome (myoclonic seizures and ataxia)
- Roussy-Lévy disease
- Spinocerebellar ataxia (SCA); olivopontocerebellar ataxias
- Vanishing white matter syndrome

ENDOCRINOLOGIC
- Acquired hypothyroidism
- Cretinism

INFECTIOUS, POSTINFECTIOUS, INFLAMMATORY
- Acute cerebellar ataxia
- Acute disseminated encephalomyelitis
- Autoimmune (anti-glutamic acid decarboxylase, anti–γ-aminobutyric $acid_B$ receptor antibodies)
- Cerebellar abscess
- Cerebellitis
- Coxsackievirus
- Diphtheria
- Echovirus
- Fisher syndrome
- Infectious mononucleosis (Epstein-Barr virus infection)
- Infectious polyneuropathy
- Japanese B encephalitis
- Mumps encephalitis
- *Mycoplasma* pneumonia
- Paraneoplastic (opsoclonus-myoclonus-ataxia syndrome)
- Pertussis
- Polio
- Postbacterial meningitis
- Rubeola
- Tuberculosis
- Typhoid
- Varicella

METABOLIC
- Abetalipoproteinemia
- Argininosuccinic aciduria
- Ataxia with vitamin E deficiency (AVED)
- Congenital disorders of glycosylation
- GM_2 gangliosidosis (late)
- Hartnup disease
- Hyperalaninemia
- Hyperammonemia I and II (urea cycle defects)
- Hypoglycemia
- Kearns-Sayre syndrome
- Leigh disease
- Maple syrup urine disease (intermittent)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Metachromatic leukodystrophy
- Mitochondrial complex defects (I, III, IV)
- Multiple carboxylase deficiency (biotinidase deficiency)
- Neuronal ceroid-lipofuscinosis
- Neuropathy, ataxia, retinitis pigmentosa (NARP)
- Niemann-Pick disease (late infantile)
- 5-Oxoprolinuria
- Pyruvate decarboxylase deficiency
- Refsum disease
- Sialidosis
- Triose-phosphate isomerase deficiency
- Tryptophanuria
- Wernicke encephalopathy

NEOPLASTIC
- Frontal lobe tumors
- Hemispheric cerebellar tumors
- Midline cerebellar tumors
- Neuroblastoma
- Pontine tumors (primarily gliomas)
- Spinal cord tumors

PRIMARY PSYCHOGENIC
- Conversion reaction

TOXIC
- Alcohol
- Benzodiazepines
- Carbamazepine
- Clonazepam
- Lead encephalopathy
- Neuroblastoma
- Phenobarbital
- Phenytoin
- Primidone
- Tic paralysis poisoning

TRAUMATIC
- Acute cerebellar edema
- Acute frontal lobe edema

VASCULAR
- Angioblastoma of cerebellum
- Basilar migraine
- Cerebellar embolism
- Cerebellar hemorrhage
- Cerebellar thrombosis
- Posterior cerebellar artery disease
- Vasculitis
- von Hippel-Lindau disease

Table 597-3 Treatable Causes of Inherited Ataxia

DISORDER	METABOLIC ABNORMALITY	DISTINGUISHING CLINICAL FEATURES	TREATMENT
Acute disseminated encephalomyelitis	Demyelination	Positive MRI findings	Steroids, IVIG, rituximab
Ataxia with vitamin E deficiency	Mutation in α-tocopherol transfer protein	Ataxia, areflexia, retinopathy	Vitamin E
Bassen-Kornzweig syndrome	Abetalipoproteinemia	Acanthocytosis, retinitis pigmentosa, fat malabsorption	Vitamin E
Hartnup disease	Tryptophan malabsorption	Pellagra rash, intermittent ataxia	Niacin
Familial episodic ataxia type 1 and type 2	Mutations in potassium channel (KCNA1) and α_{1A} voltage-gated calcium channel, respectively	Episodic attacks, worse with pregnancy or birth control pills	Acetazolamide
Multiple carboxylase deficiency	Biotinidase deficiency	Alopecia, recurrent infections, variable organic aciduria	Biotin
Mitochondrial complex defects	Complexes I, III, IV	Encephalomyelopathy	Possibly riboflavin, CoQ10, dichloroacetate
Opsoclonus-myoclonus-ataxia syndrome	Paraneoplastic or spontaneous autoimmune	Underlying neuroblastoma or autoantibodies	Steroids, IVIG, rituximab
Pyruvate dehydrogenase deficiency	Block in E-M and Krebs cycle interface	Lactic acidosis, ataxia	Ketogenic diet, possibly dichloroacetate
Refsum disease	Phytanic acid, α-hydroxylase	Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis	Dietary restriction of phytanic acid
Urea cycle defects	Urea cycle enzymes	Hyperammonemia	Protein restriction, arginine, benzoate, α-ketoacids

CoQ10, Coenzyme Q10; E-M, mitochondrial electron transport; IVIG, intravenous immunoglobulin.
Modified from Stumpf DA: The inherited ataxias. Pediatr Neurol *1:129-133, 1985, Table 1; and from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:* Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 67-1.*

Table 597-4 Autosomal-Recessive Cerebellar Ataxias

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)
Friedreich ataxia	9q13	*X25*	Frataxin	GAA repeat	2-51
Friedreich ataxia 2	9p23–p11	Unknown	Unknown	Unknown	5-20
AVED	8q13	*TTP1*	TTPA	Missense mutation, deletion, insertion	2-52
Ataxia-telangiectasia	11q22.3	*ATM*	ATM	Missense and deletion mutations	Infancy
ATLD	11q21	*hMRE11*	MRE11A	Missense and deletion mutations	9-48 mo
Ataxia-ocular apraxia 1	9p13.3	*APTX*	Aprataxin	Frameshift, missense, nonsense mutations	2-18
SCAR1	9q34	*SETX*	Senataxin	Frameshift, missense, nonsense mutations	9-22
SCAR2	9q34–qter	Unknown	Unknown	Unknown	Congenital
SCAR3	6p23–p21	Unknown	Unknown	Unknown	3-52
SCAR4	1p36	Unknown	Unknown	Unknown	23-39
SCAR5	15q24–q26	Unknown	Unknown	Unknown	1-10
SCAR6	20q11–q13	Unknown	Unknown	Unknown	Infancy
SCAR7	11p15	Unknown	Unknown	Unknown	Childhood
SCAR8	11p15	*SYNE1*	SYNE1	Splice site mutation, nonsense mutations	17-46

Continued

Table 597-4 Autosomal-Recessive Cerebellar Ataxias—cont'd

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)
SCAR9	1q41	*ADCK3*	ADCK3	Splice site mutation, missense, nonsense mutations	3-11
Ataxia, Cayman type	19q13.3	*ATCAY*	Caytaxin	Missense mutation	Birth
IOSCA	10q24	*C10orf2*	Twinkle	Missense, silent mutations	9-24 mo
Progressive myoclonic epilepsy	21q22.3	*CST6*	Cystatin B	5′ dodecamer repeat	6–13
ARSACS	13q12	*SACS*	Sacsin	Frameshift and nonsense mutations	1–20
Congenital disorders of glycosylation	Multiple	Multiple	Multiple		Birth

ARSACS, autosomal-recessive spastic ataxia of Charlevoix-Saguenay; ATLD, ataxia-telangiectasia-like disorder; AVED, ataxia with vitamin E deficiency; IOSCA, infantile-onset spinocerebellar ataxia; SCAR, spinocerebellar ataxia, autosomal-recessive.

From Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 67-2.*

Table 597-5 Autosomal-Dominant Cerebellar Ataxias

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)	NORMAL REPEAT	EXPANDED REPEAT	DURATION OF EPISODES
POLYGLUTAMINE EXPANSION								
SCA1	6p23	*SCA1*	Ataxin-1	CAG repeat	6-60	6-44*	39-82*	
SCA2	12q24	*SCA2*	Ataxin-2	CAG repeat	2-65	15-24	35-59	
SCA3/MJD	14q24.3-q31	*MJD1*	Ataxin-3	CAG repeat	11-70	13-47*	45-84*	
SCA6	19q13	*CACNA1A*	CACNA1A	CAG repeat	16-v73	4-20	21-33	
SCA7	3p21.1-p12	*SCA7*	Ataxin-7	CAG repeat	Birth-53	4-35	37-460	
SCA17	6q27	*SCA17*	TBP	CAG repeat	3-48	25-42	45-66	
DRPLA	12p13.31	*DRPLA*	Atrophin-1	CAG repeat	4-55 mo	7-34	53-93	
NONCODING EXPANSION								
SCA8	13q21	*SCA8*	SCA8 RNA	CTG repeat in 3′ UTR	18-72	2-91*	110-155*	
SCA10	22q13	*SCA10*	Ataxin-10	ATTCT repeat in intron 9	14-45	10-29	750-4500	
SCA12	5q31-q33	*SCA12*	P2R2B	CAG repeat in 5′ UTR	8-55	7-32	55-78	
SCA31	16q22.1	*BEAN/TK2*	BEAN/TK2	TGGAA repeat insertion in intron of BEAN and TK	45-72	Rarely (0.23%) 1.5-2.0 kb	2.5-3.8 kb	
OTHER MUTATIONS								
SCA14	19q13.4	*PKC-γ*	PKC-γ	Missense mutation	10-69			
SCA27	13q34	*FGF14*	FGF14	Fibroblast growth factor deficiency	15-20			
SCA5	11p11-q11	*SPTBN2*	β-3 spectrin	Deletion, missense mutations	10-68			
SCA11	15q14-q21.3	*TTBK2*	TTBK2	Truncation mutation	15-43			
SCA13	19q13.3-q13.4	*KCNC3*	KCNC3	Missense mutations	<1-60			
SCA15	3p24.2-3pter	*ITPR1*	ITPR1	Deletion, missense mutation	Child–adult			
SCA28	18p11.22-q11.2.	*AFG3L2*	AFG3L2	Missense mutations	12-36			

Table 597-8 Drugs That Can Induce Chorea

DOPAMINE RECEPTOR BLOCKING AGENTS (UPON WITHDRAWAL OR AS A TARDIVE SYNDROME) Phenothiazines Butyrophenones Benzamides	**CALCIUM CHANNEL BLOCKERS** Cinnarizine Flunarizine Verapamil
ANTIPARKINSONIAN DRUGS L-DOPA Dopamine agonists Anticholinergics	**OTHERS** Lithium Baclofen Digoxin Tricyclic antidepressants Cyclosporine Steroids/oral contraceptives Theophylline Propofol
ANTIEPILEPTIC DRUGS Phenytoin Carbamazepine Valproic acid	
PSYCHOSTIMULANTS Amphetamines Methylphenidate Cocaine	

Table 600-4 Clinical Features That May Distinguish ADEM from First Attack of MS

	ADEM	MS
Age	<10 yr	>10 yr
Stupor/coma	+	–
Encephalopathy	+	–
Fever/vomiting	+	–
Family history	No	20%
Sensory complaints	+	+
Optic neuritis	Bilateral	Unilateral
Manifestations	Polysymptomatic	Monosymptomatic
CSF	Pleocytosis (lymphocytosis)	Oligoclonal bands
Response to steroids	+	+
Follow-up	No new lesions	New lesions

Some features that may help distinguish an initial acute episode of demyelination from a first attack of MS in children. Final diagnosis of MS is based on follow-up evaluation and possibly MRI.
+, More likely to be present; –, less likely to be present; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis.

Table 597-6 Etiologic Classification of Choreic Syndromes

GENETIC CHOREAS
Huntington disease (rarely presents with chorea in childhood)
Huntington disease–like 2 and other Huntington disease –like syndromes
Dentatorubropallidoluysian atrophy
Neuroacanthocytosis
Leigh syndrome and other mitochondrial disorders
Ataxia telangiectasia
Benign hereditary chorea
Wilson disease
Spinocerebellar ataxia (types 2, 3, or 17)
Pantothene kinase–associated neurodegeneration (PKAN)
Paroxysmal kinesigenic choreoathetosis
Paroxysmal nonkinesigenic choreoathetosis
Fahr syndrome
Rett syndrome
STRUCTURAL BASAL-GANGLIA LESIONS
Vascular chorea in stroke, vasculitis, Moyamoya disease
Mass lesions (e.g., central nervous system lymphoma, metastatic brain tumors)
Joubert syndrome and related disorders
Multiple sclerosis plaques
Extrapontine myelinolysis
Trauma
PARAINFECTIOUS AND AUTOIMMUNE DISORDERS
Sydenham chorea
Systemic lupus erythematosus
Chorea gravidarum
Antiphospholipid antibody syndrome
Postinfectious or postvaccinal encephalitis
Anti–N-methyl-D-aspartate (NMDA)–receptor antibody syndrome (Limbic encephalitis)
Paraneoplastic choreas
INFECTIOUS CHOREA
HIV encephalopathy
Toxoplasmosis
Cysticercosis
Diphtheria
Bacterial endocarditis
Neurosyphilis
Scarlet fever
Viral encephalitis (mumps, measles, varicella)
METABOLIC DRUG OR TOXIC ENCEPHALOPATHIES
Acute intermittent porphyria
Hypo-/hypernatremia
Hypocalcemia
Hyperthyroidism
Hypoparathyroidism
Hepatic/renal failure
Carbon monoxide poisoning
Manganese poisoning
Mercury poisoning
Organophosphate poisoning
Pheochromocytoma
DRUG-INDUCED CHOREA (see Table 597-8)

Table 597-1 Selected Types of Involuntary Movement in Childhood

TYPE	CHARACTERISTICS
Stereotypies (see Chapter 24)	Involuntary, patterned, coordinated, repetitive, rhythmic movements that occur in the same fashion with each repetition
Tics (see Chapter 24)	Involuntary, sudden, rapid, abrupt, repetitive, nonrhythmic, simple or complex motor movements or vocalizations (phonic productions). Tics are usually preceded by an urge that is relieved by carrying out the movement
Tremor	Oscillating, rhythmic movements about a fixed point, axis, or plane
Dystonia (see Chapter 597.3)	Intermittent and sustained involuntary muscles contractions that produce abnormal postures and movements of different parts of the body, often with a twisting quality
Chorea (see Chapter 597.2)	Involuntary, continual, irregular movements or movement fragments with variable rate and direction that occur unpredictably and randomly
Ballism	Involuntary, high amplitude, flinging movements typically occurring proximally. Ballism is essentially a large amplitude chorea
Athetosis	Slow, writhing, continuous, involuntary movements
Myoclonus	Sudden, quick, involuntary muscle jerks

Table 597-7 Genetic Choreas

	MODE OF INHERITANCE	GENE, LOCATION	PROTEIN PRODUCT	USUAL AGE AT ONSET (yr)	CLINICAL SIGNS
HDL2*	AD†	*JPH3*, 16q	Junctophilin-3	20-40	Huntington disease phenotype, sometimes acanthocytosis; almost exclusively African ethnicity
SCA17	AD†	*TBP*, 6q	TBP	10-30	Cerebellar ataxia, chorea, dystonia, hyperreflexia, cognitive decline
DRPLA	AD†	*DRPLA*, 12p	Atrophin-1	About 20	Variable phenotypic picture including chorea, ataxia, seizures, psychiatric disturbances, dementia; more common in Japan than in Europe or United States
SCA3/MJD	AD†	*MJD*, 14q	Ataxin-3	35-40	Wide phenotypic variability with cerebellar ataxia, protruded eyes, chorea, dystonia, parkinsonian features, neuropathy, pyramidal tract features
SCA2	AD†	*Ataxin-2*, 12q	Ataxin-2	30-35	Cerebellar ataxia, chorea, markedly reduced velocity of saccadic eye movements, hyporeflexia
Chorea-acanthocytosis	AR	*VPS13A* (formerly *CHAC*), 9q	Chorein	20-50	Orofacial self-mutilation, dystonia, neuropathy, myopathy, seizures, acanthocytosis
McLeod syndrome	X-linked, recessive	*XK*, Xp	XK-protein	40-70	Dystonia, neuropathy, myopathy, cardiomyopathy, seizures, acanthocytosis, raised creatine kinase, weak expression of Kell antigen
Neuroferritinopathy	AD	*FTL*, 19q	FTL	20-55	Chorea, dystonia, parkinsonian features; usually reduced serum ferritin; MR abnormalities with cyst formation and increased T2 signal in globus pallidus and putamen
AT and ATLD	AR	*ATM*, 11q (*AT*) *MRE11*, 11q (*ATLD*)	ATM (AT) MRE11 (ATLD)	Childhood	Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea, dystonia, and myoclonus In AT: oculocutaneous telangiectasias; predisposition to malignancies, IgA and IgG deficiency, high α-fetoprotein in serum and high concentrations of carcinoembryonic antigen
AOA 1 and 2	AR	*APTX*, 9p (*AOA 1*) *SETX*, 9q (*AOA 2*)	Aprataxin (AOA 1) Senataxin (AOA 2)	Childhood or adolescence (later onset in AOA 2)	Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea and dystonia; ataxia with oculomotor apraxia type 1: hypoalbuminemia and hypercholesterolemia; ataxia with oculomotor apraxia type 2: raised α-fetoprotein in serum
Pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome)	AR	*PANK2*, 20p	Pantothenate kinase 2	Childhood, but also adult-onset subtype	Chorea, dystonia, parkinsonian features, pyramidal tract features; MR abnormalities with decreased T2 signal in the globus pallidus and substantia nigra, "eye of the tiger" sign (hyperintense area within the hypointense area); sometimes acanthocytosis, abnormal cytosomes in lymphocytes

Continued

Table 597-7 Genetic Choreas—cont'd

	MODE OF INHERITANCE	GENE, LOCATION	PROTEIN PRODUCT	USUAL AGE AT ONSET (yr)	CLINICAL SIGNS
Lesch-Nyhan syndrome	X-linked, recessive	*HPRT*, Xq	Hypoxanthine-guanine phosphoribosyl-transferase	Childhood	Chorea, dystonia, hypotonia, self-injurious behavior with biting of fingers and lips, mental retardation; short stature, renal calculi, hyperuricemia
Wilson disease	AR	*ATP7B*, 13q	Copper transporting P-type adenosine triphosphatase (ATPase)	<40	Parkinsonian features, dystonia, tremor, rarely chorea, behavioral and cognitive change, corneal Kayser-Fleischer rings, liver disease
PKC syndrome and ICCA syndrome	AD	Unknown, 16p	Unknown	<1-40	Paroxysmal movement disorders presenting with recurrent brief episodes of abnormal involuntary movements with dramatic response to low-dose carbamazepine (PKC); recurrent brief episodes of abnormal involuntary movements in association with infantile convulsions (ICCA)
Benign hereditary chorea	AD	*TITF-1*, 14q; other	Thyroid transcription factor 1	Childhood	Chorea, mild ataxia; genetically heterogeneous

*HDL1, HDL3, and HDL4 are very rare conditions (only 1 family known) and therefore not included in the table.
†Disorders based on expanded CAG repeats (HDL2 based on CAG/CTG repeats; SCA 17 based on CAG/CAA repeats); age of symptom onset inversely related to repeat size.
AD, autosomal dominant; AOA, ataxia with oculomotor apraxia (types 1 or 2); AR, autosomal recessive; AT, ataxia telangiectasia; ATLD, ataxia telangiectasia–like disorder; DRPLA, dentatorubropallidoluysian atrophy; ICCA, infantile convulsions and paroxysmal choreoathetosis syndrome; MJD, Machado-Joseph disease; PKC, paroxysmal kinesigenic choreoathetosis; SCA, spinocerebellar ataxia (types 2, 3, or 17).
Modified from Cardoso F, Seppi K, Mair KJ, et al: Seminar on choreas, Lancet Neurol *5:589–602, 2006.*

Table 601-2 Classification of Cerebral Vasculitis

Infectious vasculitis
- Bacterial, fungal, parasitic
- Spirochetal (syphilis, Lyme disease, leptospirosis)
- Viral, rickettsial, mycobacterial, free-living amebae, cysticercosis, other helminths

Necrotizing vasculitides
- Classic polyarteritis nodosa
- Wegener granulomatosis
- Allergic angiitis and granulomatosis (Churg-Strauss syndrome)
- Necrotizing systemic vasculitis overlap syndrome
- Lymphomatoid granulomatosis

Vasculitis associated with collagen vascular disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Scleroderma
- Sjögren syndrome

Vasculitis associated with other systemic diseases
- Behçet disease
- Ulcerative colitis
- Sarcoidosis
- Relapsing polychondritis
- Kohlmeier-Degos disease

Takayasu arteritis

Hypersensitivity vasculitides
- Henoch-Schönlein purpura
- Drug-induced vasculitides
- Chemical vasculitides
- Essential mixed cryoglobulinemia

Miscellaneous
- Vasculitis associated with neoplasia
- Vasculitis associated with radiation
- Cogan syndrome
- Dermatomyositis-polymyositis
- X-linked lymphoproliferative syndrome
- Kawasaki disease

Primary central nervous system vasculitis

From Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children, Stroke *39:2644–2691, 2008, Table 5, p. 8.*

Table 601-4 Potential Risk Factors for Hemorrhagic Stroke in Children

MAJOR CATEGORIES	EXAMPLES
Vascular disorder	Arteriovenous malformations Cavernous malformations ("cavernomas") Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm Choroid plexus angiomas (pure intraventricular hemorrhage) Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 601.1) Neoplastic lesions with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis
Blood disorder	Idiopathic thrombocytopenic purpura Hemolytic uremic syndrome Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of the newborn) Disseminated intravascular coagulopathy
Trauma	Middle meningeal artery injury (epidural hematoma) Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage Hemorrhagic contusions (coup and contrecoup) Nonaccidental trauma (subdural hematomas of different ages) Iatrogenic (neurosurgical procedures, angiography) Rupture of arachnoid cyst

Table 597-10 Causes of Dystonia in Childhood

STATIC INJURY/STRUCTURAL DISORDERS
Cerebral palsy
Hypoxic–ischemic injury
Kernicterus
Head trauma
Encephalitis
Tumors
Stroke in the basal ganglia (which may be a result of vascular abnormalities or varicella)
Congenital malformations

HEREDITARY/DEGENERATIVE DISORDERS
DYT1 (9q34, encodes torsinA)
DYT2 (autosomal-recessive)
DYT3 (X-linked dystonia-parkinsonism syndrome of Lubag–Xq13)
DYT4
DYT5 (14q22.1-2, encodes GTP cyclohydrolase I, leading to dopa-responsive dystonia or Segawa disease)
DYT6 (8p21-q22)
DYT7 (18p)
DYT8 (2q33-q35, causing paroxysmal nonkinesigenic choreoathetosis [PNKC])
DYT9 (1p, causing paroxysmal nonkinesigenic dyskinesia [PNKD] and spasticity)
DYT10 (16p11.2-q12.1, causing paroxysmal kinesigenic choreoathetosis [PKC])
DYT11 (heterogeneous, causing familial myoclonus-dystonia)
Rapid-onset dystonia-parkinsonism (DYT12)
Fahr disease (often caused by hypoparathyroid disease)
Pantothenate kinase-associated neurodegeneration (PKAN; neuronal brain iron accumulation type 1, formerly Hallervorden-Spatz disease, caused by mutations in PANK2)
Huntington disease (particularly the Westphal variant, IT15-4p16.3)
Spinocerebellar ataxias (SCAs, including SCA3/Machado-Joseph disease)
Neuronal ceroid-lipofuscinoses (NCL)
Rett syndrome
Striatal necrosis
Leigh disease
Neuroacanthocytosis
HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)
Ataxia-telangiectasia
Tay-Sachs disease
Sandhoff's disease
Niemann-Pick type C
GM_1 gangliosidosis
Metachromatic leukodystrophy (MLD)
Lesch-Nyhan disease

METABOLIC DISEASE
Glutaric aciduria types 1 and 2
Acyl-coenzyme A (CoA) dehydrogenase deficiencies
Dopa-responsive dystonia (tyrosine hydroxylase deficiency, guanosine triphosphate [GTP] cyclohydrolase 1 deficiency, DYT5)
Dopamine agonist-responsive dystonia (aromatic l-amino acid decarboxylase deficiency, aminolevulinic acid dehydrase [ALAD])
Biotin responsive basal ganglia disease
Mitochondrial disorders
Wilson disease
Vitamin E deficiency
Homocystinuria
Methylmalonic aciduria
Tyrosinemia

DRUGS/TOXINS
Neuroleptic and antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine)
Calcium channel blockers
Stimulants (amphetamine, cocaine, ergot alkaloids)
Anticonvulsants (carbamazepine, phenytoin)
Thallium
Manganese
Carbon monoxide
Ethylene glycol
Cyanide
Methanol
Wasp sting

PAROXYSMAL DISORDERS
Paroxysmal kinesigenic choreoathetosis (PKC)
Paroxysmal nonkinesigenic choreoathetosis (PNKC)
Exercise-induced dystonia
Complex migraine
Alternating hemiplegia of childhood (AHC)
Paroxysmal torticollis of infancy

DISORDERS THAT MIMIC DYSTONIA
Tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures)
Arnold-Chiari malformation type II
Atlantoaxial subluxation
Syringomyelia
Posterior fossa mass
Cervical spine malformation (including Klippel-Feil syndrome)
Skew deviation with vertical diplopia causing neck twisting
Juvenile rheumatoid arthritis
Sandifer syndrome (associated with hiatal hernia in infants)
Spasmus nutans
Tics
Infant masturbation
Spasticity
Myotonia
Rigidity
Stiff-person syndrome
Isaac syndrome (neuromyotonia)
Startle disease (hyperekplexia)
Neuroleptic malignant syndrome
Central herniation with posturing
Psychogenic dystonia

From Sanger TD, Mink JW: Movement disorders. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology: principles and practice, *ed 5, Philadelphia, 2012, WB Saunders, Box 68-2.*

Table 597-11 Examples of Primary and Secondary Dystonia in Childhood

DIAGNOSIS	ADDITIONAL CLINICAL FEATURES
Aicardi-Goutières syndrome	Encephalopathy, developmental regression Acquired microcephaly Sterile pyrexias Lesions on the digits, ears (chilblain) Epilepsy CT: calcification of the basal ganglia
Alternating hemiplegia of childhood	Episodic hemiplegia/quadriplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia
ARX gene mutation (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine
Complex regional pain syndrome	Lower limb involvement Prominent pain
Dopa-responsive dystonia (DRD)	Diurnal variation
Drug-induced dystonia	
Dystonia-deafness optic neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence
DYT1 dystonia	Lower limb onset followed by generalization
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: striatal necrosis
GM_1 gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: putaminal hyperintensity
Huntington disease	Parkinsonism Epilepsy Family history of Huntington disease
Kernicterus	Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia MRI: hyperintense lesions in the globus pallidus
Leigh syndrome	Motor delays, weakness, hypotonia Ataxia, tremor Elevated lactate MRI: bilateral symmetric hyperintense lesions in the basal ganglia or thalamus
Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment Elevated uric acid
Myoclonus dystonia	Myoclonus Head, upper limb involvement
Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Neuroacanthocytosis	Oromandibular and lingual dystonia
Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Rapid onset dystonia parkinsonism (DYT12)	Acute onset Distribution face > arm > leg Prominent bulbar signs
Rett syndrome	Female Developmental regression following a period of normal development Stereotypic hand movements Acquired microcephaly Epilepsy
Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
Tics	Stereotyped movements Premonitory urge, suppressible
Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD

Table 598-1 Classification of Cerebral Palsy and Major Causes

MOTOR SYNDROME (APPROX. % OF CP)	NEUROPATHOLOGY/MRI	MAJOR CAUSES
Spastic diplegia (35%)	Periventricular leukomalacia Periventricular cysts or scars in white matter, enlargement of ventricles, squared off posterior ventricles	Prematurity Ischemia Infection Endocrine/metabolic (e.g., thyroid)
Spastic quadriplegia (20%)	Periventricular leukomalacia Multicystic encephalomalacia Cortical malformations	Ischemia, infection Endocrine/metabolic, genetic/developmental
Hemiplegia (25%)	Stroke: in utero or neonatal Focal infarct or cortical, subcortical damage Cortical malformations	Thrombophilic disorders Infection Genetic/developmental Periventricular hemorrhagic infarction
Extrapyramidal (athetoid, dyskinetic) (15%)	Asphyxia: symmetric scars in putamen and thalamus Kernicterus: scars in globus pallidus, hippocampus Mitochondrial: scaring globus pallidus, caudate, putamen, brainstem No lesions: ? dopa-responsive dystonia	Asphyxia Kernicterus Mitochondrial Genetic/metabolic

Table 598-2 Clinical Manifestations of Mitochondrial Encephalomyopathies

TISSUE	SYMPTOMS/SIGNS	MELAS	MERRF	NARP	KSS	LEIGH	LHON
CNS	Regression	+	+		+	+	
	Seizures	+	+				
	Ataxia	+	+	+	+		
	Cortical blindness	+					
	Deafness	+		+			
	Migraine	+					
	Hemiparesis	+					
	Myoclonus	+	+				
	Movement disorder	+					+
Nerve	Peripheral neuropathy	+	+	+	+		
Muscle	Ophthalmoplegia				+		
	Weakness	+	+	+	+	+	
	RRF on muscle biopsy	+	+		+		
	Ptosis				+		
Eye	Pigmentary retinopathy			+	+		
	Optic atrophy				+	+	+
	Cataracts						
Heart	Conduction block				+		+
	Cardiomyopathy				+		
Blood	Anemia	+					
	Lactic acidosis		+		+	+	
Endocrine	Diabetes mellitus				+		
	Short stature	+	+		+		
Kidney	Fanconi syndrome	+	+		+		

KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NARP, neuropathy, ataxia and retinitis pigmentosa; RRF, ragged red fibers.

Table 598-3 Clinical Features of Congenital Leigh Syndrome or Leigh-Like Syndrome

NEUROLOGIC MANIFESTATIONS	NONNEUROLOGIC MANIFESTATIONS
Brainstem	***Dysmorphic Features***
Bradypnea, hypopnea, episodes of apnea	Lip cleft
Bradycardia	Short distal phalanges
Tetraparesis	Single palmar crease
Hypotonia (floppy infant)	Rostral vertebrae
Failure to thrive, poor sucking	Round face
Swallowing difficulties, dysphagia, poor feeding, poor sucking	Frontal bossing
Vomiting	Flat nasal root
Spasticity, brisk tendon reflexes	Microcephaly
Dysphasia, dysarthria	Thin lips
Squint	Small chin
Absence of optic or acoustic blink	Long, featureless philtrum
Other Cerebral Manifestations	Hypospadia
Stroke-like episodes	***Others***
Delay of developmental milestones	Inguinal hernia
Paralysis of vertical gaze	Stiff neck
Myoclonic jerks of limbs or eyelids	Retinal dystrophy, retinopathy
Hypothermia	Deafness, hypoacusis
Drowsiness, dizziness	Hypertrophic, dilated cardiomyopathy
Psychomotor (mental) retardation	Pancreatitis
Ataxia, tremor	Diarrhea
Seizures, convulsions	Urinary excretion of Krebs-cycle intermediates
Growth retardation	Intrauterine growth retardation
Dystonia	Hypertrichosis
Clumsiness, dullness	Villous atrophy
Nystagmus, uncoordinated eye movement, slow saccades	Nephrotic syndrome
Optic atrophy	Nephropathy
Visual loss	Hyperhidrosis
Facial dyskinesia	Scoliosis
Ocular apraxia	
Drooling	
Gaze fixation difficulty	
Peripheral Nervous System Manifestations	
Cranial nerve palsies	
Generalized wasting	
Bilateral ptoses	
Chronic progressive external ophthalmoplegia, strabismus	
Reduced tendon reflexes	
Polyneuropathy	
Muscle weakness	
Myopathy	

From Finsterer J: Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol *39:223–235, 2008, Table 1.*

Table 598-4 Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood

1. Acute encephalopathy following (1-3 days) a febrile disease. Rapid deterioration in the level of consciousness. Seizures.
2. No cerebrospinal fluid pleocytosis. Increase in cerebrospinal fluid protein.
3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum and cerebellar medulla. No involvement of other central nervous system regions.
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia.
5. Exclusion of resembling diseases.
   A. Differential diagnosis from clinical viewpoints.
   Overwhelming bacterial and viral infections, and fulminant hepatitis; toxic shock, hemolytic uremic syndrome, and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.
   B. Differential diagnosis from radiologic viewpoints.
   Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, other types of encephalitis, and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma

Table 600-1 Differential Diagnosis of Demyelinating Disorders

Acute disseminated encephalomyelitis (ADEM)
Multiple sclerosis (including tumefactive MS)
Acute hemorrhagic leukoencephalopathy
Clinically isolated syndrome (CIS)
Neuromyelitis optica spectrum disorder
N-methyl-D-aspartate receptor (NMDAR) antibody and other autoimmune encephalitis
Vasculitis/angiopathies
Hashimoto encephalitis (anti–thyroid peroxidase [TPO] antibody)
Familial hemophagocytic lymphohistiocytosis
Langerhans cell histiocytosis
Lymphoma
Gliomatosis cerebri
Glioma
Sarcoidosis
Mitochondrial disorders (Leigh syndrome)
Vitamin E deficiency
Vitamin B_{12} deficiency
Celiac disease
Herpes simplex virus (HSV), enterovirus, arbovirus, Powassan and other viral encephalitides
Rabies
Subacute sclerosing pan-encephalitis (SSPE) (chronic measles)
Charcot-Marie-Tooth syndrome
Leukoencephalopathies (Aicardi-Goutières syndrome)
Vanishing white matter disease
Schilder disease (possibly an adrenoleukodystrophy)
X-linked adrenoleukodystrophy
Griscelli syndrome type 2

Table 598-5 Autoimmune Encephalitis in Children

	MECHANISMS	TUMOR ASSOCIATION	SYNDROME	ANCILLARY TEST	TREATMENT/ PROGNOSIS
DEMONSTRATED IMMUNE MECHANISMS					
Anti-NMDAR encephalitis	Antibodies against NR1 subunit of NMDAR, disrupt function by crosslinking and internalization of receptors	Age and gender related: 41% in females older than 12 yr; <6% in girls younger than 12 yr. No tumors identified in young boys	Psychiatric symptoms, seizures, orofacial dyskinesias and other abnormal movements, autonomic dysfunction	EEG: almost always abnormal; it may show "extreme delta brush" pattern Brain MRI: nonspecific findings in ~35% CSF: pleocytosis and/or increased protein in >80%	80% complete recovery after immunotherapy and tumor removal (if appropriate). Frequently second-line drug* immunotherapy is required. Relapses in ~15% of patients
Limbic encephalitis	**Antibodies against intraneuronal antigens:** Hu, Ma2, amphiphysin, GAD **Antibodies against synaptic antigens:** $GABA_BR$, mGluR5	Extremely rare in children (see text)	Severe short-term memory loss, seizures	EEG: temporal lobe epileptic activity; focal or generalized slowing MRI: increased T2 and FLAIR signal in limbic region CSF: pleocytosis and increased proteins	If autoantigens are intracellular, poor response to immunotherapy If autoantigens are on the cell surface, ~80% are responsive to immunotherapy
STRONGLY SUSPECTED IMMUNE MECHANISMS					
Opsoclonus-myoclonus and other cerebellar-brainstem encephalitis	Most patients do not have detectable antibodies (a few patients have Hu antibodies)	Neuroblastoma occurs in 50% of children <2 year old; teratoma in teenagers and young adults	Opsoclonus often accompanied by irritability, ataxia, falling, myoclonus, tremor, and drooling	CSF abnormalities suggesting B-cell activation MRI: in some cases cerebellar atrophy	Partial response to immunotherapy in neuroblastoma-related opsoclonus High response to immunotherapy in teratoma-associated opsoclonus
Bickerstaff encephalitis	GQ1b antibodies	No tumor association	Ophthalmoplegia, ataxia, hyperreflexia. May overlap with Miller-Fisher syndrome	MRI: abnormal in ~30% (T2-signal abnormalities in the brainstem, thalamus, and cerebellum) Nerve conduction studies: abnormal in ~44% (predominant axonal degeneration, less frequent demyelination)	Often good outcome with steroids, IVIG and/or plasma exchange
Hashimoto encephalitis	TPO antibodies	No tumor association	Stroke-like symptoms, tremor, myoclonus, aphasia, sleep and behavioral problems seizures, ataxia	48% hypothyroidism, MRI often normal EEG: slow activity CSF: elevated protein	Steroid-responsive. Partial responses are frequent
Rasmussen encephalitis	Most likely immune mediated (unclear mechanism)	No tumor association	Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy	MRI: progressive unilateral hemispheric atrophy	Limited response to immunotherapy. Patients may need functional hemispherectomy
Basal ganglia encephalitis	Antibodies to D2R in some cases	No tumor association	Abnormal movement and behavior disorder	Variable basal ganglia T2/FLAIR abnormalities	Mostly monophasic, can relapse
POSSIBLE IMMUNE MECHANISMS					
CLIPPERS	No antibodies	No tumor association	Episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction	MRI: symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain, and, occasionally, spinal cord	Steroid-responsive but may require chronic steroid or other immunosuppressive therapy
ROHHAD	Unknown. Autoimmune and genetic origin postulated.	Neural crest tumor in ~50% of cases†	Rapid onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypoventilation	Brain MRI, usually normal	Symptomatic; in some patients limited response to immunotherapy

*Includes rituximab and cyclophosphamide.

†Exact frequency is unknown.

CLIPPERS, Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF, cerebrospinal fluid; D2R, dopamine 2 receptor; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; $GABA_BR$, γ-aminobutyric acid-B receptor, GAD, glutamic acid decarboxylase; IVIG, intravenous immunoglobulin; mGluR5, metabotropic glutamate receptor 5; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; ROHHAD, rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; TPO, thyroid peroxidase.

Table 598-6 Differential Diagnosis of Anti-NMDAR Encephalitis in Children

DISORDER	COMMENTS
Viral encephalitis	Viral encephalitis is often suggested by the acute onset of symptoms, CSF pleocytosis, and hyperthermia. Most viral encephalitides (except rabies) occur with higher levels of CSF pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent in viral encephalitis than in anti-NMDAR encephalitis.
Relapsing post–herpes simplex virus encephalitis	Occurs ~4-6 wk after successful treatment of herpes simplex encephalitis. This may represent a true viral relapse of encephalitis (CSF PCR-positive, progression of necrotic MRI changes, response to acyclovir), or an autoimmune disorder (CSF PCR-negative, no new necrotic lesions on MRI, lack of response to acyclovir). In a proportion of the latter patients, the disorder is anti-NMDAR encephalitis.
New-onset psychosis	Because most patients with anti-NMDAR encephalitis present with psychosis, a primarily psychiatric disorder is frequently considered. As the disease evolves, the development of neurological symptoms usually reveals the diagnosis.
Drugs/toxins	The acute development of personality and behavioral changes, and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually leads to a suspicion of drug abuse (e.g., ketamine, phencyclidine, among others). Carbon monoxide.
Neuroleptic malignant syndrome	The occurrence of altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest NMS. In addition, some patients with anti-NMDAR encephalitis have elevated serum creatine kinase and rhabdomyolysis (in the absence of antipsychotic medication). The frequent use of neuroleptics to control the abnormal behavior adds further confusion between both syndromes. The presence of dyskinesias and catatonia suggest anti-NMDAR encephalitis.
Limbic encephalitis	Criteria of LE are well defined. Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are largely restricted to the temporal lobes.
Encephalitis lethargica	This is an ill-defined entity, likely representing multiple disorders. Criteria include: acute or subacute encephalitis with at least 3 of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Approximately, 50% of patients categorized as encephalitis lethargica hyperkinetica have anti-NMDAR encephalitis.
Childhood disintegrative disorder/late-onset autism	Children with anti-NMDAR encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder. While the prognosis of CDD is poor, most patients with anti-NMDAR encephalitis respond to immunotherapy and have substantial clinical recovery.
Kleine-Levin syndrome	Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and child-like behavior, which are typical components of Kleine-Levin syndrome, may occur transiently during the process of recovery of anti-NMDAR encephalitis, or as permanent sequelae.
Inborn errors of metabolism	Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process. Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including 3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome), Wilson, and Lesch-Nyhan syndromes. Pantothenate kinase associated neurodegeneration, porphyria, and urea cycle defects should also be considered.
Monoamine neurotransmitter disorders	Deficiency of dopamine, serotonin or both can result in encephalopathy, epilepsy, and pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the CSF for levels of these neurotransmitters.
Demyelinating disorders	Acute disseminated encephalomyelitis and neuromyelitis optica are immune-mediated inflammatory and demyelinating disorders of the central nervous system. These disorders should be considered in the differential diagnosis of multifocal neurologic abnormalities and encephalopathy in children. As with anti-NMDAR encephalitis these disorders may be preceded by an infection and can show pleocytosis. The diagnosis is suggested by the MRI findings. In NMO the presence of aquaporin 4 antibodies in serum or CSF is associated with relapses and poor prognosis.
CNS vasculitis	CNS vasculitis results in neurologic deficits and psychiatric manifestations. The diagnosis is established by angiography in large vessel angiitis, and brain biopsy in small vessel angiitis. In the latter, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, Complement 3, von Willebrand factor antigen) are usually elevated, and the MRI shows FLAIR/T2 abnormalities in the white and/or gray matter, not restricted to vascular territories with frequent leptomeningeal and/or local enhancement.
Systemic rheumatic disorders	Systemic lupus erythematosus and other rheumatic disorders can result in encephalopathy and multifocal neurologic and psychiatric manifestations. These disorders are usually suggested by the presence of signs and symptoms of involvement of systemic organs: skin, joints, kidneys, blood-forming cells, and blood vessels.

CDD, childhood disintegrative disorder; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; LE, limbic encephalitis; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; NMO, neuromyelitis optica; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction.

Table 599-1 Neurometabolic Conditions Associated with Developmental Regression

AGE AT ONSET (yr)	CONDITIONS	COMMENTS
<2 with hepatomegaly	Fructose intolerance	Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)
	Galactosemia	Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)
	Glycogenosis (glycogen storage disease) types I-IV	Hypoglycemia, cardiomegaly (type II)
	Mucopolysaccharidosis types I and II	Coarse facies, stiff joints
	Niemann-Pick disease, infantile type	Gray matter disease, failure to thrive
	Tay-Sachs disease	Seizures, cherry-red macula, edema, coarse facies
	Zellweger syndrome	Hypotonia, high forehead, flat facies
	Gaucher disease (neuronopathic form)	Extensor posturing, irritability
	Carbohydrate-deficient glycoprotein syndromes	Dysmyelination, cerebellar hypoplasia
<2, without hepatomegaly	Krabbe disease	Irritability, extensor posturing, optic atrophy, and blindness
	Rett syndrome	Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia
	Maple syrup urine disease	Poor feeding, tremors, myoclonus, opisthotonos
	Phenylketonuria	Light pigmentation, eczema, seizures
	Menkes kinky hair disease	Hypertonia, irritability, seizures, abnormal hair
	Subacute necrotizing encephalopathy of Leigh disease	White matter disease
	Canavan disease	White matter disease, macrocephaly
	Neurodegeneration with brain iron accumulation disease	White matter disease, movement disorder
2-5	Niemann-Pick disease types III and IV	Hepatosplenomegaly, gait difficulty
	Wilson disease	Liver disease, Kayser-Fleischer ring; deterioration of cognition is late
	Gangliosidosis type II	Gray matter disease
	Neuronal ceroid lipofuscinosis	Gray matter disease
	Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])	Gray matter disease
	Ataxia-telangiectasia	Basal ganglia disease
	Huntington disease (chorea)	Basal ganglia disease
	Neurodegeneration with brain iron accumulation syndrome	Basal ganglia disease
	Metachromatic leukodystrophy	White matter disease
	Adrenoleukodystrophy	White matter disease, behavior problems, deteriorating school performance, quadriparesis
5-15	Adrenoleukodystrophy	Same as for adrenoleukodystrophy in 2-5 yr olds
	Multiple sclerosis	White matter disease
	Neuronal ceroid lipofuscinosis, juvenile and adult (Spielmeyer-Vogt and Kufs disease)	Gray matter disease
	Schilder disease	White matter disease, focal neurologic symptoms
	Refsum disease	Peripheral neuropathy, ataxia, retinitis pigmentosa
	Sialidosis II, juvenile form	Cherry-red macula, myoclonus, ataxia, coarse facies
	Subacute sclerosing panencephalitis	Diffuse encephalopathy, myoclonus; may occur years after measles

Table 600-5 MRI Characteristics for Dissemination in Space That Increase the Likelihood of a Pediatric Multiple Sclerosis Diagnosis

BARKHOF*	MIKAELOFF (KIDMUS)†	CALLEN (MS VS ADEM)‡	CALLEN (DIAGNOSTIC MS)§	VERHEY (DIFFERENTIAL)‖	POLMAN (2010 REVISED MCDONALD CRITERIA)¶
3 of 4: ≥9 T2 lesions or 1 gadolinium enhancing ≥3 Periventricular ≥1 Infratentorial ≥1 Juxtacortical	1 of 2: Lesions perpendicular to long axis of the corpus callosum Sole presence of well-defined lesions	2 of 3: Absence of a diffuse bilateral lesion pattern Presence of black holes ≥2 Periventricular lesions	2 of 3: ≥5 Lesions on T2-weighted images 2 Periventricular lesions ≥1 Brainstem lesions	2 of 2: ≥1 Periventricular lesions ≥1 Hypointense lesions on T1 images	2 of 4: ≥1 Periventricular ≥1 Juxtacortical ≥1 Infratentorial ≥1 Spinal cord

*Barkhof F, Filippi M, Miller DH, et al: Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 120:2059–2069, 1997.

†Mikaeloff Y, Adamsbaum C, Husson HM, et al: MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. Brain 127:1942–1947, 2004.

‡Callen DJ, Shroff MM, Branson HM, et al: Role of MRI in the differentiation of ADEM from MS in children. *Neurology* 72:968–973, 2009.

§Callen DJ, Shroff MM, Branson HM, et al: MRI in the diagnosis of pediatric multiple sclerosis. *Neurology* 72:961–967, 2009.

‖Verhay LH, Branson HM, Shroff MM, et al: MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. *Lancet Neurol* 10:1065–1073, 2011.

¶Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 69:292–302, 2011.

ADEM, acute disseminated encephalomyelitis; MS, multiple sclerosis.

From Krupp LB, Tardieu M, Amato MP, et al: International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revision to the 2007 definitions. Mult Scler *19(10):1261–1267, 2013, Appendix 3, p. 1267.*

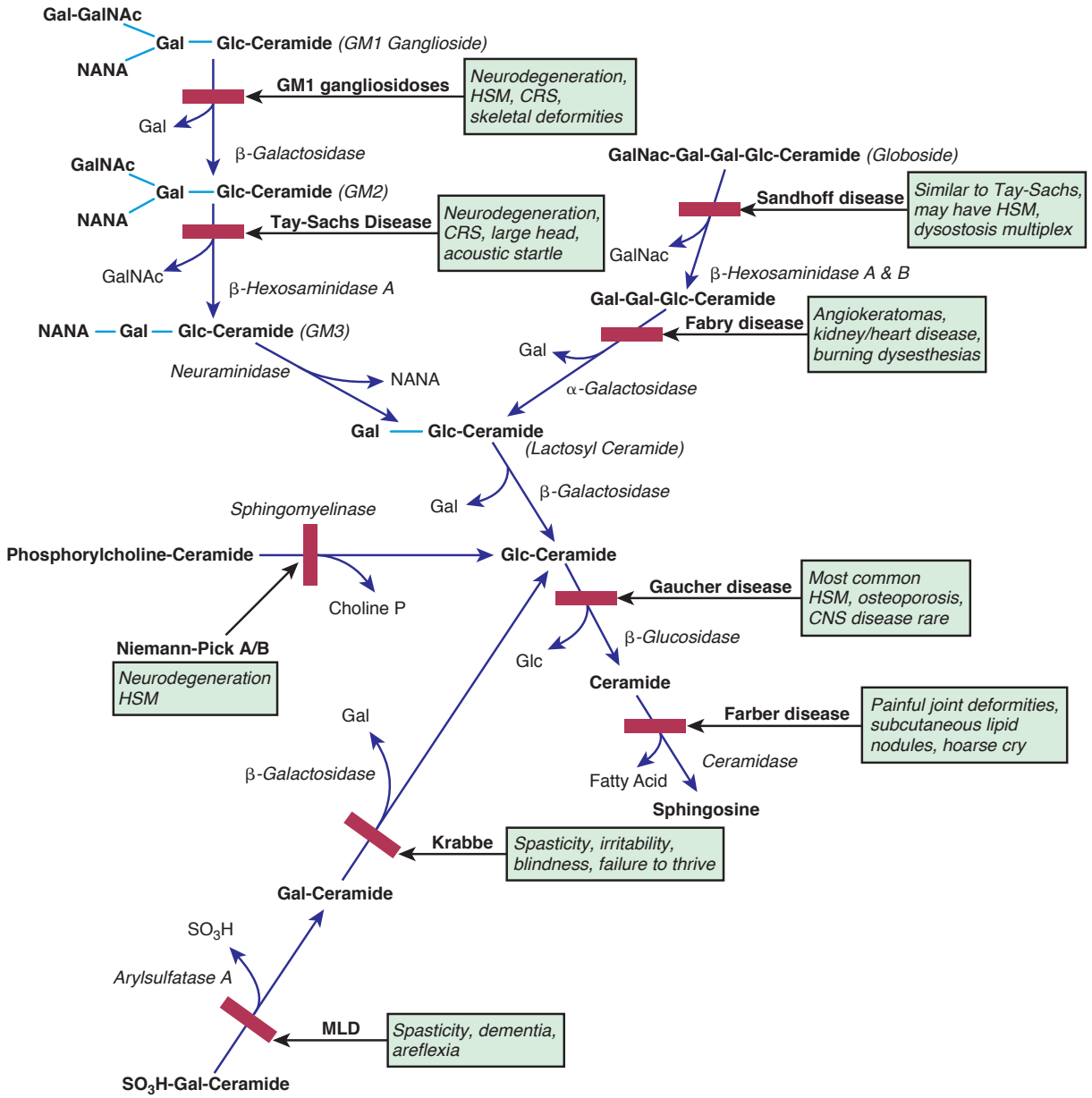

Figure 599-1 Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders. Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM, hepatosplenomegaly; MLD, metachromatic leukodystrophy; NANA, N-acetyl-neuraminic acid.

Table 599-2 Clinical and Genetic Characteristics of the Neuronal Ceroid Lipofuscinoses (NCL)

NCL TYPE	GENE*	PROTEIN	AGE OF ONSET	CLINICAL PRESENTATION
Congenital	*CLN10*	Cathepsin‡	Birth (but can present later)	Severe seizures, blindness, rigidity, early death Can also present similar to late infantile forms
Infantile	*CLN1*	Palmitoyl-protein thioesterase-1 (PPT1)‡	6-24 months	Early onset, often rapid progression of seizures; cognitive and motor decline with visual loss
Variant infantile	*CLN1*		3 yr to adulthood	Chronic course Initial visual loss followed then by slow mental and motor decline and seizures
Late infantile	*CLN2*	Tripeptidyl peptidase-1 (TPP1)‡	2-8 yr	Seizures, often severe and intractable; cognitive and motor decline; and visual loss
	CLN5	Partially soluble protein		
	CLN6	Membrane protein		
	CLN7	Membrane protein		
	CLN8	Membrane protein	5-10 yr	Severe epilepsy, progressive with mental retardation
Juvenile	*CLN3*	Membrane protein	4-10 yr	Visual loss is usually the initial presenting complaint Also have mental, motor disorder and seizures

*Note that all the NCL genes have the prefix CLN. The adult form (also called Kufs disease, with locus CLN4, caused by mutations in DNAJC5) is not well characterized and is not included in the table.
†Direct genetic testing is available for all.
‡Enzyme testing available.

Table 600-2 IPMSSG 2012 Definitions for Pediatric Acute Demyelinating Disorders of the Central Nervous System

DISORDER	IPMSSG 2012
CIS	• A first monofocal or multifocal CNS demyelinating event; encephalopathy is absent, **unless caused by fever**
Monophasic ADEM	• A first polyfocal clinical CNS event with presumed inflammatory cause • Encephalopathy that **cannot be explained by fever** is present MRI typically shows **diffuse, poorly demarcated, large, >1-2 cm lesions** involving predominantly the cerebral white matter; **T1 hypointense white matter lesions are rare**; deep gray-matter lesions (e.g., thalamus or basal ganglia) can be present • No new symptoms, signs or MRI findings after 3 mo of the incident ADEM
Recurrent ADEM	• **See multiphasic ADEM**
Multiphasic ADEM	• New event of ADEM 3 mo or more after the initial event that can be associated with **new or reemergence of prior clinical and MRI findings. Timing in relation to steroids is no longer pertinent**
MS	Any of the following: • Two or more nonencephalopathic CNS clinical events separated by more than 30 days, involving more than 1 area of the CNS • Single clinical event and MRI features rely on 2010 Revised McDonald criteria for DIS and DIT (but criteria relative for DIT for a single attack and single MRI only apply to children ages 2-12 yr and only apply to cases without an ADEM onset)
NMO	All are required: • Optic neuritis • Acute myelitis At least 2 of 3 supportive criteria • Contiguous spinal cord MRI lesion S3 vertebral segments • **Brain MRI not meeting diagnostic criteria for MS** • Anti–aquaporin-4 immunoglobulin G–seropositive status • ADEM followed 3 mo later by a nonencephalopathic clinical event with new lesions on brain MRI consistent with MS

The 2001 McDonald MRI criteria for DIS require 3 of the following 4 MRI features: 29 T2 lesions or 1 gadolinium-enhancing lesion; 23 periventricular lesions; 21 infratentorial lesion(s); 21 juxtacortical lesion(s). The DIT criteria require subsequent white-matter lesions whose timing depends on the temporal relation of the initial MRI with the onset of the clinical symptoms.

The 2010 Revised McDonald MRI criteria for DIS require the presence of at least 2 of the following 4 criteria: 21 lesions in each of the 4 locations; periventricular, juxtacortical, infratentorial, and spinal cord. The 2010 Revised McDonald MRI criteria for DIT can be satisfied either by the emergence of newT2 lesions (with or without enhancement) on serial scan(s) or can be met on a single baseline scan if there exists simultaneous presence of a clinically silent gadolinium-enhancing lesion and a nonenhancing lesion.

ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time; IPMSSG, International Pediatric Multiple Sclerosis Study Group; MS, multiple sclerosis; NMO, neuromyelitis optica.

Modified from Krupp LB, Tardieu M, Amato MP, et al: International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revision to the 2007 definitions. Mult Scler 19(10):1261–1267, 2013, Appendix 1, p. 1266.

Table 600-3 Symptoms and Signs of Multiple Sclerosis by Site

	SYMPTOMS	SIGNS
Cerebrum	Cognitive impairment	Deficits in attention, reasoning, and executive function (early); dementia (late)
	Hemisensory and motor	Upper motor neuron signs
	Affective (mainly depression)	
	Epilepsy (rare)	
	Focal cortical deficits (rare)	
Optic nerve	Unilateral painful loss of vision	Scotoma, reduced visual acuity, color vision, and relative afferent papillary defect
Cerebellum and cerebellar pathways	Tremor	Postural and action tremor, dysarthria
	Clumsiness and poor balance	Limb incoordination and gait ataxia
Brainstem	Diplopia, oscillopsia	Nystagmus, internuclear and other complex ophthalmoplegias
	Vertigo	
	Impaired swallowing	Dysarthria
	Impaired speech and emotional lability	Pseudobulbar palsy
	Paroxysmal symptoms	
Spinal cord	Weakness	Upper motor neuron signs
	Stiffness and painful spasms	Spasticity
	Bladder dysfunction	
	Erectile impotence	
	Constipation	
Other	Pain	
	Fatigue	
	Temperature sensitivity and exercise intolerance	

Modified from Compston A, Coles A: Multiple sclerosis, Lancet *372:1502–1517, 2008, p. 1503.*

Table 600-6 Overview of Available and Emerging Therapies in Pediatric Multiple Sclerosis

MEDICATION	MEDICATION CLASS	MECHANISM IN MS	SIDE EFFECTS	STUDIES DESCRIBING DRUG EFFICACY IN PEDIATRIC MS
FIRST-LINE THERAPIES				
Interferon-α or β	Immunomodulator	Modulates T cells and cytokine production	Flu-like symptoms; transaminitis; leukopenia; tissue necrosis at injection site (rare)	Retrospective Prospective multicenter
Glatiramer acetate*	Immunomodulator	Modulates T cells and reduces antigen presentation	Flushing, lipodystrophy at injection sites	Prospective single center Prospective multicenter
SECOND-LINE THERAPIES				
Natalizumab*	Monoclonal antibody	Targets α_4-integrin; prevents T-cell migration into CNS and other tissues	Overall PML rate ~1 in 500 patients, but lower in subgroups; immune reconstitution syndrome after discontinuation; melanoma; infusion reaction; transaminitis (rare)	Retrospective Prospective multicenter
Cyclophosphamide	Chemotherapeutic	DNA alkylation; effects include cytotoxic immune cell depletion	Hemorrhagic cystitis; bladder cancer; late-onset malignancy; infection; infertility	Retrospective multicenter
Mitoxantrone*	Chemotherapeutic	Disrupts DNA synthesis; effects include cytotoxic immune cell depletion	Significant long-term safety risks, including cardiotoxicity (1 in 200 patients) and secondary leukemia (1 in 125 patients); opportunistic infections	Retrospective single center
Daclizumab	Monoclonal antibody	Targets/inactivates interleukin-2 receptor; inhibits activated T cells	Glucose intolerance; pulmonary edema; infusion reaction; gastrointestinal upset; skin reactions	Retrospective multicenter
Rituximab	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	PML (rate undefined); infusion-related side effects	No efficacy assessments available in pediatric MS
Azathioprine	Chemotherapeutic	Disrupts purine metabolism; effects include cytotoxic immune cell depletion	Transaminitis; leukopenia; lymphoma	No efficacy assessments available in pediatric MS
Fingolimod*†	Immunomodulator	Sphingosine-1-phosphate agonist; causes T-cell sequestration in lymphoid compartments	Systemic viral infection; cardiac arrhythmia; macular edema; transaminitis	FDA approved for adult MS in September 2010; no reports of use in pediatric MS to date
Teriflunomide*†	Immunomodulator	Impairs immune cell proliferation via pyrimidine synthesis inhibition	Infections; headaches; diarrhea; transaminitis; alopecia; teratogenicity	FDA approved for adult MS in September 2012; no reports of use in pediatric MS to date
EMERGING THERAPIES				
Vitamin D†	Vitamin/hormone	Modulates immune cell expression	Hypercalcemia and kidney stones at a serum 25(OH) vitamin D level >100 ng/mL	Prospective trials in pediatric and adult MS are currently underway
Ocrelizumab	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Headache; infusion-related side effects; theoretical risk of PML (undefined)	Recently completed phase III trial in adult MS; no use in pediatric MS to date
Dimethyl fumarate†	Immunomodulator	Neuroprotectant; antioxidant	Flushing reaction; gastrointestinal upset; headache	FDA approved for adult MS in March 2013; no use in pediatric MS to date
Alemtuzumab	Monoclonal antibody	Anti-CD52 antibody target; depletes mature T cells	Opportunistic infection, autoimmune thyroiditis (20-30% risk), immune thrombocytopenia (1%)	Recently completed phase III trial in adult MS; no use in pediatric MS to date
Laquinimod†	Immunomodulator	Modulates T cell and cytokine production	Transaminitis	Recently completed phase III trial in adult MS; no use in pediatric MS to date

*FDA approved for the treatment of adult MS.
†Orally administered therapy.
CNS, central nervous system; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

Table 601-1 Risk Factors for Arterial Ischemic Stroke in Children

MAJOR CATEGORY	EXAMPLES
Arteriopathy	Transient cerebral arteriopathy (TCA) (synonyms: childhood primary angiitis of the central nervous system [cPACNS]; focal cerebral arteriopathy [FCA]) Postvaricella and other viruses angiopathy (PVA) Systemic/secondary vasculitis (e.g., Takayasu arteritis) Moyamoya disease/syndrome Arterial infection (e.g., bacterial meningitis, tuberculosis) Fibromuscular dysplasia Traumatic or spontaneous carotid or vertebral artery dissection Vasospasm (e.g., Call-Fleming syndrome) Migraine (migrainous infarction?) Congenital arterial hypoplasia (e.g., PHACES syndrome)
Cardiac	Complex congenital heart diseases (cyanotic ≫ acyanotic) Cardiac catheterization/procedure (e.g., balloon atrial septostomy) Ventricular assistive device use Cardiac surgery Arrhythmia Valvular heart disease Endocarditis Cardiomyopathy, severe ventricular dysfunction Intracardiac lesions (e.g., atrial myxoma) Septal defects (atrial septal defect, ventricular septal defect, patent foramen ovale [possible paradoxical emboli])
Hematologic	Sickle cell anemia Iron-deficiency anemia Inherited prothrombotic (e.g., factor V Leiden, prothrombin gene mutation 20210A) Acquired prothrombotic (e.g., protein C/S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies, oral contraceptives, pregnancy)
Other including metabolic/genetic etiologies	Acute systemic illness (e.g., dehydration, sepsis, diabetic ketoacidosis) Chronic systemic illness (e.g., systemic lupus erythematosus, leukemia) Illicit drugs and toxins (e.g., cocaine) Extracorporeal membrane oxygenation (ECMO) Hereditary dyslipoproteinemia Familial hypoalphalipoproteinemia Familial hypercholesterolemia Type IV, type III hyperlipoproteinemia Tangier disease Progeria Fabry disease (α-galactosidase A deficiency) Subacute necrotizing encephalomyelopathy (Leigh disease) Sulfite oxidase deficiency 11β-Ketoreductase deficiency 17α-Hydroxylase deficiency Purine nucleoside phosphorylase deficiency Ornithine transcarbamylase deficiency Neurofibromatosis type 1 HERNS Heritable disorders of connective tissue Ehlers-Danlos syndrome (type IV) Marfan syndrome Pseudoxanthoma elasticum Homocystinuria (cystathionine β-synthase deficiency, or 5,20-methylenetetrahydrofolate reductase) Menkes syndrome Organic acidemias Methylmalonic academia Propionic academia Isovaleric academia Glutaric aciduria type II Mitochondrial encephalomyopathies MELAS MERRF MERRF/MELAS overlap syndrome Kearns-Sayre syndrome See also: stroke mimics (see Chapter 601.4)

HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; PHACES, posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities.

Modified from Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children. Stroke *39:2644–2691, 2008, Table 2, p. 6.*

Table 601-3 Common Risk Factors for Cerebral Sinovenous Thrombosis in Children

MAJOR CATEGORIES	EXAMPLES
Blood coagulation	Prothrombotic conditions Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia Drugs and toxins (e.g., L-asparaginase, oral contraceptives) Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation) Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome Inborn errors of metabolism (e.g., homocystinuria)
Blood vessel	Infection/thrombophlebitis Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome Sepsis Trauma: skull fractures, closed hear trauma Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas)

Table 601-4 Potential Risk Factors for Hemorrhagic Stroke in Children

MAJOR CATEGORIES	EXAMPLES
Vascular disorder	Arteriovenous malformations Cavernous malformations ("cavernomas") Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm Choroid plexus angiomas (pure intraventricular hemorrhage) Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 601.1) Neoplastic lesions with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis
Blood disorder	Idiopathic thrombocytopenic purpura Hemolytic uremic syndrome Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of the newborn) Disseminated intravascular coagulopathy
Trauma	Middle meningeal artery injury (epidural hematoma) Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage Hemorrhagic contusions (coup and contrecoup) Nonaccidental trauma (subdural hematomas of different ages) Iatrogenic (neurosurgical procedures, angiography) Rupture of arachnoid cyst

Table 601-4 Potential Risk Factors for Hemorrhagic Stroke in Children

MAJOR CATEGORIES	EXAMPLES
Vascular disorder	Arteriovenous malformations Cavernous malformations ("cavernomas") Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm Choroid plexus angiomas (pure intraventricular hemorrhage) Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 601.1) Neoplastic lesions with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis
Blood disorder	Idiopathic thrombocytopenic purpura Hemolytic uremic syndrome Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of the newborn) Disseminated intravascular coagulopathy
Trauma	Middle meningeal artery injury (epidural hematoma) Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage Hemorrhagic contusions (coup and contrecoup) Nonaccidental trauma (subdural hematomas of different ages) Iatrogenic (neurosurgical procedures, angiography) Rupture of arachnoid cyst

Table 601-3 Common Risk Factors for Cerebral Sinovenous Thrombosis in Children

MAJOR CATEGORIES	EXAMPLES
Blood coagulation	Prothrombotic conditions Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia Drugs and toxins (e.g., L-asparaginase, oral contraceptives) Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation) Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome Inborn errors of metabolism (e.g., homocystinuria)
Blood vessel	Infection/thrombophlebitis Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome Sepsis Trauma: skull fractures, closed hear trauma Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas)

Table 601-3 Common Risk Factors for Cerebral Sinovenous Thrombosis in Children

MAJOR CATEGORIES	EXAMPLES
Blood coagulation	Prothrombotic conditions Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia Drugs and toxins (e.g., L-asparaginase, oral contraceptives) Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation) Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome Inborn errors of metabolism (e.g., homocystinuria)
Blood vessel	Infection/thrombophlebitis Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome Sepsis Trauma: skull fractures, closed hear trauma Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas)

Table 601-5 Differential Diagnosis of Stroke-Like Episodes in Children

DISORDER	CLINICAL DISTINCTION FROM STROKE	IMAGING DISTINCTION FROM STROKE
Migraine	Evolving or "marching" symptoms, short duration, complete resolution, headache, personal or family history of migraine	Typically normal Migrainous infarction is rare
Seizure	Positive symptoms, Todd paralysis is postseizure and limited	Normal or may identify source of seizures (e.g., malformation, old injury, etc.)
Infection	Fever, encephalopathy, gradual onset, meningismus	Normal or signs of encephalitis/cerebritis, which are typically diffuse and bilateral. Arterial ischemic stroke and cerebral sinovenous thrombosis can occur in bacterial meningitis
Demyelination	Gradual onset, multifocal symptoms, encephalopathy Accompanying optic neuritis or transverse myelitis	Multifocal lesions, characteristic appearance (e.g., patchy in acute disseminated encephalomyelitis, ovoid in multiple sclerosis), typical locations (e.g., pericallosal in multiple sclerosis), less likely to show restricted diffusion
Hypoglycemia	Risk factor (e.g., insulin therapy), related to meals, additional systemic symptoms	Bilateral, symmetrical May see restricted diffusion Posterior dominant pattern
Watershed infarction caused by global hypoxic–ischemic encephalopathy	Risk factor (e.g., hypotension, sepsis, heart disease), bilateral deficits	Bilateral, symmetric restricted diffusion in border zones between major arteries (watershed zones)
Hypertensive encephalopathy (posterior reversible leukoencephalopathy)	Documented hypertension, bilateral visual symptoms, encephalopathy	Posterior dominant, bilateral, patchy lesions involving gray and white matter, usually no restricted diffusion
Inborn errors of metabolism	Preexisting delays/regression, multisystem disease, abnormal biochemical profiles	May have restricted diffusion lesions but bilateral, symmetrical, not within vascular territories. MR spectroscopy changes (e.g., high lactate in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes)
Vestibulopathy	Symptoms limited to vertigo, imbalance (i.e., no weakness). Gradual onset	Normal
Acute cerebellar ataxia	Sudden-onset bilaterally symmetric ataxia; postviral	Normal
Channelopathy	Syndromic cluster of symptoms not localizing to single lesion. Gradual onset, progressive evolution	Normal
Alternating hemiplegia	History contralateral events Choreoathetosis/dystonia	Normal

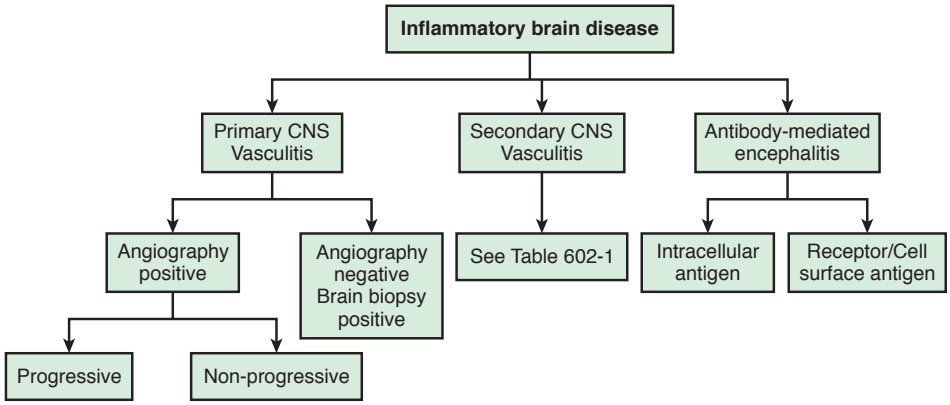

Figure 602-1 CNS vasculitis within the spectrum of immune-mediated inflammatory brain diseases.

Table 602-1 Causes of Secondary CNS Vasculitis

VIRAL INFECTIONS Varicella zoster virus, HIV, hepatitis C virus, cytomegalovirus, parvovirus B19
BACTERIAL INFECTIONS *Treponema pallidum, Borrelia burgdorferi, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Bartonella henselae, Rickettsia* spp.
FUNGAL INFECTIONS Aspergillosis, mucormycosis, coccidioidomycosis, candidosis
PARASITIC INFECTIONS Cysticercosis
SYSTEMIC VASCULITIDES Wegener granulomatosis, Churg-Strauss syndrome, Behçet disease, polyarteritis nodosa, Henoch-Schönlein purpura, Kawasaki disease, giant-cell arteritis, Takayasu arteritis
CONNECTIVE TISSUE DISEASES Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis, mixed connective tissue disease
MISCELLANEOUS Antiphospholipid antibodies syndrome, Hodgkin and non-Hodgkin lymphomas, neurosarcoidosis, inflammatory bowel disease, graft-versus-host disease, bacterial endocarditis, acute bacterial meningitis, drug-induced CNS vasculitis (cocaine, amphetamine, ephedrine, phenylpropanolamine)

Table 602-2 Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

1. Clinical evaluation: Newly acquired symptom or deficit in a previously healthy child
   - Focal neurologic deficit: hemiparesis, hemisensory loss, aphasia, ataxia, movement abnormality, paresthesia, facial droop, ataxia, vision loss, spinal cord symptoms, others
   - Seizures or (refractory) seizure status
   - Diffuse neurologic deficit including cognitive decline with loss of higher executive function, concentration difficulties, learning or memory problems, behavior or personality changes, loss of social skills or emotional/impulse control, others
   - Headaches
   - Meningitis symptoms, abnormal level of consciousness
   - Psychiatric symptoms including hallucinations, pseudoseizures

   Differential diagnosis approach:
   - Underlying illness known to cause, be associated or mimic CNS vasculitis: check all potential clinical features
2. Laboratory tests
   - Blood inflammatory markers: C-reactive protein, erythrocyte sedimentation rate and complete blood counts
   - Endothelial markers: von Willebrand factor (vWF) antigen
   - Cerebrospinal fluid (CSF) inflammatory markers: opening pressure, cell count, protein, oligoclonal bands

   Differential diagnosis approach:
   - Infections/postinfectious inflammation: cultures, serologies, Gram stains
   - Autoimmune encephalitis: check neuronal antibodies in CSF and blood
   - Systemic inflammation/rheumatic disease: characteristic laboratory markers such as complement, autoantibodies
   - Thromboembolic conditions: procoagulatory profile
3. Neuroimaging
   - Parenchymal imaging on MRI:
     - Inflammatory lesions: T2/fluid attenuated inversion recovery sequences plus gadolinium contrast (lesion enhancement)
     - Ischemic lesions: diffusion-weighted images/apparent diffusion coefficient mapping
   - Vessel imaging
4. Brain biopsy

Table 602-3 Characteristics of Primary CNS Vasculitis and Reversible Cerebral Vasoconstriction Syndrome

	PCNSV	RCVS
Precipitating factor	None	Postpartum onset or onset after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal (leucocytosis and high total protein concentration)	Normal to near normal
MRI	Abnormal in almost all patients	Normal in 70% of patients
Angiography	Possibly normal; otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetrical arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible	Always abnormal, strings of beads appearance of cerebral arteries; abnormalities reversible within 6-12 wk
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with or without cytotoxic agents	Nimodipine

CSF, cerebrospinal fluid; PCNSV, primary CNS vasculitis; RCVS, reversible cerebral vasoconstriction syndrome.
From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis. Lancet *380:767–776, 2012, Table 2.*

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders

CONDITION	PRESSURE (mm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
Normal	50-80	<5, ≥75% Lymphocytes	20-45	>50 (or 75% serum glucose)	
COMMON FORMS OF MENINGITIS					
Acute bacterial meningitis	Usually elevated (100-300)	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% serum glucose)	Organisms usually seen on Gram stain and recovered by culture
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain Pretreatment may render CSF sterile. Antigen may be detected by agglutination test
Viral meningitis or meningoencephalitis	Normal or slightly elevated (80-150)	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course	Usually 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15-20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. Enteroviruses and HSV infrequently recovered from CSF. HSV and enteroviruses may be detected by PCR of CSF
UNCOMMON FORMS OF MENINGITIS					
Tuberculous meningitis	Usually elevated	10-500; PMNs early, but lymphocytes predominate through most of the course	100-3,000; may be higher in presence of block	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms almost never seen on smear. Organisms may be recovered in culture of large volumes of CSF. *Mycobacterium tuberculosis* may be detected by PCR of CSF
Fungal meningitis	Usually elevated	5-500; PMNs early but mononuclear cells predominate through most of the course. Cryptococcal meningitis may have no cellular inflammatory response	25-500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered in culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection
Syphilis (acute) and leptospirosis	Usually elevated	50-500; lymphocytes predominate	50-200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by usual techniques of smear or culture; dark-field examination may be positive
Amebic (*Naegleria*) meningoencephalitis	Elevated	1,000-10,000 or more; PMNs predominate	50-500	Normal or slightly decreased	Mobile amebas may be seen by hanging-drop examination of CSF at room temperature
BRAIN ABSCESSES AND PARAMENINGEAL FOCUS					
Brain abscess	Usually elevated (100-300)	5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75-500	Normal unless abscess ruptures into ventricular system	No organisms on smear or culture unless abscess ruptures into ventricular system
Subdural empyema	Usually elevated (100-300)	100-5,000; PMNs predominate	100-500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10-500; lymphocytes predominate	50-200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with spinal block	10-100; lymphocytes predominate	50-400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100-1,000 or more; PMNs predominate	50-100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with dermoids

Continued

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont'd

CONDITION	PRESSURE (mm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
NONINFECTIOUS CAUSES					
Sarcoidosis	Normal or elevated slightly	0-100; mononuclear	40-100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0-500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF
Tumor, leukemia	Slightly elevated to very high	0-100 or more; mononuclear or blast cells	50-1,000	Normal to decreased (20-40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	Anti-NMDAR antibody–positive

CSF, cerebrospinal fluid; EEG, electroencephalogram; HSV, herpes simplex virus; NMDAR, *N*-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils.

Table 603-4 Antibiotics Used for the Treatment of Bacterial Meningitis*

DRUGS	Neonates 0-7 DAYS	Neonates 8-28 DAYS	INFANTS AND CHILDREN
Amikacin†‡	15-20 divided q12h	30 divided q8h	20-30 divided q8h
Ampicillin	150 divided q8h	200 divided q6h or q8h	300 divided q6h
Cefotaxime	100-150 divided q8h or q12h	150-200 divided q6h or q8h	225-300 divided q6h or q8h
Ceftriaxone§	—	—	100 divided q12h or q24h
Ceftazidime	100-150 divided q8h or q12h	150 divided q8h	150 divided q8h
Gentamicin†‡	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Meropenem	—	—	120 divided q8h
Nafcillin	75 divided q8h or q12h	100-150 divided q6h or q8h	200 divided q6h
Penicillin G	150,000 divided q8h or q12h	200,000 divided q6h or q8h	300,000 divided q4h or q6h
Rifampin	—	10-20 divided q12h	10-20 divided q12h or q24h
Tobramycin†‡	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Vancomycin†‡	20-30 divided q8h or q12h	30-45 divided q6h or q8h	60 divided q6h

*Dosages in mg/kg (units/kg for penicillin G) per day.
†Smaller doses and longer dosing intervals, especially for aminoglycosides and vancomycin for very-low-birthweight neonates, may be advisable.
‡Monitoring of serum levels is recommended to ensure safe and therapeutic values.
§Use in neonates is not recommended because of inadequate experience in neonatal meningitis.
Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al: Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 39(9):1267–1284, 2004,

Table 606-1 Clinical and Radiologic Mimics of Transverse Myelitis

EXTRAAXIAL COMPRESSION DISEASE
1. Vertebral spine disorders
   a. Trauma
      i. Blunt
      ii. Penetrating
      iii. Surfing
   b. Atlantoaxial subluxation
      i. Trisomy 21
      ii. Mucopolysaccharidosis type IV
      iii. Grisel syndrome
   c. Destructive lesions
      i. Tuberculosis
      ii. Lymphoma
      iii. Langerhans cell histiocytosis
   d. Scheuermann disease
2. Epidural disease
   a. Tumor
      i. Neuroblastoma
      ii. Wilms tumor
      iii. Ewing sarcoma
   b. Abscess
      i. Associated dermal sinus, vertebral body infection
   c. Hematoma
3. Arachnoiditis
   a. Tuberculosis
   b. Cryptococcosis
   c. Carcinomatous infiltration
4. Spinal nerve root inflammation
   a. Guillain-Barré syndrome

SPINAL CORD DISORDERS
1. Congenital malformation
   a. Neurenteric cysts
   b. Spinal cord tethering
2. Infection
   a. Nonpolio enteroviruses
   b. West Nile virus
   c. Human T-lymphocyte virus 1
   d. Neurocysticercosis
3. Vascular disorders
   a. Arteriovenous malformation
   b. Cavernomas
   c. Cobb syndrome
   d. Fibrocartilaginous embolization
   e. Spinal cord infarction
4. Vasculitis
   a. Systemic lupus erythematosus
   b. Behçet disease
5. Nutritional disorders
   a. Vitamin B_{12} deficiency (Subacute combined degeneration)
6. Toxic injury
   a. Chemotherapy (e.g., methotrexate)
   b. Radiation
7. Immune mediated
   a. Acute disseminated encephalomyelitis
   b. Neuromyelitis optica
   c. Multiple sclerosis

Modified from Thomas T, Branson HM: Childhood transverse myelitis and its mimics. Neuroimaging Clin N Am *23:267–278, 2013, Box 11.*

Table 603-2 Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis

VIRUSES
Enteroviruses (coxsackievirus, echovirus, poliovirus, enterovirus)
Arboviruses: Eastern equine, Western equine, Venezuelan equine, St. Louis encephalitis, Powassan and California encephalitis, West Nile virus, Colorado tick fever
Parechovirus
Herpes simplex (types 1, 2)
Human herpesvirus type 6
Varicella-zoster virus
Epstein-Barr virus
Parvovirus B19
Cytomegalovirus
Adenovirus
Variola (smallpox)
Measles
Mumps
Rubella
Influenza A and B
Parainfluenza
Rhinovirus
Rabies
Lymphocytic choriomeningitis
Rotaviruses
Coronaviruses
Human immunodeficiency virus type 1

BACTERIA
Mycobacterium tuberculosis (early and late)
Leptospira species (leptospirosis)
Treponema pallidum (syphilis)
Borrelia species (relapsing fever)
Borrelia burgdorferi (Lyme disease)
Nocardia species (nocardiosis)
Brucella species
Bartonella species (cat-scratch disease)
Rickettsia rickettsii (Rocky Mountain spotted fever)
Rickettsia prowazekii (typhus)
Ehrlichia canis
Coxiella burnetii
Mycoplasma pneumoniae
Mycoplasma hominis
Chlamydia trachomatis
Chlamydia psittaci
Chlamydia pneumoniae
Partially treated bacterial meningitis

BACTERIAL PARAMENINGEAL FOCUS
Sinusitis
Mastoiditis
Brain abscess
Subdural-epidural empyema
Cranial osteomyelitis

FUNGI
Coccidioides immitis (coccidioidomycosis)
Blastomyces dermatitidis (blastomycosis)
Cryptococcus neoformans (cryptococcosis)
Histoplasma capsulatum (histoplasmosis)
Candida species
Other fungi *(Alternaria, Aspergillus, Cephalosporium, Cladosporium, Drechslera hawaiiensis, Paracoccidioides brasiliensis, Petriellidium boydii, Sporotrichum schenckii, Ustilago* spp., *Zygomycetes)*

PARASITES (EOSINOPHILIC)
Angiostrongylus cantonensis
Gnathostoma spinigerum
Baylisascaris procyonis
Strongyloides stercoralis
Trichinella spiralis
Toxocara canis
Taenia solium (cysticercosis)
Paragonimus westermani
Schistosoma spp.
Fasciola spp.

PARASITES (NONEOSINOPHILIC)
Toxoplasma gondii (toxoplasmosis)
Acanthamoeba spp.
Naegleria fowleri
Malaria

POSTINFECTIOUS
Vaccines: rabies, influenza, measles, poliovirus
Demyelinating or allergic encephalitis

SYSTEMIC OR IMMUNOLOGICALLY MEDIATED
Acute Disseminated Encephalomyelitis (ADEM)
Autoimmune Encephalitis
Bacterial endocarditis
Kawasaki disease
Systemic lupus erythematosus
Vasculitis, including polyarteritis nodosa
Sjögren syndrome
Mixed connective tissue disease
Rheumatoid arthritis
Behçet syndrome
Wegener granulomatosis
Lymphomatoid granulomatosis
Granulomatous arteritis
Sarcoidosis
Familial Mediterranean fever
Vogt-Koyanagi-Harada syndrome

MALIGNANCY
Leukemia
Lymphoma
Metastatic carcinoma
Central nervous system tumor (e.g., craniopharyngioma, glioma, ependymoma, astrocytoma, medulloblastoma, teratoma)

DRUGS
Intrathecal infections (contrast media, serum, antibiotics, antineoplastic agents)
Nonsteroidal antiinflammatory agents
OKT3 monoclonal antibodies
Carbamazepine
Azathioprine
Intravenous immune globulins
Antibiotics (trimethoprim-sulfamethoxazole, sulfasalazine, ciprofloxacin, isoniazid)

MISCELLANEOUS
Heavy metal poisoning (lead, arsenic)
Foreign bodies (shunt, reservoir)
Subarachnoid hemorrhage
Postictal state
Postmigraine state
Mollaret syndrome (recurrent)
Intraventricular hemorrhage (neonate)
Familial hemophagocytic syndrome
Postneurosurgery
Dermoid–epidermoid cyst
Headache, neurologic deficits
CSF lymphocytosis (syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis [HaNDL])

Compiled from Cherry JD: Aseptic meningitis and viral meningitis. In Feigin RD, Cherry JD, editors: *Textbook of pediatric infectious diseases*, ed 4, Philadelphia, 1998, WB Saunders, p. 450; Davis LE: Aseptic and viral meningitis. In Long SS, Pickering LK, Prober CG, editors: *Principles and practice of pediatric infectious disease*, New York, 1997, Churchill Livingstone, p. 329; and Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis therapy*, ed 2, Philadelphia, 2004, Elsevier, p. 961.

Table 603-3 Classification of Encephalitis by Cause and Source

I. INFECTIONS: VIRAL
- A. Spread: person to person only
  1. Mumps: frequent in an unimmunized population; often mild
  2. Measles: may have serious sequelae
  3. Enteroviruses: frequent at all ages; more serious in newborns
  4. Parechovirus
  5. Rubella: uncommon; sequelae rare except in congenital rubella
  6. Herpesvirus group
     - a. Herpes simplex (types 1 and 2, possibly 6): relatively common; sequelae frequent; devastating in newborns
     - b. Varicella-zoster virus: uncommon; serious sequelae not rare
     - c. Cytomegalovirus, congenital or acquired: may have delayed sequelae in congenital type
     - d. Epstein-Barr virus (infectious mononucleosis): not common
  7. Pox group
     - a. Vaccinia and variola: uncommon, but serious CNS damage occurs
  8. Parvovirus (erythema infectiosum): not common
  9. Influenzas A and B
  10. Adenovirus
  11. Other: reoviruses, respiratory syncytial, parainfluenza, hepatitis B
- B. Arthropod-borne agents
- C. Arboviruses: spread to humans by mosquitoes or ticks; seasonal epidemics depend on ecology of the insect vector; the following occur in the United States:

Eastern equine	California
Western equine	Powassan
Venezuelan equine	Dengue
St. Louis	Colorado tick fever
West Nile	

- D. Spread by warm-blooded mammals
  1. Rabies: saliva of many domestic and wild mammalian species
  2. Herpesvirus simiae ("B" virus): monkeys' saliva
  3. Lymphocytic choriomeningitis: rodents' excreta

II. INFECTIONS: NONVIRAL
- A. Rickettsial: in Rocky Mountain spotted fever and typhus; encephalitic component from cerebral vasculitis
- B. *Mycoplasma pneumoniae:* interval of some days between respiratory and CNS symptoms
- C. Bacterial: tuberculous and other bacterial meningitis; often has encephalitic component
- D. Spirochetal: syphilis, congenital or acquired; leptospirosis; Lyme disease
- E. Cat-scratch disease
- F. Fungal: immunologically compromised patients at special risk: cryptococcosis; histoplasmosis; aspergillosis; mucormycosis; candidosis; coccidioidomycosis
- G. Protozoal: *Plasmodium*, *Trypanosoma*, *Naegleria*, and *Acanthamoeba* spp.; Toxoplasma gondii
- H. Metazoal: trichinosis; echinococcosis; cysticercosis; schistosomiasis

III. PARAINFECTIOUS: POSTINFECTIOUS, ALLERGIC, AUTOIMMUNE

Patients in whom an infectious agent or 1 of its components plays a contributory role in etiology, but the intact infectious agent is not isolated in vitro from the nervous system; it is postulated that in this group, the influence of cell-mediated antigen–antibody complexes plus complement is especially important in producing the observed tissue damage

- A. Associated with specific diseases (these agents may also cause direct CNS damage; see I and II)
  - Measles
  - Rickettsial infections
  - Rubella
  - Influenzas A and B
  - Mumps
  - Varicella-zoster
  - M. *pneumoniae*
- B. Associated with vaccines
  - Rabies
  - Measles
  - Vaccinia
  - Yellow fever
- C. Autoimmune encephalitis
- D. Acute disseminated encephalomyelitis (ADEM)
  - Paraneoplastic
  - Idiopathic

IV. HUMAN SLOW-VIRUS DISEASES

Accumulating evidence that viruses frequently acquired earlier in life, not necessarily with detectable acute illness, participate in later chronic neurologic disease (similar events also known to occur in animals)

- A. Subacute sclerosing panencephalitis; measles; rubella?
- B. Creutzfeldt-Jakob disease (spongiform encephalopathy)
- C. Progressive multifocal leukoencephalopathy
- D. Kuru (Fore tribe in New Guinea only)
- E. Human immunodeficiency virus

V. UNKNOWN: COMPLEX GROUP

This group constitutes more than two-thirds of the cases of encephalitis reported to the Centers for Disease Control and Prevention, Atlanta, Georgia; the yearly epidemic curve of these undiagnosed cases suggests that the majority are probably caused by enteroviruses and/or arboviruses.

There is also a miscellaneous group that is based on clinical criteria: Reye syndrome is 1 current example; others include the extinct von Economo encephalitis (epidemic during 1918-1928); myoclonic encephalopathy of infancy; retinomeningoencephalitis with papilledema and retinal hemorrhage; recurrent encephalomyelitis (? allergic or autoimmune); pseudotumor cerebri; and epidemic neuromyasthenia (Iceland disease).

An encephalitic clinical pattern may follow ingestion or absorption of a number of known and unknown toxic substances; these include ingestion of lead and mercury, and percutaneous absorption of hexachlorophene as a skin disinfectant and gamma benzene hexachloride as a scabicide.

CNS, central nervous system.

Modified from Behrman RE, editor: Nelson textbook of pediatrics, ed 14, Philadelphia, 1992, WB Saunders, p. 667. From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p. 967.

Table 605-1 Etiology of Childhood Pseudotumor Cerebri

HEMATOLOGIC
Wiskott-Aldrich syndrome
Iron-deficiency anemia
Aplastic anemia
Sickle cell disease
Polycythemia?
Bone marrow transplantation and associated treatments?
Prothrombotic states
Fanconi anemia

INFECTIONS
Acute sinusitis
Otitis media (lateral sinus thrombosis)
Mastoiditis
Tonsillitis
Measles
Roseola
Varicella, recurrent varicella-zoster virus infection
Lyme disease?
HIV or associated treatment complications?

DRUGS
Tetracyclines
Sulfonamides
Nalidixic acid
Fluoroquinolones
Corticosteroid therapy and withdrawal
Nitrofurantoin
Cytarabine
Cyclosporine
Phenytoin
Mesalamine
Isotretinoin
Amiodarone?
1-Deamino-8-D-arginine vasopressin (DDAVP)?
Lithium?
Levonorgestrel implants?
Oral contraceptive pills

RENAL
Nephrotic syndrome
Chronic renal insufficiency?
Post–renal transplantation?
Peritoneal dialysis?

NUTRITIONAL
Hypovitaminosis A
Vitamin A intoxication
Hyperalimentation in malnourished patient
Vitamin D–dependent rickets

CONNECTIVE TISSUE DISORDERS
Antiphospholipid antibody syndrome
Systemic lupus erythematosus?
Behçet disease

ENDOCRINE
Menarche
Polycystic ovarian syndrome
Hypothyroidism
Hypoparathyroidism/hyperparathyroidism
Congenital adrenal hyperplasia
Addison disease
Recombinant growth hormone

OTHER
Dural sinus thrombosis
Obesity (in pubertal patients)
Bariatric surgery
Head trauma
Superior vena cava syndrome
Arteriovenous malformation
Sleep apnea
Guillain-Barré syndrome
Crohn disease
Ulcerative colitis?
Turner syndrome

POSSIBLE ASSOCIATIONS
Cystic fibrosis
Cystinosis
Down syndrome
Hypomagnesemia–hypercalciuria
Galactokinase deficiency
Galactosemia
Atrial septal defect repair
Moebius syndrome
Sarcoidosis?

Table 607-4 Differential Diagnosis of Acute Flaccid Paralysis

Brainstem stroke
Brainstem encephalitis
Acute anterior poliomyelitis
- Caused by poliovirus
- Caused by other neurotropic viruses

Acute myelopathy
- Space-occupying lesions
- Acute transverse myelitis

Peripheral neuropathy
- Guillain-Barré syndrome
- Post–rabies vaccine neuropathy
- Diphtheritic neuropathy
- Heavy metals, biologic toxins, or drug intoxication
- Acute intermittent porphyria
- Vasculitic neuropathy
- Critical illness neuropathy
- Lymphomatous neuropathy

Disorders of neuromuscular transmission
- Myasthenia gravis
- Biologic or industrial toxins
- Tic paralysis

Disorders of muscle
- Hypokalemia
- Hypophosphatemia
- Inflammatory myopathy
- Acute rhabdomyolysis
- Trichinosis
- Familial periodic paralyses (normokalemic, hypokalemic, hyperkalemic)

Table 607-3 Differential Diagnosis of Infantile Hypotonia

Cerebral hypotonia
- Benign congenital hypotonia
- Chromosome disorders
- Prader-Willi syndrome
- Trisomy
- Chronic nonprogressive encephalopathy
- Cerebral malformation
- Perinatal distress
- Postnatal disorders
- Peroxisomal disorders
- Cerebrohepatorenal syndrome (Zellweger syndrome)
- Neonatal adrenoleukodystrophy
- Other genetic defects
- Familial dysautonomia
- Oculocerebrorenal syndrome (Lowe syndrome)
- Other metabolic defects
- Acid maltase deficiency (see "Metabolic Myopathies")
- Infantile G_M gangliosidosis

Spinal cord disorders
Spinal muscular atrophies
- Acute infantile
  - Autosomal dominant
  - Autosomal recessive
- Cytochrome-c oxidase deficiency
- X-linked
- Chronic infantile
  - Autosomal dominant
  - Autosomal recessive
- Congenital cervical spinal muscular atrophy
- Infantile neuronal degeneration
- Neurogenic arthrogryposis

Polyneuropathies
- Congenital hypomyelinating neuropathy
- Giant axonal neuropathy
- Hereditary motor-sensory neuropathies

Disorders of neuromuscular transmission
- Familial infantile myasthenia
- Infantile botulism
- Transitory myasthenia gravis

Fiber-type disproportion myopathies
- Central core disease
- Congenital fiber-type disproportion myopathy
- Myotubular (centronuclear) myopathy
- Acute
- Chronic
- Nemaline (nemaline rod) myopathy
- Autosomal dominant
- Autosomal recessive

Metabolic myopathies
- Acid maltase deficiency (Pompe disease)
- Cytochrome-c oxidase deficiency
- Other mitochondrial disorders
- Muscular dystrophies
- Bethlem myopathy
- Congenital dystrophinopathy
- Congenital muscular dystrophy
- Merosin deficiency primary
- Merosin deficiency secondary
- Merosin positive
- Congenital myotonic dystrophy

Table 607-1 Distinguishing Features of Disorders of the Motor System

LOCUS OF LESION	WEAKNESS				DEEP TENDON REFLEXES	ELECTRO-MYOGRAPHY	MUSCLE BIOPSY	OTHER
	Face	Arms	Legs	Proximal–Distal				
Central	0	+	+	≥	Normal or ↑	Normal	Normal	Seizures, hemiparesis, and delayed development
Ventral horn cell	Late	++++	++++	≥	0	Fasciculations and fibrillations	Denervation pattern	Fasciculations (tongue)
Peripheral nerve	0	+++	+++	<	↓	Fibrillations	Denervation pattern	Sensory deficit, elevated cerebrospinal fluid protein, depressed nerve biopsy
Neuromuscular junction	+++	+++	+++	=	Normal	Decremental response (myasthenia); incremental response and BSAP (botulism)	Normal	Response to neostigmine or edrophonium (myasthenia); constipation and fixed pupils (botulism)
Muscle	Variable (+ to ++++)	++	+	>	↓	Short duration, small-amplitude motor unit potentials and myopathic polyphasic potentials	Myopathic pattern*	Elevated muscle enzyme levels (variable)

*Can also show unique features, such as in central core disease, nemaline myopathy, myotubular myopathy, and congenital fiber type disproportion.
+ to ++++, varying degrees of severity; BSAP, brief duration, small amplitude, overly abundant motor unit potentials.
From Volpe J: Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders, p. 706.*

Table 607-2 Pattern of Weakness and Localization in the Floppy Infant

ANATOMIC REGION OF HYPOTONIA	CORRESPONDING DISORDERS	PATTERN OF WEAKNESS AND INVOLVEMENT
Central nervous system	Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma	Central hypotonia Axial hypotonia more prominent Hyperactive reflexes
Motor neuron	Spinal muscular atrophy	Generalized weakness; often spares the diaphragm, facial muscles, pelvis, and sphincters
Nerve	Peripheral neuropathies	Distal muscle groups involved Weakness with wasting
Neuromuscular junction	Myasthenia syndromes Infantile botulism	Bulbar, oculomotor muscles exhibit greater degree of involvement
Muscle	Congenital myopathies Metabolic myopathies Congenital muscular dystrophy Congenital myotonic dystrophy	Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures

Table 608-4 Specific Congenital Myopathies: Distinguishing Clinical Features

MYOPATHY	NEONATAL HYPOTONIA AND WEAKNESS	SEVERE FORM WITH NEONATAL DEATH	FACIAL WEAKNESS	PTOSIS	EXTRAOCULAR MUSCULAR WEAKNESS
Central core disease	+	0	±	0	0
Nemaline myopathy	+	+	+	0	0
Myotubular myopathy (centronuclear myopathy)	+	+	+	+	+
Congenital fiber-type disproportion	+	±	±	0	+

+, Often a prominent feature; ±, variably a prominent feature; 0, not a prominent feature.
From Volpe JJ: Neurology of the newborn, *ed 5, Philadelphia, 2008, Elsevier Saunders, p. 820.*

Table 608-2 Clinical Signs of Muscular Dystrophy

	MOTOR FUNCTION	DISTRIBUTION OF WEAKNESS	RIGID SPINE	CARDIOMYOPATHY	RESPIRATORY IMPAIRMENT	DISEASE COURSE	INCREASED CK	OTHER SIGNS
CONGENITAL-ONSET MUSCULAR DYSTROPHY								
Congenital muscular dystrophy with merosin deficiency	Independent ambulation generally not achieved in patients with absent merosin	Upper limbs > lower limbs	–	Not frequent	++	Slowly progressive	++	White matter changes on brain MRI
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (Walker-Warburg syndrome, muscle-eye-brain disease, congenital muscular dystrophy type 1C, etc.)	Independent ambulation generally not achieved	Upper limbs > lower limbs	–	Not frequent	+	Slowly progressive	++	Frequent structural brain changes
Congenital muscular dystrophy with rigid spine syndrome type 1 (SEPN1)	Ambulation achieved	Axial muscles > limbs	++	–	Early respiratory failure	Progression of respiratory signs > motor signs	N or +	Scoliosis
Ullrich syndrome	Ambulation achieved in ~50% but lost by middle teens	Proximal and axial	++	–	Early respiratory failure	Progression of respiratory and motor signs	N or +	Distal laxity
FROM EARLY-ONSET TO CHILDHOOD-ONSET MUSCULAR DYSTROPHY								
Duchenne muscular dystrophy	Independent ambulation achieved, but lost before age of 13 yr	Proximal > distal (pattern A)	–	++	++	Progression of motor, cardiac, and respiratory signs	++	Mental retardation in 30%
Emery-Dreifuss muscular dystrophy with lamin AC deficiency (type 2)	Ambulation achieved in all cases except for rare cases with congenital onset	Scapuloperoneal (pattern B)	++	++	In adulthood in the typical form, but also in childhood (congenital variants)	Slowly progressive	+ (+)	Frequent association with Dunningham-type lipodystrophy
Limb-girdle muscular dystrophy with lamin AC deficiency (type 1B)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	+	++	In adulthood	Progression of cardiac signs > motor signs	+ (+)	None
Limb-girdle muscular dystrophy with calpain deficiency (type 2A)	Ambulation achieved	Proximal > distal (pattern A)	+	–	Not frequent	Slow progression	++	None

Continued

Table 608-2 Clinical Signs of Muscular Dystrophy—cont'd

	MOTOR FUNCTION	DISTRIBUTION OF WEAKNESS	RIGID SPINE	CARDIOMYOPATHY	RESPIRATORY IMPAIRMENT	DISEASE COURSE	INCREASED CK	OTHER SIGNS
CHILDHOOD-ONSET AND ADULTHOOD-ONSET MUSCULAR DYSTROPHY								
Becker muscular dystrophy	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	–	++	Not frequent	Progressive with substantial variability	++	None
Limb-girdle muscular dystrophy with sarcoglycan deficiency (types 2C, 2D, 2E, 2F)	Independent ambulation achieved, generally lost in the 2nd decade	Proximal > distal (pattern A)	–	++	++	Progression of motor, cardiac, and respiratory signs	++	None
Limb-girdle muscular dystrophy with abnormal glycosylation of dystroglycan (types 2I, 2K, 2L, 2M, 2N, 2O)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	–	++	+(+)	Progressive	++	Mental retardation reported in some cases
Limb-girdle muscular dystrophy with dysferlin deficiency (type 2B)	Independent ambulation always achieved	Both pattern A and pattern E	–	–	–	Progressive in adulthood	++	None
Limb-girdle muscular dystrophy with telethonin deficiency (type 2G)	Independent ambulation achieved, generally lost in the 4th decade	Proximal > distal (pattern A); in some pattern B	–	+	+	Progressive in adulthood	+ (+)	None
Limb-girdle muscular dystrophy with titin deficiency (type 2J)	Independent ambulation achieved	Proximal > distal (pattern A) but also pattern E	–	–	–	Roughly half lose ambulation in adulthood	++	None
Facioscapulohumeral dystrophy	Independent ambulation achieved, variable progression	Pattern D	–	–	Uncommon and mild	Slowly progressive	N or +	Neurosensory hearing loss and retinal degeneration
Emery-Dreifuss muscular dystrophy with merin deficiency (type 1)	Independent ambulation achieved, variable progression	Scapuloperoneal (pattern B)	+	++	Not frequent	Progression of cardiac signs > motor signs	+ (+)	None
ADULT-ONSET MUSCULAR DYSTROPHY								
Limb-girdle muscular dystrophy with anoctamin deficiency (type 2L)	Onset in adulthood, 8:1 ratio of men to women	Mainly lower limbs pattern A, rarely pattern E	–	–	–	Slowly progressive in adulthood	++	None
Limb-girdle muscular dystrophy type 1A (myotilin)	Independent ambulation achieved	Proximal > distal (pattern A)	–	–	–	Generally slowly progressive in adulthood	+	Dysarthria in some cases
Limb-girdle muscular dystrophy with caveolin deficiency (type 1C)	Independent ambulation achieved; rippling might be seen before weakness	Proximal and distal	–	+	–	Slowly progressive, variable	++	Cramps, rippling, percussion-induced repetitive contractions

–, Absent; +, mild; ++, severe; +(+), variable; CK, creatine kinase; N, normal.
From Mercuri E, Muntoni F: Muscular dystrophies. Lancet *381:845–858, 2013, Table 2.*

Table 608-3 Cardiac Involvement in Muscular Dystrophies

	ONSET AND FIRST SIGNS	PROGRESSION	CARDIAC DEATH	SURVEILLANCE
Duchenne muscular dystrophy	Dilated cardiomyopathy with reduced left-ventricular ejection fraction after 10 yr of age	Dilated cardiomyopathy in almost all patients by 18 yr of age. Ventricular dysrhythmias occur in older patients	Congestive heart failure or sudden death in 20% of patients, although the contribution of heart to death of ventilated patients is now well established	Echocardiography every 2 yr in the 1st decade of life and annually after 10 yr of age (or more frequently if abnormalities are identified)
Becker muscular dystrophy	Dilated cardiomyopathy, generally after 10 yr of age	Present in 40% of patients older than 18 yr and more than 80% of those older than 40 yr. Most patients develop dilated cardiomyopathy followed by ventricular arrhythmias	Death from congestive heart failure and arrhythmias is estimated to occur in up to 50% of cases. Cardiac transplants reported	Echocardiography at least every 5 yr
Myotonic dystrophy	Cardiac abnormalities can occur as early as the 2nd decade of life	Conduction deficits occur in about 65% of adult patients	20-30% of patients; mean 54 yr of age. Sudden death is mainly caused by conduction blocks, but ventricular tachyarrhythmias are also a possible cause of death	ECG yearly. Holter monitoring is recommended in patients with ECG abnormalities to detect asymptomatic conduction blocks and arrhythmias
EMERY-DREIFUSS MUSCULAR DYSTROPHY				
X-linked recessive Emery-Dreifuss muscular dystrophy (type 1)	Conduction disturbances generally in the 2nd decade	Ventricular myocardium might become involved, leading to mild ventricular dilation and low-to-normal systolic function	Sudden death is by far the most common cause of death and can be very unpredictable	ECG and yearly Holter monitoring are indicated. Pacemaker implantation should be considered if sinus node or atrioventricular node disease develops. Defibrillator might be needed in some patients
Emery-Dreifuss muscular dystrophy 2 and limb-girdle muscular dystrophy 1B	Conduction disease and cardiac failure	Dysrhythmias (sinus bradycardia, atrioventricular conduction block, or atrial arrhythmias) present in 92% of patients older than 30 yr	Sudden death reported also in patients with pacemaker. Rare death with defibrillator also reported. Cardiac failure. Cardiac transplants reported	ECG and yearly Holter monitoring are indicated. Defibrillator implantation should be considered as pacemaker does not have a substantial effect on mortality
LIMB-GIRDLE MUSCULAR DYSTROPHY				
Sarcoglycanopathies	ECG and/or echocardiographic abnormalities reported in 20-30% of patients (especially β and δ variants; less common in α variant)	Severe dilated cardiomyopathy and lethal ventricular arrhythmias might occur in patients with Duchenne muscular dystrophy–like dystrophy	Typically by cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb-girdle muscular dystrophy 2I	Cardiac involvement reported in 29-62% of limb-girdle muscular dystrophy 2I. Dilated cardiomyopathy may start in teenage yr	Symptomatic cardiac failure over time, at a mean age of 38 yr (range: 18-58 yr)	Cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb-girdle muscular dystrophy 1E	Dilated, restrictive, hypertrophic cardiomyopathies and arrhythmias. Cardiac involvement can precede muscle weakness in some patients	Major cardiac signs, such as atrioventricular block, can be the presenting symptom or occur within a decade of onset of muscle weakness	Life-threatening cardiac complications in roughly 50% of patients, at a mean age of 40 yr, including sudden death, end-stage heart failure, atrioventricular block, and syncope	No evidence-based standards of care exist, but experts have made recommendations

Continued

Table 608-3 Cardiac Involvement in Muscular Dystrophies—cont'd

	ONSET AND FIRST SIGNS	PROGRESSION	CARDIAC DEATH	SURVEILLANCE
CONGENITAL MUSCULAR DYSTROPHY				
Congenital muscular dystrophy merosin muscular dystrophy type C1A	Occasional reports of reduced left ventricular systolic function	Not well characterized	Rare by cardiac failure	No evidence-based standards of care exist, but experts have made recommendations
Fukuyama congenital muscular dystrophy	Systolic left-ventricular dysfunction may develop in the 2nd decade	Symptomatic cardiac failure over time	Death from congestive heart failure might occur by the age of 20 yr	No evidence-based standards of care exist, but experts have made recommendations
Muscular dystrophy type C1C	Dilated cardiomyopathy reported in young children	Not well characterized	Not reported	No evidence-based standards of care exist, but experts have made recommendations
Facioscapulohumeral muscular dystrophy	Uncommon	Not well characterized	Not reported	No evidence-based standards of care exist, but experts have made recommendations

ECG, electrocardiogram.
From Mercuri E, Muntoni F: Muscular dystrophies. Lancet *381:845–858, 2013, Table 3.*

Table 609-1 Channelopathies and Related Disorders

DISORDER	PATTERN OF CLINICAL FEATURES	INHERITANCE	CHROMOSOME	GENE
CHLORIDE CHANNELOPATHIES				
Myotonia Congenita				
Thomsen disease	Myotonia	Autosomal dominant	7q35	*CLC1*
Becker disease	Myotonia and weakness	Autosomal recessive	7q35	*CLC1*
SODIUM CHANNELOPATHIES				
Paramyotonia congenita	Paramyotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Hyperkalemic periodic paralysis	Periodic paralysis with myotonia and paramyotonia	Autosomal dominant	17q13.1-13.3	*CNA4A*
Hypokalemic periodic paralysis	Periodic paralysis	Autosomal dominant	17q13.1-13.3	*SCNA4A*
POTASSIUM-AGGRAVATED MYOTONIAS				
Myotonia fluctuans	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Myotonia permanens	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Acetazolamide-responsive myotonia	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
CALCIUM CHANNELOPATHIES				
Hypokalemic periodic paralysis	Periodic paralysis	Autosomal dominant	1q31-32	Dihydropyridine receptor
Schwartz-Jampel syndrome (chondrodystrophic myotonia)	Myotonia; dysmorphic	Autosomal recessive	1q34.1-36.1	*Perlecan*
Rippling muscle disease	Muscle mounding, stiffness	Autosomal dominant	1q41	*Caveolin-3*
Anderson syndrome	Periodic paralysis, cardiac arrhythmia, distinctive facies	Autosomal dominant	17q23	*KCNJ2-Kir2.1*
Brody disease	Delayed relaxation, no electromyogram myotonia	Autosomal recessive	16p12	Calcium adenosine triphosphatase
Malignant hyperthermia	Anesthetic-induced delayed relaxation	Autosomal dominant	19q13.1	Ryanodine receptor

Table 609-2 Autosomal Recessive Limb-Girdle Muscular Dystrophies

TYPE	LOCATION	GENE PRODUCT	CLINICAL FEATURES
LGMD2A	15q	Calpain 3	Onset at 8-15 yr, progression variable
LGMD2B	2p13-16	Dysferlin	Onset at adolescence, mild weakness; gene site is the same as for Miyoshi myopathy
LGMD2C	13q12	Sarcoglycan	Duchenne-like, severe childhood autosomal recessive muscular dystrophy (SCARMD1)
LGMD2D	17q12	α-Sarcoglycan (adhalin)	Duchenne-like, severe childhood autosomal recessive muscular dystrophy (SCARMD2)
LGMD2E	4q12	β-Sarcoglycan	Phenotype between Duchenne and Becker muscular dystrophies
LGMD2F	5q33-34	Sarcoglycan	Slowly progressive, growth retardation

LGMD, limb-girdle muscular dystrophy.
From Fenichel GM: Clinical pediatric neurology: a signs and symptoms approach, *ed 5, Philadelphia, 2005, Elsevier Saunders, p. 176, Table 7-5.*

Table 611-2 Secondary Causes of Periodic Paralysis

HYPOKALEMIC
Thyrotoxic
Primary hyperaldosteronism (Conn syndrome)
Renal tubular acidosis (e.g., Fanconi syndrome)
Juxtaglomerular apparatus hyperplasia (Bartter syndrome)
Gastrointestinal potassium wastage
Villous adenoma
Laxative abuse
Pancreatic non–insulin-secreting tumors with diarrhea
Nontropical sprue
Barium intoxication
Potassium-depleting diuretics
Amphotericin B
Licorice
Corticosteroids
Toluene toxicity
p-Aminosalicylic acid
Carbenoxolone
HYPERKALEMIC
Addison disease
Hypoaldosteronism
Excessive potassium supplementation
Potassium-sparing diuretics
Chronic renal failure

Table 610-1 Toxic Myopathies

INFLAMMATORY	**MALIGNANT HYPERTHERMIA**
Cimetidine	Halothane
D-Penicillamine	Ethylene
Procainamide	Diethyl ether
L-Tryptophan	Methoxyflurane
L-DOPA	Ethyl chloride
NONINFLAMMATORY NECROTIZING OR VACUOLAR	Trichloroethylene
Cholesterol-lowering agents	Gallamine
Chloroquine	Succinylcholine
Colchicine	**MITOCHONDRIAL**
Emetine	Zidovudine
ε-Aminocaproic acid	**MYOTONIA**
Labetalol	2,4-*d*-Chlorophenoxyacetic acid
Cyclosporine and tacrolimus	Anthracene-9-carboxycyclic acid
Isoretinoic acid (vitamin A analog)	Cholesterol-lowering drugs
Vincristine	Chloroquine
Alcohol	Cyclosporine
RHABDOMYOLYSIS AND MYOGLOBINURIA	**MYOSIN LOSS**
Cholesterol-lowering drugs (especially statins)	Nondepolarizing neuromuscular blocking agents
Alcohol	Intravenous glucocorticoids
Heroin	
Amphetamine	
Toluene	
Cocaine	
ε-Aminocaproic acid	
Pentazocine	
Phencyclidine	

Table 611-1 Metabolic and Mitochondrial Myopathies

GLYCOGEN METABOLISM DEFICIENCIES
Type II: α-1,4-Glucosidase (acid maltase)
Type III: Debranching
Type IV: Branching
Type V: Phosphorylase (McArdle disease)*
Type VII: Phosphofructokinase (Tarui disease)*
Type VIII: Phosphorylase B kinase*
Type IX: Phosphoglycerate kinase*
Type X: Phosphoglycerate mutase*
Type XI: Lactate dehydrogenase*
LIPID METABOLISM DEFICIENCIES
Carnitine palmitoyltransferase*
Primary systemic/muscle carnitine deficiency
Secondary carnitine deficiency
β-Oxidation defects
Medications (valproic acid)
PURINE METABOLISM DEFICIENCIES
Myoadenylate deaminase deficiency
MITOCHONDRIAL MYOPATHIES
Alpers-Huttenlocher syndrome
Chronic progressive external ophthalmoplegia
Kearns-Sayre syndrome
Pearson syndrome
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
Myoclonic epilepsy with ragged red fibers (MERRF)
Leber hereditary optic neuropathy
Leigh syndrome
Infantile myopathy and lactic acidosis

*Deficiency can produce exercise intolerance and myoglobinuria.

Table 612-1 Classification of the Congenital Myasthenic Syndromes

PRESYNAPTIC DEFECTS
• Paucity of synaptic vesicles and decreased quantal release
• Congenital myasthenic syndromes with episodic apnea (choline acetyltransferase deficiency)
• Lambert-Eaton syndrome–like form
SYNAPTIC DEFECTS
• End plate acetylcholinesterase deficiency
POSTSYNAPTIC DEFECTS
• Primary acetylcholine receptor deficiency
• Reduced receptor expression as a result of acetylcholine receptor mutations
• Reduced receptor expression because of rapsyn mutations
• Reduced receptor expression with plectin deficiency
• Primary acetylcholine receptor kinetic abnormality with or without acetylcholine receptor deficiency
• Slow-channel syndrome
• Fast-channel syndrome
• Sodium-channel mutations
• *Dok7* mutations

Table 612-2 Distinctive Clinical and Electrodiagnostic Features of Congenital Myasthenic Syndromes

	Presynaptic		Synaptic	Postsynaptic			
	CHOLINE ACETYLTRANSFERASE DEFICIENCY	**LEMS-LIKE FORM**	**AChE DEFICIENCY**	**PRIMARY AChR DEFICIENCY**	**SLOW-CHANNEL CMS**	**FAST-CHANNEL CMS**	***DOK7* MUTATIONS**
Autosomal dominant inheritance					X (most mutations)		
Episodic apnea triggered by stressors	X						
Neonatal hypotonia and respiratory insufficiency	X	X	X (in severe cases)	X (in severe cases)			
Skeletal deformities			X	X		X (in severe cases)	
Delayed pupillary light responses			X				
Prominent neck, wrist, and finger extensor weakness					X		
Repetitive CMAPs after single stimulus			X		X		
Progressive decrement with prolonged exercise or repetitive stimulation	X			X			
Marked increment (>200%) with high-frequency repetitive stimulation		X					
Decrement repairs with AChE inhibitors				X		X	
Clinical improvement with AChE inhibitors						X	
Clinical worsening with AChE inhibitors			X		X		X

AChE, acetylcholinesterase; AChR, acetylcholine receptor; CMAPs, compound muscle action potentials; CMS, congenital myasthenic syndrome; LEMS, Lambert-Eaton myasthenic syndrome.

From Muppidi S, Wolfe GI, Barhon RJ: Diseases of the neuromuscular junction. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, Elsevier, Table 91-3.*

Table 612-4	Potential Therapies in Congenital Myasthenic Syndromes
AChE	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
AChR deficiency	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR fast channel	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR slow channel	Quinidine sulfate • Adults: Begin for 1 wk with 200 mg tid; gradual increase to maintain a serum level of 1-25 μg/mL • Children: 15-60 mg/kg/day in 4-6 divided doses; not available in several countries If quinidine sulfate is not available, fluoxetine 80-100 mg/day in adults Avoid AChE inhibitors
ChAT	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
Dok7	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
Laminin β_2	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries Avoid AChE inhibitors
MuSK	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses 3,4-Diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
Rapsyn	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults

Modified from Eyemard B, Hantaï D, Estounet B: Congenital myasthenic syndromes, Handb Clin Neurol *113:1469-1480, 2013.*

Table 612-3	Myasthenia Gravis Activities of Daily Living Scale (MG-ADL)			
GRADE	**0**	**1**	**2**	**3**
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking, necessitating changes in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do 1 of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant
TOTAL MG-ADL SCORE				

Table 612-5 Spinal Muscular Atrophy Variants: Progressive or Severe Neonatal Anterior Horn Cell Disease Not Linked to SMN	
VARIANT	**MAJOR FEATURES**
SMA with respiratory distress type 1 (SMARD1)	Mild hypotonia, weak cry, distal contractures initially Respiratory distress from diaphragmatic paralysis 1-6 mo, progressive distal weakness Autosomal recessive, locus 11q13.2, gene: immunoglobulin mu-binding protein 2 (IGHMBP2)
Pontocerebellar hypoplasia type 1	Arthrogryposis, hypotonia, weakness, bulbar deficits early; later, microcephaly, extraocular defects, cognitive deficits: pontocerebellar hypoplasia Molecular defect unknown Likely autosomal recessive
X-linked infantile SMA with bone fractures	Arthrogryposis, hypotonia, weakness, congenital bone fractures, respiratory failure Lethal course as in severe type 1 SMA Most cases X-linked (X9/11.3-q11.2), a few cases likely autosomal recessive
Congenital SMA with predominant lower limb involvement	Arthrogryposis, hypotonia, weakness, especially distal lower limbs early Nonprogressive but severe disability Autosomal dominant or sporadic; locus 12q23-24

SMA, spinal muscular atrophy; *SMN*, survivor motor neuron gene.

Table 613-1 Hereditary Peripheral Neuropathies

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
CMT1 (DEMYELINATING)			
CMT1 A-F (HMSN type I)	Autosomal dominant. Onset 1st-4th decade. Predominant distal weakness, decreased DTRs, mild distal sensory loss, hypertrophy of nerves common	Delayed motor and sensory conduction studies. Motor studies typically <38 m/s	
1A (118220)	Commonest form recognized, seen in all ages (but more adults)		*PMP22* duplication or point mutation
1B (118200)	Approximately 5% of CMT1 group		*MPZ*
1C (601098)	Childhood onset, starts with abnormal gait, then distal weakness and wasting, occasional nerve hypertrophy. Rarely, early-onset hearing loss		*LITAF*
1D (607678)	Possible cranial nerve involvement. Late onset in childhood or early adulthood		*EGR2*
1E (118300)	Associated with deafness (29-45%)		*PMP22*
1F (607734)			*NEFL*
Hereditary neuropathy with liability to pressure palsies (tomaculous neuropathy) (162500)	Autosomal dominant. Recurrent mononeuropathy simplex or multiplex frequently related to trauma	Significant slowing of motor and sensory conduction velocities in clinically affected nerves but also in unaffected nerves	*PMP 22* deletion
Slowed NCVs	Often a miscellaneous group. Incidentally detected with no clinical symptoms. Autosomal dominant	Moderately slowed conduction velocities	*ARHGEF10*
Asymptomatic			
CMT2 (AXONAL)			
CMT2 A-L (HMSN type II)	Autosomal dominant (A, B, D, E, F, G, I) Autosomal recessive (BI, B2, H, K) Clinically similar to CMT type 1, except for later onset, absence of peripheral nerve enlargement, and less marked weakness	Nerve conduction velocities greater than HMSN type I (>38 m/s) but below normal range occasionally	
2A1 (118210)	CMT2A: prominent distal weakness, proximal weakness also present in 60%. Optic atrophy and central involvement reported. Main form related to *MFN2* mutations		2A1: *KIF1B* (one family)
2A2 (609260)			2A2: *MFN2*
2B (600882)	CMT2B: severe sensory loss: often complications with infections, arthropathy, amputations, foot ulcers, distal weakness		2B: *RAB7*
2B1 (605588)			2B1: *LMNA*
2B2 (605589)	Average onset 34 yr (Costa Rican family)		*?MED25*
2C (606071)	Vocal cord, diaphragm, and respiratory involvement, decreased longevity. Allelic with congenital dSMA (600175) and scapuloperoneal muscular atrophy (181405)		*TRP4* 12q23–q24 *TRP4*
2D (601472) (allelic to dSMA)	Upper limb predominance		*GARS*
2E (607684) (1F dominant is allelic to CMT2E)	30% associated with deafness, early childhood onset with gait abnormalities, occasional hyperkeratosis, increased sensory involvement	Intermediate/slow nerve conduction studies	*NEFL*

Continued

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
2F (606595)	Trophic changes feet and knees		*HSPB1* (*HSP27*)
2G (608591)	Onset age 9-76 yr, average age 20 yr, large Spanish family. Also severe form with early onset		12q12–q13
2H (607731) 2H (allelic to CMT4A–CMT4C2 in original publication)	Pyramidal involvement, vocal cord involvement	Intermediate/slow nerve conduction studies	*GDAP1*
2I (607677)	CMT I and J: possible late onset, pupillary anomalies, pain, hearing loss, dysphagia		*MPZ*
2J (607736)	Vocal cord paralysis, more severe early-onset form		*MPZ*
2K (607831)	Occasional proximal leg weakness (like dHMN II), large Chinese family, with onset at age 15-33 yr. Scoliosis		*GDAP1*
2L (608673)			*HSPB8* 12q24
HMSN II with onset in early childhood (EOHMSN) Severe early-onset axonal neuropathy (SEOAN)	Autosomal dominant or recessive. Weakness within 1st 5 yr, rapid progression of weakness, usually complete paralysis below elbows and knees by teens, absent DTRs, moderate sensory changes in most cases. Normal CSF protein. Occasional optic atrophy or spasticity	Axonal pattern with axonal-degenerative polyneuropathy. Absent SNAPs, no response to stimulation in cerebral palsy nerve, upper limb nerves normal or mildly slowed. EMG: denervation	*MFN2*; *GDAP1* Heterogeneous
Spinal muscular atrophy with respiratory distress type 1 (SMARD1)/severe infantile axonal neuropathy with respiratory failure (SIANR) Allelic to dHMN6 dSMA1 (604320)	Autosomal recessive. Onset in infancy (3-6 mo), respiratory failure, progressive distal weakness, eventual plateau. No recovery	Absent conduction in most cases	*IGHMBP2*
Hereditary motor and sensory neuropathy (HMSN-P) (Okinawa type)	Adult onset (after 30 yr). Autosomal dominant. Slowly progressive proximal dominant area of weakness. Fasciculations of extremities and trunk. Raised creatine kinase, hyperlipidemia, diabetes mellitus, eventual loss of ambulation, absent DTRs, sensory disturbances. Most patients described from Japan	Motor and sensory axonal neuropathy. SNAPs, CMAPs, MNCVs, and SNCVs reduced or absent EMG: fasciculations, fibrillations, and neuromyotonic picture early on	3q13
CMT3* AND 4			
CMT3 (Dejerine-Sottas syndrome) (145900)	Onset 1st 2 yr, overall disability ?less severe than CMT4. Hypotonia, motor delay by 1st yr, poor coordination, ataxia, distal weakness (max. lower limbs), short stature. By 2nd decade, proximal weakness, hand and foot deformities. Nerve hypertrophy. Moderate to severe sensory loss. Scoliosis. Common cranial nerve involvement, nystagmus, deafness, and mild bifacial weakness. Raised CSF protein	Motor conduction velocities usually <10 m/s. SAPs absent. EMG: chronic denervation	*PMP22, MPZ, PRX, EGR2, FIG4*
CMT4 (A-J) Autosomal recessive	Clinical picture similar to or slightly more severe than in CMT1 form, increased ataxia, areflexia, scoliosis. Nerve hypertrophy rare	Moderate slowing of nerve conduction studies	
4A (214400)	Onset <2 yr, Tunisian and Moroccan families. Severe progressive. Less-severe European phenotypes	25-35 m/s	*GDAP1*
4B1 (601382)	Ophthalmoplegia, vocal cord paralysis, facial, bulbar weakness (all infrequent). Weakness below 5 yr, proximal and distal weakness, absent DTRs	9-20 m/s	*MTMR2, (MPZ)*
4B2 (604563)	Early onset: 1st decade; glaucoma and deafness sometimes. Recorded in Tunisia, Japan, and Turkey	15-30 m/s	*SBF2, MTMR13*
4C (601596)	Early-onset scoliosis, commoner in Algerians, glaucoma and neutropenia. 1st and 2nd decades	4-37 m/s	*SH3TC2* (*KIAA1985*)
4D (601455) (HMSN-Lom)	Closed gypsy pedigree; onset <10 yr. Deafness (by 2nd-3rd decade). Tongue atrophy	10-20 m/s	*NDRG1*
4E (605253)	Congenital hypomyelinating neuropathy	5-20 m/s	*ERG2/KROX 20, MPZ*

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
4F (145900)	Severely affected at birth or by 7 yr; arthrogryposis multiplex congenita common; respiratory and feeding difficulties; often die young	<5 m/s	*PRX*
4G (605285)	Type Russe. Onset 8-16 yr. Origin Bulgaria	30-35 m/s	10q22
4H (609311)	Increased in Lebanese/Turkish. Onset infancy to childhood (1-2 yr). Delayed motor milestones. Occasional scoliosis, increased distal weakness, usually absent DTRs	<10 m/s or absent	*FDG4*
4J (611228)	Onset by 5 yr. Severe disorder. Similarities to motor neuron disease	2-7 m/s; some cases higher	*FIG4*
CCFDN (604168)	Congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy	19-33 m/s	*CTDP1*
MIXED PATHOLOGY (AXONAL AND DEMYELINATING)			
CMT X X-linked CMT X1 (302800)	X-linked dominant. Onset 1st-2nd decade. Progressive wasting and weakness of distal limb musculature, especially hands, more marked in affected males than carrier females	Median nerve motor conduction studies <40 m/s (but faster than CMT1A). Intermediate slowing less uniform along nerves with dispersion more pronounced	*GJB1*
X2 (302801)	X-linked recessive. Rare infantile onset, intellectual disability, females very mildly affected	Mixed demyelinating/axonal	Xp22.2
X3 (302802)	X-linked recessive. ± Spasticity. Females unaffected	Mixed demyelinating/axonal	Xq26
X4 (310490)	X-linked (Cowchock syndrome). Severe neuropathy, females very mildly affected. Isolated case reports. Onset birth to early childhood. Slowly progressive. Many develop deafness by 5 yr. Mental retardation commonly seen. Occasional optic atrophy	Axonal neuropathy. Motor conduction velocities: mild delay (33-56 m/s). Sensory very abnormal. EMG: denervation, large motor unit potential, and fasciculation	Xq24–26.1
X5 (311070)	X-linked. Mild to moderate neuropathy, deafness, optic atrophy. Allelic with Rosenberg-Chutorian (opticoacoustic neuropathy) and Arts syndromes	Axonal neuropathy–mild demyelinating changes	Xq21.32–q24 *PRPS1*
Intermediate forms of CMT	Patients have neurophysiologic results that fall between axonal and demyelinating ranges	"Intermediate values" 30-40 m/s–most accurate from median motor nerves. Some forms have normal nerve conduction studies (DI-CMTB)	
DI-CMTA	Italian family		10q24.1–q25.1
DI-CMTB (606482)	American family		*DNM2*
DI-CMTC (608323)			*YARS*
DI-CMTD (607791)	Myelin protein zero		*MPZ*
A–autosomal recessive form (608340)	Overlap conditions: Recessive CMT with *GADP1* mutations: (CMT2K and 4A) Spanish and Tunisian family–severe childhood forms reported. Also called DI-CMTA autosomal recessive form CMT with NF-L: (CMT1F and 2E)		Overlap: *GJB1* *NF-L* *GDAP1*
OTHER HMSN AND HMN SYNDROMES			
HMSN V/spastic paraplegia with HMSN type V/CMT5 (CMT with pyramidal signs) (600631)	Variable inheritance. Spasticity in lower limbs causing difficulty walking and toe walking. Autosomal recessive form associated with mental retardation. Lower limb marked spasticity with little weakness, increased DTRs, extensor plantars, pes cavus, often distal amyotrophy. Expanding field with multiple subforms, n = 37. Not all associated with peripheral neuropathy CMT with pyramidal signs: part of HMSN V but described without spasticity	Small/absent SNAPs. Motor studies axonal in type	*SPG3A, SPAST, NIPA1, BSCL2, SPG4, SPG7, SPG20, SPG21, SPG30, PLP1* CMT with pyramidal signs: *MFN2*
HMSN VI (allelic CMT2A)	Visual impairment due to optic atrophy. Dominant and recessive forms. Onset in 1st decade. Distal weakness, often proximal involvement too. Less sensory involvement. Scoliosis	No response or motor conduction around 45 m/s. Sensory nerves often cannot be stimulated	*MFN2*
HMSN VII	HMSN with retinitis pigmentosa. CSF protein raised. Usually adult onset. Rare entity described in a few families, mainly of adult onset		

Continued

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
DISTAL HEREDITARY MOTOR NEURONOPATHIES (DHMN)			
dHMNI (182960)	Autosomal dominant. Juvenile onset. Distal weakness and wasting	Normal nerve conduction studies, occasional mild slowing. EMG neurogenic	*HSPB1* 7q34–q36
dHMNII (608634)	Autosomal dominant. Adult onset, distal weakness and wasting		*HSPB8, HSPB3*
dHMNIIjuv (158590)	(Allelic CMT2F, CMT2L)		*HSPB1*
dHMNIII	Autosomal recessive. Infantile to adult onset. Slow, progressive muscle wasting and weakness, variable diaphragmatic paralysis		11q13.3
dHMNIV (607088) Distal SMA type 3	Autosomal recessive. Juvenile onset. Severe muscle wasting and weakness and diaphragmatic paralysis		11q13
dHMNV (600794)	(Allelic CMT2D) Autosomal dominant. Upper limb predominance, occasional pyramidal features		*GARS*
dHMN type V (Silver syndrome) (270685)	Autosomal dominant. Prominent hand muscle weakness and wasting, mild to severe spasticity of lower limbs		*BSCL2*
dHMNVI (604320)	(Allelic SMARD1) Autosomal recessive. Severe infantile form with respiratory distress		*IGHMBP2*
dHMNVIIA (158580)	Autosomal dominant. Onset with vocal cord paralysis		*DCTN1*
dHMNVIIB (607641)	Autosomal dominant. Onset with vocal cord paralysis and facial weakness		2q14 Xq13–q21
X-linked dHMN			
dHMN/ALS4 (602433)	X-linked recessive. Juvenile onset with distal wasting and weakness		*SETX*
dHMN-J (Jerash)	Autosomal dominant. Early onset symptomatic in 2nd decade with pyramidal tract signs		9p21.1–p12
Congenital distal SMA (600175)	Autosomal recessive. Onset from 6-10 yr with pyramidal features in 1 Jordanian family Autosomal dominant congenital nonprogressive distal HMN with contractures		12q23–q24
Peripheral neuropathy with agenesis of corpus callosum (Charlevoix disease or Andermann syndrome) (218000)	Autosomal recessive. Increased in French Canadian populations. Progressive axonal neuropathy. CNS malformations—absence/hypoplasia of corpus callosum in most, early onset, developmental delay, areflexia, dysmorphology. Later, increased motor disability, hallucinatory psychosis. Death by 3rd decade	EMG: denervation. Axonal neuropathy	*SLC12A6 (KCC3)*
Hereditary neuralgic amyotrophy (brachial plexus neuropathy) (162100)	Autosomal dominant. Episodes of paralysis and muscle weakness initiated by severe pain. Onset can be from birth or later childhood but usually adult onset. Outcome usually good but some left with residual dysfunction. Episodes often triggered by infections, immunizations, and stress. Some pedigrees dysmorphic with hypotelorism	Normal or mildly prolonged MNCVs distal to affected brachial plexus	*SEPT9*
HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES			
HSN (HSAN) 1 (162400)	Type 1: Autosomal dominant. Onset 2nd–5th decade. Predominant loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement	Normal to low-normal MNCVs, disturbance of sensory conduction of variable severity Type 1B: Autosomal dominant. Predominantly sensory neuropathy with cough and gastroesophageal reflux, rarely foot ulcers. More often adult onset. Hearing often abnormal	*SPTLC1* *RAB7* 3p24–p22
HSN (HSAN) 2(A) (201300)	Autosomal recessive. Onset in infancy/early childhood–1st 2 decades. Mutilating acropathy. Often unrecognized fractures. Marked sensory loss affecting all cutaneous modalities, most marked distally in all limbs. Autonomic dysfunction less marked. Absent or decreased DTRs	Normal MNCVs; SNAPs are absent	*WNK1*
HSN (HSAN) 2B (223900)	Autosomal recessive. Impaired sensation, ulcers, and arthropathy develop in childhood		*FAM134B*

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
HSN (HSAN) 3 (Riley-Day syndrome, familial dysautonomia) (223900)	Autosomal recessive. History of neurologic abnormality and of difficult feeding from birth. Failure to produce tears regularly. Absent or reduced DTRs. Absent corneal reflexes, postural hypotension, emotional lability. Relative indifference to pain, absence of fungiform papillae on tongue, absence of flare with intradermal histamine. Normal intelligence	Motor conduction velocities usually slightly below control values. Sensory conduction normal or decreased	*IKBAP*
HSN (HSAN) 4 (congenital insensitivity to pain with anhidrosis, CIPA) (256800)	Autosomal recessive. Onset from infancy, often high fevers due to truncal anhidrosis during hot weather. Painless injuries of extremities and oral structures, often self-mutilation. Lack of pain sensation, both peripheral and visceral, inability to distinguish hot and cold. Preservation of DTRs. Mild mental retardation. Hyperactivity and emotional lability common	Nerve conduction studies normal. Sympathetic skin responses are absent (histamine test)	*NTRK1*
HSN (HSAN) 5 (608654)	Autosomal recessive. Onset in early life. Rare disorder. Painless injuries of the extremities. Lack of pain and thermal sensitivity in the limbs but preservation of response to tactile and mechanical stimuli. Preservation of muscle strength and DTRs. Distal anhidrosis. Bone and joint fractures; arthropathy. Normal intelligence	Normal motor and sensory nerve conduction studies	*NGFβ*

*The term CMT3 should be reserved for hereditary neuropathies in which hypomyelination is the dominant feature. This would include congenital hypomyelinating neuropathy, Dejerine-Sottas disease, and congenital amyelinating neuropathy.

CCFDN, congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy; CIPA, congenital insensitivity to pain with anhidrosis; CMAP, compound motor unit action potential; CMT, Charcot-Marie-Tooth disease; CP, common peroneal; CSF, cerebrospinal fluid; dHMN, distal hereditary motor neuronopathy; DI, dominant intermediate; dSMA, distal spinal muscular atrophy; DTR, deep tendon reflex; EMG, electromyography; EOHMSN, early-onset HMSN; HMN, hereditary motor neuropathy; HMSN, hereditary motor and sensory neuropathy; HSAN, hereditary sensory and autonomic neuropathy; HSN, hereditary sensory neuropathy; MNCV, motor nerve conduction velocity; OMIM, Online Mendelian Inheritance in Man; SAP, sensory action potential; SEOAN, severe early-onset axonal neuropathy; SMA, spinal muscular atrophy; SNAP, sensory nerve action potential.

From Wilmshurst JM, Ouvrier R: Hereditary peripheral neuropathies of childhood: an overview for clinicians, Neuromuscul Disord *21(11):763–775, 2011.*

Table 616-1 Differential Diagnosis of Childhood Guillain-Barré Syndrome

SPINAL CORD LESIONS
Acute transverse myelitis
Epidural abscess
Tumors
Poliomyelitis (natural or live virus)
Enteroviruses
Hopkins syndrome
Vascular malformations
Cord infarction
Fibrocartilaginous embolism
Cord compression from vertebral subluxation related to congenital abnormalities or trauma
Acute disseminated encephalomyelitis
Bickerstaff brainstem encephalitis for Miller-Fisher syndrome
PERIPHERAL NEUROPATHIES
Toxic
• Vincristine
• Glue sniffing
• Heavy metal: gold, arsenic, lead, thallium
• Organophosphate pesticides
• Fluoroquinolones
Infections
• HIV
• Diphtheria
• Lyme disease
Inborn errors of metabolism
• Leigh disease
• Tangier disease
• Porphyria
Critical illness: polyneuropathy/myopathy
Vasculitis syndromes
Porphyria
Mitochondrial neurogastrointestinal encephalomyopathy
CD59 deficiency
NEUROMUSCULAR JUNCTION DISORDERS
Tick paralysis
Myasthenia gravis
Botulism
Hypercalcemia
Myopathies
Periodic paralyses
Dermatomyositis
Critical illness myopathy/polyneuropathy

From Agrawal S, Peake D, Whitehouse WP: Management of children with Guillain Barré syndrome, Arch Dis Child Educ Pract Ed *92:161–168, 2007.*

Table 617-1 Etiologies of Acute Peripheral Facial Palsy

COMMON	**OTHER LESS-COMMON CONDITIONS**
Idiopathic	Trauma
Herpes simplex virus type 1*	Schwannoma of facial nerve
Varicella-zoster virus*	Infiltrative tumor
LESS-COMMON INFECTIONS	Aneurysm or vascular malformation
Otitis media ± cholesteatoma	Anomalous narrowing of facial canal
Lyme disease	Hypertension
Epstein-Barr virus	Sjögren syndrome
Cytomegalovirus	Diabetes mellitus, type 1
Mumps	Guillain-Barré syndrome
Human herpesvirus 6	Sarcoidosis
Intranasal influenza vaccine	Melkersson-Rosenthal syndrome†
Mycoplasma	Ribavirin
Toxocara	Interferon
Rickettsia	
AIDS/HIV	

*Implicated in idiopathic Bell palsy.
†Noncaseating granulomas with facial (lips, eyelids) edema, recurrent alternating facial paralysis, family history, migraines, or headaches.

Table 614-1 Toxic and Metabolic Neuropathies

METALS	Nitrofurantoin
Arsenic (insecticide, herbicide)	Nitrous oxide
Lead (paint, batteries, pottery)	Nucleosides (antiretroviral agents dideoxycytidine [ddC], didanosine [ddI], d4T, others)
Mercury (metallic, vapor)	Penicillamine
Thallium (rodenticides)	Pentamidine
Gold	Phenytoin
OCCUPATIONAL OR INDUSTRIAL CHEMICALS	Pyridoxine (excessive)
Acrylamide (grouting, flocculation)	Statins
Carbon disulfide (solvent)	Stilbamidine
Cyanide	Suramin
Dichlorophenoxyacetate	Tacrolimus
Dimethylaminopropionitrite	Taxanes (paclitaxel, docetaxel)
Ethylene oxide (gas sterilization)	Thalidomide
Hexacarbons (glue, solvents)	Tryptophan (eosinophilia-myalgia syndrome)
Organophosphates (insecticides, petroleum additive)	Vincristine
Polychlorinated biphenyls	**METABOLIC DISORDERS**
Tetrachlorbiphenyl	Fabry disease
Trichloroethylene	Krabbe disease
DRUGS	Leukodystrophies
Amiodarone	Porphyria
Chloramphenicol	Tangier disease
Chloroquine	Tyrosinemia
Cisplatin	Uremia
Colchicine	**BIOLOGIC AND INFECTIOUS NEUROPATHIES**
Dapsone	Diphtheria
Ethambutol	Herpesviruses
Ethanol	HIV
Fluoroquinolones	Leprosy
Gold	Lyme disease
Hydralazine	Rabies
Isoniazid	West Nile virus
Metronidazole	

Table 616-2 Classification of Guillain-Barré Syndrome and Related Disorders and Typical Antiganglioside Antibodies By Pathology

DISORDER	ANTIBODIES
Acute inflammatory demyelinating polyradiculoneuropathy	Unknown
Acute motor and sensory axonal neuropathy	GM_1, GM_{1b}, GD_{1a}
Acute motor axonal neuropathy	GM_1, GM_{1b}, GD_{1a}, GalNac-GD_{1a}
Acute sensory neuronopathy	GD_{1b}
ACUTE PANDYSAUTONOMIA	
Regional Variants	
Fisher syndrome	GQ_{1b}, GT_{1a}
Oropharyngeal	GT_{1a}
Overlap	
Fisher/Guillain-Barré overlap syndrome	GQ_{1b}, GM_1, GM_{1b}, GD_{1a}, GalNac-GD_{1a}

From Hughes RAC: Treatment of Guillain-Barré syndrome with corticosteroids: lack of benefit? Lancet *363:181–182, 2004.*

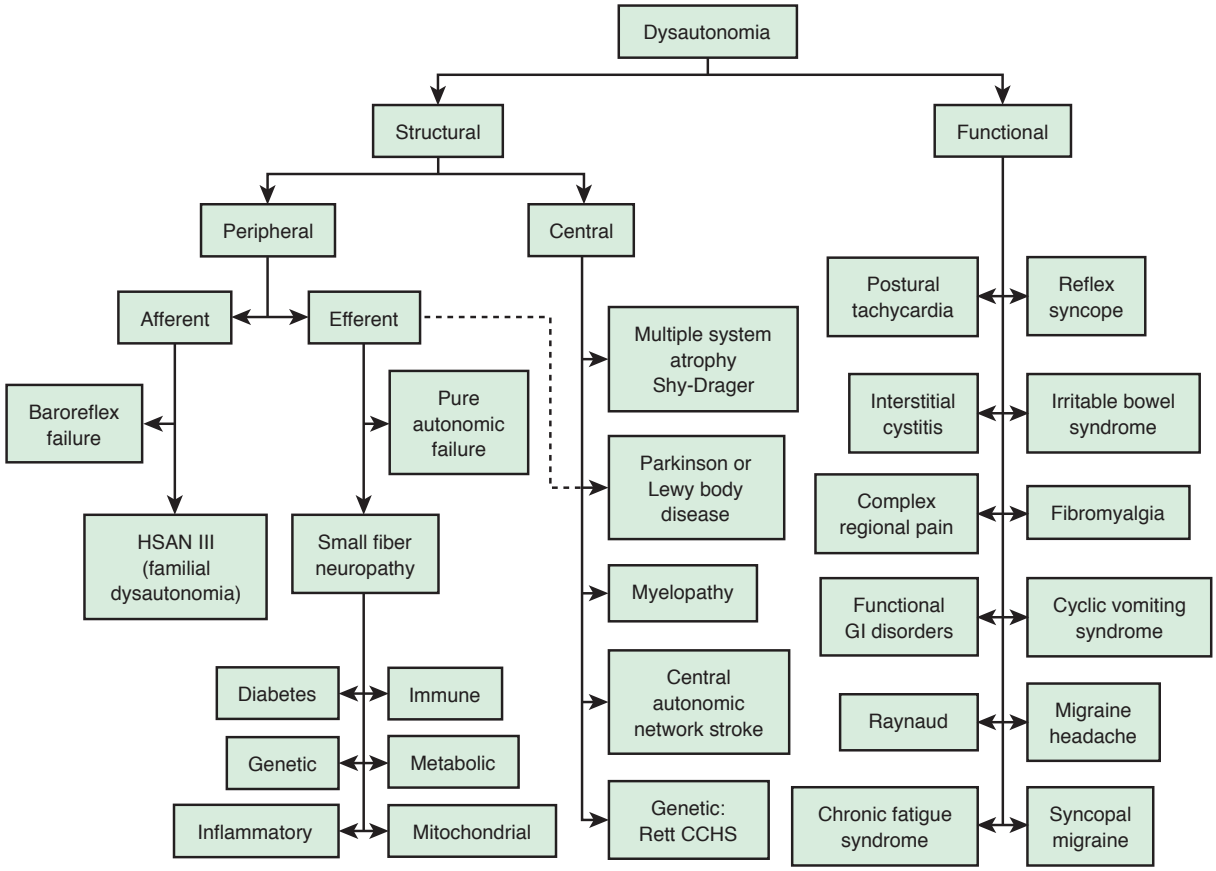

Figure 615-1 Classification of autonomic disorders or dysautonomias. The first conceptual division is between a structural and functional disorder. The word "functional" is being used in its true meaning of a disturbance in autonomic function, without clear evidence of structural damage to the autonomic nervous system, akin to the use of the word "functional" in functional gastrointestinal disorders, and without implication of a psychiatric etiology. In the absence of any evidence of consistent structural abnormalities functional disorders clearly cannot be localized in the nervous system. In contrast, structural disorders can be further divided into those localized in the central and peripheral nervous systems, with the division point usually taken at the sympathetic ganglion. Finally, peripheral nervous system disorders can be further classified based on whether they primarily involve afferent or efferent nerves. It should be emphasized that there is overlap between these groups, for example, diabetes will often involve afferent nerve fibers, but this classification emphasizes the predominant fiber involvement. A *dotted line* links Parkinson disease to a peripheral efferent group as Lewy bodies are present in the both parasympathetic and sympathetic ganglia, impairing peripheral autonomic function. See below for discussion of specific disorders. *CCHS*, Congenital central hypoventilation syndrome; *HSAN*, hereditary sensory autonomic neuropathy. *(From Chelimsky T, Robertson D, Chelimsky G: Disorders of the autonomic nervous system. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors*: Bradley's neurology in clinical practice, *ed 6, Philadelphia, 2012, WB Saunders, Fig. 77-1, p. 2018.)*

Table 615-1 Autonomic Neuropathies

Guillain-Barré syndrome (see Chapter 608)
Non–Guillain-Barré syndrome autoimmunity
- Paraneoplastic (type I antineuronal nuclear antibody)
- Lambert-Eaton syndrome
- Antibodies to neuronal nicotinic acetylcholine receptors
- Antibodies to P/Q-type calcium channels
- Other autoantibodies
- Systemic lupus erythematosus

Hereditary sensory and autonomic neuropathies
- Type I autosomal dominant
- Type II autosomal recessive (Morvan disease)
- Type III autosomal recessive (Riley-Day)
- Type IV autosomal recessive (congenital insensitivity to pain with anhidrosis)
- Type V absence of pain

Metabolic
- Fabry disease
- Diabetes mellitus
- Tangier disease
- Porphyria

Infectious
- HIV
- Chagas disease
- Botulism
- Leprosy
- Diphtheria

Other
- Triple A (Allgrove) syndrome
- Navajo Indian neuropathy
- Multiple endocrine neoplasia type 2b

Toxins (see Table 614-1 in Chapter 614)

Table 615-2 Major Clinical Features of Hereditary Sensory-Autonomic Neuropathy Types II, III, and IV

CLINICAL FEATURES	HSAN TYPE II	HSAN TYPE III	HSAN TYPE IV
Onset	Birth	Birth	Birth
Initial symptoms (from birth to age 3 yr)	Swallowing problems Self-mutilation (65%) Delayed development	Swallowing problems Aspiration pneumonia Breech presentation (37%) Hypothermia Delayed development	Fevers Self-mutilation (88%)
Unique features	No axon flare Lack of fungiform papilla Hearing loss (30%)	No axon flare Lack of fungiform papilla Alacrima	No axon flare Anhidrosis Consanguinity 50%
Sensory dysfunction			
Depressed deep tendon reflexes	Frequent (71%)	Almost consistent (99%)	Infrequent (9%)
Pain perception	Absent	Mild to moderate decrease	Absent
Temperature perception	Severe decrease	Mild to moderate decrease	Absent
Vibration sense	Normal	Normal	Normal to moderate decrease
Autonomic			
Gastroesophageal reflux	Frequent (71%)	Frequent (67%)	Uncommon (24%)
Postural hypotension	Uncommon (25%)	Almost consistent (99%)	Uncommon (29%)
Episodic hypertension	Rare	Frequent	Rare
Ectodermal features			
Dry skin	No	No	Consistent
Fractures	29%	40%	71%
Scoliosis	59%	85%	23%
Intelligence			
IQ <65	Common (38%)	Uncommon (10%)	Common (33%)
Hyperactivity	Common (41%)	Uncommon	Common (54%)

Frequency definitions: rare = <1%; infrequent = <10%; uncommon = <30%; common = 30-65%; frequent = >65%.
From Axelrod FB, Gold-von Simson G: Hereditary sensory and autonomic neuropathies: types II, III, and IV, Orphanet J Rare Dis *2:39, 2007, Table 2.*

Table 615-3 Autonomic Function Testing

Sympathetic and parasympathetic divisions of the autonomic nervous system are involved in all tests of autonomic function
CARDIAC PARASYMPATHETIC NERVOUS SYSTEM FUNCTION
Heart rate variability with deep respiration (respiratory sinus arrhythmia); time-domain and frequency-domain assessments
Heart rate response to Valsalva maneuver
Heart rate response to standing
SYMPATHETIC ADRENERGIC FUNCTION
Blood pressure response to upright posture (standing or tilt table)
Blood pressure response to Valsalva maneuver
Microneurography
SYMPATHETIC CHOLINERGIC FUNCTION
Thermoregulatory sweat testing
Quantitative sudomotor-axon reflex test
Sweat imprint methods
Sympathetic skin response

Table 615-4 Management of Autonomic Neuropathies

PROBLEM	TREATMENT
Orthostatic hypotension	Volume and salt supplements Fluorohydrocortisone (mineralocorticoid) Midodrine (α agonist)
Gastroparesis	Prokinetic agents (metoclopramide, domperidone, erythromycin)
Hypomotility	Fiber, laxatives
Urinary dysfunction	Timed voiding; bladder catheterization
Hyperhidrosis	Anticholinergic agents (glycopyrrolate, propantheline) Intracutaneous botulism toxin

Disorders of the Eye

Table 619-1 Vision Screening Guidelines

FUNCTION	RECOMMENDED TESTS	REFERRAL CRITERIA	COMMENTS
AGES 3-5 YR			
Distance visual acuity	Snellen letters Snellen numbers Tumbling E test HOTV test	<4 of 6 correct on 20-ft line with either eye tested at 10 ft monocularly (i.e., <10/20 or 20/40), or Two-line difference between eyes, even within the passing range (i.e., 10/12.5 and 10/20 or 20/25 and 20/40)	Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages 6 yr and older.
	Picture tests -Allen figures -Lea symbols		Testing distance of 3 m (10 ft) is recommended for all visual acuity tests. A line of figures is preferred over a single figure. The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to eye; the examiner must ensure that it is not possible to peek with the nontested eye.
Ocular alignment	Cross cover test at 3 m (10 ft) or Random dot E stereo test at 40 cm (630 sec of arc)	Any eye movement <4 of 6 correct	
	Simultaneous red reflex test (Bruckner test)	Any asymmetry of pupil color, size, brightness	Direct ophthalmoscope used to view both red reflexes simultaneously in a darkened room from 2-3 ft away; detects asymmetric refractive errors as well.
Ocular media clarity (cataracts, tumors, etc.)	Red reflex	White pupil, dark spots, absent reflex	Direct ophthalmoscope, darkened room. View eyes separately at 12-18 inches; white reflex indicates possible retinoblastoma.
AGES 6 YR AND OLDER			
Distance visual acuity	Snellen letters Snellen numbers Tumbling E test HOTV test	<4 of 6 correct on 4.5 m (15 ft) line with either eye tested at 3 m (10 ft) monocularly (i.e., <10/15 or 20/30)	Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages 6 yr and older.
	Picture tests -Allen figures -Lea symbols	Two-line difference between eyes, even within the passing range (i.e., 10/10 and 10/15 or 20/20 and 20/30)	Testing distance of 3 m (10 ft) is recommended for all visual acuity tests. A line of figures is preferred over a single figure. The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to the eye; the examiner must ensure that it is not possible to peek with the nontested eye.
Ocular alignment	Cross cover test at 3 m (10 ft) or Random dot E stereo test at 40 cm (630 sec of arc)	Any eye movement <4 of 6 correct	

Table 621-1 Causes of Childhood Severe Visual Impairment or Blindness

CONGENITAL
Optic nerve hypoplasia or aplasia
Septooptic dysplasia
Optic coloboma
Congenital hydrocephalus
Hydranencephaly
Porencephaly
Micrencephaly
Encephalocele, particularly occipital
Morning glory disc
Aniridia
Microphthalmia/anophthalmia
Peters anomaly
Rieger anomaly
Persistent pupillary membrane
Glaucoma
Cataracts
Persistent hyperplastic primary vitreous

PHAKOMATOSES
Tuberous sclerosis
Neurofibromatosis (special association with optic glioma)
Sturge-Weber syndrome
von Hippel-Lindau disease

TUMORS
Retinoblastoma
Optic glioma
Perioptic meningioma
Craniopharyngioma
Cerebral glioma
Astrocytoma
Posterior and intraventricular tumors when complicated by hydrocephalus
Pseudotumor cerebri

NEURODEGENERATIVE DISEASES
Cerebral storage disease
Gangliosidoses, particularly Tay-Sachs disease, Sandhoff variant, generalized gangliosidosis
Other lipidoses and ceroid lipofuscinoses, particularly the late-onset disorders such as those of Jansky-Bielschowsky and of Batten-Mayou-Spielmeyer-Vogt
Mucopolysaccharidoses, particularly Hurler syndrome and Hunter syndrome
Leukodystrophies (dysmyelination disorders), particularly metachromatic leukodystrophy and Canavan disease
Demyelinating sclerosis (myelinoclastic diseases), especially Schilder disease and Devic neuromyelitis optica
Special types: Dawson disease, Leigh disease, the Bassen-Kornzweig syndrome, Refsum disease
Retinal degenerations: retinitis pigmentosa and its variants and Leber congenital type
Optic atrophies: congenital autosomal recessive type, infantile and congenital autosomal dominant types, Leber disease, and atrophies associated with hereditary ataxias—the types of Behr, of Marie, and of Sanger-Brown

INFECTIOUS/INFLAMMATORY PROCESSES
Encephalitis, especially in the prenatal infection syndromes caused by *Toxoplasma gondii*, cytomegalovirus, rubella virus, *Treponema pallidum*, herpes simplex virus
Meningitis; arachnoiditis
Chorioretinitis
Endophthalmitis
Trachoma
Keratitis
Uveitis

HEMATOLOGIC DISORDERS
Leukemia with central nervous system involvement

VASCULAR AND CIRCULATORY DISORDERS
Collagen vascular diseases
Arteriovenous malformations—intracerebral hemorrhage, subarachnoid hemorrhage
Central retinal occlusion

TRAUMA
Contusion or avulsion of optic nerves, chiasm, globe, cornea
Cerebral contusion or laceration
Intracerebral, subarachnoid, or subdural hemorrhage
Retinal detachment
Laser injury

DRUGS AND TOXINS
Quinine
Ethambutol
Methanol
Many others

OTHER
Retinopathy of prematurity
Sclerocornea
Conversion reaction
Optic neuritis
Osteopetrosis

Table 623-1 Specific Patterns of Nystagmus

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Latent nystagmus	Conjugate jerk nystagmus toward viewing eye	Congenital vision defects, occurs with occlusion of eye
Manifest latent nystagmus	Fast jerk to viewing eye	Strabismus, congenital idiopathic nystagmus
Periodic alternating	Cycles of horizontal or horizontal-rotary that change direction	Caused by both visual and neurologic conditions
Seesaw nystagmus	One eye rises and intorts as other eye falls and extorts	Usually associated with optic chiasm defects
Nystagmus retractorius	Eyes jerk back into orbit or toward each other	Caused by pressure on mesencephalic tegmentum (Parinaud syndrome)
Gaze-evoked nystagmus	Jerk nystagmus in direction of gaze	Caused by medications, brainstem lesion, or labyrinthine dysfunction
Gaze-paretic nystagmus	Eyes jerk back to maintain eccentric gaze	Cerebellar disease
Downbeat nystagmus	Fast phase beating downward	Posterior fossa disease, drugs
Upbeat nystagmus	Fast phase beating upward	Brainstem and cerebellar disease; some visual conditions
Vestibular nystagmus	Horizontal-torsional or horizontal jerks	Vestibular system dysfunction
Asymmetric or monocular nystagmus	Pendular vertical nystagmus	Disease of retina and visual pathways
Spasmus nutans	Fine, rapid, pendular nystagmus	Torticollis, head nodding; idiopathic or gliomas of visual pathways

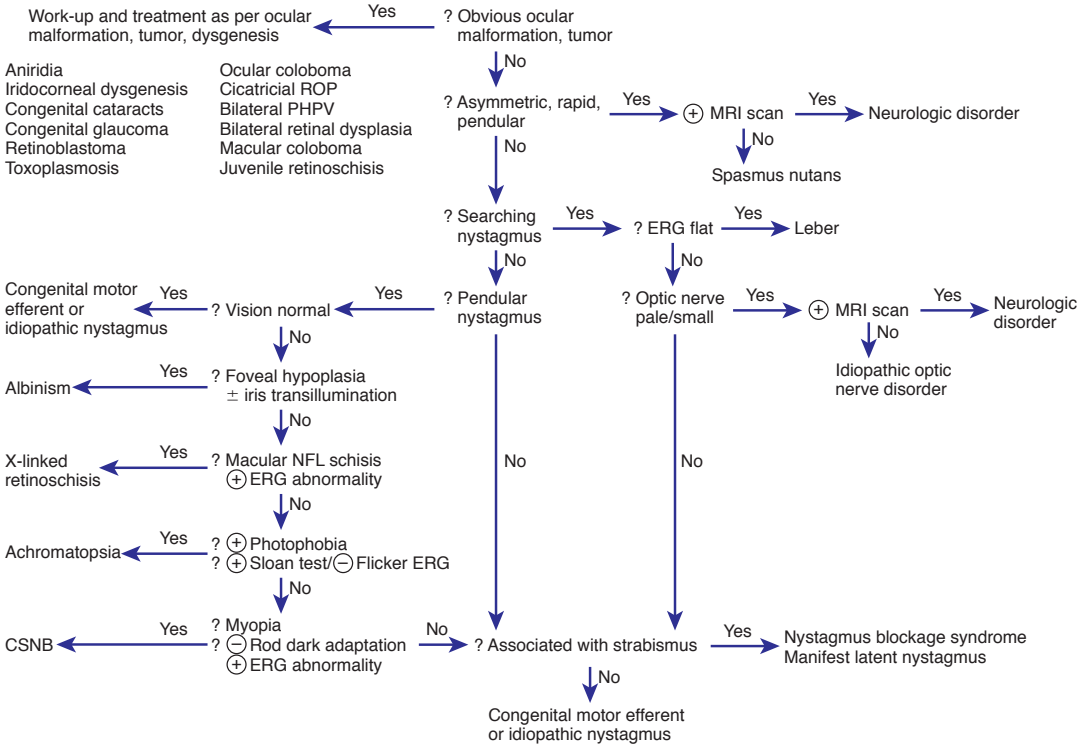

Figure 623-7 Algorithm for the work-up of an infant with nystagmus. ⊕, positive; ⊖, negative; CSNB, congenital stationary night blindness; ERG, electroretinogram; NFL, nerve fiber layer; PHPV, persistent hyperplastic primary vitreous; ROP, retinopathy of prematurity. *(From Nelson LB: Harley's pediatric ophthalmology, ed 4, Philadelphia, 1998, WB Saunders, p. 470.)*

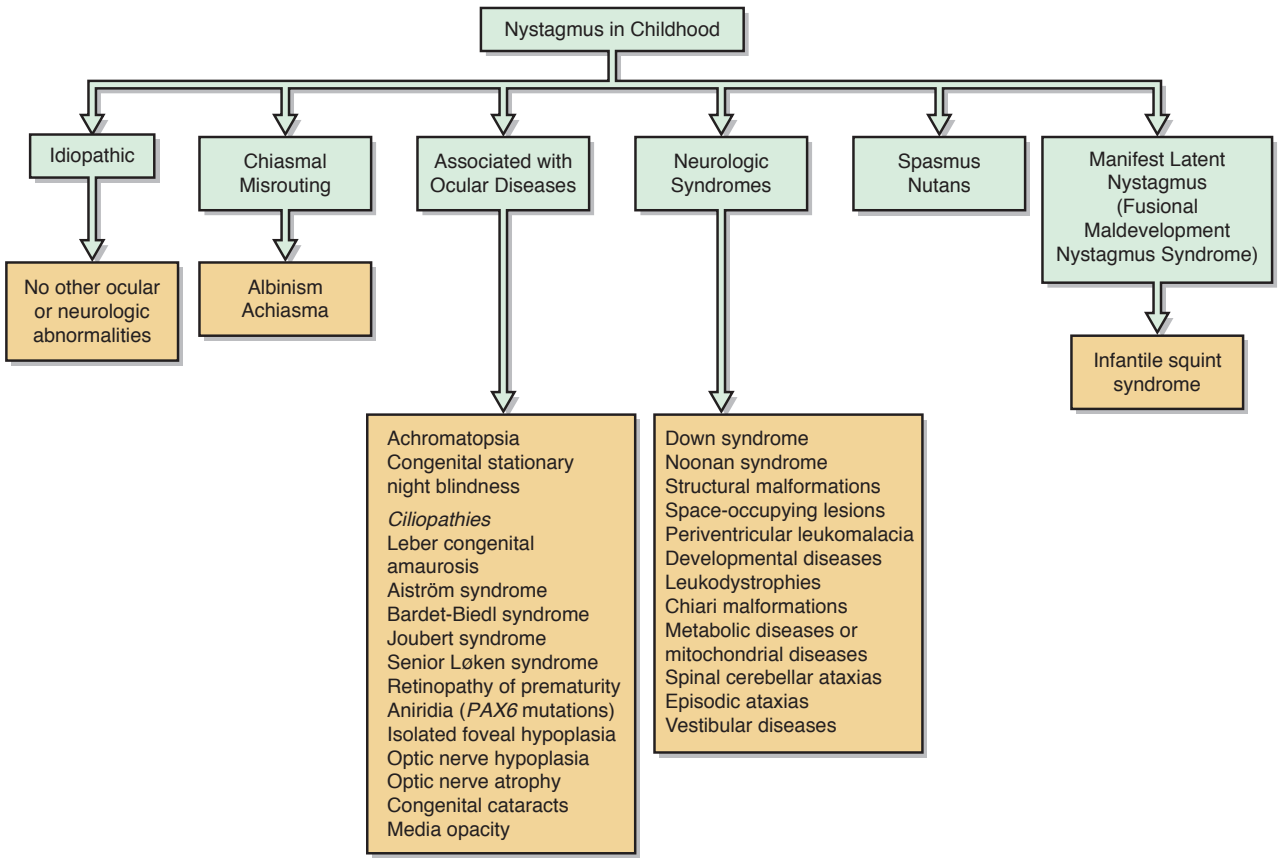

Figure 623-8 Classification of nystagmus based on associated diseases. *(From Hoyt CS, Taylor D, editors:* Pediatric ophthalmology and strabismus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 89.2, p. 910.)*

Table 626-1 The Red Eye

CONDITION	ETIOLOGY	SIGNS AND SYMPTOMS	TREATMENT
Bacterial conjunctivitis	*Haemophilus influenzae, Haemophilus aegyptius, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis*	Mucopurulent unilateral or bilateral discharge, normal vision, photophobia	Topical antibiotics, parenteral ceftriaxone for gonococcus, *H. influenzae*
Hyperacute bacterial conjunctivitis	*Neisseria gonorrhoeae, Neisseria meningitides*	Conjunctival injection and edema (chemosis); gritty sensation	
Viral conjunctivitis	Adenovirus, ECHO virus, coxsackievirus, herpes simplex virus	As above; may be hemorrhagic, unilateral	Self-limited
Neonatal conjunctivitis	*Chlamydia trachomatis*, gonococcus, chemical (silver nitrate), *S. aureus*	Palpebral conjunctival follicle or papillae; as above	Ceftriaxone for gonococcus and erythromycin for *C. trachomatis*
Allergic conjunctivitis	Seasonal pollens or allergen exposure	Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae	Antihistamines, topical mast cell stabilizers or prostaglandin inhibitors, steroids
Keratitis	Herpes simplex virus, adenovirus, *S. pneumoniae, S. aureus, Pseudomonas, Acanthamoeba*, chemicals	Severe pain, corneal swelling, clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection	Specific antibiotics for bacterial/fungal infections; keratoplasty, acyclovir for herpes
Endophthalmitis	*S. aureus, S. pneumoniae, Candida albicans*, associated surgery or trauma	Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze	Antibiotics
Anterior uveitis (iridocyclitis)	JIA, postinfectious with arthritis and rash, sarcoidosis, Behçet disease, Kawasaki disease, inflammatory bowel disease	Unilateral/bilateral; erythema, ciliary flush, irregular pupil, iris adhesions; pain, photophobia, small pupil, poor vision	Topical steroids, plus therapy for primary disease
Posterior uveitis (choroiditis)	Toxoplasmosis, histoplasmosis, *Toxocara canis*	No signs of erythema, decreased vision	Specific therapy for pathogen
Episcleritis/scleritis	Idiopathic autoimmune disease (e.g., SLE, Henoch-Schönlein purpura)	Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation	Episcleritis is self-limiting; topical steroids for fast relief
Foreign body	Occupational exposure	Unilateral, red, gritty feeling; visible or microscopic size	Irrigation, removal; check for ulceration
Blepharitis	*S. aureus, Staphylococcus epidermidis*, seborrheic, blocked lacrimal duct; rarely molluscum contagiosum, *Phthirus pubis, Pediculus capitis*	Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins	Topical antibiotics, warm compresses, lid hygiene
Dacryocystitis	Obstructed lacrimal sac: *S. aureus, H. influenzae*, pneumococcus	Pain, tenderness, erythema, and exudates in area of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis	Systemic, topical antibiotics; surgical drainage
Dacryoadenitis	*S. aureus, Streptococcus*, CMV, measles, EBV, enteroviruses; trauma, sarcoidosis, leukemia	Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis	Systemic antibiotics; drainage of orbital abscesses
Orbital cellulitis (postseptal cellulitis)	Paranasal sinusitis: *H. influenzae, S. aureus, S. pneumoniae*, streptococci Trauma: *S. aureus* Fungi: *Aspergillus, Mucor* spp. if immunodeficient	Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, ophthalmoplegia, fever, lid edema, leukocytosis	Systemic antibiotics, drainage of orbital abscesses
Periorbital cellulitis (preseptal cellulitis)	Trauma: *S. aureus*, streptococci Bacteremia: pneumococcus, streptococci, *H. influenzae, S. aureus*	Cutaneous erythema, warmth, normal vision, minimal involvement of orbit; fever, leukocytosis, toxic appearance	Systemic antibiotics

CMV, cytomegalovirus; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.
From Behrman R, Kliegman R: Nelson's essentials of pediatrics, *ed 3, Philadelphia, 1998, WB Saunders.*

Table 626-2 Topical Antibiotics Used to Treat Bacterial Conjunctivitis: Adult Dosages

DRUG	DOSAGE
Bacitracin (AK-Tracin, Bacticin) ointment	Apply 0.5 inch in eye q3-4h
Ciprofloxacin (Ciloxan) 0.3% ophthalmic solution	1-2 gtt in eye q15min × 6h, then q30min × 18h, then q1h × 1 day, then q4h × 12 days*
Gatifloxacin (Zymar) 0.3% ophthalmic solution	1 gt in eye q2h up to 8 × per day × 2 days, then 1 gt qid × 5 days
Gentamicin (Gentak, Gentasol) 0.3% ophthalmic solution or ointment	Ointment: 0.5 inch applied to eye 2-3 × per day Solution: 1-2 gtt in eye q4h
Levofloxacin (Quixin) 0.5% ophthalmic solution	1-2 gtt in eye q2h × 2 days while awake, then q4h × 5 days while awake
Moxifloxacin (Vigamox) 0.5% ophthalmic solution	1 gt in eye tid × 7 days
Neomycin/polymyxin B/gramicidin (Neosporin) ophthalmic solution	1-2 gtt in eye q4h × 7-10 days
Ofloxacin (Ocuflox) 0.3% ophthalmic solution	1-2 gtt in eye q2-4h × 2 days, then 1-2 gtt in eye qid × 5 days
Polymyxin B and trimethoprim (Polytrim) ophthalmic solution	1 gt in eye q3h × 7-10 days
Sulfacetamide (Isopto Cetamide, Ocusulf-10, Sodium Sulamyd, Sulf-10, AK-Sulf) 10% ophthalmic solution, ointment	Ointment: 0.5-inch ribbon in eye q3-4h and qhs × 7 days Solution: 1-2 gtt in eye q2-3h × 7-10 days
Tobramycin (AK-Tob, Tobrex) 0.3% ophthalmic solution	1-2 gtt in eye q4h

*

Table 623-2 Specific Patterns of Nonnystagmus Eye Movements

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Opsoclonus	Multidirectional conjugate movements of varying rate and amplitude	Hydrocephalus, diseases of brainstem and cerebellum, neuroblastoma, paraneoplasia syndrome
Ocular dysmetria	Overshoot of eyes on rapid fixation	Cerebellar dysfunction
Ocular flutter	Horizontal oscillations with forward gaze and sometimes with blinking	Cerebellar disease, hydrocephalus, or central nervous system neoplasm
Ocular bobbing	Downward jerk from primary gaze, remains for a few sec, then drifts back	Pontine disease
Ocular myoclonus	Rhythmic to-and-fro pendular oscillations of the eyes, with synchronous nonocular muscle movement	Damage to red nucleus, inferior olivary nucleus, and ipsilateral dentate nucleus

Table 627-1 STUMPED: Differential Diagnosis of Neonatal Corneal Opacities

DIAGNOSIS	LATERALITY	OPACITY	OCULAR PRESSURE	OTHER OCULAR ABNORMALITIES	NATURAL HISTORY	INHERITANCE
S—Sclerocornea	Unilateral or bilateral	Vascularized, blends with sclera, clearer centrally	Normal (or elevated)	Cornea plana	Nonprogressive	Sporadic
T—Tears in endothelium and Descemet membrane						
Birth trauma	Unilateral	Diffuse edema	Normal	Possible hyphema, periorbital ecchymoses	Spontaneous improvement in 1 mo	Sporadic
Infantile glaucoma	Bilateral	Diffuse edema	Elevated	Megalocornea, photophobia and tearing, abnormal angle	Progressive unless treated	Autosomal recessive
U—Ulcers						
Herpes simplex keratitis	Unilateral	Diffuse with geographic epithelial defect	Normal	None	Progressive	Sporadic
Congenital rubella	Bilateral	Disciform or diffuse edema, no frank ulceration	Normal or elevated	Microphthalmos, cataract, pigment epithelial mottling	Stable, may clear	Sporadic
Neurotrophic exposure	Unilateral or bilateral	Central ulcer	Normal	Lid anomalies, congenital sensory neuropathy	Progressive	Sporadic
M—Metabolic (rarely present at birth) (mucopolysaccharidoses IH, IS; mucolipidosis type IV)*	Bilateral	Diffuse haze, denser peripherally	Normal	Few	Progressive	Autosomal dominant
P—Posterior corneal defect	Unilateral or bilateral	Central, diffuse haze or vascularized leukoma	Normal or elevated	Anterior chamber cleavage syndrome	Stable, sometimes early clearing or vascularization	Sporadic, autosomal recessive
E—Endothelial dystrophy						
Congenital hereditary endothelial dystrophy	Bilateral	Diffuse corneal edema, marked corneal thickening	Normal	None	Stable	Autosomal dominant or recessive
Posterior polymorphous dystrophy	Bilateral	Diffuse haze, normal corneal thickness	Normal	Occasional peripheral anterior synechiae	Slowly progressive	Autosomal dominant
Congenital hereditary stromal dystrophy	Bilateral	Flaky, feathery stromal opacities; normal corneal thickness	Normal	None	Stable	Autosomal dominant
D—Dermoid	Unilateral or bilateral	White vascularized mass, hair, lipid arc	Normal	None	Stable	Sporadic

*Mucopolysaccharidosis IH (Hurler syndrome); mucopolysaccharidosis IS (Scheie syndrome).
From Nelson LB, Calhoun JH, Harley RD: Pediatric ophthalmology, *ed 3, Philadelphia, 1991, WB Saunders, p. 210.*

Table 628-1 Differential Diagnosis of Cataracts

DEVELOPMENTAL VARIANTS
Prematurity (Y-suture vacuoles) with or without retinopathy of prematurity
Mittendorf dot (remnant of hyaloid artery)
Persistent pupillary membrane (remnant of embryonic lens vasculature)

GENETIC DISORDERS
Simple Mendelian Inheritance
Autosomal dominant (most common)
Autosomal recessive
X-linked
Major Chromosomal Defects
Trisomy disorders (13, 18, 21)
Turner syndrome (45X)
Deletion syndromes (11p13, 18p, 18q)
Duplication syndromes (3q, 20p, 10q)
Multisystem Genetic Disorders
Alport syndrome (hearing loss, renal disease)
Alström syndrome (nerve deafness, diabetes mellitus)
Apert disease (craniosynostosis, syndactyly)
Cerebrooculofacial syndrome
Cockayne syndrome (premature senility, skin photosensitivity)
Conradi disease (chondrodysplasia punctata)
Crouzon disease (dysostosis craniofacialis)
Ectodermal dysplasia
Hallermann-Streiff syndrome (microphthalmia, small pinched nose, skin atrophy, and hypotrichosis)
Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis)
Ichthyosis (keratinizing disorder with thick, scaly skin)
Incontinentia pigmenti (dental anomalies, mental retardation, cutaneous lesions)
Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal disease)
Marfan syndrome
Meckel-Gruber syndrome (renal dysplasia, encephalocele)
Myotonic dystrophy
Nail–patella syndrome (renal dysfunction, dysplastic nails, hypoplastic patella)
Marinesco-Sjögren syndrome (cerebellar ataxia, hypotonia)
Nevoid basal cell carcinoma syndrome (autosomal dominant, basal cell carcinoma erupts in childhood)
Peters anomaly (corneal opacifications with iris-corneal dysgenesis)
Progeria
Rieger syndrome (iris dysplasia, myotonic dystrophy)
Rothmund-Thomson syndrome (poikiloderma: skin atrophy)
Rubinstein-Taybi syndrome (broad great toe, mental retardation)
Smith-Lemli-Opitz syndrome (toe syndactyly, hypospadias, mental retardation)
Sotos syndrome (cerebral gigantism)
Spondyloepiphyseal dysplasia (dwarfism, short trunk)
Werner syndrome (premature aging in 2nd decade of life)
Inborn Errors of Metabolism
Abetalipoproteinemia (absent chylomicrons, retinal degeneration)
Fabry disease (α-galactosidase A deficiency)
Galactokinase deficiency
Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Homocystinemia (subluxation of lens, mental retardation)
Infantile neuronal ceroid lipofuscinosis
Mannosidosis (acid α-mannosidase deficiency)
Niemann-Pick disease (sphingomyelinase deficiency)
Refsum disease (phytanic acid α-hydrolase deficiency)
Wilson disease (accumulation of copper leads to cirrhosis and neurologic symptoms)
Zellweger syndrome

ENDOCRINOPATHIES
Hypocalcemia (hypoparathyroidism)
Hypoglycemia
Diabetes mellitus

CONGENITAL INFECTIONS
Toxoplasmosis
Cytomegalovirus infection
Syphilis
Rubella
Perinatal herpes simplex infection
Measles (rubeola)
Poliomyelitis
Influenza
Varicella-zoster

OCULAR ANOMALIES
Microphthalmia
Coloboma
Aniridia
Mesodermal dysgenesis
Persistent pupillary membrane
Posterior lenticonus
Persistent fetal vasculature
Primitive hyaloid vascular system
Retinitis pigmentosa

MISCELLANEOUS DISORDERS
Atopic dermatitis
Drugs (corticosteroids)
Radiation
Trauma
Juvenile idiopathic arthritis
Retinopathy of prematurity

IDIOPATHIC

Table 629-1 Uveitis in Childhood

ANTERIOR UVEITIS
Juvenile idiopathic arthritis (pauciarticular)
Sarcoidosis
Trauma
Tuberculosis
Kawasaki disease
Ulcerative colitis
Crohn syndrome
Postinfectious (enteric or genital) with arthritis and rash
Spirochetal (syphilis, leptospiral)
Brucellosis
Heterochromic iridocyclitis (Fuchs)
Viral (herpes simplex, herpes zoster)
Ankylosing spondylitis
Stevens-Johnson syndrome
Chronic infantile neurologic cutaneous arthritis syndrome (CINCA)
Familial Mediterranean fever
Hyperimmunoglobulin D syndrome
Tumor necrosis factor receptor–associated periodic syndrome
Muckle-Wells syndrome
Blau syndrome
Psoriasis
Multiple sclerosis
Cyclic neutropenia
Chronic granulomatous disease
X-linked lymphoproliferative disease
Hypocomplementemic vasculitis
Idiopathic
Drugs
POSTERIOR UVEITIS (CHOROIDITIS—MAY INVOLVE RETINA)
Toxoplasmosis
Toxocariasis
Parasites (toxocariasis)
Sarcoidosis
Cat-scratch disease
Tuberculosis
Viral (rubella, herpes simplex, HIV, cytomegalovirus, West Nile)
Subacute sclerosing panencephalitis
Tubulointestinal nephritis and uveitis syndrome
Idiopathic
ANTERIOR AND/OR POSTERIOR UVEITIS
Sympathetic ophthalmia (trauma to other eye)
Vogt-Koyanagi-Harada syndrome (uveootocutaneous syndrome: poliosis, vitiligo, deafness, tinnitus, uveitis, aseptic meningitis, retinitis)
Behçet syndrome
Lyme disease

Table 634-1 Chandler Classification of Orbital Complications of Sinusitis, a Clinical Description

CHANDLER CLASS	STAGE	CLINICAL DESCRIPTION AND DEFINITION
I	Inflammatory edema	Eyelid edema and erythema Normal extraocular movement Normal visual acuity
II	Orbital cellulitis	Diffuse edema of orbital contents without discrete abscess formation
III	Subperiosteal abscess	Collection of purulent exudate* beneath periosteum of lamina papyracea Displacement of globe downward/laterally
IV	Orbital abscess	Purulent collection within orbit* Proptosis Chemosis Ophthalmoplegia Decreased vision
V	Cavernous sinus thrombosis	Bilateral eye findings Prostration Meningismus

*The radiographic correlation of a subperiosteal or orbital abscess seen with CT is a contrast-enhancing mass in the extraconal or intraconal space, possibly with areas of cavitation, because purulence cannot be determined with CT scanning.

Table 629-2 Examination Schedule for Children with JIA Without Known Iridocyclitis

	AGE OF ONSET	
JIA SUBTYPE	**≤6 yr**	**>6 yr**
OLIGOARTHRITIS OR POLYARTHRITIS		
Positive ANA		
Less than 4 yr duration	Every 3 mo	Every 6 mo
4-7 yr duration	Every 6 mo	Annually
More than 7 yr duration	Annually	Annually
Negative ANA		
Less than 4 yr duration	Every 6 mo	Annually
4-7 yr duration	Annually	Annually
More than 7 yr duration	Annually	Annually
Systemic	Annually regardless of duration	Annually regardless of duration

Table 632-1 Primary and Secondary Childhood Glaucomas

I. PRIMARY GLAUCOMAS
A. Congenital open-angle glaucoma
  1. Congenital
  2. Infantile
  3. Late recognized
B. Autosomal dominant juvenile glaucoma
C. Primary angle-closure glaucoma
D. Associated with systemic abnormalities
  1. Sturge-Weber syndrome
  2. Neurofibromatosis type 1 (NF-1)
  3. Stickler syndrome
  4. Oculocerebrorenal (Lowe) syndrome
  5. Rieger syndrome
  6. Hepatocerebrorenal syndrome
  7. Marfan syndrome
  8. Rubinstein-Taybi syndrome
  9. Infantile glaucoma associated with mental retardation and paralysis
  10. Oculodentodigital dysplasia
  11. Open-angle glaucoma associated with microcornea and absence of frontal sinuses
  12. Mucopolysaccharidosis
  13. Trisomy 13
  14. Cutis marmorata telangiectasia congenita
  15. Warburg syndrome
  16. Kniest syndrome (skeletal dysplasia)
  17. Michel syndrome
  18. Nonprogressive hemiatrophy
E. Associated with ocular abnormalities
  1. Congenital glaucoma with iris and pupillary abnormalities
  2. Aniridia
    a. Congenital glaucoma
    b. Acquired glaucoma
  3. Congenital ocular melanosis
  4. Sclerocornea
  5. Iridotrabecular dysgenesis
  6. Peters syndrome
  7. Iridotrabecular dysgenesis and ectropion uveae
  8. Posterior polymorphous dystrophy
  9. Idiopathic or familial elevated episcleral venous pressure
  10. Anterior corneal staphyloma
  11. Congenital microcornea with myopia
  12. Congenital hereditary endothelial dystrophy
  13. Congenital hereditary iris stromal hypoplasia

II. SECONDARY GLAUCOMAS
A. Traumatic glaucoma
  1. Acute glaucoma
    a. Angle concussion
    b. Hyphema
    c. Ghost cell glaucoma
  2. Late-onset glaucoma with angle recession
  3. Arteriovenous fistula
B. Secondary to intraocular neoplasm
  1. Retinoblastoma
  2. Juvenile xanthogranuloma
  3. Leukemia
  4. Melanoma
  5. Melanocytoma
  6. Iris rhabdomyosarcoma
  7. Aggressive nevi of the iris
C. Secondary to uveitis
  1. Open-angle glaucoma
  2. Angle-blockage glaucoma
    a. Synechial angle closure
    b. Iris bombé with pupillary block
D. Lens-induced glaucoma
  1. Subluxation–dislocation and pupillary block
    a. Marfan syndrome
    b. Homocystinuria
  2. Spherophakia and pupillary block
  3. Phacolytic glaucoma
E. Secondary to surgery for congenital cataract
  1. Lens material blockage of the trabecular meshwork (acute or subacute)
  2. Pupillary block
  3. Chronic open-angle glaucoma associated with angle defects
F. Steroid-induced glaucoma
G. Secondary to rubeosis
  1. Retinoblastoma
  2. Coats disease
  3. Medulloepithelioma
  4. Familial exudative vitreoretinopathy
H. Secondary angle-closure glaucoma
  1. Retinopathy of prematurity
  2. Microphthalmos
  3. Nanophthalmos
  4. Retinoblastoma
  5. Persistent hyperplastic primary vitreous
  6. Congenital pupillary iris–lens membrane
I. Glaucoma associated with increased venous pressure
  1. Carotid or dural-venous fistula
  2. Orbital disease
J. Secondary to maternal rubella
K. Secondary to intraocular infection
  1. Acute recurrent toxoplasmosis
  2. Acute herpetic iritis

From Nelson LB: Harley's pediatric ophthalmology, *ed 4, Philadelphia, 1998, WB Saunders, p. 294.*

Table 637-9 Recommended Pneumococcal Vaccination Schedule for Persons with Cochlear Implants

AGE AT FIRST PCV13 DOSE (mo)*	PCV12 PRIMARY SERIES	PCV13 ADDITIONAL DOSE	PPV23 DOSE
2-6	3 doses, 2 mo apart†	1 dose at 12-15 mo of age‡	Indicated at ≥24 mo of age§
7-11	2 doses, 2 mo apart†	1 dose at 12-15 mo of age‡	Indicated at ≥24 mo of age§
12-23	2 doses, 2 mo apart¶	Not indicated	Indicated at ≥24 mo of age§
24-59	2 doses, 2 mo apart¶	Not indicated	Indicated§
≥60	Not indicated‖	Not indicated‖	Indicated

*A schedule with a reduced number of total 13-valent pneumococcal conjugate vaccine (PCV13) doses is indicated if children start late or are incompletely vaccinated. Children with a lapse in vaccination should be vaccinated according to the catch-up schedule (see Chapter 182).
†For children vaccinated at younger than age 1 yr, minimum interval between doses is 4 wk.
‡The additional dose should be administered 8 wk or more after the primary series has been completed.
§Children younger than age 5 yr should complete the PCV13 series first; 23-valent pneumococcal polysaccharide vaccine (PPV23) should be administered to children 24 mo of age or older 8 wk or more after the last dose of PCV13 (see Chapter 182). (Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR Recomm Rep* 49[RR-9]:1–35, 2000, and Licensure of a 13-valent pneumococcal conjugate vaccine [PCV13] and recommendations for use among children—Advisory Committee on Immunization Practices [ACIP], 2010, *MMWR Morb Mortal Wkly Rep* 59(9);258–261, 2010.)
¶Minimum interval between doses is 8 wk.
‖PCV13 is not recommended generally for children age 5 yr or older.
PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.
From Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Pneumococcal vaccination for cochlear implant candidates and recipients: Updated recommendations of the Advisory Committee on Immunization Practices, MMWR Morb Mortal Wkly Rep *52(31):739–740, 2003.*

The Ear

Table 637-1 Indicators Associated with Hearing Loss

INDICATORS ASSOCIATED WITH SENSORINEURAL AND/OR CONDUCTIVE HEARING LOSS
Neonates (Birth-28 Days) When Universal Screening Is Not Available
Family history of hereditary childhood sensorineural hearing loss
In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis
Craniofacial anomalies, including those with morphologic abnormalities of the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
Birthweight <1500 g (3.3 lb)
Hyperbilirubinemia at a serum level requiring exchange transfusion
Ototoxic medications, including but not limited to the aminoglycosides, used in multiple courses or in combination with loop diuretics
Bacterial meningitis
Apgar scores of 0-4 at 1 min or 0-6 at 5 min
Mechanical ventilation lasting ≥5 days; extracorporeal membrane oxygenation
Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; white forelock
Infants and Toddlers (Age 29 Days-2 Yr) When Certain Health Conditions Develop That Require Rescreening
Parent or caregiver concern regarding hearing, speech, language, and/or developmental delay
Bacterial meningitis and other infections associated with sensorineural hearing loss
Head trauma associated with loss of consciousness or skull fracture
Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; neurofibromatosis, osteopetrosis, and Usher Hunter, Waardenburg, Alport, Pendred, or Jervell and Lange-Nielsen syndrome
Ototoxic medications, including but not limited to chemotherapeutic agents or aminoglycosides used in multiple courses or in combination with loop diuretics
Recurrent or persistent otitis media with effusion for 3 mo or longer
Skeletal dysplasia
Infants and Toddlers (Age 29 Days-3 Yr) Who Require Periodic Monitoring of Hearing
Some newborns and infants pass initial hearing screening but require periodic monitoring of hearing to detect delayed-onset sensorineural and/or conductive hearing loss. Infants with these indicators require hearing evaluation at least every 6 mo until age 3 yr, and at appropriate intervals thereafter
INDICATORS ASSOCIATED WITH DELAYED-ONSET SENSORINEURAL HEARING LOSS
Family history of hereditary childhood hearing loss
In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis
Neurofibromatosis type 2 and neurodegenerative disorders
Cogan syndrome (vasculitis: keratitis, uveitis, vertigo, arthritis, dermatitis)
INDICATORS ASSOCIATED WITH CONDUCTIVE HEARING LOSS
Recurrent or persistent otitis media with effusion
Anatomic deformities and other disorders that affect eustachian tube function
Neurodegenerative disorders

Note: At all ages, parents' concern about hearing loss must be taken seriously even in the absence of risk factors.
Adapted from American Academy of Pediatrics, Joint Committee on Infant Hearing: Joint Committee on Infant Hearing 1994 position statement, Pediatrics *95:152, 1995.*

Table 637-2 Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss

LOCUS	GENE	AUDIO PHENOTYPE
DFN3	*POU3F4*	Conductive hearing loss as a result of stapes fixation mimicking otosclerosis; superimposed progressive SNHL
DFNA1	*DIAPH1*	Low-frequency loss beginning in the 1st decade and progressing to all frequencies to produce a flat audio profile with profound losses throughout the auditory range
DFNA2	*KCNQ4*	Symmetric high-frequency sensorineural loss beginning in the 1st decade and progressing over all frequencies
	GJB3	Symmetric high-frequency sensorineural loss beginning in the 3rd decade
DFNA3	*GJB2*	Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment
	GJB6	Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment
DFNA6, 14, and 38	*WFS1*	Early-onset low-frequency sensorineural loss; approximately 75% of families dominantly segregating this audio profile carry missense mutations in the C-terminal domain of wolframin
DFNA8, and 12	*TECTA*	Early-onset stable bilateral hearing loss, affecting mainly mid to high frequencies
DFNA10	*EYA4*	Progressive loss beginning in the 2nd decade as a flat to gently sloping audio profile that becomes steeply sloping with age
DFNA11	*MYO7A*	Ascending audiogram affecting low and middle frequencies at young ages and then affecting all frequencies with increasing age
DFNA13	*COL11A2*	Congenital midfrequency sensorineural loss that shows age-related progression across the auditory range
DFNA15	*POU4F3*	Bilateral progressive sensorineural loss beginning in the 2nd decade

Table 637-2 Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss—cont'd

LOCUS	GENE	AUDIO PHENOTYPE
DFNA20, and 26	*ACTG1*	Bilateral progressive sensorineural loss beginning in the 2nd decade; with age, the loss increases with threshold shifts in all frequencies, although a sloping configuration is maintained in most cases
DFNA22	*MYO6*	Postlingual, slowly progressive, moderate to severe hearing loss
DFNB1	*GJB2, GJB6*	Hearing loss varies from mild to profound. The most common genotype, 35delG/35delG, is associated with severe to profound SNHL in about 90% of affected children; severe to profound deafness is observed in only 60% of children who are compound heterozygotes carrying 1 35delG allele and any other *GJB2* SNHL-causing allele variant; in children carrying 2 *GJB2* SNHL-causing missense mutations, severe to profound deafness is not observed
DFNB3	*MYO7A*	Severe to profound sensorineural hearing loss
DFNB4	*SLC26A4*	DFNB4 and Pendred syndrome (see Table 637-3) are allelic. DFNB4 hearing loss is associated with dilation of the vestibular aqueduct and can be unilateral or bilateral. In the high frequencies, the loss is severe to profound; in the low frequencies, the degree of loss varies widely. Onset can be congenital (prelingual), but progressive postlingual loss also is common
DFNB7, and 11	*TMC1*	Severe-to-profound prelingual hearing impairment
DFNB9	*OTOF*	*OTOF*-related deafness is characterized by 2 phenotypes: prelingual nonsyndromic hearing loss and, less frequently, temperature-sensitive nonsyndromic auditory neuropathy. The nonsyndromic hearing loss is bilateral severe-to-profound congenital deafness
DFNB12	*CDH23*	Depending on the type of mutation, recessive mutations of *CDH23* can cause nonsyndromic deafness or type 1 Usher syndrome (USH1), which is characterized by deafness, vestibular areflexia, and vision loss as a result of retinitis pigmentosa
DFNB16	*STRC*	Early-onset nonsyndromic autosomal recessive sensorineural hearing loss
mtDNA 1555A > G	*12S rRNA*	Degree of hearing loss varies from mild to profound but usually is symmetric; high frequencies are preferentially affected; precipitous loss in hearing can occur after aminoglycoside therapy

SNHL, sensorineural hearing loss.
Adapted from Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children, Lancet *365:879–890, 2005.*

Table 637-3 Common Types of Syndromic Sensorineural Hearing Loss

SYNDROME	GENE	PHENOTYPE
DOMINANT		
Waardenburg (WS1)	*PAX3*	Major diagnostic criteria include dystopia canthorum, congenital hearing loss, heterochromic irises, white forelock, and an affected 1st-degree relative. Approximately 60% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Waardenburg (WS2)	*MITF*, others	Major diagnostic criteria are as for WS1 but without dystopia canthorum. Approximately 80% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Branchiootorenal	*EYA1*	Diagnostic criteria include hearing loss (98%), preauricular pits (85%), and branchial (70%), renal (40%), and external-ear (30%) abnormalities. The hearing loss can be conductive, sensorineural, or mixed, and mild to profound in degree.
CHARGE syndrome	*CHD7*	Choanal atresia, colobomas, heart defect, retardation, genital hypoplasia, ear anomalies, deafness. Can lead to sensorineural or mixed hearing loss. Can be autosomal dominant or isolated cases.
Goldenhar syndrome	Unknown	Part of the hemifacial microsomia spectrum. Facial hypoplasia, ear anomalies, hemivertebrae, parotid gland dysfunction. Can cause conductive or mixed hearing loss. Can be autosomal dominant or sporadic.
RECESSIVE		
Pendred syndrome	*SLC26A4*	Diagnostic criteria include sensorineural hearing loss that is congenital, nonprogressive, and severe to profound in many cases, but can be late-onset and progressive; bilateral dilation of the vestibular aqueduct with or without cochlear hypoplasia; and an abnormal perchlorate discharge test or goiter.
Alport syndrome	*COL4A3, COL4A4,* and *COL4A5*	Nephritis, deafness, lens defects, retinitis. Can lead to bilateral sensorineural hearing loss in the 2,000-8,000 Hz range. The hearing loss develops gradually and is not generally present in early infancy.
Usher syndrome type 1 (USH1)	*USH1A, MYO7A, USH1C, CDH23, USH1E, PCDH15, USH1G*	Diagnostic criteria include congenital, bilateral, and profound hearing loss, vestibular areflexia, and retinitis pigmentosa (commonly not diagnosed until tunnel vision and nyctalopia become severe enough to be noticeable).
Usher syndrome type 2 (USH2)	*USH2A, USH2B, USH2C,* others	Diagnostic criteria include mild to severe, congenital, bilateral hearing loss and retinitis pigmentosa; hearing loss may be perceived as progressing over time because speech perception decreases as diminishing vision interferes with subconscious lip reading.
Usher syndrome type 3 (USH3)	*USH3*	Diagnostic criteria include postlingual, progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable impairment of vestibular function.

Adapted from Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children, Lancet *365:879–890, 2005.*

Table 637-5 Hearing Handicap as a Function of Average Hearing Threshold Level of the Better Ear

AVERAGE THRESHOLD LEVEL (dB) AT 500-2,000 Hz (ANSI)	DESCRIPTION	COMMON CAUSES	WHAT CAN BE HEARD WITHOUT AMPLIFICATION	DEGREE OF HANDICAP (IF NOT TREATED IN 1ST YR OF LIFE)	PROBABLE NEEDS
0-15	Normal range	Conductive hearing loss	All speech sounds	None	None
16-25	Slight hearing loss	Otitis media, TM perforation, tympanosclerosis; eustachian tube dysfunction; some SNHL	Vowel sounds heard clearly, may miss unvoiced consonant sounds	Mild auditory dysfunction in language learning Difficulty in perceiving some speech sounds	Consideration of need for hearing aid, speech reading, auditory training, speech therapy, appropriate surgery, preferential seating
26-30	Mild	Otitis media, TM perforation, tympanosclerosis, severe eustachian dysfunction, SNHL	Hears only some speech sounds, the louder voiced sounds	Auditory learning dysfunction Mild language retardation Mild speech problems Inattention	Hearing aid Lip reading Auditory training Speech therapy Appropriate surgery
31-50	Moderate hearing loss	Chronic otitis, ear canal/middle ear anomaly, SNHL	Misses most speech sounds at normal conversational level	Speech problems Language retardation Learning dysfunction Inattention	All of the above, plus consideration of special classroom situation
51-70	Severe hearing loss	SNHL or mixed loss due to a combination of middle-ear disease and sensorineural involvement	Hears no speech sound of normal conversations	Severe speech problems Language retardation Learning dysfunction Inattention	All of the above; probable assignment to special classes
71+	Profound hearing loss	SNHL or mixed	Hears no speech or other sounds	Severe speech problems Language retardation Learning dysfunction Inattention	All of the above; probable assignment to special classes or schools

ANSI, American National Standards Institute; SNHL, sensorineural hearing loss; TM, tympanic membrane.
Modified from Northern JL, Downs MP: Hearing in children, *ed 4, Baltimore, 1991, Williams & Wilkins.*

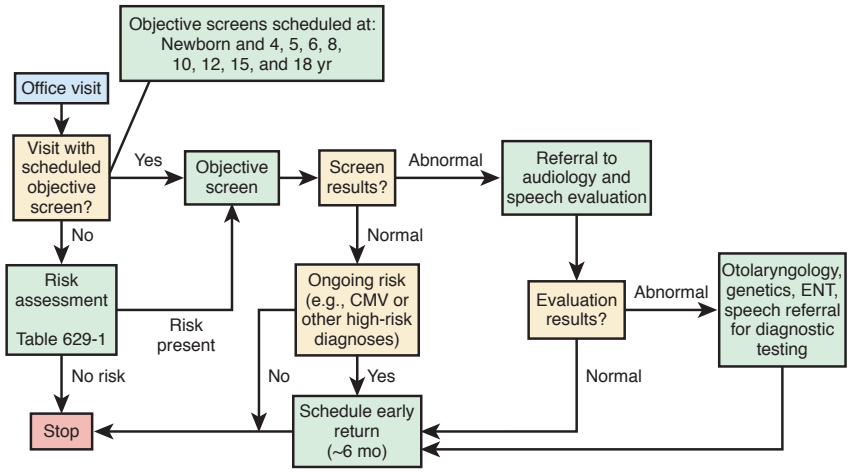

Figure 637-2 Hearing-assessment algorithm within an office visit. CMV, cytomegalovirus; ENT, ear, nose, and throat. *(From Harlor AD Jr, Bower C: Clinical report—hearing assessment in infants and children: recommendations beyond neonatal screening,* Pediatrics *124:1252–1263, 2009, Fig. 1, p. 1254.)*

Table 637-6 Criteria for Referral for Audiologic Assessment

AGE (mo)	REFERRAL GUIDELINES FOR CHILDREN WITH "SPEECH" DELAY
12	No differentiated babbling or vocal imitation
18	No use of single words
24	Single-word vocabulary of ≤10 words
30	<100 words; no evidence of 2 word combinations; unintelligible
36	<200 words; no use of telegraphic sentences; clarity <50%
48	<600 words; no use of simple sentences; clarity ≤80%

From Matkin ND: Early recognition and referral of hearing-impaired children, Pediatr Rev 6:151–156, 1984. Reproduced by permission of Pediatrics.

Table 637-7 Guidelines for Referral of Children with Suspected Hearing Loss

AGE (mo)	NORMAL DEVELOPMENT
0-4	Should startle to loud sounds, quiet to mother's voice, momentarily cease activity when sound is presented at a conversational level
5-6	Should correctly localize to sound presented in a horizontal plane, begin to imitate sounds in own speech repertoire or at least reciprocally vocalize with an adult
7-12	Should correctly localize to sound presented in any plane Should respond to name, even when spoken quietly
13-15	Should point toward an unexpected sound or to familiar objects or persons when asked
16-18	Should follow simple directions without gestural or other visual cues; can be trained to reach toward an interesting toy at midline when a sound is presented
19-24	Should point to body parts when asked; by 21-24 mo, can be trained to perform play audiometry

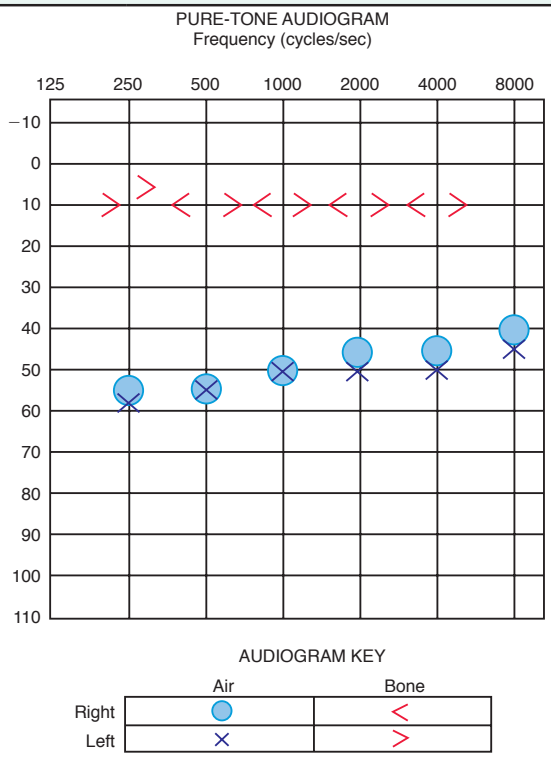

Figure 637-3 Audiogram showing bilateral conductive hearing loss.

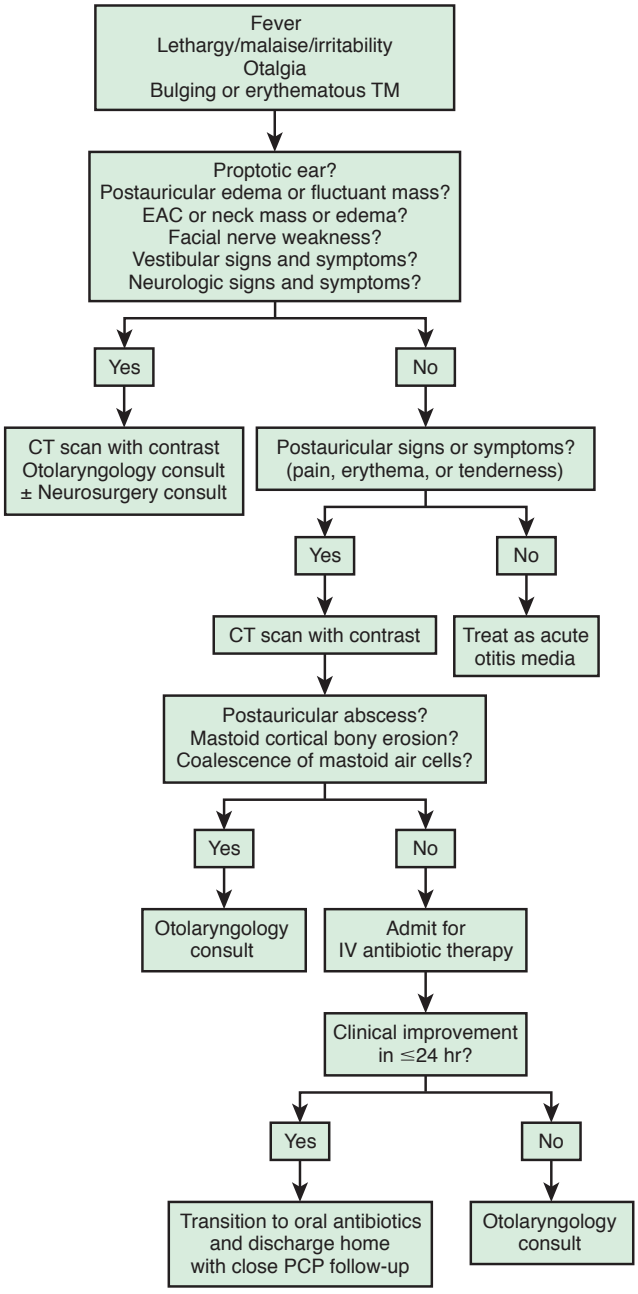

Figure 640-7 Diagnosis and treatment algorithm for cases of sus-pected acute mastoiditis.

Table 640-1 Treatments for Otalgia in Acute Otitis Media

TREATMENT MODALITY	COMMENTS
Acetaminophen, ibuprofen	Effective analgesia for mild to moderate pain. Readily available. Mainstay of pain management for AOM
Home remedies (no controlled studies that directly address effectiveness) Distraction External application of heat or cold Oil drops in external auditory canal	May have limited effectiveness
Benzocaine, procaine, lidocaine (topical)	Additional, but brief, benefit over acetaminophen in patients older than 5 yr
Naturopathic agents	Comparable to amethocaine/phenazone drops in patients older than 6 yr
Homeopathic agents	No controlled studies that directly address pain
Narcotic analgesia with codeine or analogs	Effective for moderate or severe pain. Requires prescription; risk of respiratory depression, altered mental status, gastrointestinal tract upset, and constipation
Tympanostomy/myringotomy	Requires skill and entails potential risk

From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics *131:e964-e999, 2013, Table 3.*

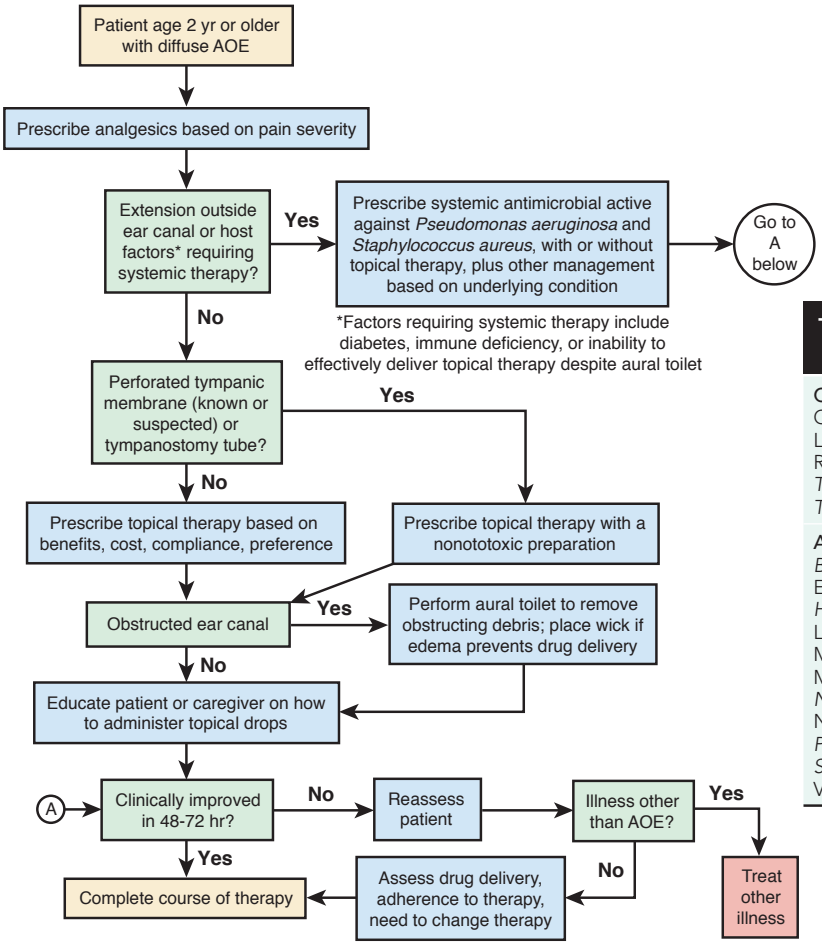

Figure 639-1 Flow chart for managing acute otitis externa (AOE). *(From Rosenfeld RM, Brown L, Cannon CR, et al: Clinical practice guideline: acute otitis externa,* Otolaryngol Head Neck Surg *134:S4–S23, 2006. Copyright 2006 American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc.)*

Table 637-4 Infectious Pathogens Implicated in Sensorineural Hearing Loss in Children

CONGENITAL INFECTIONS
Cytomegalovirus
Lymphocytic choriomeningitis virus
Rubella virus
Toxoplasma gondii
Treponema pallidum
ACQUIRED INFECTIONS
Borrelia burgdorferi
Epstein-Barr virus
Haemophilus influenzae
Lassa virus
Measles virus
Mumps virus
Neisseria meningitidis
Nonpolio enteroviruses
Plasmodium falciparum
Streptococcus pneumoniae
Varicella-zoster virus

Table 640-2 Recommendations for Initial Management for Uncomplicated Acute Otitis Media*

AGE	OTORRHEA WITH AOM*	UNILATERAL OR BILATERAL AOM* WITH SEVERE SYMPTOMS†	BILATERAL AOM* WITHOUT OTORRHEA	UNILATERAL AOM* WITHOUT OTORRHEA
6 mo to 2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation‡

*Applies only to children with well-documented AOM with high certainty of diagnosis.
†A toxic-appearing child, persistent otalgia more than 48 hr, temperature ≥39°C (102.2°F) in the past 48 hr, or if there is uncertain access to follow-up after the visit.
‡This plan of initial management provides an opportunity for shared decision making with the child's family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48-72 hr of AOM onset.
NOTE: For infants younger than age 6 mo, a suspicion of AOM should result in antibiotic therapy.
From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics *131:e964–e999, 2013, Table 4.*

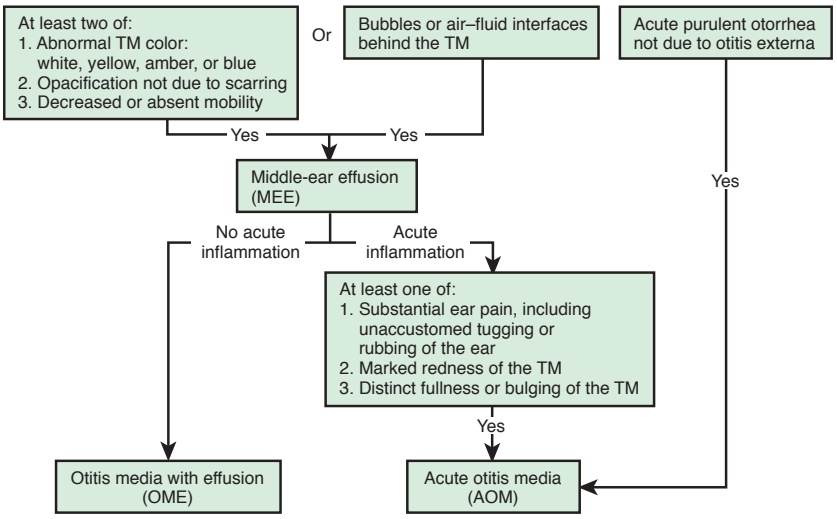

Figure 640-1 Algorithm for distinguishing between acute otitis media and otitis media with effusion. TM, tympanic membrane.

Table 640-3 Recommended Antibiotics for (Initial or Delayed) Treatment and for Patients Who Have Failed Initial Antibiotic Treatment

Initial Immediate or Delayed Antibiotic Treatment		Antibiotic Treatment After 48-72 hr of Failure of Initial Antibiotic Treatment	
RECOMMENDED FIRST-LINE TREATMENT	**ALTERNATIVE TREATMENT (IF PENICILLIN ALLERGY)**	**RECOMMENDED FIRST-LINE TREATMENT**	**ALTERNATIVE TREATMENT**
Amoxicillin (80-90 mg/kg/day in 2 divided doses)	Cefdinir‡ (14 mg/kg/day in 1 or 2 doses)	Amoxicillin-clavulanate* (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate in 2 divided doses)	Ceftriaxone (50 mg IM or IV for 3 days, every other day until clinical improvement; max 3 doses) Clindamycin (30-40 mg/kg/day in 3 divided doses), with or without third-generation cephalosporin
or	Cefuroxime‡ (30 mg/kg/day in 2 divided doses)	or	Failure of second antibiotic
Amoxicillin-clavulanate* (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate [amoxicillin : clavulanate ratio, 14 : 1] in 2 divided doses) or Ceftriaxone (50 mg IM or IV for 3 days, every other day until improvement; max 3 doses)	Cefpodoxime‡ (10 mg/kg/day in 2 divided doses) Ceftriaxone‡ (50 mg IM or IV per day for 1 or 3 days)	Ceftriaxone (50 mg IM or IV for 3 days, every other day until clinical improvement or for a maximum of 3 doses)	Clindamycin (30-40 mg/kg/day in 3 divided doses) with or without third-generation cephalosporin Tympanocentesis† Consult specialist†

IM, intramuscular; IV, intravenous.
*May be considered in patients who have received amoxicillin in the previous 30 days or who have the otitis–conjunctivitis syndrome.
†Perform tympanocentesis/drainage if skilled in the procedure, or seek a consultation from an otolaryngologist for tympanocentesis/drainage. If the tympanocentesis reveals multidrug-resistant bacteria, seek an infectious disease specialist consultation.
‡Cefdinir, cefuroxime, cefpodoxime, and ceftriaxone are highly unlikely to be associated with cross reactivity with penicillin allergy on the basis of their distinct chemical structures.
From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics *131:e964–e999, 2013, Table 5.*

Table 640-5 Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis with Periosteitis/Abscess

	Postauricular Signs and Symptoms					
DISEASE	**CREASE***	**ERYTHEMA**	**MASS**	**TENDERNESS**	**EXTERNAL CANAL INFECTION**	**MIDDLE-EAR EFFUSION**
Acute mastoiditis with periosteitis	May be absent	Yes	No	Usually	No	Usually
Acute mastoiditis with subperiosteal abscess	Absent	Maybe	Yes	Yes	No	Usually
Periosteitis of pinna with postauricular extension	Intact	Yes	No	Usually	No	No
External otitis with postauricular extension	Intact	Yes	No	Usually	Yes	No
Postauricular lymphadenitis	Intact	No	Yes (circumscribed)	Maybe	No	No

*Postauricular crease (fold) between pinna and postauricular area.
From Bluestone CD, Klein JO, editors: Otitis media in infants and children, *ed 3, Philadelphia, 2001, WB Saunders, p. 333.*

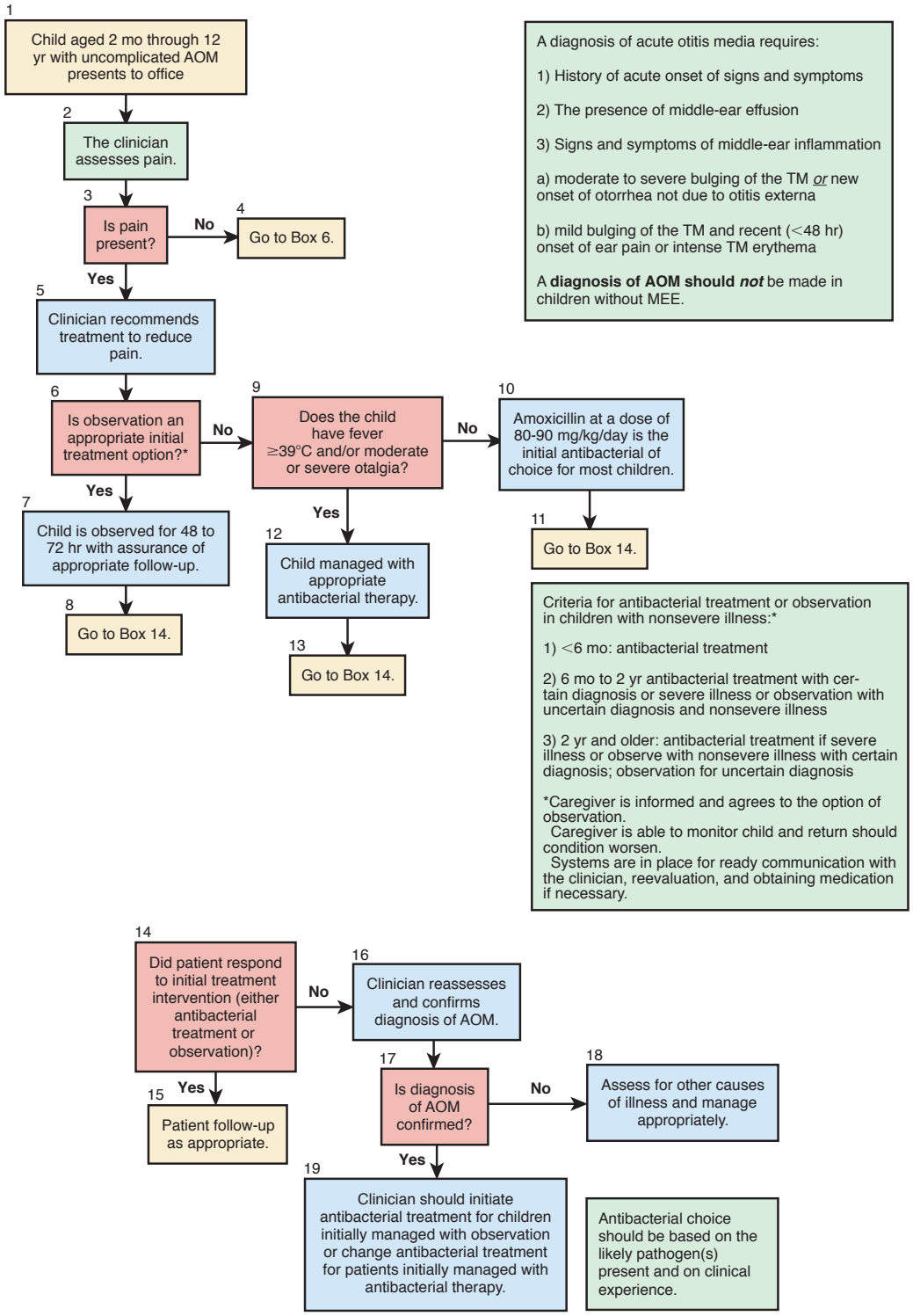

Figure 640-6 Management of acute otitis media. *(From Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media,* Pediatrics *113:1451–1465, 2004.)*

The Skin

Table 645-2 Characteristics of Cutaneous Signs of Systemic Diseases

DISEASE	AGE OF ONSET	SKIN LESIONS	DISTRIBUTION	DIAGNOSTIC EVALUATION(S) AND FINDINGS	ASSOCIATED SYMPTOMS/SIGNS	DIFFERENTIAL DIAGNOSIS
Systemic lupus erythematosus	Any	Erythematous patches; palpable purpura; livedo reticularis; Raynaud phenomenon; thrombocytopenic and nonthrombocytopenic purpura	Photodistribution; "malar" face	ANA panel Anti–dsDNA Leukopenia/lymphopenia Thrombocytopenia Complement levels Urinalysis	Arthritis Nephritis Cerebritis Serositis	Seborrheic dermatitis Atopic dermatitis Juvenile dermatomyositis
Discoid lupus erythematosus	Any	Annular, scaly plaques; atrophy; dyspigmentation	Photodistribution	ANA	Scarring	Subacute cutaneous lupus Polymorphous light eruption Juvenile dermatomyositis
Neonatal lupus erythematosus	Newborn	Annular, erythematous, scaly plaques	Head/neck	ANA Anti-Ro (SSA), anti-La (SSB)	Heart block Thrombocytopenia	Tinea capitis Atopic dermatitis Seborrheic dermatitis
Juvenile dermatomyositis	Any	Erythematous to violaceous scaly, macules; discrete papules overlying knuckles	Periocular face; shoulder girdle; extensor extremities; knuckles; palms	ANA AST ALT Aldolase Creatine kinase Lactate dehydrogenase	Proximal muscle weakness Calcifications Vasculopathy	Atopic dermatitis Allergic contact dermatitis Lupus erythematosus
Henoch-Schönlein purpura	Childhood and adolescence	Purpuric papules and plaques	Buttocks; lower extremities	Urinalysis Blood urea nitrogen/creatinine ratio Skin biopsy	Abdominal pain Arthritis	Vasculitis Drug eruption Infantile hemorrhagic edema Viral exanthem
Kawasaki disease	Infancy, childhood	Erythematous maculopapular to urticarial plaques; acral and groin erythema, edema, desquamation	Diffuse	Leukocytosis ESR C-reactive protein Thrombocytosis	Strawberry tongue Conjunctivitis Lymphadenopathy Cardiovascular complications	Viral syndrome Drug eruption Staphylococcal/ streptococcal illness
Inflammatory bowel disease	Childhood and adolescence	Aphthae; erythema nodosum; pyoderma gangrenosum; thrombophlebitis	Oral ulcers; perianal fissures	Skin biopsy	Abdominal pain Diarrhea Cramping Arthritis Conjunctivitis	Behçet syndrome Vasculitis *Yersinia* colitis
Sweet syndrome	Any	Infiltrated erythematous, edematous plaques	Diffuse	Skin biopsy Leukocytosis ESR	Fever Flu-like illness Conjunctivitis	Infection Urticaria Erythema multiforme Urticarial vasculitis
Graft-versus-host disease	Any	Acute: erythema, papules, vesicles, bulla	Head and neck; palms/soles; diffuse	Skin biopsy Liver function	Fever Mucositis Hepatitis	Drug eruption Infectious exanthem
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Any	Erythema; urticarial macules and plaques	Diffuse	Liver function Eosinophilia Atypical lymphocytosis	Perioral edema Lymphadenopathy Fever Hepatitis	Stevens-Johnson syndrome Infectious exanthem
Serum sickness–like reaction (SSLR)	Any	Edematous, urticarial plaques	Acral; diffuse	None	Fever Lymphadenopathy Arthritis, nephritis	Kawasaki disease Urticaria

ANA, antinuclear antibodies; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dsDNA, double-stranded deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; SSA/SSB, Sjögren's syndrome A/B.

Table 645-3 Drug Eruptions in Pediatric Patients

ERUPTION	KEY DRUGS	LESIONAL PATTERN	MUCOSAL CHANGES
Urticaria	Penicillins, cephalosporins, sulfonamides, aspirin/NSAIDs, radiocontrast media, TNF inhibitors	Pruritic erythematous wheals	None
Angioedema	Aspirin/NSAIDs, angiotensin-converting enzyme inhibitors	Swelling of subcutaneous and deep dermal tissues	May be present
Serum sickness–like reaction	Cephalosporins, penicillins, minocycline, bupropion, sulfonamides	Annular urticarial plaques	None
Exanthematous	Any drug	Erythematous macules and/or papules	None
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Phenytoin, phenobarbital, carbamazepine, lamotrigine, allopurinol, sulfonamides, dapsone, minocycline	Edema; erythematous macules and/or papules; sometimes vesicles or bullae	May be present
Lichenoid	Captopril, enalapril, β-blockers, gold salts, hydrochlorothiazide, hydroxychloroquine, penicillamine, griseofulvin, tetracycline, carbamazepine, phenytoin, NSAIDs	Discrete flat-topped, reddish purple papules and plaques	May be present
Fixed drug	Sulfonamides, ibuprofen, acetaminophen, tetracyclines, pseudoephedrine, barbiturates, lamotrigine, metronidazole, penicillin	Solitary to few erythematous, hyperpigmented plaques	Unusual
Pustular (acute generalized exanthematous pustulosis)	β-Lactam antibiotics, macrolides, clindamycin, terbinafine, calcium channel blockers, antimalarials	Generalized small pustules and papules	Unusual
Acneiform	Corticosteroids, androgens, lithium, iodides, phenytoin, isoniazid, tetracycline, B vitamins, azathioprine	Follicle-based inflammatory papules and pustules predominate	None
Pseudoporphyria	NSAIDs, cyclooxygenase-2 inhibitors, tetracyclines, furosemide	Photodistributed blistering and skin fragility	None
Vasculitis	Penicillins, NSAIDs, sulfonamides, cephalosporins	Purpuric papules, especially on the lower extremities; urticaria, hemorrhagic bullae, digital necrosis, pustules, ulcers	Rarely
Stevens-Johnson/toxic epidermal necrolysis	Sulfonamides, anticonvulsants, NSAIDs, allopurinol, dapsone	Target lesions, bullae, epidermal necrosis with detachment	Present
Drug-induced lupus	Minocycline, procainamide, hydralazine, isoniazid, penicillamine, carbamazepine, chlorpromazine, infliximab	Rarely has skin manifestations but may be urticarial, vasculitic, erythematous	Rare

NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor.

Table 646-1 Potency of Topical Glucocorticosteroids

CLASS 1—SUPERPOTENT Betamethasone dipropionate, 0.05% gel, ointment Clobetasol propionate cream, ointment, 0.05% Halobetasol propionate cream, ointment, 0.05%
CLASS 2—POTENT Betamethasone dipropionate cream 0.05% Desoximetasone cream, ointment, gel 0.05% and 0.25% Fluocinonide cream, ointment, gel, 0.05%
CLASS 3—UPPER MID-STRENGTH Betamethasone dipropionate cream, 0.05% Betamethasone valerate ointment, 0.1% Fluticasone propionate ointment, 0.005% Mometasone furoate ointment, 0.1% Triamcinolone acetonide cream, 0.5%
CLASS 4—MID-STRENGTH Desoximetasone cream, 0.05% Fluocinolone acetonide ointment, 0.025% Triamcinolone acetonide ointment, 0.1%
CLASS 5—LOWER MID-STRENGTH Betamethasone valerate cream/lotion, 0.1% Fluocinolone acetonide cream, 0.025% Fluticasone propionate cream, 0.05% Triamcinolone acetonide cream/lotion, 0.1%
CLASS 6—MILD STRENGTH Desonide cream, 0.05%
CLASS 7—LEAST POTENT Topicals with hydrocortisone, dexamethasone, flumethasone, methylprednisolone, and prednisolone

Table 648-1 Freiden's Classification of Aplasia Cutis Congenita

GROUP	DEFINITION	INHERITANCE
1	Isolated scalp involvement; may be associated with single defects	AD
2	Scalp ACC with limb reduction defects (Adams-Oliver syndrome); may be associated with encephalocele	AD
3	Scalp ACC with epidermal nevus	Sporadic
4	ACC overlying occult spinal dysraphism, spina bifida, or meningoencephalocele	Sporadic
5	ACC with placental infarcts, and/or fetus papyraceus	Sporadic
6	ACC with epidermolysis bullosa	AD or AR
7	ACC localized to extremities without blistering; usually affecting pretibial areas and dorsum of hands and feet	AD or AR
8	ACC caused by teratogens (e.g., varicella, herpes, methimazole)	Sporadic
9	ACC associated with malformation syndromes (e.g., trisomy 13, deletion 4p–, deletion Xp22.1, ectodermal dysplasia, Johanson-Blizzard syndrome, Adams-Oliver syndrome)	Variable

ACC, Aplasia cutis congenital; AD, autosomal dominant; AR, autosomal recessive.

Table 650-1 International Society for the Study of Vascular Anomalies (ISSVA) Classification System

VASCULAR MALFORMATION	VASCULAR TUMOR
Slow-flow malformations Capillary malformation Venous malformation Lymphatic malformation Fast-flow malformations Arterial malformation Arteriovenous malformation Arteriovenous fistula Combined vascular malformations	Infantile hemangioma Congenital hemangioma Rapidly involuting congenital hemangioma Noninvoluting congenital hemangioma Kaposiform hemangioendothelioma Tufted angioma Spindle cell hemangioendothelioma Epithelioid hemangioendothelioma Other rare hemangioendotheliomas Angiosarcoma Acquired vascular tumors: pyogenic granuloma

Table 653-2 Typical Features of Segmental and Nonsegmental Vitiligo

SEGMENTAL VITILIGO	NONSEGMENTAL VITILIGO
Often begins in childhood	Can begin in childhood, but later onset is more common
Has rapid onset and stabilizes	Is progressive, with flare-ups
Involves hair compartment soon after onset	Involves hair compartment in later stages
Is usually not accompanied by other autoimmune diseases	Is often associated with personal or family history of autoimmunity
Often occurs in the face	Commonly occurs at sites sensitive to pressure and friction and prone to trauma
Is usually responsive to autologous grafting, with stable repigmentation	Frequently relapses in situ after autologous grafting
Can be difficult to distinguish from nevus depigmentosus, especially in cases with early onset	

Table 650-2 Complications of Hemangioma and Their Treatment

CLINICAL FINDING	RECOMMENDED TREATMENT
Severe ulceration/ maceration	Encourage twice-daily cleansing regimen Dilute sodium bicarbonate soaks ± Flashlamp pulsed-dye laser ± Oral corticosteroids or propranolol ± Culture-directed systemic antibiotics for infection
Bleeding (not KMP)	Gelfoam or Surgifoam or propranolol Compression therapy ± embolization
Hemangioma with ophthalmologic sequelae	Patching therapy as directed by ophthalmologist Intralesional vs oral corticosteroids vs propranolol
Subglottic hemangioma	Oral corticosteroids, propranolol, ± potassium titanyl phosphate (KtP) laser Tracheotomy if required
KMP	Corticosteroids, aminocaproic acid, vincristine, interferon-α ± embolization
High-flow hepatic hemangioma	Corticosteroids or interferon ± embolization

KMP, Kasabach-Merritt phenomenon.

Table 650-3 Clinical "Red Flags" Associated with Hemangiomas

CLINICAL FINDING	RECOMMENDED EVALUATION
Facial hemangioma involving significant area of face	Evaluate for PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities): MRI for orbital hemangioma ± posterior fossa malformation Cardiac, ophthalmologic evaluation Evaluate for midline abnormality: supraumbilical raphe, sternal atresia, cleft palate, thyroid abnormality
Cutaneous hemangiomas in beard distribution	Evaluate for airway hemangioma, especially if manifesting with stridor
Periocular hemangioma	MRI of orbit Ophthalmologic evaluation
Paraspinal midline vascular lesion	Ultrasonography or MRI to evaluate for occult spinal dysraphism
Hemangiomatosis (multiple small cutaneous hemangiomas)	Evaluate for parenchymal hemangiomas, especially hepatic/ central nervous system Guaiac stool test
Large hemangioma, especially hepatic	Ultrasonography with Doppler flow study MRI Thyroid function studies
Thrill and/or bruit associated with hemangioma	Consider cardiac evaluation and echocardiography to rule out diastolic reversal of flow in aorta MRI to evaluate extent and flow characteristics
Head tilting	Evaluate appropriately for specific site of lesion, and consider physical therapy evaluation
Delayed milestones	Consider side effect of corticosteroids (myopathy, weight-related) Consider side effect of interferon (especially spastic diplegia)
LUMBAR syndrome	MRI of spine, kidneys

LUMBAR, lower body infantile hemangiomas and other skin defects, urogenital anomalies and ulceration, myelopathy, boney deformities, anorectal malformations and arterial anomalies, renal anomalies.

Table 654-2 Clinical Presentation and Diagnosis of Selected Epidermolysis Bullosa Subtypes in the Neonatal Period

EB SUBTYPE (USUAL INHERITANCE)	CLINICAL FEATURES		DIAGNOSIS
	Cutaneous	Extracutaneous	
EB simplex–generalized (AD)	Mild to moderate blistering, often generalized Rare scarring, milia	Occasional mucosal blistering	EM: Intrabasal layer split IF: BPAG1 (BP230), BP-180 (BPAG2, collagen XVII), $\alpha_6\beta_4$ integrin, laminin 1, laminin 332, type IV collagen, type VII collagen (EBA antigen) at base of blister
EB simplex–localized (AD)	Mild blistering, often localized, sometimes in 1st 24 mo, but often not until later infancy or childhood Rare scarring, milia	Rare mucosal involvement	EM: Intrastratum basale split IF: Same as for EB simplex—generalized
EB simplex–Dowling-Meara (AD)	Moderate to severe blistering, which starts generalized, then is grouped (herpetiform); milia; nail dystrophy, shedding	Mild mucosal blistering	EM: Intrastratum basale split; clumped keratin filaments IF: Same as for EB simplex—generalized
Junctional EB–non-Herlitz (AR)	Moderate blistering; atrophic scars; nail dystrophy	Mild mucosal blistering; enamel hypoplasia	EM: Intralamina lucida cleavage; variable reduction in hemidesmosomes IF: Absence of staining with 19-DEJ-1 (uncein); variable staining with GB3 and other laminin 332 antibodies, including 46 and K140; BPAG1 (BP230) BP180 (BPAG2, type XVII collagen), $\alpha_6\beta_4$ integrin in blister roof; laminin 1, type IV collagen, type VII collagen (EBA antigen) at base of blister
Junctional EB–Herlitz (AR)	Severe generalized blistering that heals poorly; granulation tissue; scarring; nail dystrophy	Severe mucosal blistering; GI involvement common; laryngeal involvement with airway obstruction; urologic involvement	EM: Cleavage intralamina lucida; markedly reduced or no hemidesmosomes; absence of sub-basal dense plates IF: Absence of staining with 19-DEJ-1 (uncein) and GB3 (laminin 332) and of staining with other laminin 332 antibodies, including 46 and K140; BPAG1 (BP230) and BP180 (BPAG2, type XVII collagen) in blister roof; laminin-1, type IV collagen, and type VII collagen at base of blister
Junctional EB–pyloric atresia (AR)	Severe blistering	Polyhydramnios; pyloric atresia; urologic involvement: uretovesicular obstruction, hydronephrosis	EM: Cleavage intralamina lucida and intraplasma membrane; small hemidesmosomes IF: BPAG1 (BP230) and BP180 (BPAG2, type XVII collagen) in blister roof; laminin-1, type IV collagen, and type VII collagen at base of blister; Absence of 19-DEJ-1(uncein), $\alpha_6\beta_4$ integrin absent or reduced
Dominant dystrophic EB (AD)	Mild to moderate blistering (but may be more severe in newborn period) Milia, scarring Nail dystrophy	Mild mucosal blistering	EM: Cleavage sublamina densa; variable reduction in anchoring fibrils IF: BPAG1 (BP230), BPAG2 (BP180, type XVII collagen), $\alpha_6\beta_4$ integrin, laminin 1, type IV collagen at top of blister Staining for type VII collagen (EBA antigen) is normal, variable, or absent
Recessive dystrophic EB–Hallopeau-Siemens (AR)	Severe blistering Milia, scarring	Severe mucosal blistering; GI involvement common; urologic involvement	EM: Cleavage sublamina densa; absence of anchoring fibrils IF: BPAG1 (BP230), BP-180 (BPAG2, type XVII collagen), $\alpha_6\beta_4$ integrin, laminin 1, type IV collagen at top of blister Variability or absence of staining for type VII collagen (EBA antigen)

AD, autosomal dominant; AR, autosomal recessive; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; EM, electron microscopy; GI, gastrointestinal; IF, immunohistochemical and immunofluorescence antigen mapping findings.

Table 658-1 Disorders of Cornification That Usually Manifest in the First Weeks of Life

DISORDER	INHERITANCE	CLINICAL FEATURES	MUTATION	VISUAL METHOD OF DIAGNOSIS
Harlequin ichthyosis	AR	Thick, armor-like scale with fissuring	*ABCA12*	Clinical
Collodion baby	Usually AR	Shiny collodion membrane	Various	Clinical
Recessive X-linked ichthyosis	Recessive X-linked	Collodion membrane May have genital anomalies	Steroid sulfatase	Plasma cholesterol sulfate
Lamellar ichthyosis	Usually AR	Collodion membrane	Transglutaminase I *ABCA12* *CYP4F22*	Clinical
Congenital ichthyosiform erythroderma	AR	Collodion membrane	Transglutaminase 1 *ALOX12B* *ALOXE3*	Clinical
Epidermolytic ichthyosis	AD	Scaling and blistering	Keratins 1, 10, 2e	Clinical and histologic
Ichthyosis hystrix	AD	Plaques of hyperkeratosis	Keratin 1, *GJB2*	Clinical
Familial peeling skin	AR	Superficial peeling	Unknown	Clinical and histologic
Sjögren-Larsson syndrome	AR	Variable skin thickening Mental, developmental retardation Spastic diplegia Seizures "Glistening dots"	*FAD*	Clinical and fibroblast cultures for FAD
Neutral lipid storage disease	AR	Collodion membrane or ichthyosiform erythroderma	*CGI58*	Blood smear for vacuolated polymorphonuclear leukocytes
Netherton syndrome	AR	Ichthyosiform erythroderma Scant hair, often failure to thrive	*SPINK 5* Unknown	Clinical; hair exam later in infancy Clinical and hair microscopy; hair sulfur content
Trichothiodystrophy	AR	Collodion membrane Broken hair	*XPB* *XPD*	
KID (keratitis with ichthyosis and deafness) syndrome	May be AD, AR	Erythrokeratodermatous or thick, leathery skin with stippled papules	*GJB2*	Clinical; auditory evoked potentials
CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome	X-linked dominant	Alopecia Unilateral waxy yellow, scaling Hemidysplasia Limb defects	*NSDHL*	Clinical
Conradi-Hünermann syndrome	X-linked dominant	Thick, psoriasiform scale over erythroderma, patterned along Blaschko lines Proximal limb shortening	*ARSE*	Clinical
Ichthyosis follicularis	Usually X-linked recessive	Prominent follicular hyperkeratoses Alopecia Photophobia	*MBTPS2*	Clinical
CHIME (colobomas of the eyes, heart defects, ichthyosiform dermatosis, mental retardation, and ear abnormalities) syndrome	AR	Ichthyotic erythematous plaques Cardiac defects; typical facies Retinal colobomas	Unknown	Clinical
Gaucher disease	AR	Collodion membrane Hepatosplenomegaly	β-Glucocerebrosidase	Clinical; fibroblast cultures

AD, autosomal dominant; AR, autosomal recessive.; FAD, fatty aldehyde.

Table 659-1 Ehlers-Danlos Syndrome

TYPE	FORMER NAME	CLINICAL FEATURES*	INHERITANCE	OMIM†	MOLECULAR DEFECT
Classic	EDS I and II	Joint hypermobility; skin hyperextensibility; atrophic scars; smooth, velvety skin; subcutaneous spheroids	AD	130000 130010	Structure of type V collagen because of mutations in *COL5A1, COL5A2*
Hypermobility	EDS III	Joint hypermobility; some skin hyperextensibility, with or without smooth, velvety texture	AD AR	130020 225320	? Tenascin-X *(TNX)*
Vascular	EDS IV	Thin skin; easy bruising; pinched nose; acrogeria; rupture of large-caliber and medium-caliber arteries, uterus, and large bowel	AD	130050 (225350) (225360)	Deficient type III collagen *(COL3A1)*
Kyphoscoliotic	EDS VI	Joint hypermobility; congenital, progressive rupture; scoliosis; scleral fragility with globe rupture; tissue fragility, aortic dilation, MVP	AR	225400	Deficiency of lysyl hydroxylase
Arthrochalasis	EDS VII A	Joint hypermobility, severe, with subluxations, congenital hip dislocation; skin hyperextensibility; tissue fragility	AD	130060	No cleavage of amino terminus of type I procollagen because of mutations in *COL1A1* or *COL1A2*
Dermatosparaxis	EDS VII C	Severe skin fragility; decreased skin elasticity, easy bruising; hernias; premature rupture of fetal membranes	AR	225410	No cleavage of amino terminus of type I procollagen because of deficiency of peptidase
Unclassified types	EDS V	Classic features	XL	305200	?
	EDS VIII	Classic features and periodontal disease	AD	130080	?
	EDS X	Mild classic features, MVP	?	225310	?
	EDS XI	Joint instability	AD	147900	?
	EDS IX	Classic features; occipital horns	XL	309400	Allelic to Menkes syndrome
	EDS, progeroid form	Classic features and premature aging	AR	130700	Deficiency of galactosyltransferase I

*Listed in order of diagnostic importance.
†Entries in Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). Available at: http://omim.org/
AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers-Danlos syndrome; MVP, mitral valve prolapse; XL, X-linked.

Table 668-3 Drugs for Head Lice

DRUG	RESISTANCE	FDA-APPROVED LOWER AGE OR WEIGHT LIMIT	DOSAGE AND ADMINISTRATION	COST[a]/SIZE
Ivermectin 0.5% lotion–Sklice (Sanofi Pasteur)	No[b]	6 months	Apply to dry hair and scalp for 10 min, then rinse	$257.88/4 oz
Ivermectin tablets[c]–Stromectol (Merck)	No	15 kg	200-400 µg/kg PO once; repeat 7-10 days later	9.97[d]
Spinosad 0.9% suspension–Natroba (ParaPro)	No[b]	4 yr	Apply to dry hair for 10 min, then rinse; repeat 7 days later if necessary	219.00/4 oz
Benzyl alcohol 5% lotion–Ulesfia (Shionogi)	No	6 months	Apply to dry hair for 10 min, then rinse; repeat 7 days later	52.62/8 oz
Pyrethrins with piperonyl butoxide shampoo[e,f]–Generic Rid (Bayer)	Yes	2 yr	Apply to dry hair for 10 min, then shampoo; repeat 7-10 days later	12.49/8 oz 19.99/8 oz[g]
Permethrin 1% creme rinse[e]–Generic Nix (Insight)	Yes	2 months	Apply to shampooed, towel-dried hair for 10 min, then rinse; repeat 7 days later	18.49/4 oz 19.99/4 oz[g]
Malathion 0.5% lotion– Generic Ovide (Taro)	Not in U.S.	6 yr	Apply to dry hair for 8-12 hr,[h] then shampoo; repeat 7-9 days later if necessary	152.67/2 oz 160.46/2 oz

[a]Wholesale acquisition cost (WAC). Source: PricePointRx. Reprinted with permission by FDB, Inc. All rights reserved. Copyright 2012. www.firstdatabank.com/support/drug-pricing-policy.aspx. Actual retail prices may be higher. Amount needed may vary.
[b]Product new to market: currently no reports of resistance.
[c]Not FDA-approved for treatment of head lice. Stromectol is available in 3 mg tablets.
[d]Cost of 1 dose for a 30 kg child at the lowest dosage.
[e]Available without a prescription.
[f]Products that contain benzyl alcohol as their vehicle may be more effective.
[g]Cost according to drugstore.com.
[h]One or two 20 min applications have also been effective (Meinking TL, Vicaria M, Eyerdam DH,, et al: Efficacy of a reduced application time of Ovide lotion (0.5% malathion) compared to Nix creme rinse (1% permethrin) for the treatment of head lice, Pediatr Dermatol 21:670–674, 2004.)

Table 656-2 Cutaneous Reactions to Sunlight

SUNBURN

Photoallergic drug eruptions:
- Systemic drugs include tetracyclines, psoralens, chlorothiazides, sulfonamides, barbiturates, griseofulvin, thiazides, quinidine, phenothiazines
- Topical agents include coal tar derivatives, psoralens, halogenated salicylanilides (soaps), perfume oils (e.g., oil of bergamot), sunscreens (e.g., para-aminobenzoic acid [PABA], cinnamates, benzophenones)

Phototoxic drug eruptions:
- Systemic agents include nalidixic acid, furosemide, nonsteroidal antiinflammatory agents (naproxen, piroxicam), and high doses of agents causing photoallergic eruptions
- Topical agents include 5-fluorouracial, furocoumarins (e.g., lime, lemon, carrot, celery, dill, parsnip, parsley), and high doses of agents causing photoallergic eruptions

Genetic disorders with photosensitivity:
- Xeroderma pigmentosum
- Bloom syndrome
- Cockayne syndrome
- Rothmund-Thomson syndrome
- Trichothiodystrophy
- Smith-Lemli-Opitz syndrome
- Kindler syndrome

Inborn errors of metabolism:
- Porphyrias, protoporphyria
- Hartnup disease and pellagra

Infectious diseases associated with photosensitivity:
- Recurrent herpes simplex infection
- Viral exanthems (accentuated photodistribution; e.g., varicella)

Skin disease exacerbated or precipitated by light:
- Lichen planus
- Darier disease
- Lupus erythematosus including neonatal
- Dermatomyositis
- Psoriasis
- Erythema multiforme
- Atopic dermatitis
- Hailey-Hailey disease

Deficient protection because of a lack of pigment:
- Vitiligo
- Oculocutaneous albinism
- Phenylketonuria
- Chédiak-Higashi syndrome
- Hermansky-Pudlak syndrome
- Waardenburg syndrome
- Piebaldism

Table 659-4 Mastocytosis Classification

Cutaneous mastocytosis:
1. Urticaria pigmentosa:
   (a) Classic infantile type; (b) Chronic with stem cell factor mutations
2. Diffuse cutaneous mastocytosis
3. Mastocytoma of the skin
4. Telangiectasia macularis eruptive perstans

Systemic mastocytosis (without an associated hematologic non–mast cell disorder or leukemic mast cell disease):
1. Systemic indolent mastocytosis
2. Systemic smoldering mastocytosis

Systemic mastocytosis with an associated hematologic non–mast cell disorder:
1. Myeloproliferative syndrome
2. Myelodysplastic syndrome
3. Acute myeloid leukemia
4. Non-Hodgkin lymphoma

Systemic aggressive mastocytosis
Mast cell leukemia
Mast cell sarcoma
Extracutaneous mastocytoma

Table 661-1 Causes of Hyperhidrosis

CORTICAL
Emotional
Familial dysautonomia
Congenital ichthyosiform erythroderma
Epidermolysis bullosa
Nail-patella syndrome
Jadassohn-Lewandowsky syndrome
Pachyonychia congenita
Palmoplantar keratoderma
Stroke

HYPOTHALAMIC
Drugs:
- Alcohol
- Antipyretics
- Cocaine
- Emetics
- Insulin
- Opiates (including withdrawal)
- Ciprofloxacin

Exercise
Infection:
- Defervescence
- Chronic illness

Metabolic:
- Carcinoid syndrome
- Debility
- Diabetes mellitus
- Hyperpituitarism
- Hyperthyroidism
- Hypoglycemia
- Obesity
- Pheochromocytoma
- Porphyria
- Pregnancy
- Rickets
- Infantile scurvy

Cardiovascular:
- Heart failure
- Shock
- Vasomotor
- Cold injury
- Raynaud phenomenon
- Rheumatoid arthritis

Neurologic:
- Abscess
- Familial dysautonomia
- Postencephalitic
- Tumor

Miscellaneous:
- Chédiak-Higashi syndrome
- Compensatory
- Lymphoma
- Phenylketonuria
- Vitiligo

MEDULLARY
Physiologic gustatory sweating
Encephalitis
Granulosis rubra nasi
Syringomyelia
Thoracic sympathetic trunk injury

SPINAL
Cord transection
Syringomyelia

CHANGES IN BLOOD FLOW
Maffucci syndrome
Arteriovenous fistula
Klippel-Trenaunay syndrome
Glomus tumor
Blue rubber-bleb nevus syndrome

Table 663-1 White Nail or Nail Bed Changes

DISEASE	CLINICAL APPEARANCE
Anemia	Diffuse white
Arsenic	Mees lines: transverse white lines
Cirrhosis	Terry nails: most of nail, zone of pink at distal end (see Fig. 663-3)
Congenital leukonychia (autosomal dominant; variety of patterns)	Syndrome of leukonychia, knuckle pads, deafness; isolated finding; partial white
Darier disease	Longitudinal white streaks
Half-and-half nail	Proximal white, distal pink azotemia
High fevers (some diseases)	Transverse white lines
Hypoalbuminemia	Muehrcke lines: stationary paired transverse bands
Hypocalcemia	Variable white
Malnutrition	Diffuse white
Pellagra	Diffuse milky white
Punctate leukonychia	Common white spots
Tinea and yeast	Variable patterns
Thallium toxicity (rat poison)	Variable white
Trauma	Repeated manicure: transverse striations
Zinc deficiency	Diffuse white

Table 663-3 Differential Diagnosis of Onychomycosis

Psoriasis
- As in onychomycosis: onycholysis, subungual hyperkeratosis, splinter hemorrhages, leuconychia, dystrophy
- Pitting
- Oil drop sign (a translucent yellow-red discoloration seen in the nail bed)
- Other cutaneous features of psoriasis, family history of psoriasis

Lichen planus
- Cutaneous disease at other sites
- Thin nail plate and ridging
- Dorsal pterygium—scarring at proximal aspect of nail

Trauma
- Nail plate can appear abnormal
- Nail bed should be normal
- Distal onycholysis with repeated trauma
- Single nail affected, shape of nail changed, homogenous alteration of nail color

Eczema
- Irregular buckled nails with ridging
- Cutaneous signs of eczema

Yellow nail syndrome
- Nail plate is discolored green-yellow
- Nails are hard with elevated longitudinal curvature
- Nails may be shed, painful
- Associations with bronchiectasis, lymphoedema, and chronic sinusitis

Lamellar onychoschizia (lamellar splitting)
- History of repeated soaking in water
- Usually distal portion of nail

Periungual squamous cell carcinoma/Bowens disease
- Single nail, warty changes of nail fold, ooze from edge of nail

Malignant melanoma
- Black discoloration of nail plate or nail bed
- Pigment can extend onto nail fold
- Can get associated bleeding

Myxoid (mucous) cyst
- Cyst at base of nail, groove in nail extending length of nail

Alopecia areata
- Pits, longitudinal ridging, brittleness
- Hair loss

Table 662-1 Causes of and Conditions Associated with Hypertrichosis

INTRINSIC FACTORS
Racial and familial forms such as hairy ears, hairy elbows, intraphalangeal hair, or generalized hirsutism

EXTRINSIC FACTORS
Local trauma
Malnutrition
Anorexia nervosa
Long-standing inflammatory dermatoses
Drugs: Diazoxide, phenytoin, corticosteroids, Cortisporin, cyclosporine, androgens, anabolic agents, hexachlorobenzene, minoxidil, psoralens, penicillamine, streptomycin

HAMARTOMAS OR NEVI
Congenital pigmented nevocytic nevus, hair follicle nevus, Becker nevus, congenital smooth muscle hamartoma, fawn-tail nevus associated with diastematomyelia

ENDOCRINE DISORDERS
Virilizing ovarian tumors, Cushing syndrome, acromegaly, hyperthyroidism, hypothyroidism, congenital adrenal hyperplasia, adrenal tumors, gonadal dysgenesis, male pseudohermaphroditism, non–endocrine hormone–secreting tumors, polycystic ovary syndrome

CONGENITAL AND GENETIC DISORDERS
Hypertrichosis lanuginosa, mucopolysaccharidosis, leprechaunism, congenital generalized lipodystrophy, de Lange syndrome, trisomy 18, Rubinstein-Taybi syndrome, Bloom syndrome, congenital hemihypertrophy, gingival fibromatosis with hypertrichosis, Winchester syndrome, lipoatrophic diabetes (Lawrence-Seip syndrome), fetal hydantoin syndrome, fetal alcohol syndrome, congenital erythropoietic or variegate porphyria (sun-exposed areas), porphyria cutanea tarda (sun-exposed areas), Cowden syndrome, Seckel syndrome, Gorlin syndrome, partial trisomy 3q, Ambras syndrome

Table 662-2 Disorders Associated with Alopecia and Hypotrichosis

Congenital total alopecia: Atrichia with papules, Moynahan alopecia syndrome
Congenital localized alopecia: Aplasia cutis, triangular alopecia, sebaceous nevus
Hereditary hypotrichosis: Marie-Unna syndrome, hypotrichosis with juvenile macular dystrophy, hypotrichosis–Mari type, ichthyosis with hypotrichosis, cartilage-hair hypoplasia, Hallermann-Streiff syndrome, trichorhinophalangeal syndrome, ectodermal dysplasia "pure" hair and nail and other ectodermal dysplasias
Diffuse alopecia of endocrine origin: Hypopituitarism, hypothyroidism, hypoparathyroidism, hyperthyroidism
Alopecia of nutritional origin: Marasmus, kwashiorkor, iron deficiency, zinc deficiency (acrodermatitis enteropathica), gluten-sensitive enteropathy, essential fatty acid deficiency, biotinidase deficiency
Disturbances of the hair cycle: Telogen effluvium
Toxic alopecia: Anagen effluvium
Autoimmune alopecia: Alopecia areata
Traumatic alopecia: Traction alopecia, trichotillomania
Cicatricial alopecia: Lupus erythematosus, lichen planopilaris, pseudopelade, morphea (en coup de saber) dermatomyositis, infection (kerion, favus, tuberculosis, syphilis, folliculitis, leishmaniasis, herpes zoster, varicella), acne keloidalis, follicular mucinosis, sarcoidosis
Hair shaft abnormalities: Monilethrix, pili annulati, pili torti, trichorrhexis invaginata, trichorrhexis nodosa, woolly hair syndrome, Menkes disease, trichothiodystrophy, trichodento-osseous syndrome, uncombable hair syndrome (spun-glass hair, pili trianguli et canaliculi)

Table 663-2

Large nails	Pachyonychia congenita, Rubinstein-Taybi syndrome, hemihypertrophy
Smallness or absence of nails	Ectodermal dysplasias, nail-patella, dyskeratosis congenita, focal dermal hypoplasia, cartilage-hair hypoplasia, Ellis–van Creveld, Larsen, epidermolysis bullosa, incontinentia pigmenti, Rothmund-Thomson, Turner, popliteal web, trisomy 13, trisomy 18, Apert, Gorlin-Pindborg, long arm 21 deletion, otopalatodigital, fetal alcohol, fetal hydantoin, elfin facies, anonychia, acrodermatitis enteropathica
Other	Congenital malalignment of the great toenails, familial dystrophic shedding of the nails

Bone and Joint Disorders

Table 666-1 Primary Immunodeficiencies Underlying Fungal Infections

DISEASE	ASSOCIATED INFECTIONS	IMMUNOLOGIC PHENOTYPE	GENE, TRANSMISSION
CMC			
SCID	Bacteria, viruses, fungi, mycobacteria	No T cells, with or without B and/or NK cell lymphopenia	>30 genes: *IL2RG,* X-linked; *JAK3,* autosomal recessive; RAG1, autosomal recessive; *RAG2,* autosomal recessive; *ARTEMIS,* autosomal recessive; *ADA,* autosomal recessive; *CD3,* autosomal recessive, etc.
CID		T-cell defect	
CD25 deficiency	Viruses and bacteria		*IL2RA,* autosomal recessive
NEMO or iκBγ deficiency	Pyogenic bacteria, mycobacteria, viruses		*NEMO* or *IKBG* X-linked
IκBα GOF mutation			*IKBA,* autosomal dominant
DOCK8 deficiency	Viruses, bacteria and fungi		*DOCK8,* autosomal recessive
TCR-α deficiency	Viruses and bacteria		*TCRA,* autosomal recessive
CRACM1 deficiency	Viruses, mycobacteria, bacteria and fungi		*CRACM1,* autosomal recessive
MST1/STK4 deficiency	Viruses and bacteria		*MST1/STK4,* autosomal recessive
MHC class II deficiency	Viruses, bacteria and fungi		*CIITA, RFXANK, RFXC, RFXAP,* all autosomal recessive
Idiopathic CD4 lymphopenia	*Pneumocystis, Cryptococcus,* virus	CD4 T cells <300 cells/mm^3	*UNC119,* autosomal dominant, *MAGT1* X-linked, *RAG1,* autosomal recessive
SYNDROMIC CMC			
Interleukin-12Rβ1 and interleukin-12p40 deficiencies	*Mycobacteria, Salmonella*	Deficit of interleukin-17–producing T cells	*IL12RB1,* autosomal recessive, *IL12B,* autosomal recessive
STAT3 deficiency (autosomal dominant-HIES)	*Staphylococcus aureus, Aspergillus*	Hyperimmunoglobulin E, deficit of interleukin-17–producing T cells	*STAT3,* autosomal dominant
APECED/APS-1	No	Neutralizing anti–interleukin-17A, anti–interleukin-17F, and/or anti–interleukin-22 autoantibodies	*AIRE,* autosomal recessive
CARD9 deficiency	Dermatophytes, *Candida,* brain abscess	Deficit of interleukin-17–producing T cells	*CARD9,* autosomal recessive
CMCD			
Complete interleukin-17RA deficiency	*S. aureus*	No interleukin-17 response	*IL17RA,* autosomal recessive
Partial interleukin-17F deficiency	*S. aureus*	Impaired interleukin-17F, interleukin-17A/F function	*IL17F,* autosomal dominant
STAT1 GOF mutations	Bacteria, viruses, fungi, mycobacteria	Low interleukin-17–producing T cells	*STAT1,* autosomal dominant

AIRE, autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS-1, autoimmune polyendocrinopathy syndrome type 1; CARD9, caspase recruitment domain-containing protein 9; CID, combined immunodeficiency; CMC, chronic mucocutaneous candidiasis; CMCD, chronic mucocutaneous candidiasis disease; CRACM1, calcium release-activated calcium modulator 1; GOF, gain-of-function; HIES, hyperimmunoglobulin E syndrome; IκBα, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B-cells, alpha; iκBγ, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B-cells, gamma; MHC, major histocompatibility complex; MST1, macrophage stimulating 1; NEMO, nuclear factor κB essential modulator; NK, natural killer; SCID, severe combined immunodeficiency; STAT, signal transducer and activator of transcription; STK4, serine/threonine protein kinase 4; TCR, T-cell receptor.

Table 672-1 Terminologies for Deviations

TERMINOLOGY	DESCRIPTION
Congenital	Anomaly that is apparent at birth
Deformation	A normally formed structure that is pushed out of shape by mechanical forces
Deformity	A body part altered in shape from normal, outside the normal range
Developmental	A deviation that occurs over time; one that might not be present or apparent at birth
Disruption	A structure undergoing normal development that stops developing or is destroyed or removed
Dysplasia	A tissue that is abnormal or wrongly constructed
Malformation	A structure that is wrongly built; failure of embryologic development or differentiation resulting in abnormal or missing structures

Table 672-2 Skeletal Growth Considerations

- Abnormal stature can be assessed as "proportionate" or "disproportionate" based on comparing the ratio of sitting height with subischial height (lower limbs).
- Normally the arm span is almost equal to standing height.
- The head is disproportionately large at birth and ratio of head height to total height is approximately 1:4 at birth, which changes to 1:7.5 at skeletal maturity.
- Lower extremities account for approximately 15% of height at birth and 30% at skeletal maturity.
- The rate of height and growth increase is not constant and varies with growth spurts.
- By age 5 yr, birth height usually doubles and the child is approximately 60% of adult height. The child is approximately 80% of final height at 9 yr. During puberty, the standing height increases by approximately 1 cm/mo.
- Bone age is more important than chronologic age in determining future growth potential.

Table 673-3 Causes of Abnormal Gait

Limp
Pain
Torsional variations
Toe walking
Joint abnormalities
Leg-length discrepancy
Neuromuscular disorders

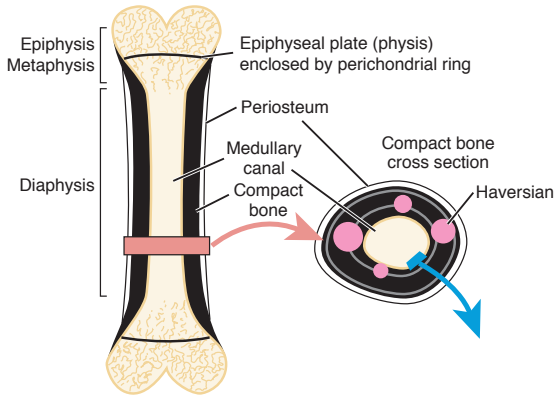

Figure 672-1 Diagram showing typical long bone divisions.

Table 672-3 Functional Milestones

MILESTONE	ACHIEVED BY
Head control	3-6 months
Sitting	6-9 months
Crawling	8 months
Pulling to stand	8-12 months
Ambulating	12-18 months

Table 673-4 Common Causes of Limping According to Age

ANTALGIC	TRENDELENBURG	LEG-LENGTH DISCREPANCY
TODDLER (1-3 YR)		
Infection Septic arthritis Hip Knee Osteomyelitis Diskitis Occult trauma Toddler's fracture Neoplasia	Hip dislocation (DDH) Neuromuscular disease Cerebral palsy Poliomyelitis	–
CHILD (4-10 YR)		
Infection Septic arthritis Hip Knee Osteomyelitis Diskitis Transient synovitis, hip LCPD Tarsal coalition Rheumatologic disorder JRA Trauma Neoplasia	Hip dislocation (DDH) Neuromuscular disease Cerebral palsy Poliomyelitis	+
ADOLESCENT (11+ YR)		
SCFE Rheumatologic disorder JRA Trauma: fracture, overuse Tarsal coalition Neoplasia		+

–, Absent; +, present; DDH, developmental dysplasia of the hip; JRA, juvenile rheumatoid arthritis; LCPD, Legg-Calvé-Perthes disease; SCFE, slipped capital femoral epiphysis.

From Thompson GH: Gait disturbances. In Kliegman RM, editor: Practical strategies of pediatric diagnosis and therapy, *Philadelphia, 1996, WB Saunders, pp. 757–778.*

Table 673-5 Differential Diagnosis of Limping

ANTALGIC GAIT
Congenital
Tarsal coalition
Acquired
Legg-Calvé-Perthes disease
Slipped capital femoral epiphysis
Trauma
Sprains, strains, contusions
Fractures
Occult
Toddler's fracture
Abuse
Neoplasia
Benign
- Unicameral bone cyst
- Osteoid osteoma

Malignant
- Osteogenic sarcoma
- Ewing sarcoma
- Leukemia
- Neuroblastoma
- Spinal cord tumors

Infectious
Septic arthritis
Reactive arthritis
Osteomyelitis
- Acute
- Subacute

Diskitis
Rheumatologic
Juvenile rheumatoid arthritis
Hip monoarticular synovitis (toxic transient synovitis)

TRENDELENBURG
Developmental
Developmental dysplasia of the hip
Leg-length discrepancy
Neuromuscular
Cerebral palsy
Poliomyelitis

Table 676-1 Causes of Leg-Length Discrepancy

CONGENITAL CAUSES
Defects in Growth
Proximal femoral focal deficiency
Congenital pseudarthrosis of the tibia
Fibular hemimelia (see Fig. 676-8)
Bone Tumors/Disease
Skeletal dysplasia
Multiple hereditary exostoses
Neurofibromatosis
Enchondromatosis (Ollier disease)
Osteogenesis imperfecta
Vascular
Klippel-Trenaunay-Weber syndrome
Russell-Silver syndrome
Miscellaneous
Congenital coxa vara
Proteus syndrome

ACQUIRED CAUSES
Trauma
Overriding fractures
Epiphyseal fractures with growth plate damage
Developmental
Developmental dysplasia of the hip
Neoplastic
Malignant tumors
Tumors across epiphysis
Neurologic
Myelodysplasia
Cerebral palsy
Infections/Inflammatory
Septic arthritis of hip
Osteomyelitis
Rheumatoid arthritis
Miscellaneous
Acquired coxa vara
Fixed pelvic obliquity in scoliosis

Table 673-6 Ashworth Scale of Spasticity

0	No increase in muscle tone
1	Slight increase in muscle tone, usually a catch or minimal resistance at end range of motion
2	Moderate tone throughout range of motion
3	Considerable increase in tone; passive range of motion difficult
4	Rigid in flexion or extension

Table 673-7 Clinical Scale of Upper-Extremity Motor Control

GRADE	DEFINITION
Grade 1	Hypotonic, no volitional motion
Grade 2	Hypertonic, no volitional motion
Grade 3	Mass flexion or extension in response to a stimulus
Grade 4	Patient can initiate movement but results in mass flexion or extension
Grade 5	Slow volitional movement; stress or rapid movement results in mass action
Grade 6	Volitional control of specific joints/muscles

Table 674-2 Differential Diagnosis of Foot Pain By Age

0-6 YR	6-12 YR	12-20 YR
Poorly fitting shoes	Poorly fitting shoes	Poorly fitting shoes
Foreign body	Sever disease	Stress fracture
Fracture	Enthesopathy (JIA)	Foreign body
Osteomyelitis	Foreign body	Ingrown toenail
Leukemia	Accessory navicular	Metatarsalgia
Puncture wound	Tarsal coalition	Plantar fasciitis
Drawing of blood	Ewing sarcoma	Osteochondroses (avascular necrosis)
Dactylitis	Hypermobile flatfoot	Freiberg
JIA	Trauma (sprains, fractures) Puncture wound	Köhler Achilles tendinitis Trauma (sprains) Plantar warts Tarsal coalition

Table 679-1 Classification of Spinal Deformities

SCOLIOSIS
Idiopathic
Infantile
Juvenile
Adolescent
Congenital
Failure of formation
  Wedge vertebrae
  Hemivertebrae
Failure of segmentation
  Unilateral bar
  Block vertebra
  Mixed
Neuromuscular
Neuropathic diseases
  Upper motor neuron
  Cerebral palsy
  Spinocerebellar degeneration (Friedreich ataxia, Charcot-Marie-Tooth disease)
  Syringomyelia
  Spinal cord tumor
  Spinal cord trauma
  Lower motor neuron
  Poliomyelitis
  Spinal muscular atrophy
Myopathies
Duchenne muscular dystrophy
Arthrogryposis
Other muscular dystrophies
Syndromes
Neurofibromatosis
Marfan syndrome
Compensatory
Leg-length discrepancy

KYPHOSIS
Postural kyphosis (flexible)
Scheuermann disease
Congenital kyphosis
  Failure of formation
  Failure of segmentation
  Mixed

Table 678-1 Differential Diagnosis of Legg-Calvé-Perthes Disease

OTHER CAUSES OF AVASCULAR NECROSIS
Sickle cell disease
Other hemoglobinopathies (e.g., thalassemia)
Chronic myelogenous leukemia
Steroid medication
Sequela of traumatic hip dislocation
Treatment of developmental dysplasia of the hip
Septic arthritis

EPIPHYSEAL DYSPLASIAS
Multiple epiphyseal dysplasia
Spondyloepiphyseal dysplasia
Mucopolysaccharidoses
Hypothyroidism

OTHER SYNDROMES
Osteochondromatosis
Metachondromatosis
Schwartz-Jampel syndrome
Trichorhinophalangeal syndrome
Maroteaux-Lamy syndrome
Martsolf syndrome

Table 679-3 Differential Diagnosis of Back Pain

INFLAMMATORY/INFECTIOUS
Diskitis
Vertebral osteomyelitis (pyogenic, tuberculous)
Spinal epidural abscess
Pyelonephritis
Pancreatitis
Psoas abscess

RHEUMATOLOGIC
Pauciarticular juvenile idiopathic arthritis
Reiter syndrome
Ankylosing spondylitis
Psoriatic arthritis

DEVELOPMENTAL
Spondylolysis
Spondylolisthesis
Scheuermann disease
Scoliosis

TRAUMATIC (ACUTE VERSUS REPETITIVE)
Hip–pelvic anomalies
Herniated disk
Overuse syndromes
Vertebral stress fractures
Upper cervical spine instability

NEOPLASTIC
Vertebral tumors
  Benign
  Eosinophilic granuloma
  Aneurysmal bone cyst
  Osteoid osteoma
  Osteoblastoma
Malignant
  Osteogenic sarcoma
  Leukemia
  Lymphoma
  Metastatic tumor
Spinal cord, ganglia, and nerve roots
  Intramedullary spinal cord tumor
  Sympathetic chain
  Ganglioneuroma
  Ganglioneuroblastoma
  Neuroblastoma

OTHER
Intraabdominal or pelvic pathology
Following lumbar puncture
Conversion reaction
Juvenile osteoporosis

Table 679-2 Conditions Associated with Hyperkyphosis

- Trauma causing spinal fractures
- Spinal infections resulting from bacterial, tuberculosis, and fungal diseases
- Metabolic diseases such as osteogenesis imperfecta or osteoporosis
- Iatrogenic (laminectomy, spinal irradiation)
- Neuromuscular diseases
- Neoplasms
- Congenital/developmental
  - Disorders of collagen such as Marfan syndrome
  - Dysplasias such as neurofibromatosis, achondroplasia, and mucopolysaccharidoses

Table 679-4 Findings Consistent with a Nonmechanical Etiology Warranting Further Evaluation

- History of trauma
- Pain that wakes the patient from sleep
- Constant pain unrelieved by rest
- Constitutional or systemic symptoms of fevers, chills, malaise, weight loss
- Any neurologic dysfunction including weakness, numbness, radicular pain, gait changes, or bowel and bladder changes
- Abnormalities in spinal alignment
- Bony tenderness to palpation or vertebral step-offs
- Significant pain with provocative tests (spinal flexion or extension)
- Positive straight-leg raise test for neurologic symptoms below the knee
- Abnormal neurologic exam

Table 680-1 Differential Diagnosis of Torticollis

CONGENITAL
Muscular torticollis
Positional deformation
Vertebral anomalies (failure segmentation, formation or both)
Unilateral atlantooccipital fusion
Klippel-Feil syndrome
Unilateral absence of sternocleidomastoid
Pterygium colli
TRAUMA
Muscular injury (cervical muscles)
Atlantooccipital subluxation
Atlantoaxial subluxation
C2-3 subluxation
Rotary subluxation
Fractures (C1, others)
INFLAMMATION
Cervical lymphadenitis
Retropharyngeal abscess
Cervical vertebral osteomyelitis or diskitis
Juvenile idiopathic arthritis
Grisel syndrome (nontraumatic rotary subluxation of the atlantoaxial joint caused by inflammation)
Upper lobe pneumonia
NEUROLOGIC
Visual disturbances (nystagmus, superior oblique or lateral rectus paresis)
Dystonic oculogyric drug reactions (phenothiazines, haloperidol, metoclopramide)
Cervical cord tumor
Posterior fossa brain tumor
Acoustic neuroma
Syringomyelia
Wilson disease
Dystonia musculorum deformans
OTHER
Acute cervical disk calcification
Sandifer syndrome (gastroesophageal reflux, hiatal hernia)
Benign paroxysmal torticollis
Bone tumors (eosinophilic granuloma, osteoid osteoma)
Soft-tissue tumor
Psychogenic

Table 680-2 Causes of Pediatric Cervical Instability

CAUSES	SUBTYPES
Congenital	Cranio-occipital defects (occipital vertebrae, basilar impression, occipital dysplasias, condylar hypoplasia, occipitalized atlas) Atlantoaxial defects (aplasia of atlas arch, aplasia of odontoid process) Subaxial anomalies (failure of segmentation and/or fusion, spina bifida, spondylolisthesis) Syndromic disorders (i.e., Down syndrome, Klippel-Feil syndrome, 22q11.2 deletion syndrome, Larsen syndrome, Marfan syndrome, Ehlers-Danlos syndrome)
Acquired	Trauma Infection (pyogenic/granulomatous) Tumor (including neurofibromatosis) Inflammatory conditions (i.e., juvenile idiopathic arthritis) Osteochondrodysplasias (i.e., achondroplasia, diastrophic dysplasia, metatropic dysplasia, spondyloepiphyseal dysplasia) Storage disorders (i.e., mucopolysaccharidoses) Metabolic disorders (rickets) Miscellaneous (including osteogenesis imperfecta, postsurgery)

Chapter 682

Arthrogryposis

Helen M. Horstmann, Christine M. Conroy, and Richard S. Davidson

Table 682-2 Current Labels and OMIM Numbers for the Distal Arthrogryposis Syndromes

SYNDROME	OMIM NUMBER
Distal arthrogryposis type 1	108120
Distal arthrogryposis type 2A (Freeman-Sheldon syndrome)	193700
Distal arthrogryposis type 2B (Sheldon-Hall syndrome)	601680
Distal arthrogryposis type 3 (Gordon syndrome)	114300
Distal arthrogryposis type 4 (scoliosis)	609128
Distal arthrogryposis type 5 (ophthalmoplegia, ptosis)	108145
Distal arthrogryposis type 6 (sensorineural hearing loss)	108200
Distal arthrogryposis type 7 (trismus-pseudocamptodactyly)	158300
Distal arthrogryposis type 8 (autosomal dominant multiple pterygium syndrome)	178110
Distal arthrogryposis type 9 (congenital contractural arachnodactyly)	121050
Distal arthrogryposis type 10 (congenital plantar contractures)	187370

From Bamshad M, Van Heest AE, Pleasure D: Arthrogryposis: a review and update. J Bone Joint Surg Am *91 Suppl 4:40–46, 2009, Table 1, p. 43.*

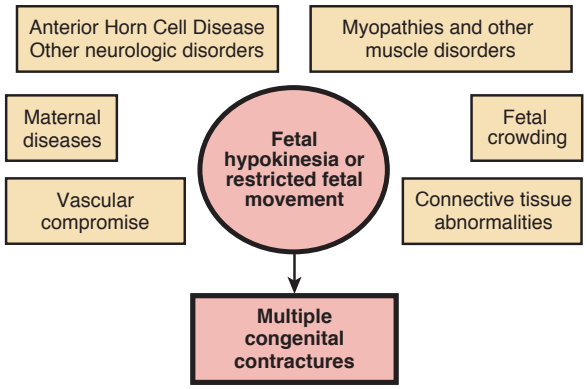

Figure 682-1 Etiology of arthrogryposis. *(Modified from Hall JG: Arthrogryposis multiplex congenital: Etiology, genetics, classification, diagnostic approach, and general aspects.* J Pediatr Orthop B *6:159–166, 1996.)*

Table 682-1 Associated Etiologies of Arthrogryposis

ARTHROGRYPOSIS CAUSED BY NERVOUS SYSTEM DISORDERS
- Focal anterior horn cell deficiency
- Generalized anterior horn cell deficiency
- Structural brain disorder/damage
- Uncertain location

(Spastic conditions are excluded)

DISTAL ARTHROGRYPOSIS SYNDROMES
- Type I dominant distal
- Type IIa dominant distal (Gordon syndrome)
- Type IIe distal
- Digitotalar dysmorphism
- Trismus pseudocamptodactyly
- Distal distribution, type not specified

PTERYGIUM SYNDROMES
- Multiple pterygium syndrome
- Lethal multiple pterygium syndrome
- Popliteal pterygium syndrome
- Ptosis, scoliosis, pterygia
- Antecubital webbing syndrome (Liebenberg)

MYOPATHIES
- Emery-Dreifuss muscular dystrophy
- Hypotonia, myopathy, mild contractures

ABNORMALITIES OF JOINTS AND CONTIGUOUS TISSUE
- Congenital contractural arachnodactyly
- Freeman-Sheldon syndrome
- Laxity or hypertonicity with intrauterine dislocation and contractures
- Larsen syndrome
- Spondyloepimetaphyseal dysplasia with joint laxity
- Trisomy 18, extended breech position with bilateral hip dislocation
- Siblings with bifid humeri, hypertelorism, and hip and knee joint dislocations

SKELETAL DISORDERS
- Diastrophic dysplasia
- Parastremmatic dysplasia
- Kniest dysplasia
- Metatropic dysplasia
- Campomelic dysplasia
- Schwartz syndrome
- Fetal alcohol syndrome with synostoses
- Osteogenesis imperfecta with bowing/contractures

INTRAUTERINE/MATERNAL FACTORS
- Fetal alcohol syndrome with contractures
- Infections
- Untreated maternal systemic lupus erythematosus
- Intrauterine fetal constraint
- Deformity (pressure)
- Amniotic fluid leakage
- Multiple pregnancies
- Intrauterine tumors
- Disruption (bands)

MISCELLANEOUS
- Pseudotrisomy 18 with contractures
- Roberts pseudothalidomide syndrome
- Deafness with distal contractures
- VACTERL association
- Multiple abnormalities and contractures not otherwise specified
- ARC

SINGLE JOINT
- Campomelia
- Symphalangism
- "Trigger" finger

ARC, arthrogryposis, renal tubular acidosis, cholestasis; VACTERL, vertebral defects, imperforate anus, congenital heart disease, tracheoesophageal fistula, renal and limb defects.

Modified from Mennen U, Van Heest A, Ezaki MB, et al: Arthrogryposis multiplex congenita. J Hand Surg Br *30:5:468–474, 2005. Copyright 2005 The British Society for Surgery of the Hand.*

Table 687-1 Staging of Overuse Injuries

GRADE	GRADING SYMPTOMS	TREATMENT
I	Pain only after activity Does not interfere with performance or intensity Generalized tenderness Disappears before next session	Modification of activity, consider cross-training, home rehabilitation program
II	Minimal pain with activity Does not interfere with performance More localized tenderness	Modification of activity, cross-training, home rehabilitation program
III	Pain interferes with activity and performance Definite area of tenderness Usually disappears between sessions	Significant modification of activity, strongly encourage cross-training, home rehabilitation program, and outpatient physical therapy
IV	Pain with activities of daily living Pain does not disappear between sessions Marked interference with performance and training intensity	Discontinue activity temporarily, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy
V	Pain interferes with activities of daily living Signs of tissue injury (e.g., edema) Chronic or recurrent symptoms	Prolonged discontinuation of activity, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy

Table 701-1 Osteogenesis Type, Gene Defects, and Phenotypes

OSTEOGENESIS IMPERFECTA TYPE	GENE DEFECT	PHENOTYPE
DOMINANT INHERITANCE		
Classical Sillence Types		
I	*COL1A1* null allele	Mild, nondeforming
II	*COL1A1* or *COL1A2*	Lethal perinatal
III	*COL1A1* or *COL1A2*	Progressively deforming
IV	*COL1A1* or *COL1A2*	Moderately deforming
COL1-Mutation Negative		
V	*IFITM5*	Distinct histology
RECESSIVE INHERITANCE		
Mineralization Defect		
VI	*SERPINF1*	Distinct histology
3-Hydroxylation Defects		
VII	*CRTAP*	Severe to lethal
VIII	*LEPRE1*	Severe to lethal
IX	*PPIB*	Moderate to lethal
Chaperone Defects		
X	*SERPINH1*	Severe
XI	*FKBP10*	Progressive deforming, Bruck syndrome 1
C-Propeptide Cleavage Defect		
XII	*BMP1*	Severe, high bone mass case
UNCLASSIFIED		
Zinc-finger transcription factor defect	*SP7*	Moderate
Cation channel defect	*TMEM38B*	Moderate to severe
WNT signaling pathway defect	*WNT1*	Moderate, progressively deforming

From Marini JC, Blissett AR: New genes in bone development: what's new in osteogenesis imperfecta. J Clin Endocrinol Metab *98:3095–3103, 2013, Table 1, p. 3096.*

Table 702-1 Diagnostic Criteria for Marfan Syndrome

In the absence of a family history of MFS, a diagnosis can be established in 4 distinct scenarios:
1. Aortic root Z score >2 *and* ectopia Lentis*
2. Aortic root Z score >2 *and* a bona fide *FBN1* mutation
3. Aortic root Z score >2 *and* a systemic score >7*
4. Ectopia lentis *and* a bona fide *FBN1* mutation known to cause aortic disease

In the presence of a family history of MFS, a diagnosis can be established in the presence of:
1. Ectopia lentis
2. A systemic score >7*
3. Aortic root Z score >2 if older than 20 yr or >3 if younger than 20 yr*

In the absence of a family history of MFS, alternative diagnoses include:
1. Ectopia lentis ± systemic score *and FBN1* mutation not known to associate with aortic aneurysm or no *FBN1* mutation = ectopia lentis syndrome
2. Aortic root Z score <2 *and* a systemic score >5 (with at least 1 skeletal feature) without ectopia lentis = MASS (mitral valve prolapse, myopia, borderline and nonprogressive aortic enlargement, and nonspecific skin and skeletal findings) phenotype
3. Mitral valve prolapse *and* aortic root Z score <2 *and* a systemic score <5 without ectopia lentis = mitral valve prolapse syndrome

*Denotes caveat that features suggestive of an alternative diagnosis must be excluded and appropriate alternative molecular testing should be performed.

Table 702-2 Scoring of Systemic Features in Points

- Wrist *and* thumb sign = 3 (wrist *or* thumb sign = 1)
- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hind foot deformity = 2 (plain pes planus = 1)
- Pneumothorax = 2
- Dural ectasia = 2
- Protrusio acetabuli = 2
- Reduced US:LS *and* increased arm:height *and* no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (3/5) = 1 (dolichocephaly, enophthalmos, down-slanting palpebral fissures, midface hypoplasia, retrognathia)
- Skin striae = 1
- Myopia >3 diopters = 1
- Mitral valve prolapse (all types) = 1

Maximum total: 20 points; score ≥7 indicates systemic involvement.
US:LS, upper segment:lower segment ratio.

Table 689-1 Return to Play (RTP) Table

NO CONTRAINDICATION TO RTP	
Healed fractures including:	Healed C1 or C2 fracture with normal cervical spine range of motion (ROM)
	Healed subaxial fracture without sagittal plane deformity
	Asymptomatic clay-shoveler's (C7) spinous process avulsion fracture
Congenital conditions	Klippel-Feil (single-level anomaly not C0/C1 articulation)
	Spina bifida occulta
Degenerative/ postsurgical conditions	Cervical disc disease (no change in baseline neurologic status)
	Single-level anterior cervical fusion (ACF) with/without instrumentation
	Single- or multiple-level posterior cervical laminotomy
Recurrent stingers	Less than 3 episodes lasting <24 hr
	Must have full cervical range of motion
	No persisting neurologic deficit
Transient quadriparesis	Single episode
	Full cervical range of motion
	Normal neurologic exam
	No radiologic instability
	Normal spinal reserve (as evidenced on MRI)
RELATIVE CONTRAINDICATION TO RTP	
Stingers/Burners	Prolonged symptomatic burner/stinger
	Three or more stingers
Transient quadriparesis	Transient quadriparesis lasting >24 hr
	More than 1 episode with symptoms of any duration
Postsurgical	Healed 2-level ACF
	Posterior cervical fusion (PCF) with/ without instrumentation
ABSOLUTE CONTRAINDICATION TO RTP	
Transient quadriparesis and any 1 or more of:	Cervical myelopathy
	Continued neck discomfort
	Reduced ROM
	Neurologic deficit from baseline after injury
Surgical procedures	C1 + C2 fusion
	Cervical laminectomy
	Three-level ACF or PCF
Soft-tissue injuries	Asymptomatic ligamentous laxity (>11 degrees of kyphotic deformity)
	C1 + C2 hypermobility with anterior dens >3.5 mm (adult), >4 mm (child), i.e., Down syndrome (see Chapter 680)
	Symptomatic cervical disc herniation
Other conditions including:	Spear tackler's spine
	Multilevel Klippel-Feil anomaly (see Chapter 680)
	Healed subaxial fracture with sagittal kyphosis coronal plane abnormality, or cord encroachment
	Ankylosing spondylitis
	Rheumatoid arthritis with spinal abnormalities
	Spinal cord abnormality (cord edema, compression, etc.)
	Arnold-Chiari syndrome
	Basilar invagination
	Occipital-C1 assimilation (occipitalization or connection)
	Spinal stenosis (canal width <13 mm between C3 and C7)

Adapted from Cantu R, Li YM, Abdulhamid M, Chin LS: Return to play after cervical spine injury in sports. Curr Sports Med Rep *12:14–17, 2013.*

Table 694-2 Major Problems Associated with Skeletal Dysplasias

PROBLEM	EXAMPLE
Lethality*	Thanatophoric dysplasia
Associated anomalies†	Ellis-van Creveld syndrome
Short stature	Common to almost all
Cervical spine dislocations	Larsen syndrome
Severe limb bowing	Metaphyseal dysplasia, Schmid type
Spine curvatures	Metatropic dysplasia
Clubfeet	Diastrophic dysplasia
Fractures	Osteogenesis imperfecta
Pneumonias, aspirations	Camptomelic dysplasia
Spinal cord compression	Achondroplasia
Joint problems (hips, knees)	Most skeletal dysplasias
Hearing loss	Common (greatest with cleft palate)
Myopia/cataracts	Stickler syndrome
Immunodeficiency‡	Cartilage-hair hypoplasia, Schimke immunoosseous dysplasia
Poor body image	Variable, but common to all
Sex reversal	Camptomelic dysplasia

*Mostly a result of severely reduced size of thorax.

Table 694-5 Usually Nonlethal Dwarfing Conditions Recognizable at Birth or Within 1st Few Mo of Life

MOST COMMON
Achondroplasia
Osteogenesis imperfecta (types I, III, IV)
Spondyloepiphyseal dysplasia congenita
Diastrophic dysplasia
Ellis-van Creveld syndrome
LESS COMMON
Chondrodysplasia punctata (some forms)
Kniest dysplasia
Metatropic dysplasia
Langer mesomelic dysplasia

Table 694-3 Associated Anomalies in Skeletal Dysplasias

ANOMALY	EXAMPLE
Heart defects	Ellis-van Creveld syndrome, Jeune syndrome
Polydactyly	Short rib polydactyly, Majewski type
Cleft palate	Diastrophic dysplasia
Ear cysts	Diastrophic dysplasia
Spinal cord compression	Achondroplasia
Encephalocele	Dyssegmental dysplasia
Hemivertebrae	Dyssegmental dysplasia
Micrognathia	Camptomelic dysplasia
Nail dysplasia	Ellis-van Creveld syndrome
Conical teeth, oligodontia	Ellis-van Creveld syndrome
Multiple oral frenula	Ellis-van Creveld syndrome
Dentinogenesis imperfecta	Osteogenesis imperfecta
Pretibial skin dimples	Camptomelic dysplasia
Cataracts, retinal detachment	Stickler syndrome
Intestinal atresia	Saldino-Noonan
Renal cysts	Saldino-Noonan
Camptodactyly	Diastrophic dysplasia
Craniosynostosis	Thanatophoric dysplasia
Ichthyosis	Chondrodystrophia punctata
Hitchhiker thumb	Diastrophic dysplasia
Sparse scalp hair	Cartilage-hair hypoplasia
Hypertelorism	Robinow syndrome
Hypoplastic nasal bridge	Acrodysostosis
Clavicular agenesis	Cleidocranial dysplasia
Genital hypoplasia	Robinow syndrome
Tail	Metatropic dysplasia
Omphalocele	Beemer-Langer syndrome
Blue sclera	Osteogenesis imperfecta

Table 694-4 Lethal Neonatal Dwarfism

USUALLY FATAL*
Achondrogenesis (different types)
Thanatophoric dysplasia
Short rib polydactyly (different types)
Homozygous achondroplasia
Camptomelic dysplasia
Dyssegmental dysplasia, Silverman-Handmaker type
Osteogenesis imperfecta, type II
Hypophosphatasia (congenital form)
Chondrodysplasia punctata (rhizomelic form)
OFTEN FATAL
Asphyxiating thoracic dystrophy (Jeune syndrome)
OCCASIONALLY FATAL
Ellis-van Creveld syndrome
Diastrophic dysplasia
Metatropic dwarfism
Kniest dysplasia

*A few prolonged survivors have been reported in most of these disorders.

Table 702-4 Differential Diagnosis of Marfan Syndrome

DIFFERENTIAL DIAGNOSIS	CARDIAC FEATURES	VASCULAR FEATURES	SYSTEMIC FEATURES
AORTIC ANEURYSM SYNDROMES			
Loeys-Dietz syndrome (MIM 609192)	Patent ductus arteriosus Atrial septal defect Bicuspid aortic valve	Aortic root aneurysm Arterial tortuosity Widespread aneurysms Vascular dissection at relatively young ages and small aortic dimensions	Hypertelorism Cleft palate Broad or bifid uvula Craniosynostosis Midface hypoplasia Blue sclerae Arachnodactyly Pectus deformity Scoliosis Joint hypermobility Pes planus Rarely Easy bruising Dystrophic scars Translucent skin Rarely developmental delay
Familial thoracic aortic aneurysm (MIM 132900)	Generally none Rare forms with patent ductus arteriosus	Aortic root aneurysm Ascending aortic aneurysm	Generally none Rarely livedo reticularis and iris flocculi
Shprintzen-Goldberg syndrome (MIM 182212)	None	Aortic root aneurysm	Hypertelorism Craniosynostosis Arched palate Arachnodactyly Pectus deformity Scoliosis Joint hypermobility Developmental delay
Bicuspid aortic valve with aortic aneurysm (MIM: 109730)	Bicuspid aortic valve	Aortic root aneurysm Ascending aortic aneurysm	
Ehlers-Danlos syndrome, type IV (MIM: 130050)	Mitral valve prolapse	Aneurysm and rupture of any medium to large muscular artery No predisposition for aortic root enlargement	Joint hypermobility Atrophic scars Translucent skin Easy bruising Hernias Rupture of hollow organs
ECTOPIA LENTIS SYNDROMES			
Familial ectopia lentis (MIM 129600)	None	None	Nonspecific skeletal features
Homocystinuria (MIM 236200)	Mitral valve prolapse	Intravascular thrombosis	Tall stature Ectopia lentis Long-bone overgrowth Developmental delay
SYNDROMES WITH SYSTEMIC MANIFESTATIONS OF MFS			
MASS phenotype (MIM 604308)	Mitral valve prolapse	Borderline or nonprogressive	Nonspecific skin and skeletal findings Myopia

Table 703-2 Clinical Variants of Rickets and Related Conditions

TYPE	SERUM CALCIUM LEVEL	SERUM PHOSPHORUS LEVEL	ALKALINE PHOSPHATASE ACTIVITY	URINE CONCENTRATION OF AMINO ACIDS	GENETICS	GENE DEFECT KNOWN
CALCIUM DEFICIENCY WITH SECONDARY HYPERPARATHYROIDISM [DEFICIENCY OF VITAMIN D; LOW 25(OH)D AND NO STIMULATION OF HIGHER $1,25(OH)_2D$ VALUES]						
Lack of Vitamin D						
Lack of exposure to sunlight	N or L	L	E	E		
Dietary deficiency of vitamin D	N or L	L	E	E		
Congenital	N or L	L	E	E		
Other Deficiencies						
Malabsorption of vitamin D	N or L	L	E	E		
Liver diseases	N or L	L	E	E		
Anticonvulsant drug	N or L	L	E	E		
Renal osteodystrophy	N or L	E	E	V		
Vitamin D–dependent type I	L	N or L	E	E	AR	Y
PRIMARY PHOSPHATE DEFICIENCY (NO SECONDARY HYPERPARATHYROIDISM)						
Genetic Primary Hypophosphatemia	N	L	E	N	XI, AD, AR	Y
X-linked hypophosphatemic rickets					XL	Y
Autosomal dominant hypophosphatemic rickets					AD	Y
Autosomal recessive hypophosphatemic rickets					AR	Y
Fanconi Syndrome						
Cystinosis	N	L	E	E	AR	Y
Tyrosinosis	N	L	E	E	AR	Y
Lowe syndrome	N	L	E	E	XR	Y
Acquired	N	L	E	E		
Phosphate Deficiency or Malabsorption						
Parenteral hyperalimentation	N	L	E	N		
Low phosphate intake	N	L	E	N		
Other						
Renal tubular acidosis, type II proximal	N	L	E	N		Y
Tumor-induced osteomalacia	N	L	E	N		Y
END-ORGAN RESISTANCE TO $1,25(OH)_2D_3$						
Vitamin D-dependent type II (several variants)	L	L or N	E	E	AR	Y
RELATED CONDITIONS RESEMBLING RICKETS						
Hypophosphatasia	N	N	L	Phosphoethanolamine elevated	AR	Y
Metaphyseal Dysostosis						
Jansen type		N	E	N	AD	Y
Schmid type		N	E	N	AD	Y

AD, autosomal dominant; AR, autosomal recessive; E, elevated; L, low; N, normal; V, variable; XL, X-linked; Y, yes.

Table 715-1 Prognosticating in Myelomeningocele

MOTOR LEVEL SPINAL CORD SEGMENT	CRITICAL MOTOR FUNCTION PRESENT	MOBILITY: SCHOOL AGE	RANGE: ADULT	ACTIVITY: ADOLESCENT
T12	Totally paralyzed lower limbs	Standing brace, wheelchair	Wheelchair	Wheelchair, no ambulation
L1-2	Hip flexor muscles	Crutches, braces, wheelchair	Wheelchair, household ambulation	Wheelchair, nonfunctional ambulation
L3-4	Quadriceps muscles	Crutches, braces, household ambulation, wheelchair	Crutches, household ambulation, wheelchair	50% Wheelchair, household ambulation with crutches
L5	Medical hamstrings, anterior tibial muscles	Crutches, braces, community ambulation	Crutches, community ambulation	Community ambulation with crutches
S1	Lateral hamstring and peroneal muscles	Community ambulation	Community ambulation	Community ambulation 50% crutch or cane
S2-3	Mild loss of intrinsic foot muscles possible	Normal	Normal	Limited endurance because of late foot deformities

From Braddon RL, editor: Physical medicine & rehabilitation, *ed 4, Philadelphia, 2011, WB Saunders, Table 54-1, p. 1284.*

Table 707-1 Risks for Osteoporosis

ENDOCRINE DISORDERS
Female Hypogonadism
Turner syndrome
Hypothalamic amenorrhea (athletic triad)
Anorexia nervosa
Premature and primary ovarian failure
Depot medroxyprogesterone acetate therapy
Estrogen receptor α *(ESR1)* mutations
Hyperprolactinemia
Male Hypogonadism
Primary gonadal failure (Klinefelter syndrome)
Secondary gonadal failure (idiopathic hypogonadotropic hypogonadism)
Delayed puberty
Hyperthyroidism
Hyperparathyroidism
Hypercortisolism (therapeutic or Cushing disease)
Growth hormone deficiency
Thyrotoxicosis

INFLAMMATORY DISORDERS
Dermatomyositis
Chronic hepatitis
Systemic lupus erythematosus

GASTROINTESTINAL DISORDERS
Malabsorption syndromes (cystic fibrosis, celiac disease, biliary atresia)
True or perceived milk intolerance
Inflammatory bowel disease
Chronic obstructive jaundice
Primary biliary cirrhosis and other cirrhoses
Alactasia
Subtotal gastrectomy

BONE MARROW DISORDERS
Bone marrow transplant
Lymphoma
Leukemia
Hemolytic anemias (sickle cell anemia, thalassemia)
Systemic mastocytosis

CONNECTIVE TISSUE/BONE DISORDERS
Juvenile osteoporosis
Osteogenesis imperfecta
Ehlers-Danlos syndrome
Marfan syndrome
Homocystinuria
Fibrous dysplasia
Previous or recurrent low impact fractures
Early onset osteoporosis with *WNT1* mutations
X-linked osteoporosis with fractures with *PLS3* mutations

DRUGS
Alcohol
Heparin
Glucocorticosteroids
Thyroxine
Anticonvulsants
Gonadotropin-releasing hormone agonists
Cyclosporine
Chemotherapy
Cigarettes

MISCELLANEOUS DISORDERS
Immobilization (cerebral palsy, spinal muscular atrophy, Duchenne dystrophy)
Rheumatoid arthritis
Renal disease
Glycogen storage disease type 1
Chronic hepatitis
Low calcium dietary intake
Gaucher disease
Severe congenital neutropenia

Table 723-1 Diseases Caused By Agents of Chemical and Biologic Terrorism, Classified By Syndrome

	NEUROMUSCULAR SYMPTOMS PROMINENT	RESPIRATORY SYMPTOMS PROMINENT	DERMATOLOGIC FINDINGS PROMINENT
Sudden-onset	Nerve agents	Chlorine Phosgene Cyanide	Mustard Lewisite
Delayed-onset	Botulism	Anthrax Plague Tularemia Ricin	Smallpox

Rehabilitation Medicine and Others

Table 712-1 Dosing Guidelines, Pharmacologic Actions, and Adverse Event Profile of Commonly Prescribed Oral Antispasmodic Medications for Children

ORAL MEDICATION (DOSE/FREQ., AGE/ WEIGHT RANGE)	MODE OF ACTION	ADVERSE EVENTS/PRECAUTIONS
Baclofen (0.125-1 mg/kg/day) *Dosing guideline* *2-7 yr* 2.5-10 mg tid-qid (10-40 mg/day) *8-12 yr* 5-15 mg tid-qid (15-60 mg/day) *12-16 yr* 5-20 mg tid-qid (20-80 mg/day) *Note:* Caution advised with renal impairment, consider reducing dose.	Centrally acting, structural analog of γ-aminobutyric acid (GABA), binds to $GABA_B$ receptors of presynaptic excitatory interneurons (and postsynaptic primary afferents) causing presynaptic inhibition of monosynaptic/polysynaptic spinal reflexes. Rapid absorption, blood level peaks in 1 hr, half-life 5.5 hr. Renal (70-80% unchanged) and hepatic (15%) excretion.	Central nervous system (CNS) depression (sedation, drowsiness, fatigue), nausea, headache, dizziness, confusion, euphoria, hallucinations, hypotonia, ataxia, paresthesias. **Note: Abrupt withdrawal** may cause seizures, hallucinations, rebound muscle spasms, and hyperpyrexia.
Diazepam (0.12-0.8 mg/kg/day) *Dosing guideline* 6 mo-12 yr 0.12-0.8 mg/kg/day PO divided q6-8h >12 yr 2-10 mg PO bid-qid *Note:* Prescription of a *qhs* dose only or proportionately larger dose at bedtime may limit excessive daytime sedation.	Centrally acting; binds to $GABA_A$ receptors mediating presynaptic inhibition in brainstem reticular formation and spinal polysynaptic pathways. Rapid absorption; blood level peaks in 1 hr, with half-life of 30-60 hr. Metabolized in liver, producing pharmacologically active metabolites with long duration of action. Increased potential for adverse effects with low albumin levels as a result of being 98% protein bound.	CNS depression (sedation, impaired memory and attention), ataxia. Dependence/potential for substance abuse/ overdose. Withdrawal syndrome (including anxiety, agitation, irritability, tremor, muscle twitching, nausea, insomnia, seizures, hyperpyrexia).
Dantrolene Sodium (3-12 mg/kg/day) *Dosing guideline (for children >5 yr old):* *6-8 mg/kg/day PO divided bid-qid* In children >5 yr old Start 0.5 mg/kg qd-bid for 7 days, then 0.5 mg/kg tid for 7 days, then 1 mg/kg tid for 7 days, then 2 mg/kg tid to a maximum of 12 mg/kg/day or 400 mg/day.	Peripheral action, blocking release of calcium from sarcoplasmic reticulum with uncoupling of nerve excitation and skeletal muscle contraction. Blood level peaks in 3-6 hr (active metabolite 4-8 hr), with half-life of approximately 15 hr. Metabolized largely in liver, with 15-25% of nonmetabolized drug excreted in urine.	Malaise, fatigue, nausea, vomiting, diarrhea, muscle weakness with high dose. *Note:* Hepatotoxicity (baseline liver function tests **must** be checked prior to starting dantrolene, tested weekly during dose titration, and regularly every 1-2 mo thereafter). Drug *should be discontinued* promptly if liver enzymes become elevated.
Tizanidine *Dosing guideline* In children <10 yr: Commence 1 mg orally at bedtime initially, increasing to 0.3-0.5 mg/ kg in 4 divided doses. In children >10 yr: Commence 2 mg orally at bedtime initially, increased according to response, maximum 24 mg/day in 3-4 divided doses.	Centrally acting, α_2-adrenoceptor agonist activity at both spinal and supraspinal sites. Prevents release of excitatory amino acids, facilitating presynaptic inhibition. Good oral absorption, blood level peaks in 1-2 hr, with a half-life of 2.5 hr. Extensive first-pass hepatic metabolism with urinary excretion of inactive metabolites.	Dry mouth, drowsiness, tiredness, headache, dizziness, insomnia, anxiety, aggression, mood swings, visual hallucinations, risk of hypotension (although 10 times less antihypertensive potency than clonidine), nausea, vomiting, and constipation. Liver function tests should be monitored at baseline, 1, 3, and 6 mo. Then periodically.
Clonidine *Dosing guideline* 0.025-0.1 mg in 2-3 divided doses. *Note:* A retrospective chart review of literature about clonidine in children reported an average dosage based on weight was 0.02-0.03 mg/kg/day (0.4-0.5 mg/day), with a range of 0.0014-0.15 mg/kg/day.	Centrally acting, mixed α-adrenoceptor agonist with predominant α_2 activity causing membrane hyperpolarization at multiple sites in brain, brainstem, and dorsal horns of spinal cord. Inhibition of substance P may also contribute to tone reduction via an antinociceptive effect. Rapidly absorbed orally, blood level peaks in 1-1.5 hr, with a half-life of 6-20 hr.	Drowsiness, dry mouth, bradycardia, orthostatic hypotension. Abrupt cessation may result in rebound hypertension.

Table 720-3 Differential Characteristics of Mercury Exposure

	ELEMENTAL	INORGANIC (SALT)	ORGANIC (ALKYL)
Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Kidney	CNS, kidney, liver
Clearance	Renal, GI	Renal, GI	Methyl: GI Aryl: renal, GI
Clinical effects:			
CNS	Tremor	Tremor, erethism (irritability)	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+++	—	—
Gastrointestinal	+	+++ (caustic)	+
Renal	+	+++ (acute tubular necrosis)	+
Acrodynia	+	++	—
Therapy	BAL, DMSA	BAL, DMSA	DMSA (early)

BAL, British antilewisite; CNS, central nervous system; DMSA, 2,3-dimercaptosuccinic acid; GI, gastrointestinal; +, mild; ++, moderate; +++, severe.

Table 719-1 Effects of Selected Chemical Pollutants on Infants and Children

CHEMICAL POLLUTANT	EFFECT(S)
Air pollution	Asthma, other respiratory diseases, sudden infant death syndrome
Asbestos	Mesothelioma and lung cancer
Benzene, nitrosamine, vinyl chloride, ionizing radiation	Cancer
Diethylstilbestrol	Adenocarcinoma of the vagina after intrauterine exposure
Environmental tobacco smoke	Increased risk of sudden infant death syndrome and asthma
Ethyl alcohol	Fetal alcohol syndrome after intrauterine exposure
Lead	Neurobehavioral toxicity from low-dose exposure
Methyl mercury	Developmental neurotoxicity
Organophosphate insecticides	Developmental neurotoxicity
Polychlorinated biphenyls	Developmental neurotoxicity
Polybrominated diphenyl ethers	Developmental neurotoxicity
Phthalates	Developmental neurotoxicity and reproductive impairment
Thalidomide	Phocomelia after intrauterine exposure
Trichloroethylene	Elevated risk of leukemia after intrauterine exposure

Table 720-1 Effects of Arsenic on Organ Systems

ORGAN SYSTEM	EFFECTS OF ARSENIC
Gastrointestinal system	Submucosal vesicles, watery or bloody diarrhea, severe hematemesis
Cardiovascular system	Reduced myocardial contractility, prolonged QT intervals, tachyarrhythmias
	Vasodilation, hypotension
Kidneys	Hematuria, proteinuria, acute tubular necrosis
Nervous system	Toxic encephalopathy with seizures, cerebral edema, and coma
	Chronic exposure: peripheral painful sensorimotor neuropathy
Hematologic and lymphatic system	Anemia and thrombocytopenia; acute hemolysis with arsine gas
Liver	Fatty degeneration with central necrosis
Skin	Desquamation, alopecia, hyperkeratosis, nail changes
	Chronic exposure: hyperkeratosis, hyperpigmentation
Teratogenic	Neural tube defects in the fetus
Oncologic	Urologic cancer, other malignancies

Table 720-2 Acceptable and Toxic Levels of Arsenic and Mercury

	ARSENIC	MERCURY
Molecular weight	74.9 Da	200.59 Da
Acceptable blood level	<5 μg/L (<0.665 nmol/L)	<10 μg/L (<50 nmol/L)
Acceptable urine level	<50 μg/L (<6.65 nmol/L) 24 hr urine sample	<20 μg/L (<100 nmol/L)
Intervene at blood level		>35 μg/L (>175 nmol/L)
Intervene at urine level	>100 μg/L (>13.3 nmol/L) 24 hr urine sample	>150 μg/L (>750 nmol/L)

Table 721-4 Chelation Therapy

NAME	SYNONYM	DOSE	TOXICITY
Succimer	Chemet, 2,3-dimercaptosuccinic acid (DMSA)	350 mg/m^2 body surface area/dose ***(not 10 mg/kg)*** q8h, PO for 5 days, then q12h for 14 days	Gastrointestinal distress, rashes; elevated LFTs, depressed white blood cell count
Edetate*	$CaNa_2EDTA$ (calcium disodium edetate), versenate	1,000-1,500 mg/m^2 body surface area/day; IV infusion—continuous or intermittent; IM divided q6h or q12h for 5 days	Proteinuria, pyuria, rising blood urea nitrogen/creatinine—all rare Hypercalcemia if too rapid an infusion Tissue inflammation if infusion infiltrates
British antilewisite (BAL)	Dimercaprol	300-500 mg/m^2 body surface area/day; **IM only** divided q4h for 3-5 days. Only for BLL ≥70 μg/dL	Gastrointestinal distress, altered mentation; elevated LFTs, hemolysis if glucose-6-phosphate dehydrogenase deficiency; no concomitant iron treatment
D-Pen	Penicillamine	10 mg/kg/day for 2 wk increasing to 25-40 mg/kg/day; oral, divided q12h. For 12-20 wk	Rashes, fever; blood dyscrasias, elevated LFTs, proteinuria Allergic cross reactivity with penicillin

*Always given as the calcium salt; never as the sodium salt without calcium.
BLL, blood lead level; IM, intramuscularly; IV, intravenously; LFT, liver function test; PO, by mouth.
From Markowitz ME: Lead poisoning, Pediatr Rev *21:327–335, 2000.*

Table 723-3 Critical Chemical Agents of Terrorism

AGENT	TOXICITY	CLINICAL FINDINGS	ONSET	DECONTAMINATION*	MANAGEMENT
NERVE AGENTS					
Tabun, sarin, soman, VX	Anticholinesterase: muscarinic, nicotinic, central nervous system effects	Vapor: miosis, rhinorrhea, dyspnea Liquid: diaphoresis, vomiting Both: coma, paralysis, seizures, apnea	Seconds: vapor Minutes to hours: liquid	Vapor: fresh air, remove clothes, wash hair Liquid: remove clothes, wash skin, hair with copious soap and water, ocular irrigation	ABCs. Atropine: 0.05 mg/kg IV†, IM‡ (min: 0.1 mg, max: 5 mg), repeat q2-5 min prn for marked secretions, bronchospasm Pralidoxime: 25 mg/kg IV, IM§ (max: 1 g IV; 2 g IM), may repeat within 30-60 min prn, then again q1h for 1 or 2 doses prn for persistent weakness, high atropine requirement Diazepam: 0.3 mg/kg (max: 10 mg) IV; lorazepam: 0.1 mg/kg IV, IM (max: 4 mg); midazolam: 0.2 mg/kg (max: 10 mg) IM prn for seizures or severe exposure
VESICANTS					
Mustard	Alkylation	Skin: erythema, vesicles Eye: inflammation Respiratory tract: inflammation	Hours	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Symptomatic care
Lewisite	Arsenical		Immediate pain		Possibly British antilewisite (BAL) 3 mg/kg IM q4-6h for systemic effects of lewisite in severe cases
PULMONARY AGENTS					
Chlorine, phosgene	Liberate hydrochloric acid, alkylation	Eye, nose, and throat irritation (especially chlorine) Respiratory: bronchospasm, pulmonary edema (especially phosgene)	Minutes: eye, nose, and throat irritation, bronchospasm Hours: pulmonary edema	Fresh air Skin: water	Symptomatic care (see text)
CYANIDE					
	Cytochrome oxidase Inhibition: cellular anoxia, lactic acidosis	Tachypnea, coma, seizures, apnea	Seconds	Fresh air	ABCs, 100% oxygen
				Skin: soap and water	Na bicarbonate prn metabolic acidosis; hydroxycobalamin 70 mg/kg IV (max: 5 g) *or* nitrite/thiosulfate, given as follows (see text): *Na nitrite (3%): dose (mL/kg)* (max: 10 mL) — *Estimated hemoglobin concentration (g/dL)* 0.27 — 10 0.33 — 12 (estimated for average child) 0.39 — 14 followed by Na thiosulfate (25%): 1.65 mL/kg (max: 50 mL)

*Decontamination, especially for patients with significant nerve agent or vesicant exposure, should be performed by healthcare providers garbed in adequate personal protective equipment. For emergency department staff, this equipment consists of a nonencapsulated, chemically resistant body suit, boots, and gloves with a full-face air-purifier mask/hood.

†Intraosseous route is likely equivalent to intravenous.

‡Atropine might have some benefit via endotracheal tube or inhalation, as might aerosolized ipratropium. See also Table 723-4.

§Pralidoxime is reconstituted to 50 mg/mL (1 g in 20 mL water) for IV administration, and the total dose infused over 30 min, or may be given by continuous infusion (loading dose 25 mg/kg over 30 min, and then 10 mg/kg/hr). For IM use, it might be diluted to a concentration of 300 mg/mL (1 g added to 3 mL water—by analogy to the U.S. Army's Mark 1 autoinjector concentration), to effect a reasonable volume for injection. See also Table 723-4.

ABCs, airway, breathing, and circulatory support; max, maximum; min, minimum; prn, as needed.

Adapted from Henretig FH, Cieslak TJ, Eitzen EM: Biological and chemical terrorism, J Pediatr *141:311–326, 2002.*

Table 724-2 Microorganisms Associated with Bites

DOG BITES
Staphylococcus species
Streptococcus species
Eikenella species
Pasteurella species
Proteus species
Klebsiella species
Haemophilus species
Enterobacter species
Capnocytophaga canimorsus
Bacteroides species
Moraxella species
Corynebacterium species
Neisseria species
Fusobacterium species
Prevotella species
Porphyromonas species

CAT BITES
Pasteurella species
Actinomyces species
Propionibacterium species
Bacteroides species
Fusobacterium species
Clostridium species
Wolinella species
Peptostreptococcus species
Staphylococcus species
Streptococcus species

HERBIVORE BITES
Actinobacillus lignieresii
Actinobacillus suis
Pasteurella multocida
Pasteurella caballi
Staphylococcus hyicus subsp. *hyicus*

SWINE BITES
Pasteurella aerogenes
Pasteurella multocida
Bacteroides species
Proteus species
Actinobacillus suis
Streptococcus species
Flavobacterium species
Mycoplasma species

RODENT BITES—RAT BITE FEVER
Streptobacillus moniliformis
Spirillum minus

PRIMATE BITES
Bacteroides species
Fusobacterium species
Eikenella corrodens
Streptococcus species
Enterococcus species
Staphylococcus species
Enterobacteriaceae
Simian herpesvirus

LARGE REPTILE (CROCODILE, ALLIGATOR) BITES
Aeromonas hydrophila
Pseudomonas pseudomallei
Pseudomonas aeruginosa
Proteus species
Enterococcus species
Clostridium species

Table 724-3 Prophylactic Management of Human or Animal Bite Wounds to Prevent Infection

CATEGORY OF MANAGEMENT	MANAGEMENT
Cleansing	Remove visible dirt. Cleanse the wound surface with soap and water, saline, 1% povidone–iodine, or 1% benzalkonium chloride. Irrigate with a copious volume of sterile saline solution by high-pressure syringe irrigation.* Do not irrigate puncture wounds; Standard Precautions should be used.
Wound culture	No, for fresh wounds, unless signs of infection exist. Yes for wounds that appear infected.†
Diagnostic Imaging	Indicated for penetrating injuries overlying bones or joints, for suspected fracture, or to assess foreign body inoculation.
Debridement	Remove superficial devitalized tissue.
Operative debridement and exploration	Yes if any of the following: • Extensive wounds (devitalized tissue) • Involvement of the metacarpophalangeal joint (clenched-fist injury) • Cranial bites by large animal
Wound closure	Yes for selected fresh, nonpuncture bite wounds.
Assess tetanus immunization status	Yes.
Assess risk of rabies from animal bites	Yes.
Assess risk of hepatitis B virus infection from human bites	Yes.
Assess risk of human immunodeficiency virus from human bites	Yes.
Initiate antimicrobial therapy	Yes for: • Moderate or severe bite wounds, especially if edema or crush injury is present • Puncture wounds, especially if penetration of bone, tendon sheath, or joint has occurred • Face, hand, foot, and genital bites • Wounds in immunocompromised and asplenic persons • Wounds with signs of infection
Follow-up	Inspect wound for signs of infection within 48 hr

*Use of an 18-gauge needle with a large-volume syringe is effective. Antimicrobial or antiinfective solutions offer no advantage and may increase tissue irritation.

†Both aerobic and anaerobic bacterial culture should be performed.