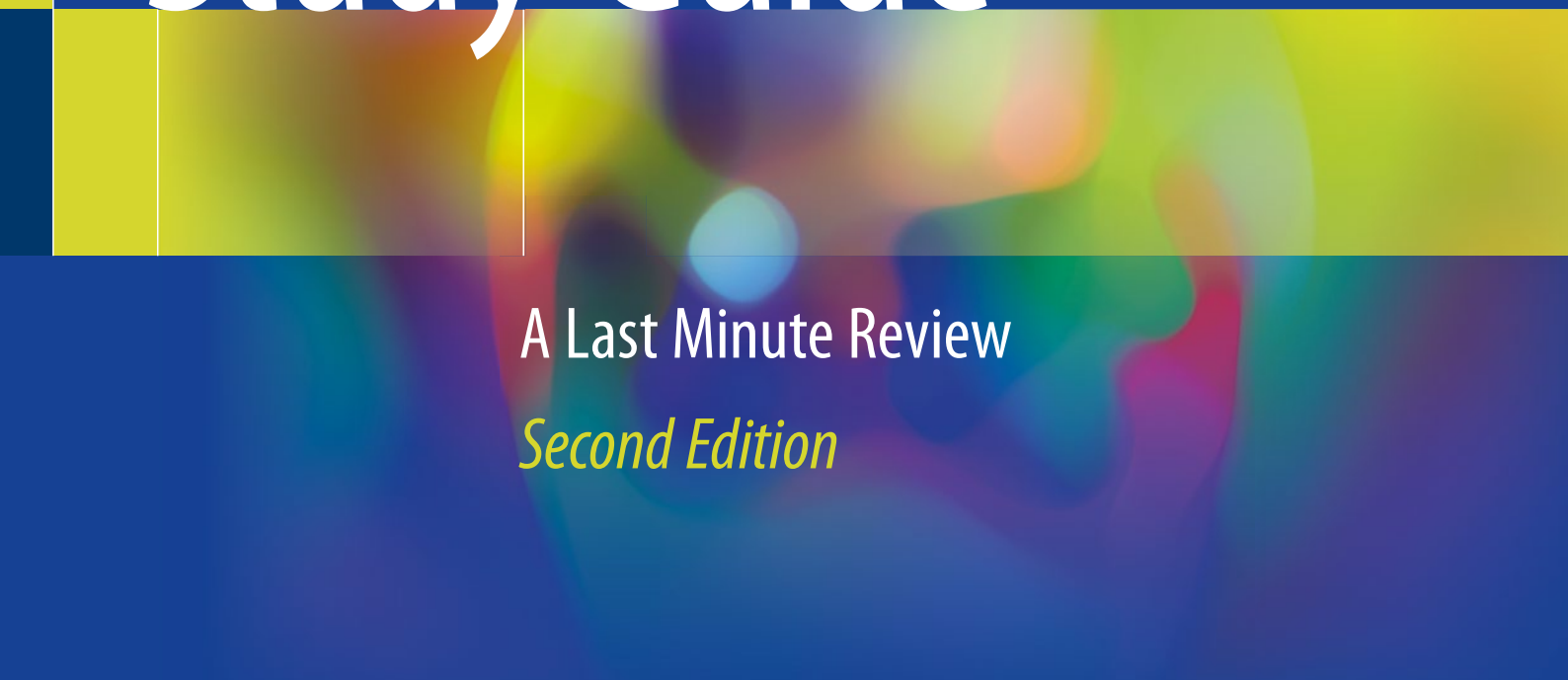
Osama I. Naga
Editor

Pediatric Board Study Guide



A Last Minute Review

Second Edition

Springer

Pediatric Board Study Guide

Osama I. Naga
Editor

Pediatric Board Study Guide

A Last Minute Review

Second Edition

Springer

Editor
Osama I. Naga, MD
Department of Pediatrics
Paul L. Foster School of Medicine
Texas Tech University Health Sciences Center
El Paso, TX
USA

ISBN 978-3-030-21266-7 ISBN 978-3-030-21267-4 (eBook)
https://doi.org/10.1007/978-3-030-21267-4

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

I owe my deepest gratitude to the contributors whose expertise helped bring this pediatric resource to life.

To all the pediatricians who keep on learning for the sake of the children!

Preface

The *Pediatric Board Study Guide: A Last Minute Review* provides the core material needed to pass the General Pediatrics Certifying Examination by the American Board of Pediatrics (ABP) and to meet the requirements required for the ABP Maintenance of Certification. This book contains a total of 33 chapters; the first 31 chapters discuss all aspects of pediatric medicine and are all updated according to the most recent content specifications provided by the ABP. Chapter 32 reviews common pediatric radiology cases, while Chapter 33, the final chapter, consists of high-yield last minute review cases.

The second edition is notably more comprehensive and detailed than the first. Improvements over the previous edition include more illustrations and added chapters. Each chapter has been either written or reviewed by an expert in that specific field from a top academic institution in the United States. New chapters include Sports Medicine, Nutrition, Fluids and Electrolytes, Ethics, Patient Safety and Quality Improvement, and Pharmacology. Finally, to make the chapters even more incisive, "Pearls and Pitfalls" have been added at the end of each chapter.

The 80 clinical case scenarios in the Radiology Review (Chap. 32), with its distinct images and radiological findings, should not only improve exam performance but also help the general pediatrician to identify common radiological findings.

The final chapter, Last Minute Review, has been expanded in this new edition. These high-yield cases are arranged in the same sequence as the book chapters and placed in a way that allows the reader to discriminate among diseases and conditions, helping the test taker to distinguish between similar presenting cases on the exam. The final chapter allows the reader to review in the shortest time possible more than 1700 critical facts for the pediatric board exam, making it the ideal resource for the week prior to the exam.

This book is of particular interest to pediatricians, fellows, pediatric subspecialists preparing for the board examination or certification maintenance, pediatric residents preparing for the in-service exam, daily rounds, and real-life clinical encounters.

About the ABP board-certifying exam

- The board exam is offered once a year, usually in October.
- The exam consists of four sections.
- There is a total of 330–350 multiple-choice questions with normally five answer choices for each question.
- There are currently four sections with each section lasting 105 minutes. There is a 15-minute break between the first two sections.
- After the second section, there is a 60-minute lunch break.
- There is another 15-minute break between section 3 and section 4
- The exam is scored from 0 to 300 with 180 being a passing score.

How to study for the ABP board-certifying exam

- Read the text of the *Pediatric Board Study Guide: A Last Minute Review* thoroughly multiple times throughout your residency.
- Chapters can be read sequentially or can be read in conjunction with a rotation.

- For example, a resident doing a 1-month pediatric cardiology rotation could usefully read in Chap. 19, Cardiology.
- After finishing a chapter, turn to Chap. 33 to review the Last Minute Review cases for that particular specialty.
- Make sure to study the most recent self-assessment curricula of the Pediatric Review and Education Program (PREP): https://shop.aap.org/professional-education/self-assessments.
- Simulate the test-taking experience by answering timed questions.
- Read the critiques/explanations after each question, including the PREP Pearls at the end of each question.
- Read the new articles in *Pediatrics in Review* and answer their CME questions.
- Two to three months before the exam, read the *Pediatric Board Study Guide* one more time.
- One week before the exam, read for one final time Chap. 33, the Last Minute Review.
- Rest at least 24 hours before the exam.

The day of the exam

- Have a good breakfast.
- Arrive early to the testing center.
- Make sure to have all the documents with you (ID, exam ticket, etc.).
- Make sure to dress appropriately; sometimes the testing room may be cold.
- During the exam, make sure to answer all questions. Do not leave any question unanswered even if you do not know the answer. There is no penalty for guessing.
- Pace yourself: once the time has expired in a section, you cannot go back.

El Paso, TX, USA Osama Naga

Contents

Editor

Osama I. Naga, MD Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, USA

Contributors

Amr Abdelgawad, MD, MBA Department of Orthopaedic Surgery and Rehabilitation, Texas Tech University Health Sciences Center, El Paso, TX, USA

Marwa Abdou, MD Department of Pediatrics, Texas Tech University Health Sciences Center, El Paso, TX, USA

Jessica Addison, MD, MS Division of Adolescent/Young Adult Medicine, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Mohamed Hamdy Ataalla, MD Department of Child and Adolescent Psychiatry, Texas Tech University Health Sciences Center, El Paso, TX, USA

Robert D. Baker, MD, PhD Department of Pediatrics, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Amherst, NY, USA

Susan S. Baker, MD, PhD Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

Amanda G. Brown, MD Division of Rheumatology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Catherine J. Chen, MD Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Megan Craddock, MD Department of Dermatology and Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA

Ellen Fraint, MD Division of Pediatric Hematology, Oncology, Marrow and Blood Cell Transplantation, Department of Pediatrics, Children's Hospital at Montefiore, Bronx, NY, USA

Mamta Fuloria, MD Division of Neonatology, Department of Pediatrics, The Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA

Maria I. Garcia Lloret, MD, MSc Division of Pediatric Allergy/Immunology and Rheumatology, Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA, USA

Michael George, MD Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Beatrice Goilav, MD Pediatric Nephrology, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA

Ivet Hartonian, MD, MS Pediatric Neurology, Department of Pediatrics, Adventist Health White Memorial, Los Angeles, CA, USA

Allison Hill, MD Division of Cardiology, Department of Pediatrics, Children's Hospital of Los Angeles, USC Keck School of Medicine, Los Angeles, CA, USA

Micah A. Jacobs, MD, MPH Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Wendy G. Kim, MD Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Sitratullah O. Kukoyi-Maiyegun, MD Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Science Center, El Paso, TX, USA

Grace Kung, MD Division of Cardiology, Department of Pediatrics, Children's Hospital of Los Angeles, USC Keck School of Medicine, Los Angeles, CA, USA

Caroline Y. Kuo, MD Division of Pediatric Allergy/Immunology and Rheumatology, Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA, USA

William Blaine Lapin, MD Division of Rheumatology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Matthew B. Laurens, MD, MPH Division of Infectious Diseases and Tropical Pediatrics, Department of Pediatrics, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA

Jason T. Lerner, MD Pediatric Neurology, Department of Pediatrics, UCLA Mattel Children's Hospital, Los Angeles, CA, USA

Tanya Martínez-Fernández, MD Division Respiratory Medicine, Department of Pediatrics, University of Texas Southwestern Medical Center/Children's Medical Center Dallas, Dallas, TX, USA

Jennifer McConnell, MD Division of Pediatric Emergency Medicine, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA

Kara D. Meister, MD Department of Otolaryngology-Head & Neck Surgery, Pediatrics Division, Lucile Packard Children's Hospital, Stanford University, Stanford, CA, USA

Anna H. Messner, MD, FACS, FAAP Professor of Otolaryngology/Head & Neck Surgery, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Kyle E. Miller, MC(FS) USN, MD Department of Ophthalmology, Naval Medical Center Portsmouth, Portsmouth, VA, USA

Scott Moerdler, MD Pediatric Hematology/Oncology Program, Department of Pediatrics, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ, USA

Kerry Morrone, MD Division of Pediatric Hematology, Oncology, Marrow and Blood Cell Transplantation, Department of Pediatrics, Children's Hospital at Montefiore, Bronx, NY, USA

Amr Morsi, MD Division of Endocrinology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

Daniel Murphy, MD, CAQ-Sports Medicine Department of Family and Community Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Center, El Paso, TX, USA

Osama I. Naga, MD Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, USA

Jo-Ann O. Nesiama, MD, MS Division of Pediatric Emergency Medicine, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA

Violeta Radenovich, MD, MPH Children's Eye Center of El Paso, Pediatric Ophthalmology, Texas Tech University Health Science Center, El Paso, TX, USA

Nora E. Rahmani, MD Division of Pediatric Hematology, Oncology, Marrow and Blood Cell Transplantation, Department of Pediatrics, Children's Hospital at Montefiore, Bronx, NY, USA

Andrea A. Ramirez, MD Division of Rheumatology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Jennifer L. Rammel, MD Division of Rheumatology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Yadira Rivera-Sánchez, MD Division Respiratory Medicine, Department of Pediatrics, University of Texas Southwestern Medical Center/Children's Medical Center Dallas, Dallas, TX, USA

Shira L. Robbins, MD, FAAO, FAAP Department of Ophthalmology, Ratner Children's Eye Center, University of California San Diego, La Jolla, CA, USA

Jennifer Ruth, MD Department of Dermatology and Pediatrics, Dell Children's Medical Group, Austin, TX, USA

Preeti Sharma, MD Division Respiratory Medicine, Department of Pediatrics, University of Texas Southwestern Medical Center/Children's Medical Center Dallas, Dallas, TX, USA

Arpan A. Sinha, MBBS, MD Jimmy Everest Center of Pediatric Hematology and Oncology, Department of Pediatrics, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Benjamin Steinman, DO Department of Pediatrics, The Children's Hospital at SUNY Downstate, SUNY Downstate Medical Center, Brooklyn, NY, USA

Jennifer Su, MD Division of Cardiology, Department of Pediatrics, Children's Hospital of Los Angeles, USC Keck School of Medicine, Los Angeles, CA, USA

Adit Tal, MD Division of Pediatric Hematology, Oncology, Marrow and Blood Cell Transplantation, Department of Pediatrics, Children's Hospital at Montefiore, Bronx, NY, USA

Hina J. Talib, MD Division of Adolescent Medicine, Department of Pediatrics, Children's Hospital at Montefiore, Bronx, NY, USA

M. Hossein Tcharmtchi, MD Department of Pediatrics, Section of Critical Care, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Vijay S. Tonk, PhD Department of Pediatrics, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Manpreet K. Virk, MD Department of Pediatrics, Section of Critical Care, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

Dawn M. Wahezi, MD, MS Pediatric Rheumatology, Children's Hospital at Montefiore, Bronx, NY, USA

Golder N. Wilson, MD, PhD Department of Pediatrics, Texas Tech University Health Sciences Center and KinderGenome Medical Genetics, Dallas, TX, USA

Kenneth Yen, MD, MS Division of Pediatric Emergency Medicine, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA

Jong W. Yoo, MD Pediatric Neurology, Department of Pediatrics, UCLA Mattel Children's Hospital, Los Angeles, CA, USA

Mohamed A. Zebda, DO, MPH Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, Galveston, TX, USA

General Pediatrics

1

Osama I. Naga

GROWTH

Background

- Growth is affected by maternal nutrition and uterine size
- Genetic growth potential is inherited from parents and also depends on nutrition throughout childhood
- Growth is affected by growth hormone, thyroid hormone, insulin, and sex hormones, all of which have varying influence at different stages of growth
- Deviation from normally expected patterns of growth often can be the first indication of an underlying disorder
- Carefully documented growth charts serve as powerful tools for monitoring the overall health and well-being of patients
- Key to diagnosing abnormal growth is the understanding of normal growth, which can be classified into 4 primary areas: fetal, postnatal/infant, childhood, and pubertal

Weight

- Healthy term infants may lose up to 10% of birth weight within the first 10 days after birth
- Newborns quickly regain this weight by 2 weeks of age
- 0–3 months: weight gain is approximately 30 g/day
- 3–6 months: weight gain is approximately 15 g/day
- 6–12 months: weight gain is approximately 10 g/day
- Birth weight is expected to double by 5–6 months

Height [1]

- The height of a newborn increases by 50% or by 25.4 cm (10 in.) in the 1st year
- The height of a newborn doubles within 3–4 years
- After 2 years the height increases by an average 5–6 cm/year
- There is a range of pubertal peak growth velocities of around 7–12 cm per year in boys and 6–10.5 cm per year in girls

Measurements [2]

- The length or supine height should be measured in infants and toddlers < 2 years
- Standing heights should be used if age > 3 years
- For children between 2 and 3 years of age, it is best to measure both supine length and standing height and compare the 2 measurements
- Plot gestational age rather than chronological age for preterm infants
- Specific growth charts are available for special populations, e.g., trisomy 21, Turner syndrome, Klinefelter syndrome, and achondroplasia

O. I. Naga (✉)
Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, USA
e-mail: osama.naga@ttuhsc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_1

Head circumference

- Head circumference will increase by 12.7 cm (5 in.) in the 1st year

Growth curve reading

- Shifts across 2 or more percentile lines may indicate an abnormality in growth
- Weight loss is one of the first signs of malabsorption and of cases of malnourishment or neglect
- Primary linear growth problems often have some congenital, genetic, or endocrine abnormalities (see also Chap. 12 Endocrinology)
- Genetic channeling: downward percentile crossing of a large baby born to short parents or upward percentile crossing of a small baby born to tall parents typically accomplished by 9–12 months

Macrocephaly

Definition

- Head circumference 2 standard deviations above the mean

Causes

- Benign familial macrocephaly with enlargement of subarachnoid space
- Hydrocephalus
- Intracranial hemorrhage or mass
- Genetic causes e.g., Soto syndrome, or "cerebral gigantism"

Benign familial macrocephaly (Table 1.1)

- Most common cause (50%)
- Autosomal dominant; usually seen in one or both parents
- Document parental head size
- Reassure parents and child if child's head size is congruent with familial sizes
- Periodic monitoring of the head size
- Periodic monitoring of physical growth and neurological development
- If the child's head size is not congruent with familial sizes:
  - Full history, including prenatal, birth, past medical, and family
  - Head ultrasound is the study of choice if anterior fontanelle is still open
  - Skull radiography
  - Brain magnetic resonance imaging (MRI) if the anterior fontanelle is closed

Table 1.1 Difference between benign familial macrocephaly and hydrocephalus

Benign familial macrocephaly	Hydrocephalus
Family history of macrocephaly	History of prematurity, IVH, trauma, or CNS infection
Normal growth and development	Spasticity, gait disturbance, cognitive deterioration, hypertonia
No signs of increased ICP	Bulging AF, ocular globes deviate downward (sun-setting sign), headaches, vomiting, irritability
Reassurance	Referral to neurosurgeon

CNS Central nervous system, *IVH* Intraventricular hemorrhage, *ICP* Intracranial pressure, *AF* Anterior fontanelle

Hydrocephalus (see Table 1.1)

- Referral to a pediatric neurosurgeon

Microcephaly (See Also Chap. 16 Neurology)

Definition

- Head circumference 2 standard deviations below the mean

Causes

- Congenital infections, e.g., TORCH (Toxoplasmosis, Others, Rubella, Cytomegalovirus [CMV]), Herpes simplex), Zika virus
- Maternal deprivation (folate deficiency, malnutrition, hypothyroidism)
- Maternal hyperphenylalaninemia
- Toxic or metabolic disorders
- Genetic conditions, e.g., trisomy 21, Cornelia de Lange syndrome
- Acquired or postnatal onset of microcephaly, e.g., hypoxic-ischemic encephalopathy

Plagiocephaly (Fig. 1.1) [3]

Background

- Deformational flattening from lack of changes in head positions is the most common cause of asymmetric head shape

Causes

- Positional or supine sleeping is the most common cause of plagiocephaly
- Causes of persistent head tilt, e.g., congenital muscular torticollis, ocular torticollis, Klippel-Feil syndrome (See also Chap. 13 Orthopedics.)
- Craniosynostosis

Craniosynostosis (See Also Chap. 4 Genetic Disorders)

Primary craniosynostosis

- One or more sutures fuse prematurely while the brain still increasing in size
- If one suture is involved, it is usually isolated
- If more than one suture is involved, it is commonly associated with genetic disorders
- Asymmetric skull (head growth is limited in the plane perpendicular to the fused suture)
- Bony ridging overlying the fused suture
- Commonly associated with an increase in head size asymmetrically
- Scaphocephaly (elongated head) is the most common type of craniosynostosis, due to early fusion of the sagittal suture; ridging of the sagittal suture is palpable

Secondary craniosynostosis

- Primary failure of brain growth leads to early fusion of sutures and microcephaly

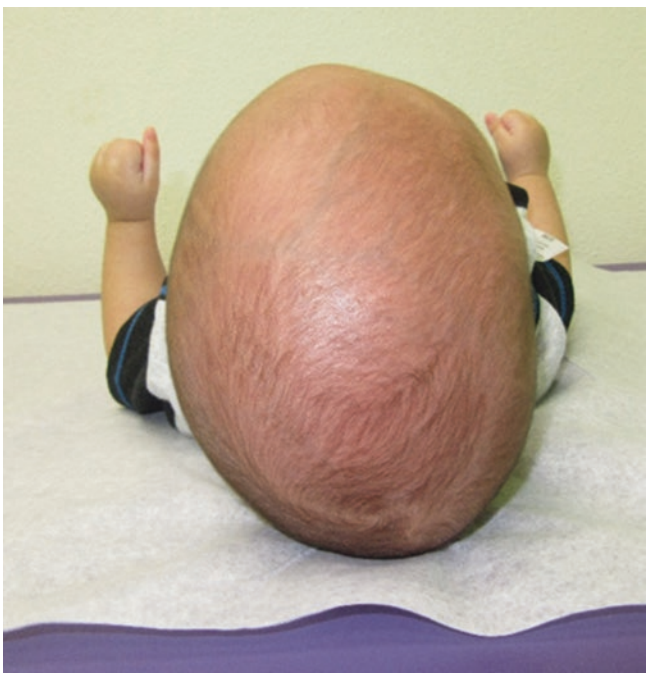


Fig. 1.1 A 5-month-old-boy with deformational plagiocephaly, flattening on the left side, and ipsilateral frontal bossing

Deformational plagiocephaly (Fig. 1.2, Table 1.2)

- Anterior displacement of the occiput and the frontal region on the same side (parallelogram)
- Ear position is more anterior on the side of flattening in positional plagiocephaly
- Supine sleeping recommendations ("baby on back") have increased the prevalence of posterior plagiocephaly

Diagnosis

- Neonatal examination to exclude syndromes with cranial and brain anomalies
- Careful examination alone can make the diagnosis
- Referral to a pediatric neurosurgeon if craniosynostosis is clinically suspected
- Plain skull radiography or CT scan can confirm the diagnosis of craniosynostosis if the diagnosis is not clear
- Cranial CT scan with 3-dimensional reconstruction is not required to make the diagnosis of craniosynostosis in most cases

Treatment

- Deformational plagiocephaly
  - Observation; usually resolves spontaneously
  - The helmet may be beneficial in severe cases of deformational plagiocephaly

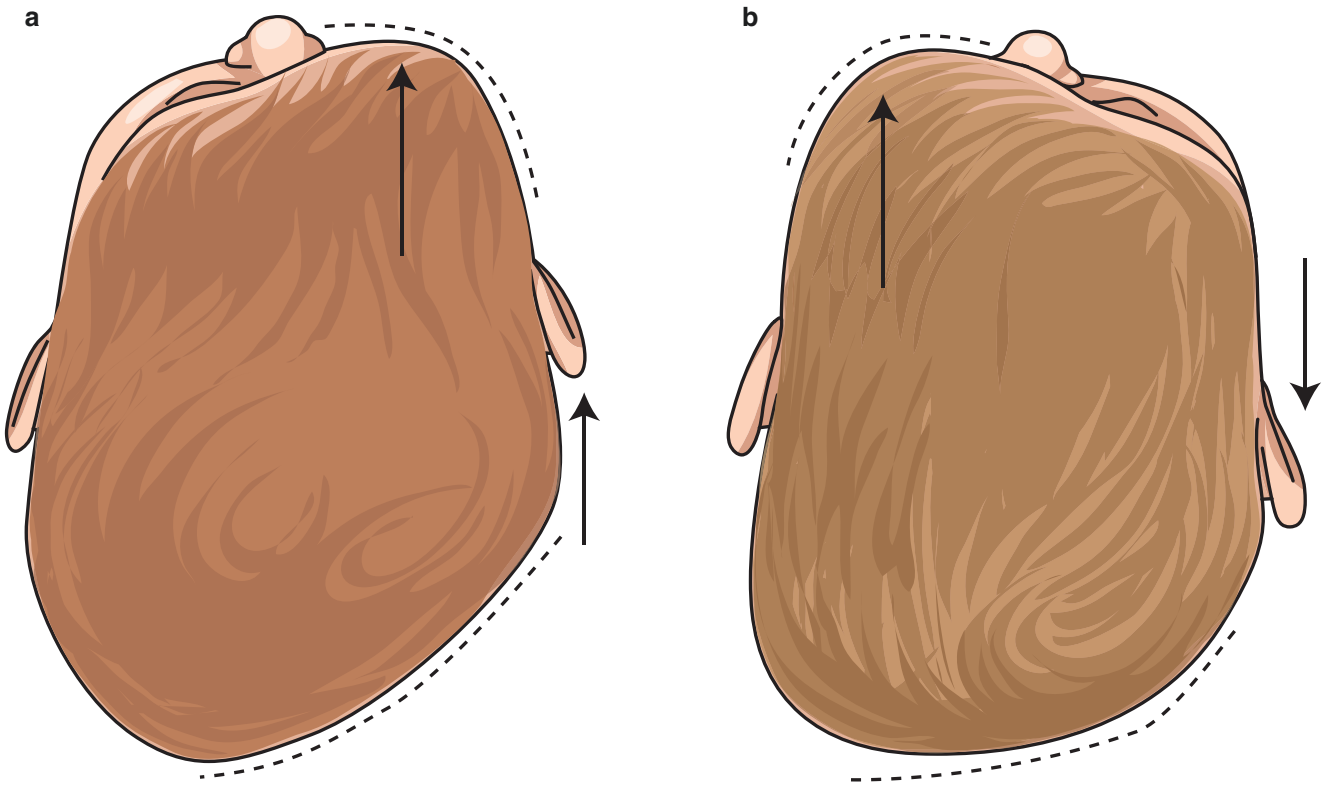


Fig. 1.2 **(a)** Deformational plagiocephaly; **(b)** Unilambdoid synostosis

Table 1.2 Difference between deformational plagiocephaly and plagiocephaly due to unilambdoid synostosis

Deformational plagiocephaly	Plagiocephaly due to unilambdoid synostosis
Parallelogram-shaped head	Trapezoid-shaped head
Occipital flattening on one side	Occipital flattening on one side
Frontal bossing on the same side	Frontal bossing on the contralateral side
Anterior displacement of the ear on the same side	Posterior displacement of the ear on the same side
Palpable suture, no palpable ridging	Absence of suture or palpable ridging of fused lambdoid suture

  - Treatment of underlying causes, e.g., congenital muscular torticollis or other causes of head tilt
  - Emphasis on floor ("tummy") time, occupational/physical therapy
- Craniosynostosis
  - Surgery, usually between 6 and 12 months

DEVELOPMENTAL MILESTONES [4, 5]

The American Academy of Pediatrics (AAP) recommends that clinicians screen children for general development using standardized, validated tools at 9, 18, and 30 months and for autism at 18 and 24 months or at any point when a caregiver or the clinician has a concern

Tools for screening

- Denver Developmental Screening Test
- Ages & Stages Questionnaires (ASQs)
- Modified Checklist for Autism in Toddlers (M-CHAT)

Newborn

Gross motor

- Lies in flexed position

- Turns head from side to side; head sags on ventral suspension

Social/communication
- Visual preference for human face

Visual
- Able to fixate face on light in line of vision; "doll's-eye" movement of eyes on turning the body
- Responds to visual threats by blinking
- Visual acuity is 20/400

Reflex
- Moro, stepping, placing, and grasp reflexes are all active

1 Month

Gross motor
- Legs more extended
- Head lifted momentarily to plane of body on ventral suspension
- Chin up in the prone position
- Turns head in the supine position

Fine motor
- Hands fisted near the face
- Sucks well

Social/communication/problem-solving
- Begins to smile
- Gazes at black-white objects
- Watches person; follows moving object
- Body movements following the sound of others

Language
- Startles to voice or sound

2 Months

Gross motor
- Raises head slightly farther in prone position
- Head sustained in plane of body on ventral suspension
- Begins to push up when lying on tummy
- Head lags when pulled to sitting position

Fine motor
- Hands unfisted 50% of the time
- Retains an object or finger if placed in the hand
- Brings hands to mouth, sucks on hand, and may hold hands together

Social/communication/problem solving
- Follows moving object 180°
- Able to fixate on the face and follow it briefly
- Tries to look at parents
- Stares momentarily where object disappeared
- Smiles on social contact; listen to voice and coos
- Turns toward sounds

Language
- Coos and makes gurgling sounds
- Begins to act bored (crying, fussy)

3 Months

Gross motor
- Lifts head and chest with arms in prone position
- May roll to the side

Fine motor
- Brings hands together in the midline and to the mouth
- Inspects their own fingers
- Bats at objects or toys

Social/communication/problem solving
- Follows parents across the room
- Expression of dislike for a taste or a loud sound
- Regards hands and toys

Language
- Regards and vocalizes to parents when talking
- Chuckles

4 Months

Gross motor

- Holds head steady and no head lag when pulled from lying down to sitting position (Fig. 1.3)
- May be able to roll over from front to back
- Pushes tummy, with elbows lifting the head and chest (Fig. 1.4)

Fig. 1.3 Holds head steady and no head lag when pulled from lying down to sitting position

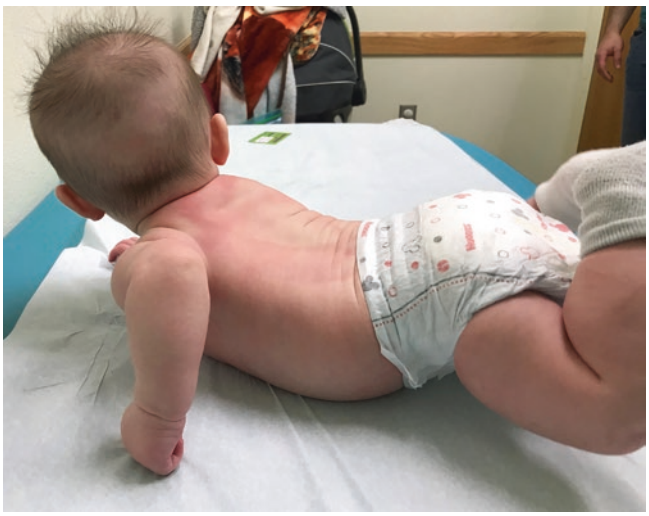


Fig. 1.4 Developmental milestone at 4 months: Pushes tummy, with elbows lifting the head and chest

- Pushes down on legs when feet are on a hard surface

Fine motor

- Brings hands to mouth
- Uses hands and eyes together, such as seeing a toy and reaching for it
- Shakes rattle

Social/communication/problem solving

- Responds to affection
- Begins to babble
- Laughs out loud
- Excited at sight of a bottle
- Recognizes familiar people and things at a distance
- Likes to play with people and might cry when playing stops

Language

- Vocalizes when alone

Reflexes

- Asymmetric tonic reflex is gone
- Palmar grasp is gone

6 Months

Gross motor

- Begins to sit with minimal support
- Rolls over from back to front and front to back
- Supports weight on legs and might bounce

Fine motor

- Transfers objects from one hand to another
- Brings objects or food to the mouth
- Places hands on the bottle
- Bangs and shakes toys
- Rakes pellets
- Removes cloth on face

Social/communication/problem-solving

- Stranger anxiety
- Responds to own name
- Responds to sounds by making sounds showing joy and displeasure

Language
- Monosyllabic babble
- Looks at self in mirror and smiles

7 Months

Gross motor
- Sits steady without support (Fig. 1.5)
- Bounces when held upright
- Puts arms out to the side for balance

Fine motor
- Radial palmar grasp

Social/communication/problem-solving
- Explores different aspects of toy and observes toy block in each hand
- Finds partially hidden toys or objects
- Looks from object to parents and back when wanting help
- Looks at familial objects or toys
- Attends to sounds and music
- Prefers mother
- Inhibits to "no"

Language
- More vowels and more variety of sounds

9 Months

Gross motor
- Can get into sitting position from lying down
- Pulls to stand
- Begins to crawl (Fig. 1.6)
- Bears walk with all limbs straight

Fine motor
- Radial-digital grasps of a block
- Bangs 2 blocks together
- Bites and chews cookie
- Inspects and rings a bell
- Pulls string to obtain a ring

Social/communication/problem-solving
- Separation anxiety
- Recognizes familiar people
- May be afraid of strangers

Fig. 1.5 Developmental milestone at 7 months: Sits steady without support

Fig. 1.6 Developmental milestone at 9 months: Begins to crawl

- Uses sound to get attention
- Plays peek-a-boo
- Orients to name well

Language

- Says "mamama" and "bababa" nonspecific
- Copies sounds and gestures of others

12 Months

Gross motor

- Walks with one hand held
- Pulls up to stand, walks holding on to furniture ("cruising")
- May stand alone and make a few steps without holding (Fig. 1.7)

Fine motor

- Fine pincer grasps of pellet
- Holds crayon and scribbles after demonstration
- Attempts tower of 2 blocks
- Finger feeds part of a meal
- Takes off a hat
- Puts out arm or leg to help with dressing
- Rattles spoon in a cup
- Puts a toy in a container, takes it out of the container

Social/communication/problem-solving

- Shows parents object to share interest
- Follows one-step command with a gesture
- Looks at the right picture or thing when it is named
- Points to get desired object (proto-imperative pointing) and to share interest
- Uses several gestures when vocalizing (e.g., waving, reaching)

Language

- Says a few words, including "mama," "dada," and exclamations like "uh-oh!"

Fig. 1.7 Developmental milestone at 12 months: May stand alone and make a few steps without holding

14 Months

Gross motor

- Walks well
- Stands without pulling

Fine motor
- Imitates back and forth scribbling
- May add the third block to a 2-block tower
- Puts round peg in and out of a hole
- Removes socks and shoes
- Chews well
- Puts a spoon in the mouth upside down
- Dumps pellet out of a bottle after a demonstration

Social/communication/problem-solving
- Points at an object to express interest (proto-declarative pointing)
- Purposeful exploration of toys through trial and error
- Follows one-step commands without gesture

Language
- Names one object

15 Months

Gross motor
- Stoops to pick up an object from the floor
- Runs stiff-legged
- Climbs on furniture and may be able to creep upstairs

Fine motor
- Builds 3- to 4-block tower
- Places 10 blocks in a cup
- Drinks from a cup
- Releases pellet into a bottle
- Eats with a spoon with some spilling
- Places circle in a single-shape puzzle
- Turns pages in a book

Social/communication/problem-solving
- Hugs parents in reciprocation
- Shows empathy (may cry when someone else is crying)
- Recognizes without demonstration that a toy requires activation, then hands it to an adult if it cannot operate
- Points to one body part
- Gets an object from another room upon demand

Language
- Uses 3–5 words
- Mature jargoning with real words

18 Months

Gross motor
- Runs well
- Creeps downstairs
- Gets onto a chair without assistance

Fine motor
- Throws a ball while standing
- Makes 4-block tower
- Imitates vertical stroke
- Can help undress him/herself
- Eats with a spoon
- Matches pairs of objects

Social/communication/problem-solving
- Normal M-CHAT
- Plays simple pretend, such as feeding a doll
- Begins to have temper tantrum and shows shame when does wrong
- Points to 2 of 3 objects when named and 3 body parts
- Points to familiar people with the name
- Understands “mine”

Language
- Uses 10–25 words
- Imitates animal sounds
- Names object in one picture on demand

24 Months

Gross motor
- Walks upstairs and downstairs holding rail
- Kicks a ball
- Throws ball overhand
- Stands on tiptoes

Fine motor
- Makes a single line of blocks
- In drawing, imitates horizontal line
- Begins to sort shapes and colors
- Opens door using the knob
- Takes off clothes without buttons
- Pulls off pants
- Builds a tower of 6 blocks
- Parallel play

Social/communication/problem-solving
- Begins to mask emotions for social etiquette
- Follows 2-step instructions or commands such as "Sit on your chair and eat your food"
- Points to 5–10 objects in pictures

Language
- Uses 2-word sentence
- Uses 50 or more words
- 50% intelligible speech

3 Years

Gross motor
- Walks up and down stairs, 1 foot on each step, no rails
- Climbs well
- Pedals a tricycle (3-wheeled bike)
- Balances on 1 foot for 3 seconds

Fine motor
- Copies a circle with pencil or crayon
- Can work toys with buttons, levers, and moving parts
- Screws and unscrews jar lids and turns door handle
- Understands what "2" means
- Imitates bridge of blocks
- Independent eating
- Puts on shoes without laces and able to unbutton clothing
- Draws man with 2 to 3 parts

Social/communication/problem-solving
- Understands long/short, big/small, more/less
- Knows own gender and age
- Follows 3-step instructions or commands
- Fears imaginary things

Language
- Uses words to describe what someone else is thinking ("Dad thought I was crying")
- Names body parts with function
- Uses 3-word sentences
- Says words like "I," "me," "we," and "you" and some plurals ("cars", "dogs," "cats")
- Names body parts by use
- 75% intelligible speech

4 Years

Gross motor
- Balances on 1 foot for 8 seconds
- Hops and stands on 1 foot up to 2 seconds

Fine motor
- Throws ball overhand more than 3 yards
- Catches a bounced ball most of the time
- Copies a square
- Goes to the toilet alone
- Wipes after a bowel movement
- Draws man with 4 to 6 parts

Social/communication/problem solving
- Group play
- Follows 3-steps commands and instructions
- Tells story and accurately counts 4 pennies

Language
- Knows some basic rules of grammar, such as correctly using "he," "she," "his," "her"
- 100% intelligible speech

5 Years

Gross motor
- Walks downstairs with rail, alternating feet
- Skips

Fine motor
- Copies a triangle
- Cuts with scissors
- Builds stairs with blocks from model
- Dresses and undresses

Social/communication/problem-solving
- Apologizes for mistakes
- Draws man with 8 to 10 parts
- Names 10 colors and counts to 10, counts 10 pennies correctly

Language
- Knows right from left
- Asks questions about the meanings of words and responds to questions
- Repeats 6 to 8 words in sentences

6 Years

Gross motor
- Tandem gait (heel-to-toe walks)

Fine motor
- Builds stairs from memory
- Copies a diamond shape
- Writes first and the last name

Social/communication/problem-solving
- Has a best friend of same gender
- Looks both ways at street when crossing
- Draws man with 12–14 parts
- Able to do simple additions and subtractions

Language
- Knows days of the week
- Able to describe events in sequence

Key Points to Developmental Milestones

Primitive reflexes
- Moro is absent around 3–4 months of age
- Palmar grasp absent around 2–3 months of age
- Parachute starts around 6–9 months of age

Following objects
- 1 month: Follows to the midline
- 2 months: Follows past midline
- 3 months: Follows 180°
- 4 months: Circular tracking 360°

Speech intelligibility
- 50% intelligible at 2 years
- 75% intelligible at 3 years
- 100% intelligible at 4 years

Language: receptive
- 1 month
  - Startles to voice or sound
- 2 months
  - Alerts to voice or sound
- 4 months
  - Orients head to the direction of a voice or sound
- 8 months
  - Responds to parents
- 9 months
  - Orients attentively to his or her name
- 10 months
  - Waves “bye-bye” in return
- 12 months
  - Follows one-step command with a gesture
- 14 months
  - Follows one-step command without a gesture

Language: expressive
- Coos
  - 2 months (2–4 months)
- Laughs out loud
  - 4 months
- Babbles
  - 6 months
- “Mama” or “dada” nonspecific
  - 9 months
- “Mama” and “dada” specific, plus a few words
  - 12 months
- Vocabulary of 10–25 words
  - 18 months
- Two-word sentences
  - 2 years (18–24 months)

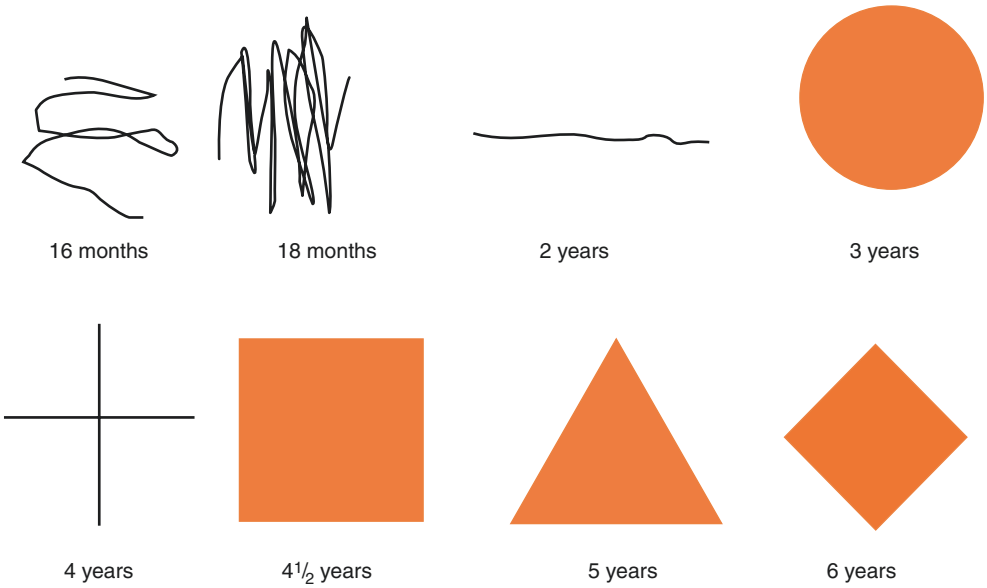


Fig. 1.8 Fine motor developmental milestones and ability to draw at different ages

- Three-word sentences
  - 3 years (2–3 year)
- Four-word sentences
  - 4 years (3–4 year)

Drawing (Fig. 1.8)

- Scribbles spontaneously
  - 16 months
- Imitates vertical lines
  - 18 months
- Imitates horizontal lines
  - 2 years
- Circle
  - 3 years
- Cross
  - 4 years
- Square
  - 4.5 years
- Triangle
  - 5 years
- Diamond
  - 6 years

Social skills

- Reciprocal smiling
  - 2 months
- Follows the person who is moving across the room
  - 3 months
- Smiles spontaneously at a pleasurable sight/sound
  - 4 months
- Recognizes caregiver socially
  - 5 months
- Stranger anxiety
  - 6 months
- Separation anxiety; gaze follows caregiver's pointing to object, "Oh, look!"
  - 9 months
- Waves "bye-bye" in return
  - 10 months
- Shows objects to parents to share interests
  - 12 months
- Parallel play
  - 2 years
- Reduction in separation anxiety
  - 28 months
- Cooperative play
  - 3–4 years
- Ties shoelaces
  - 5 years
- Distinguishes fantasy from reality
  - 6 years

Block play (Fig. 1.9)

- Passes blocks
  - More than 6 months

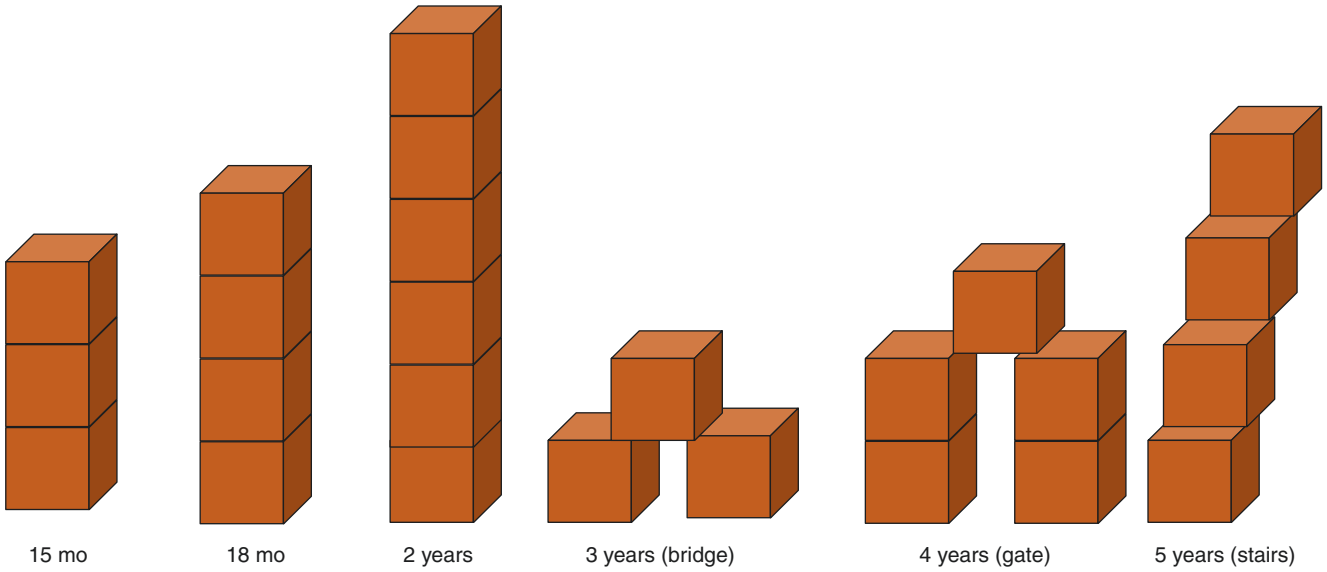


Fig. 1.9 Fine motor skills and ability to use blocks at different ages

- Bangs blocks
  - 9 months
- Block in a cup
  - 12 months
- Tower 3 blocks
  - 15 months
- Tower 4 blocks
  - 18 months
- Tower 6 blocks
  - 24 months
- Builds bridge with blocks
  - 3 years
- Builds gate with blocks
  - 4 years
- Builds stairs from model
  - 5 years

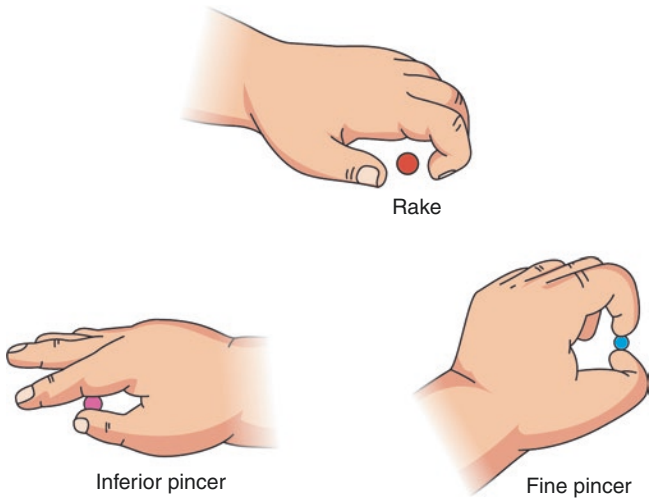


Fig. 1.10 Fine motor skills of catching an object at different ages

Catching objects (Fig. 1.10)

- Rakes
  - 5–6 months
- Radial-palmar grasp of pellet
  - 7–8 months
- Inferior pincer grasp of pellet
  - 10 months
- Fine pincer grasp of pellet
  - 12 months

Walking and running

- Independent steps
  - 12 months
- Walks well
  - 14 months
- Runs stiff-legged
  - 15 months
- Runs well
  - 18 months
- Kicks ball without demonstration
  - 2 years
- Skips and walks backward heel-toe
  - 5 years
- Heel to toe walks (tandem gait)
  - 6 years

Climbing stairs

- Creeps upstairs
  - 15 months
- Creeps downstairs
  - 18 months
- Walks downstairs holding rail, both feet on each step
  - 2 years
- Goes up stairs, alternating feet, no rail
  - 3 years
- Walks downstairs with rail, alternating feet
  - 5 years

Developmental red flags (Tables 1.3 and 1.4) [4]

Table 1.3 Developmental red flags for motor skills by age [4]

Age	Motor red flags
Newborn	Hypotonia and feeding difficulty
2 months	Unable to hold head up when pushing up when on tummy
4 months	Unable to hold head steady Unable to bring things to the mouth Persistent fisting (a predictor of neurological dysfunction)
6 months	Unable to pass an object from one hand to another and does not try to reach an object Floppy like a rag doll
9 months	Unable to sit, not rolling
12 months	Unable to stand or bear weight on legs when supported Unable to crawl
15 months	Unable to do pincer grasps
18 months	Unable to walk
24 months	Unable to walk well
36 months	Unable to climb stairs well and frequent falling
4 years	Unable to jump in place
5 years	Unable to draw pictures, a cross, or a square Poor balance
6–12 years	Unable to skip or hop on one foot Unable to write name
All ages	Loss of skills they once had

Table 1.4 Developmental red flags for language and social skills by age [4]

Age	Language and social red flags
Newborn	Does not respond to loud sounds
2 months	Does not alert to voice, lack of looking at faces Does not watch things as they move
4 months	Does not coo or make sounds Does not smile at people
6 months	Does not turn toward sounds; no smiling, laughing, or expression
9 months	Does not babble (“mama,” “baba,” “dada”)
12 months	Does not respond to name Does not understand “no” Indifferent or resistant attachment to the caregiver Does not look where caregiver points
15 months	Does not use words “mama,” “papa,” “dada” Does not point to the desired object
18 months	Does not gain new words Does not have at least 6 words Does not point to show things to other or share interest
24 months	Unable to use two-word phrases (e.g., “drink water”) Unable to follow simple instructions Unable to imitate actions or words Unable to maintain eye contact
36 months	Unable to use a three-word sentence Unable to pretend, play, or make-believe
4 years	Unable to speak clearly Unable to answer simple questions Unable to use pronouns (“I”, “me”, “you”, “he”, and “she”) correctly Ignores other children or does not respond to people outside the family
5 years	Unable to use plurals or past tense properly Unable to recognize shapes, letters, colors Unable to brush teeth, use toilet, wash and dry hands, or get undressed without help Unable to distinguish between reality and fantasy Shows extreme behavior (unusually fearful, aggressive, shy, or sad)
6–12 years	Unable retell or summarize a story Unable to name friends Unable to recognize the feelings of others
All ages	Loss of skills they once had

IMMUNIZATION [6, 7] (TABLE 1.5)

Responding to parents who refuse immunization for their children

- Listen to parents and address all their concerns about vaccines
- Explain all risks and benefits of the vaccinations:
  - Unimmunized, delay in vaccination, and use of alternative immunization schedules have caused a resurgence of many infectious diseases due to the loss of herd immunity, which puts many communities at risk
  - Vaccines are very safe, but they are not risk-free, nor are they 100% effective
  - Compare the risks of vaccines to the risks of diseases they protect against, some of which can cause death or permanent disability
- Refer parents to reputable sources and database about vaccines
- Discuss risks and benefits in each subsequent visit along with proper documentation
- Unimmunized children may be prevented from attending schools during outbreaks of vaccine-preventable diseases
- Advise parents to inform health-care providers that their child is not immunized during acute illness (e.g., emergency room visit)
- Have parents sign vaccine refusal form in every subsequent well visit
- Continued refusal after adequate discussion should be respected unless the child is put at significant risk of serious harm, e.g., refuses rabies vaccines after the child was bitten by a stray dog
- In general, the pediatrician should not refuse a child care because caregivers reject vaccines unless a strong sense of distrust develops that impacts the child's overall care

Table 1.5 Immunization schedule summary

Immunization schedule	Vaccine
Birth	HepB
2 months	DTap, IPV, HepB, Hib, PCV, RV
4 months	DTap, IPV, HIB, PCV, RV
6 months	DTap, IPV, HepB, Hib[a], PCV, RV[b], Influenza[c]
12 months	MMR, Varicella, Hib, PCV, HepA
15–18 months	DTap
18 months	HepA (1st and 2nd dose must be 6 months apart)
4–6 years	MMR, Varicella, DTap, IPV
11–12 years	Tdap, MCV4 HPV (2-dose series 6–12 months apart)[d]
16 years	Second dose of MCV4
High risk	PPSV23 2–18 years MCV4 2–10 years Meningococcal B (10 years and older)

DTaP Diphtheria and tetanus toxoids and acellular pertussis vaccine, *DTP* Diphtheria, pertussis, and tetanus, *HepA* Hepatitis A, *HepB* Hepatitis B, *Hib Haemophilus influenzae* type b (Hib) conjugate, *HPV* Human papillomavirus vaccine, *IPV* Inactivated poliovirus vaccine, *MCV4* Meningococcal conjugate ACWY vaccine, *MMR* Measles, mumps, and rubella, *PCV* Pneumococcal conjugate vaccine, *PPSV23* Pneumococcal polysaccharide vaccine, *Tdap* Tetanus and diphtheria toxoids and acellular pertussis vaccine, *RV* Rotavirus vaccine

[a]Hib dose at 6 months is not required if using PedvaxHIB (Merck)

[b]Dose at 6 months is not required if using Rotarix (GSK)

[c]Influenza every year beginning at 6 months

[d]3 doses of HPV for persons initiating vaccination at age 15 years or older

Recommended immunization schedule for children and adolescents ages 18 years or younger, United States, 2018 (US Department of Health and Human Services, Centers for Disease Control and Prevention) https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

Hepatitis B Vaccine (HepB)

First dose of HepB is at birth

- Birth dose (monovalent HepB vaccine only)

Doses following birth dose

- Administer the second dose 1–2 months after the first dose (minimum interval of 4 weeks)
- Administration of four doses of HepB is permissible if the combination is used after birth dose

- The final third or fourth dose in the HepB series should not be administered before 6 months of age

Mother is HBsAg-negative

- One dose within 24 h of birth for medically stable infants ≥ 2000 g. For infants < 2000 g, administer one dose at chronological age 1 month or hospital discharge.

Mother is HBsAg-positive

- Give one dose HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) (at separate anatomic sites) within 12 h of birth, regardless of birth weight.
- Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.

Mother's HBsAg status is unknown:

- Give HepB vaccine within 12 h of birth, regardless of birth weight.
- For infants < 2000 g, give 0.5 mL of HBIG in addition to HepB vaccine within 12 h of birth
- Give 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month
- Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, give 0.5 mL of HBIG to infants ≥ 2000 g as soon as possible, but no later than 7 days of age.

Catch-up vaccination

- An unvaccinated person should complete a three-dose series

Rotavirus Vaccine (Two Available in the USA)

Minimum age is 6 weeks

- If Rotarix (RV1; GlaxoSmithKline [GSK]) is used, administer a two-dose series at 2 and 4 months of age
- If RotaTeq (RV5; Merck & Co.) is used, administer a 3-dose series at age 2, 4, and 6 months
- 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 in infants of age 15 weeks, 0 days, or older
- The maximum age for the final dose is 8 months, 0 days

DTaP/Tdap

DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine)

Administration

- Minimum age 6 weeks (exception, DTaP-IPV [Kinrix, GSK; Quadracel, Sanofi Pasteur], 4 years)
- *Not* given to children 7 years and older
- Five-dose series DTaP vaccine at ages 2, 4, 6, 15–18 months, and 4–6 years
- The fourth dose may be administered as early as 12 months, if at least 6 months have elapsed since dose 3

Catch-up vaccination

- The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older

Tdap (tetanus and diphtheria toxoids and acellular pertussis vaccine)

- Similar to DTaP but contain a smaller amount of pertussis antigen
- Minimum age: 10 years for both Boostrix (GSK) and Adacel (Sanofi Pasteur)

Administration
- Administer one dose of Tdap vaccine to all adolescents aged 11–12 years

Catch-up vaccination
- A child 7 years and older who is not fully immunized with DTaP vaccine should receive Tdap vaccine as one dose in the catch-up series; if additional doses needed, use tetanus and diphtheria vaccine, adult/adolescent formulation (Td).
- For children between 7 and 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11–12 years should *not* be administered. Td should be administered instead, 10 years after Tdap dose.

DTaP inadvertently given after 7th birthday
- Child age 7–10 years: DTaP may count as part of catch-up series. Routine Tdap dose at 11–12 should be administered
- Adolescent age 11–18 years: Count dose of DTaP as the adolescent Tdap booster.

Absolute contraindication
- History of encephalopathy within 7 days of dosing

Relative contraindication
- History of fever > 40.5 °C (105 °F) within 48 h after prior dose
- Seizure within 3 days
- A shock-like condition within 2 days
- Persistent crying for more than 3 h within 2 days

Vaccination may be administered under these conditions
- Fever of < 105 °F (< 40.5 °C), fussiness, or mild drowsiness after a previous dose of DTaP
- Family history of seizures
- Family history of sudden infant death syndrome
- Family history of an adverse event after DTaP administration
- Stable neurologic conditions (e.g., cerebral palsy, well-controlled seizures, or developmental delay)

Haemophilus influenzae Type B (Hib) Conjugate

Vaccine
- Hib vaccine prevents invasive bacterial infections usually caused by *H. influenzae* type b

Routine vaccination of Hib
- 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 12–15 months to complete a full Hib vaccine series

Special situations
- Do not immunize immunocompetent children 5 years of age or older, even if they never had Hib vaccine
- Give one dose of Hib to unimmunized children 5 years of age or older with HIV, functional/anatomical asplenia
- Give one dose of Hib to unimmunized children who are going for elective splenectomy, preferably at least 14 days before the procedure
- Children who are going for hematopoietic stem cell transplant will need 3-dose series with doses 4 weeks apart, starting 6–12 months after successful transplant (regardless of Hib vaccination history)

Pneumococcal Vaccines

13-Valent pneumococcal conjugate vaccine (PCV13)

Routine vaccination
- Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months, and at age 12–15 months

- PCV13 is recommended for all children younger than 5 years

Catch-up vaccination with PCV13

- Administer 1 dose of PCV13 to all healthy children aged 24–59 months who are not completely vaccinated for their age

23-Valent pneumococcal polysaccharide vaccine (PPSV23)

- Protects children older than 2 years of age against invasive disease caused by the 23 capsular serotypes contained in the vaccine

Special situations: high-risk conditions (Table 1.6)

- When both PCV13 and PPSV23 are indicated, administer PCV13 first
- PCV13 and PPSV23 should not be administered during same visit

Methods of vaccine administration (Table 1.7)

Inactivated Poliovirus Vaccine (IPV)

Routine vaccination

- Administer a 4-dose series of IPV at ages 2, 4, 6–18 months, and 4–6 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

- Minimum age is 6 weeks
- The minimum interval between dose 1 to dose 2 and dose 2 to dose 3 is 4 weeks, the minimum interval between dose 3 to dose 4 is 6 months
- The minimum age for final dose is 4 years

Oral Poliovirus Vaccine (OPV)

- Live oral vaccine
- No longer used in the USA

Contraindication

- Children with immunodeficiency
- Children who live with adult HIV-infected or immunocompromised

Table 1.7 Methods of vaccine administration

Method of vaccine administration	Vaccine
Oral	Rotavirus Oral polio vaccine (not used in the USA)
Subcutaneous	MMR Varicella IPV
Intramuscular	All other vaccines, including IPV

MMR Measles, mumps, and rubella, *IPV* Inactivated poliovirus vaccine

Table 1.6 PCV13 and PPSV23 administration to children with an underlying medical condition

Group and risks	PCV13	PPSV23 Dose#1	PPSV23 Dose #2
Healthy children < 5 years	Routine	None	None
Immunocompetent children and teens with underlying medical conditions, e.g., chronic heart disease, chronic lung disease, (including asthma treated with high-dose, oral corticosteroids), diabetes mellitus, cerebrospinal fluid leak; cochlear implant	1 dose 8 weeks before PPSV23[a]	Age 2 years and older: Administer 1 dose at least 8 weeks after any prior PCV13 dose	None
Children and teens with *immunocompromising* conditions, nephrotic syndrome, malignant neoplasms, functional or anatomic asplenia	1 dose 8 weeks before PPSV23[a]	Age 2 years and older: Administer 1 dose at least 8 weeks after any prior PCV13 dose	1 additional dose at least 5 years following the first PPSV23

PCV13 13-Valent pneumococcal conjugate vaccine, *PPSV23* 23-Valent pneumococcal polysaccharide vaccine

[a]Children 2–5 years with any incomplete series of PCV13; not having received all doses in either the recommended series or an age-appropriate catch-up series will need one PCV13 booster dose (if received 3 PCV13 doses series), and two PCV13 booster doses 8 weeks apart (if received < 3 PCV13 doses series), at least 8 weeks after any prior PCV13 dose

Influenza Vaccines

Minimum age

- 6 months: inactivated influenza vaccine (IIV)
- 2 years: live attenuated influenza vaccine (LAIV)
- 18 years: recombinant influenza vaccine (RIV)

Routine vaccination

- 1 dose any influenza vaccine appropriate for age and health status annually (2 doses separated by at least 4 weeks for children 6 months–8 years who did not receive at least 2 doses of influenza vaccine before July 1, 2018)

Special situations

- Egg allergy, hives only
  - Give any influenza vaccine appropriate for age and health status annually
- Egg allergy more severe than hives (e.g., angioedema, respiratory distress)
  - Give any influenza vaccine appropriate for age and health status annually in medical setting under supervision of health-care provider who can recognize and manage severe allergic conditions
- LAIV should **NOT** be used in the following conditions
  - History of severe allergic reaction to any component of the vaccine (excluding egg) or to a previous dose of any influenza vaccine
  - Children and adolescents receiving concomitant aspirin or salicylate-containing medications
  - Children age 2–4 years with a history of asthma or wheezing, those who are immunocompromised due to any cause (including immunosuppression caused by medications and HIV infection)
  - Anatomic and functional asplenia, cochlear implants, cerebrospinal fluid-oropharyngeal communication
  - Close contacts and caregivers of severely immunosuppressed persons who require a protected environment
  - Pregnancy
  - Persons who have received influenza antiviral medications within the previous 48 hours.

Measles, Mumps, and Rubella (MMR) Vaccine

Background

- MMR is a combination of 3 attenuated live viruses
- Not contraindicated in children with egg allergy

Routine vaccination

- Administer a 2-dose series of MMR vaccine at ages 12–15 months and 4–6 years

International travel to high-risk countries

- Age 6–11 months
  - Administer 1 dose of MMR vaccine before departure from the USA
  - If the child remains in the high-risk area, the second dose should be given at least 4 weeks later
  - The dose before age of 12 months does not count towards the routine MMR vaccine series
- Age 12 months and older
  - Administer 2 doses of MMR vaccine 4 weeks apart before departure from the USA

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
- May not be given within 4 weeks of other live vaccines, but it can be given together or in combination with varicella vaccine at the same time

Contraindication

- Anaphylactic reaction to neomycin or gelatin
- Pregnancy; however, it is not an indication for abortion
- Immunodeficiency, e.g., AIDS; however, HIV-infected children can receive MMR live vaccine if not immunodeficient

Vaccination may be administered under these conditions

- Positive tuberculin skin test
- Simultaneous tuberculin skin testing
- Breastfeeding
- Pregnancy of recipient's mother or other close or household contact
- A recipient is female of childbearing age
- Immunodeficient family member or household contact
- Asymptomatic or mildly symptomatic HIV infection
- Allergy to eggs

Varicella (VAR)

Background

- Live attenuated virus vaccine contains a small amount of neomycin and gelatin
- Two doses are recommended
- Minimum age is 12 months, second dose at 4–6 years
- The combination with MMR vaccine is now available (MMRV)

Routine vaccination

- Administer a 2-dose series of VAR vaccine at ages 12–15 months and 4–6 years
- The second dose may be given as early as 3 months after the first dose (a dose given after a 4-week interval may be counted)

Catch-up vaccination

- Ages 7–12 years: Routine interval 3 months (minimum interval, 4 weeks)
- Ages 13 years and older: Minimum interval 4 weeks

Contraindication

- Immunocompromised children
- Pregnant women

Vaccination may be administered under these conditions

- Pregnancy of a recipient's mother or other close or household contact
- Immunodeficient family member or household contact
- Asymptomatic or mildly symptomatic HIV infection
- Humoral immunodeficiency (e.g., agammaglobulinemia)
- Children with HIV or who live with an immunocompromised adult can take the vaccine
- The vaccine can be given to children who live with a pregnant woman.

Varicella Zoster Immune Globulin (VariZIG)

- Post-exposure to measles and varicella prophylaxis (Table 1.8)

Hepatitis A (HepA) Vaccine

Routine vaccination

- Initiate the 2-dose HepA vaccine series at 12–23 months; separate the 2 doses by 6–18 months
- Minimum age: 12 months for routine vaccination

Catch-up vaccination

- Anyone 2 years of age or older may receive HepA vaccine if desired. Minimum interval between doses is 6 months.

International traveling to countries with high or intermediate endemic hepatitis A

- Infants age 6–11 months: 1 dose before departure; revaccinate with 2 doses, separated by

Table 1.8 Post-exposure to measles and varicella prophylaxis

Exposure of individuals who have no evidence of immunity	Vaccine	Immunoglobulin
Measles	MMR vaccine within 72 hours of exposure MMR vaccine should be offered at any interval after exposure, as it may provide some protection MMR vaccination of infants 6–11 months if many measles cases appeared in infants < 12 months	Immunoglobulin can be given within 6 days of exposure to people at risk of severe illness or infants younger than 12 months; 6–11 months old, MMR vaccine can be given within 72 hours instead of immunoglobulin
Varicella	To healthy individuals with no history of immunization who are 12 months or older within 3–5 days after varicella or herpes zoster exposure	VariZIG within 10 days to the newborn infant whose mother had chickenpox (not zoster) within 5 days before delivery or within 48 hours after delivery To immunocompromised children

MMR Measles, mumps, and rubella, *VariZIG* Varicella zoster immune globulin

6–18 months, between 12 and 23 months of age
- Unvaccinated age 12 months and older: first dose as soon as travel considered

Post-exposure prophylaxis
- < 12 months: administer a single dose of Ig as soon as possible
- ≥ 12 months: administer a dose of single-antigen vaccine or Ig as soon as possible (the efficacy of Ig or vaccine when administered > 2 weeks after exposure has not been established)

Meningococcal Conjugate Vaccines

Background
- MCV4 or meningococcal conjugate vaccines (Men ACWY: Menactra, Sanofi Pasteur; Menveo, GSK), reduce morbidity and mortality from meningococcal disease caused by serotypes A, C, W, or Y (does not cover for B serotype)

Routine vaccination
- Administer a single dose of Menactra or Menveo vaccine at age 11–12 years, with a booster dose at age 16 years

Catch-up vaccination
- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval, 8 weeks)
- Age 16–18 years: 1 dose

Special situations
- Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, eculizumab use

Menveo
- Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months
- Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after the 1st birthday)
- Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart

Menactra
- Persistent complement component deficiency:
  - Age 9–23 months: 2 doses at least 12 weeks apart
  - Age 24 months or older: 2 doses at least 8 weeks apart
- Anatomic or functional asplenia, sickle cell disease, or HIV infection
  - Age 9–23 months: Not recommended

  - 24 months or older: 2 doses at least 8 weeks apart
  - Menactra must be administered at least 4 weeks after completion of PCV13 series.

Travel in countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj

- Children age less than 24 months:
  - Menveo (age 2–23 months):
    - Dose 1 at 8 weeks: 4-dose series at 2, 4, 6, 12 months
    - Dose 1 at 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after the 1st birthday)
  - Menactra (age 9–23 months):
    - Two-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose of Menveo or Menactra

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits: 1 dose of Menveo or Menactra

Serogroup B meningococcal vaccines

- MenB vaccine may be administered based on individual clinical decision to *adolescents not at increased risk* age 16–23 years (preferred age 16–18 years): (Bexsero, GSK; Trumenba, Pfizer)
- Children 10 years or older who are at increased risk for serogroup B meningococcal infections should be vaccinated, e.g.:
  - Asplenia (functional or anatomic)
  - Persistent complement deficiency
  - Eculizumab use

Administration

- Bexsero: 2-dose series at least 1 month apart
- Trumenba: 3-dose series at 0, 1–2, and 6 months
- Bexsero and Trumenba are not interchangeable

Human Papillomavirus (HPV) Vaccines

Background

- Prevent cervical cancer, precancerous genital lesions, and genital warts due to HPV type 6, 11, 16, and 18
- 4vHPV (Gardasil, Merck & Co.) and 9vHPV (Gardasil 9)

Routine vaccination

- Administer a 2-dose series of HPV vaccine on a schedule of 0 and 6–12 months to all adolescents aged 11 or 12 years
- The vaccination series can start at age 9 years

Catch-up vaccination

- For persons initiating vaccination at age 15 years or older, the recommended immunization schedule is 3 doses of HPV vaccine at 0, 1–2, and 6 months

Special situations

- History of sexual abuse or assault: Begin series at age 9 years
- Immunocompromised (including HIV) aged 9–26 years: 3-dose series at 0, 1–2, and 6 months

Vaccine content that may cause an allergic reaction (Table 1.9)

Common Adverse Reaction of Vaccines

- Low-grade fever
- Local reaction and tenderness

Table 1.9 Vaccine content that may cause an allergic reaction

Contents in the vaccine that may cause allergies	Type of vaccine
Egg	Influenza, yellow fever *Egg allergy is no longer a contraindication to influenza vaccine* "In severe egg allergies (e.g., angioedema, respiratory distress) influenza vaccine can be given under supervision of health care provider who can recognize and manage severe allergic conditions"
Gelatin, neomycin	MMR and varicella
Streptomycin, neomycin	IPV and OPV

MMR Measles, mumps, and rubella, *IPV* Inactivated poliovirus vaccine, *OPV* Oral poliovirus vaccine

Table 1.10 Contraindications to vaccinations

Vaccine	Contraindications
Any vaccine	Life-threatening allergic reaction after a previous dose
Live vaccines, e.g., MMR, varicella, rotavirus	Known severe immunodeficiency
Rotavirus	Personal history of intussusception (not family history)
DTP, DTaP, or Tdap	Encephalopathy not attributable to another identifiable cause, within 7 days of administration of the previous dose

MMR Measles, mumps, and rubella, *DTP* Diphtheria, pertussis, and tetanus, *DTaP* Diphtheria and tetanus toxoids and acellular pertussis vaccine, *Tdap* Tetanus and diphtheria toxoids and acellular pertussis vaccine

Contraindications to Vaccinations (Table 1.10)

General conditions commonly misperceived as contraindications (i.e., vaccination may be administered under these conditions)

- Mild acute illness with or without fever
- Mild-to-moderate local reaction (i.e., swelling, redness, soreness); low-grade or moderate fever after the previous dose
- Fever of < 105 °F (< 40.5 °C); fussiness or mild drowsiness after a previous dose of DTP/DTaP
- Current antimicrobial therapy
- A family history of seizures, autism, or developmental delay
- Preterm birth (HepB vaccine is an exception in certain circumstances)
- Recent exposure to an infectious disease
- History of penicillin allergy, other non-vaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy
- Positive purified protein derivative (PPD) test

Special considerations

- If PPD not given with MMR on the same day, PPD test should wait for 4–6 weeks (MMR may alter result if not done on the same day)
- If the infant vomited the rotavirus vaccine, there is no need to re-administer the dose again; complete the series normally
- Family history of intussusception or anaphylaxis is not a contraindication to give rotavirus vaccine

PREVENTIVE MEDICINE [8]

Newborn Screening

- All 50 states in the USA screen for:
  - Congenital hypothyroidism
  - Phenylketonuria
- Some states screen for more diseases, e.g., metabolic and hemoglobinopathies

History (initial/interval), length/height, and weight

- From birth and at all child well visits

Head circumference measurements

- From birth and at all child well visits until 24 months of age or at any time if any concern about the head growth

Newborn Bilirubin Screening

- Screening for hyperbilirubinemia is recommended for all term and late preterm infants
- Assessment of jaundice, risk factors for severe hyperbilirubinemia
- Measure total serum bilirubin or transcutaneous bilirubin before discharging any newborn from the newborn nursery

Blood Pressure Screening

- All children on yearly basis starting at 3 years of age
- Blood pressure measurements at visits before 3 years if coexisting medical conditions associated with hypertension

Pediatric cuff size (Fig. 1.11)

- Minimum bladder width
  - Bladder width should be at least 40% of mid arm circumference (MAC)
- Bladder length
  - Bladder length should encircle 80–100% of MAC, but no more than 100%

Normal blood pressure (BP)

- < 90th percentile for age and sex
- Children whose BP is > 90th percentile for age, sex, and height require further evaluation

Vision Screening

- Examination of eyes and visual system should begin in the nursery and continue throughout childhood and into adolescence
- Newborn infants should be examined using inspection and red reflex testing to detect structural ocular abnormalities such as cataract, corneal opacity, and ptosis before discharge from the newborn nursery
- Instrument-based screening should be attempted between 12 months and 3 years of age and at annual well child visits until visual acuity can be tested directly
- Visual acuity testing is now recommended for children beginning at 3 years of age (if cooperative), 4, 5, 6, 8, 10, 12, and 15 years

Screening tools

- Ophthalmoscope
- Photo-screening device
- Lea symbols, Allen figures, HOTV letters, Tumbling E, Snellen chart

Cover and uncover test

- The child should be looking at an object from a distance of 10 ft
- Movement in the uncovered eye when the opposite is covered or uncovered suggests potential strabismus

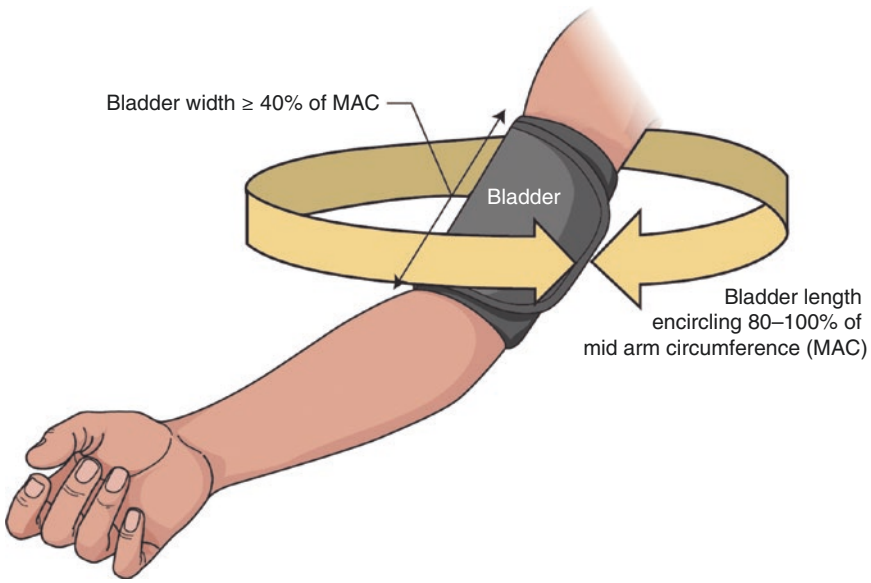


Fig. 1.11 Pediatric cuff size and accurate blood pressure measurement: Relative sizes of patient's mid arm circumference, cuff bladder width and length

Hearing Screening

Periodicity

- All newborns must receive newborn hearing screening before discharge from the newborn nursery or NICU
- At age of 3–5 days, confirm initial screen was completed, verify results, and follow-up as appropriate
- Formal hearing screening is recommended at age 4, 5, 6, 8, 10, and once between 11–14, 15–17, 18–21 years

Goal of screening

- Identify hearing loss of 35 dB or greater in 500–4000 Hz range

Indication for hearing screening in special situations

- Speech delay
- Parental expression of concern on hearing problem, language, or developmental delay
- History of bacterial meningitis
- Neonatal CMV infection
- Head trauma
- Syndromes associated with hearing loss, e.g., Alport syndrome
- Exposure to ototoxic medications

Developmental Screening

- Developmental screening at 9, 18, and 30 months of age

Autism screening

- AAP Bright Futures recommends autism screening at 18 and 24 months of age
- Repeat specific screening whenever parental concern raised
- Positive screening: If < 3 years of age, refer to early intervention (EI); if > 3 years of age, refer to the school district for further evaluation
- Screening tool at 18 and 24 months (See also Chap. 6 Mental and Behavioral Health.)
  - M-CHAT: Modified Checklist for Autism in Toddlers (https://www.autismspeaks.org/screen-your-child; Autism Speaks)

Lead Screening [9, 10]

Ages of screening

- All Medicaid-eligible children and those whose families receive any governmental assistance must be screened at age 1 and 2 years

Elevated blood lead level (BLL)

- There is no safe BLL
- Lead poisoning is diagnosed if the BLL is ≥ 5 mcg/dL (0.24 mmol/L)
- BLL for children 1–5 years old should be less than 2 mcg/dL
- An elevated capillary BLL should be confirmed with a venous sample

Risk factors for lead poisoning

- Living in or regularly visiting a house built before 1950 or remodeled before 1978
- Other sibling or family member with a high lead level
- Immigrant or adopted children
- Use of folk remedies
- Environment with high or unknown lead level
- Children eligible for Medicaid are at high risk

Effect of lead intoxication

- A decline in academic achievement, intelligence quotient (IQ) scores, attention-related behaviors with BLL < 10 mcg/dL
- Microcytic anemia
  - Concomitant iron deficiency anemia; increased lead absorption
- Abdominal colic
- Constipation
- Growth failure
- Dental caries
- Hearing loss

- Renal disease
- Neurotoxicity
- Seizures
- Encephalopathy
- Death

Management of lead poisoning, any detectable or elevated BLL (Table 1.11)

Iron Deficiency Anemia Screening

- AAP Bright Future recommends universal anemia screening with determination of hemoglobin concentration at 1 year of age

Screening of high-risk children

- Prematurity
- Low birth weight
- Early introduction of cow's milk
- Strict vegans
- Poverty
- Limited access to food
- Associated medical conditions

Urinalysis (UA) Screening

- No routine screening recommended by AAP Bright Futures at this time

Sexually Transmitted Diseases

- Recommendations for screening sexually active adolescents for sexually transmitted infections vary with age, sex, and sexual behavior.

HIV Screening

- The US Preventive Services Task Force recommends that clinicians screen for HIV infection in all adolescents once between 15 and 18 years of age
  - Younger adolescents who are at increased risk should also be screened
  - Risk factors, e.g., male-to-male sexual contact, injection drug use, heterosexual contact

Table 1.11 Management of lead poisoning, any detectable or elevated blood lead level (BLL)

BLL	Management	Re-testing venous BLL
Any detectable or elevated BLL	Education Environmental investigations	Periodic follow-up
BLL > 5 mcg/dL	Education Environmental investigations	In 6–12 months if the child is at high risk In 3–6 months if < 12 months old
BLL 5–14 mcg/dL	Refer to local health authorities CBC, CRP, and serum ferritin Iron-rich food and vitamin C	Re-test venous BLL within 1–3 months
BLL 15-44 mcg/dL	In addition to previous steps of BLL 5–14 mcg/dL, if pica for paint chips or mouthing behaviors, perform KUB; bowel decontamination if foreign bodies containing lead are visualized	Re-test venous BLL within 1–4 weeks
BLL > 44 mcg/dL	Perform chelation therapy	Re-test venous BLL within 48 h if no symptoms
BLL > 69 mcg/dL	Hospitalization and chelation therapy	Re-test venous BLL within 24 h if no symptoms
Symptomatic lead intoxication	Hospitalize for full investigations, decontamination, and chelation therapy. PICU admission if lead encephalopathy	Medical emergency Confirm with a stat BLL

CBC Complete blood count, *CRP* C-reactive protein, *KUB* Kidneys, ureters, and urinary bladder, abdominal radiograph, *PICU* pediatric ICU

Screening test for HIV

- Rapid HIV testing or HIV immunoassay
- The reactive test followed by confirmatory Western blot or immunofluorescent assay

Tobacco, Alcohol, And Substance Use

- Annual screening for tobacco, alcohol, and substance use, beginning at age 11 years

Depression Screening

- Universal screening for depression annually from age 12 to 21 years
- Screening for depression in children ≥ 10 years and adolescents at high risk of depression

Tuberculosis (TB) Screening

- The AAP/Bright Futures guidelines suggest tuberculosis risk assessment by 1 month of age; at ages 6, 12, and 24 months; and annually thereafter

Dyslipidemia

- Routine screening for dyslipidemia in all children once between 9 and 11 years and once between 17 and 21 years

Screening methods

- Non-fasting non-HDL-cholesterol
- Screen for dyslipidemia in a child between 2 and 8 years of age if parent has a total cholesterol of 240 mg/dL or higher: A fasting lipid profile should be obtained and then repeated after 2 weeks to 3 months (See also Chap. 19 Cardiology.)

Oral Health Screening

- Perform dental risk assessment at 6 and 9 months of age
- The AAP recommends repeat oral health assessment at 12, 18, 24, and 30 months and 3, 4, 5, and 6 years of age if the child has not yet established a dental home
- The AAP recommends the initial dental visit at 12 months of age

Fluoride supplementation

- Periodic application of fluoride varnish between 6 months and 5 years of age
- No fluoride should be given to an infant of less than 6 months
- If the fluoride in the water supply < 0.3 PPM begin supplementation at 6 months of age
- If fluoride in the water supply is > 0.6 PPM, no need for taking extra fluoride

Tooth care

- Once tooth erupts, it should be brushed twice daily with plain water
- Once the child reaches 2 years of age, brush teeth twice daily with a pea-sized amount of fluoride toothpaste
- Daily flossing

Prevention of bacterial transmission (*Streptococcus mutans* or *S. sobrinus*)

- Practice good oral hygiene and seek dental care
- Do not share utensils, cups, spoons, or toothbrushes with an infant
- Do not clean a pacifier by mouth before giving it to an infant

Risk group infants should be referred to a dentist as early as 6 months of age and no later than 6 months after the first tooth erupts or 12 months of age (whichever comes first) for the establishment of a dental home. Examples of risk group infants:

- Children with special health-care needs
- Children of mothers with a high caries rate

- Children with demonstrable caries, plaque, demineralization, and/or staining
- Children who sleep with a bottle or are breast-feed throughout the night
- Children in families of low socioeconomic status

Summary of Routine screening in Pediatrics (Table 1.12)

WELL CHILD VISITS

Well Visit Schedule

Infancy
- Newborn
- 3–5 days old
- 1, 2, 4, 6, and 9 months

Early childhood
- 12, 15, 18, 24, 30 months; 3 and 4 years

Middle childhood
- Yearly from 5 to 10 years

Adolescents
- Yearly from 11 to 21 years

Counseling during each well visit is very important
- Bath safety
- Sun exposure
- Fluoride supplementation
- Nutrition
- Immunization
- Common cold management

Age-appropriate anticipatory guidance, e.g.:
- Feeding the newborn
- Dental care when the first tooth appears
- Dental appointment at 12 months if pediatric dentist is available
- Limitations on screen time (TV, computer, phone)
- Encourage reading to the child, and by the child

Table 1.12 Routine screening in pediatrics

Screening	Ages to be performed	Special considerations
Length/height and weight	From birth and in each well visit	Repeat and confirm any abnormal reading
Head circumference	From birth until the age of 2 years	Repeat and confirm any abnormal reading or any time if any concern about head size
Blood pressure	3 years of age, then yearly after	Before 3 years of age visits if any risk factor of hypertension
Hearing	Newborn, 4, 5, 6, 8, 10, and once at 11–14, 15–17, 18–21 year	Any time if any risk factor
Vision	3, 4, 5, 6, 8, 10, 12, 15 year	Any time if any concern
Developmental screening	9, 18, and 30 months	Any time if any concern
Autism screening	18 and 24 months	Any time if any concern
Depression	12 years of age, then yearly after	Any time if any signs of depression
Maternal depression	1, 2, 4, and 6-month visits	Any time if any signs of depression
Bilirubin	Newborn	Any time if indicated
Anemia	12 months	Any time if indicated
Lead	12 and 24 months if Medicaid or high risk of prevalence area	Any time if any risk factor
Tuberculosis	Risk assessment at 1, 6, 12, and 24 months, and annually thereafter	Any time if any risk factor
Dyslipidemia	9–11, and once at 17–21 years	Any time if indicated
HIV	Once between 15 and18 years	Younger if increased risk of HIV infection
Oral health	Perform dental risk assessment at 6 and 9 months, fluoride varnish every 3-6 months between 6 months and 5 years of age	Refer to establish a dental home at 12 months of age
Anticipatory guidance	From birth and in each well visit	Any time if parents have a concern

- Helmet for bicycle
- Discussion about tobacco, alcohol, drug use, and sex at age of 11 and up

ENVIRONMENTAL SAFETY COUNSELING

Preventing Motor Vehicle Injuries in Children [11]

Children should be properly buckled up in a car seat, booster seat, or seat belt, whichever is appropriate for their age, height, and weight

- All children aged 12 years and under should be buckled in the back seat
- Airbags can kill young children riding in the front seat
- Never place a rear-facing car seat in front of an airbag

Rear-facing car seat

- Birth until 2–4 years of age
- Buckle children in a rear-facing car seat until they reach the maximum weight or height limit of their car seat
- Keep children rear-facing as long as possible

Forward-facing car seat

- After out-growing rear-facing car seat until at least 5 years of age

Booster seat

- After outgrowing the forward-facing car seat until seat belts fit properly
- The recommended height for proper seat belt fit is 57 in. (4 ft 9 in.) tall and 9–12 years of age

Seat belt

- Once seat belts fit properly without a booster seat
- Children no longer need to use a booster seat if the seat belts fit properly when the lap belt lays across the upper thighs (not the stomach) and the shoulder belt lays across the chest (not the neck)

Car seat or bed screen before discharging a pre-term baby from NICU [12]

- Indications for screening
  - Infants < 37 weeks gestation
  - At risk for obstructive apnea, bradycardia, or hypoxemia, including infants with hypotonia (e.g., Down syndrome), micrognathia (e.g., Pierre Robin sequence)
  - After cardiac surgery
- Infants "fail" the screen if they have
  - Oxygen desaturation below 90% or 93% for more than 10 s
  - Apnea greater than or equal to 20 s
  - Bradycardia less than or equal to 80 beats per minute

Preventing Drowning

- Enclose pools entirely with fence and least 4 ft high and self-closing gate
- Wear life jackets on boats and when playing near water
- Do not leave children unattended in baths
- Supervise closely (adults within one arm's reach of a child in or near water)

Preventing Fire and Burns

- Install a smoke detector on every level of the home and near sleeping areas
- Reduce water heater temperature to 120 °F
- Do not drink hot fluids near children
- Never leave the stove unattended

Preventing Gun Accidents

- If parents choose to keep a firearm in the home, the unloaded gun and ammunition must be kept in separate locked cabinets

Preventing Poisoning

- Keep all potential poisons in original containers and out of reach
- Keep all medications out of reach
- Place child-resistant caps on medications
- Install carbon monoxide detectors on every level of the home
- Keep the 24-h Poison Control number near the phone: 1-800-222-1222 (National Capital Poison Center).
- Online: webPoison Control. https://triage.webpoisoncontrol.org/#/exclusions

Preventing Threats to Breathing [13]

- Remove comforters, pillows, bumpers, and stuffed animals from crib
- The AAP recommends:
  - Hard candy and gum not be given to children younger than age 5 years
  - Raw vegetables and fruit be cut up into small pieces
  - Children should always be supervised while eating and that children be seated when eating—not running, walking, or lying down
  - Caregivers should be familiar with choking-related rescue maneuvers

Preventing Falls

- No baby walkers with wheels
- Baby walkers increase risk of falls and skull fracture

Preventing Bicycle Injuries [14]

- Children between the ages of 5 and 14 years are at the highest risk for bicycle injury
- Head injuries account for the majority of bicycle-related deaths and hospital admissions
- Children < 1 year should not ride in bicycle-mounted carriers or trailers
- Children < 3 years do not have the developmental skills necessary to ride a tricycle
- Children aged 4–5 usually can ride a bicycle with training wheels and foot-operated brakes; they should not ride in traffic and must always be supervised
- Children 6 years or older usually can ride a bicycle without training wheels and operate hand brakes
- Children should not be permitted to ride in traffic until they have demonstrated that they can control the bicycle, understand and follow the rules of the road, and exercise good judgment
- Reflectors are important to increase visibility in the dark; however, bicycling in the dark should be discouraged
- Use bicycle lanes and bicycle paths
- Keep children < 10 years off the road

Bicycle helmets

- Reduce the risk of head, brain, and severe brain injuries for bicyclists of all ages
- Should be encouraged for riders and passengers of all ages, on every occasion that they ride a bicycle
- Should fit properly and be worn in the proper position
- Only those that meet US Consumer Product Safety Commission standards should be used
- Helmets that have been involved in a crash should be discarded
- Helmets should be replaced every 5 years

Preventing Sunburn [15]

- Sunburn increases risk of melanoma at all ages

Sun avoidance

- Wear protective clothing
- Seek shade or reduce exposure to the sun between 10:00 AM–2:00 PM, when sunlight intensity is greatest, especially in the summer
- Protective clothing such as long sleeves and wide-brim hats should be worn while outdoors

Sunscreens

- Broad spectrum sunscreens with a sun protection factor (SPF) of at least 30 or higher on both cloudy and sunny days
- Sunscreen rated SPF 30 filters 97% of UVB rays while SPF 50 blocks 98%.
- Sunscreens should be applied 15–30 min before sun exposure to allow the formation of a protective film on the skin
- Reapply sunscreen every 2 h and after swimming or sweating

Infants younger than 6 months

- For infants younger than 6 months, the AAP recommends avoidance of sun exposure and the use of clothing (e.g., lightweight pants, long-sleeved shirts, brimmed hats)
- A minimal amount of sunscreen with an SPF of $\geq$ 15 may be applied to small areas (e.g., face, back of the hands) when adequate clothing and shade are not available

Artificial Ultraviolet Rays (Tanning)

- Artificial ultraviolet rays may cause sunburn, skin dryness, pruritus, and photokeratitis
- Long-term exposure may cause cataracts, skin aging, and cancer

Preventing Mosquito Bites [16]

Example of effective repellents

- DEET (N,N-diethyl-3-methylbenzamide) repels mosquitoes, ticks and other bugs; used on the skin only
- Permethrin products (repel mosquitoes and ticks and can be used on clothing)
- Picaridin (can be used on the skin or clothing)

DEET

- Repellents with 10–30% DEET should be safe and effective when used according to the directions on the product labels
- Repellents with 10% DEET concentration are effective for periods of approximately 2 h
- Repellents with 24% DEET concentration are effective for periods of approximately 4 h
- Higher concentrations provide longer durations of protection
- Protection is shortened by swimming, washing, rainfall, sweating, and wiping

Recommended age for repellents

- Children 2 months or older
- Children younger than 2 months of age should not use products with DEET

Adverse effects

- Dermatitis, allergic reactions, and rare neurotoxicity from excessive absorption through the skin
- Avoid using sunscreen products containing DEET because of possibility of reapplication and excessive absorption of DEET
- Once the child is indoors, wash off the skin with water to avoid excessive absorption

Complications of mosquito bites

- Urticarial reaction
- Large local reaction; itchy or even painful area of redness, warmth, swelling, and/or induration that ranges from 2 cm to more than 10 cm in diameter
- Malaria and West Nile virus infections in high-risk areas

- Bacterial cellulitis:
  - It is not common
  - Malaise, chills, fever, and toxicity may be present
  - The involved area is red, hot, swollen, and tender
  - May take days to develop versus minutes to hours in cases of local reaction
  - Without treatment, bacterial cellulitis will continue to get worse versus local reaction, which will improve with time

Prevention of large local reaction
- Mosquito avoidance
- Prophylaxis with an oral non-sedating H1 antihistamine

Treatment of large local reactions
- Antihistamines
- Ice in a wet washcloth for 20 min
- Topical hydrocortisone cream
- Systemic glucocorticoids in severe cases

CRYING INFANT

Infantile Colic

Background
- Colic begins during the 2nd week of life, peaks at 6 weeks, and resolves between 12 and 16 weeks
- Equally common in both breast- and bottle-fed infants
- Average crying per day: 2.2 h
- May cause parental anxiety and may increase the risk of postpartum depression

Normal physical findings
- Weight gain:
  - Infants with colic often have accelerated growth; failure to thrive should make one suspicious about the diagnosis of colic
  - Exclusion of organic causes, e.g., infection, occult fractures, or maternal drug effects
- Should respond to comforting
- Baby acts happy between bouts of crying

Differential diagnosis
- Gastrointestinal causes (e.g., gastroesophageal reflux disease [GERD], over- or underfeeding, milk protein allergy, early introduction of solids)
- Exposure to cigarette smoke and its metabolites
- Food allergy

Management of infantile colic [17]
- Parents need to be reassured that they have a healthy infant
- Effective swaddling, and decreased stimulation of the infant
- Hold and comfort, e.g., gentle rocking, dancing with the baby, wind-up swing, or vibrating chair
- Cautioning overtired and frustrated parents never to shake their infant and giving them permission to allow the infant to cry are essential components of any treatment plan and can decrease the risk of child abuse
- A breastfeeding mother should avoid caffeine
- Probiotics and/or simethicone may help (no data to support the routine use of these therapies)

Dietary changes may include the following
- Elimination of cow's milk protein in cases of suspected intolerance of the protein
- In infants with suspected cow's milk allergy, a protein hydrolysate formula is indicated
- Soy-based formulas are not recommended, because many infants who are allergic to cow's milk protein may also become intolerant of soy protein

PEARLS AND PITFALLS

- Crossing percentiles in the growth curve for any child must be investigated initially by repeating the measurement to ensure accuracy.
- Rotavirus vaccine is contraindicated in infants with personal history of intussusception or personal history of anaphylaxis to rotavirus vaccine.

- Family history of intussusception or anaphylaxis to rotavirus is not a contraindication to rotavirus vaccine.
- For any child with abnormal red reflex, or any parental concern about white pupil reflex, the most prudent action is to refer the patient for a complete ocular examination.
- Any new-onset strabismus is a red flag for ocular or intracranial structural abnormalities e.g., brain tumor.
- Screen all adolescents for HIV once between age 15 and 18 years.
- To prevent drowning, children should be supervised closely (adults within one arm's reach of a child in or near water).
- If parents choose to keep a firearm in the home, the unloaded gun and ammunition must be kept in separate locked cabinets.
- Hard candy and gum should not be given to children younger than age 5 years and raw vegetables and fruit should be cut into small pieces.
- Baby walkers with wheels increase risk of falls and skull fracture.
- Bicycle helmets reduce the risk of severe head and brain injuries for bicyclists of all ages.
- Broad-spectrum sunscreens with SPF 30 or higher should be regularly used when performing outdoor activities in sunny weather, especially in regions with high levels of insolation.
- Keep infants younger than 6 months away from the sun.
- To prevent mosquito bites, repellents with 10–30% DEET are recommended for children 2 months and older.
- Children younger than 2 months of age should not use products with DEET.
- Infantile colic is a self-limited condition that will spontaneously resolves between 12 and 16 weeks.
- Effective swaddling, gentle rocking, and decreased stimulation of the infant are helpful measures in the management of infantile colic.
- Simethicone, considered by many as a mainstay of colic treatment, is a safe but relatively ineffective remedy for the treatment of infantile colic.
- There is no safe blood lead level (BLL). Any detectable BLL must be managed and investigated further.
- Intake of milk above 16–24 oz is associated with increased risk of iron deficiency and subsequent anemia.
- Growing pains is a diagnosis of exclusion, requires that symptoms only occur at night, and that the patient has no limp, no joint swelling, or symptoms during the day.

References

1. Braun LR, Marino R. Disorders of growth and stature. Pediatr Rev. 2017;38(7):293–304.
2. Nicol L, Allen DB, Czernichow P, Zeitler P. Normal growth and growth disorders. In: Kappy MS, Allen DB, Geffner ME, editors. Pediatric practice endocrinology. New York: McGraw-Hill; 2010. p. 23–76.
3. Losee JE, Mason AC. Deformational plagiocephaly: diagnosis, prevention, and treatment. Clin Plast Surg. 2005;32(1):53–64, viii.
4. Scharf RJ, Scharf GJ, Strousup A. Developmental milestones. Pediatr Rev. 2016;37(1):25–37; quiz 38, 47.
5. Feigelman S. Growth, development, and behavior. In: Kliegman RM, Stanton BF, Schor NF, St. Geme III JW, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier Saunders; 2011. p. 26–32.
6. U.S. Department of Health and Human Services Centers for Disease Control and Prevention. Recommended immunization schedule for children and adolescents aged 18 years or younger—United States 2019. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html. Accessed 16 Feb 2019.8.
7. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. Immunization schedules for health care professionals. 26 May 2016. https://www.

cdc.gov/vaccines/schedules/hcp/index.html. Accessed 29 Sep 2018.
8. Bright Futures/American Academy of Pediatrics. Recommendations for Preventive Pediatric Health Care (periodicity schedule). 2017. https://www.aap.org/en-us/Documents/periodicity_schedule.pdf. Accessed 23 Sep 2018.
9. Academy of Pediatrics. Committee on environmental health. Lead exposure in children: prevention, detection, and management. Pediatrics. 2005;116(4):1036–46.
10. Lowry JA. Childhood lead poisoning: Management. Post TW, editor. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed 14 Oct 2018.
11. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. Child passenger safety: get the facts. 11 2017. https://www.cdc.gov/motorvehiclesafety/child_passenger_safety/cps-factsheet.html. Accessed 29 Oct 2018.
12. Smith VC, Stewart J. Discharge planning for high-risk newborns. Post TW, editor. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed 14 Oct 2018.
13. Green SS. Ingested and aspirated foreign bodies. Pediatr Rev. 2015;36(10):430–6.
14. Gill AC. Bicycle injuries in children: Prevention. Post TW, editor. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed 14 Oct 2018.
15. Young AR, Tewari A. Sunburn. Post TW, editor. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed 14 Oct 2018.
16. Breisch NL. Post TW, editor. Prevention of arthropod and insect bites: repellents and other measures. Waltham: UpToDate Inc.. http://www.uptodate.com. (Accessed 14 Oct 2018
17. Cohen GM, Albertini LW. Colic. Pediatr Rev. 2012;33(7):332–3.

Suggested Reading

Kelly NR. Screening tests in children and adolescents. Post TW, editor. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on 14 Oct 2018.

Olney AH. Macrocephaly syndromes. Semin Pediatr Neurol. 2007;14(3):128–35.

Neonatology

2

Mamta Fuloria

DEFINITIONS

Live birth

- Live birth occurs when a fetus, whatever its gestational age, exits the maternal body and subsequently shows any signs of life, such as voluntary movement, heartbeat, or pulsation of the umbilical cord, for however brief a time and regardless of whether the umbilical cord or placenta is intact

Gestational age (GA)

- The number of weeks in a pregnancy since the 1st day of the last menstrual period or the corresponding age of gestation as estimated by a more accurate method if available. Such methods include an early obstetric ultrasonography or by adding 14 days to a known duration since fertilization (in patients who have undergone in vitro fertilization)

Small for gestational age (SGA)

- Birth weight (BW) < 10th percentile for the given GA

Large for gestational age (LGA)

- BW > 90th percentile for the given GA

Low birth weight (LBW)

- BW < 2500 g regardless of the GA

Very low birth weight (VLBW)

- BW < 1500 g

Extreme low birth weight (ELBW)

- BW of less than 1000 g (2 lb., 3 oz)

Preterm

- An infant born at < 37 weeks GA

Term

- An infant born between the 37 0/7 and 41 6/7 weeks of gestation
  - Early term: Between 37 0/7 and 38 6/7 weeks of gestation
  - Full term: Between 39 0/7 and 40 6/7 weeks of gestation
  - Late term: Between 41 0/7 and 41 6/7 weeks of gestation

Post-term

- An infant born after 42 0/7 weeks of gestation

PRENATAL CARE

Routine Prenatal Laboratory Tests

- Urine for protein, glucose, and bacteriuria
- Complete blood count (CBC)
- Blood type and Rh
- Red blood cell (RBC) antibodies
- Hepatitis B surface antigen
- Rapid plasma reagin (RPR) or venereal disease research laboratory test (VDRL)

M. Fuloria (✉)
Division of Neonatology, Department of Pediatrics, The Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA
e-mail: mfuloria@montefiore.org

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_2

Table 2.1 Significant fetal ultrasonographic anatomic findings and postnatal management

Prenatal US finding	Causes	Postnatal evaluation
Dilated cerebral ventricles	Hydrocephalus, Dandy-Walker cyst, agenesis of corpus callosum	Serial head US or MRI, evaluation for other system anomalies
Choroid plexus cyst	Trisomy 18; can be a normal variant	Karyotype if indicated, Head US or MRI scan, evaluation for other system anomalies
Nuchal pad thickening	Cystic hygroma, Turner syndrome, trisomy 18 or 21	Evaluation for other system malformation, karyotype if indicated
Dilated renal pelvis	Ureteropelvic junction obstruction, vesicoureteral reflux, posterior urethral valve, ectopic ureterocele	Renal ultrasound between day 5 and 7 and at 4–6 weeks of age; voiding cystourethrogram and prophylactic antibiotic if indicated

MRI magnetic resonance imaging, *US* ultrasonography

- Human immunodeficiency virus (HIV) screening
- Rubella antibodies
- Blood work for neural tube defects and chromosomal abnormalities, if indicated
- Ultrasound at 18–20 weeks, if indicated (Table 2.1)
- Glucose challenge and/or glucose tolerance tests between 24 and 28 weeks gestation (for diagnosing gestational diabetes)
- Vaginal and rectal culture for group B streptococcus (GBS) between 35 and 37 weeks gestation, and intrapartum antibiotics if indicated
- Education about nutrition, vitamins, and pregnancy course
- Prenatal care delayed until after the first trimester is associated with higher infant mortality rate

General neonatal risks

- Delayed prenatal care
- Maternal age: Teens and > 40 years of age
- Male infants have higher mortality rates than female infants
- Multiple births
- Placental bleeding – placenta previa, placental abruption
- Uterine abnormalities
- Premature rupture of membranes
- Preterm delivery
- Chorioamnionitis
- Maternal drug abuse, e.g., cocaine
- Bacterial vaginosis

Known risk factors for prematurity

- Placental bleeding
- Uterine abnormalities
- Use of drugs such as cocaine
- Smoking
- Alcohol intake
- Maternal chronic disease
- Premature rupture of membranes
- Prior history of preterm delivery
- Chorioamnionitis
- Bacterial vaginosis
- Preeclampsia or hypertension
- Maternal age: < 18 years and > 35 years

Factors associated with high mortality rate in preterm infants

- Younger GA
- Male sex
- 5 min Apgar < 4
- Persistent bradycardia at 5 min
- Hypothermia
- Intrauterine growth restriction

Umbilical Cord

- Umbilical cord has two arteries and one vein
- Single artery umbilical cord can be associated with other organ anomalies, e.g., heart and kidneys
- Umbilical cord length is about 55 cm; umbilical cord < 40 cm is short and can be associated with fetal complications, e.g., amniotic band and arthrogryposis
- Longer cord more than 55 cm may be associated with knots, prolapse, or may entwine the fetus

Placenta

- **Placenta accreta**: Develops when the chorionic villi attaches to the myometrium of the uterine wall rather than being restricted within the decidua basalis; may occur because of previous trauma, e.g., previous cesarean section, and curettage
- **Placenta increta**: Develops when the chorionic villi invades into the myometrium
- **Placenta percreta**: Develops when the chorionic villi invades through the myometrium, sometimes extending to nearby organs such as the bladder, resulting in serious bleeding
- **Placental abruption**:
  - Develops when the placenta separates from the wall of the uterus, either partially or completely, before birth of the infant
  - Hemorrhage into the decidua basalis occurs as the placenta separates from the uterus
  - Vaginal bleeding usually follows, although a concealed retroplacental hemorrhage is possible

Cesarean Section (C-section): Indications

- Previous C-section
- Fetal distress
- Dystocia
- Fetal malpresentation
- Placenta previa
- Placenta accreta, increta, and percreta
- Other

Fetal Distress

Definitions

- **Nonstress test** is the most common noninvasive test; it monitors fetal heart rate accelerations that follow fetal movement over time
- **Early deceleration** is associated with head compression during uterine contraction, resulting in vagal stimulation and slowing of the heart rate
- **Variable deceleration** is associated with compression of the umbilical cord
- **Late deceleration** is associated with uteroplacental insufficiency. Thus, maternal hypotension, uterine hyperstimulation, preeclampsia, or any other factor that reduces uterine blood flow and limits effective oxygenations of the fetus will result in late decelerations and decreased baseline variability.
  - Persistent late decelerations associated with decreased beat-to-beat variability is an ominous pattern
  - If late deceleration is not responding to oxygen supplementation, hydration, position change, and discontinuation of labor stimulation, prompt delivery is indicated
- **Contraction stress test** is performed to determine how well a fetus will tolerate uterine contractions during delivery. It is important for testing the wellbeing of fetus, e.g., in uteroplacental insufficiency, IUGR
  - Contraction stress test measures the heart rate in relation to uterine contraction by giving oxytocin or nipple stimulation
- **Biophysical profile test** assesses fetal heart rate, movement, breathing, muscle tone, and amniotic fluid volume. It does not assess fetal growth

Causes of abnormal alpha-fetoprotein (AFP) during pregnancy

- Increased AFP
  - Neural tube defect
    - Anencephaly
    - Spina bifida
  - Abdominal wall defects
    - Gastroschisis
    - Omphalocele
  - Cystic hygroma
  - Placental abnormalities
  - Renal abnormalities, e.g.:
    - Polycystic kidney or absent kidney
    - Urinary obstruction
  - Multiple pregnancy
- Decreased AFP
  - Incorrect GA calculation
  - Trisomy 21 (Down syndrome)
  - Trisomy 18 (Edward syndrome)

DELIVERY ROOM CARE [1]

Temperature control

- To minimize heat loss, the delivered infant is first placed in a warmed towel or blanket
- Raising the environmental (room) temperature to 26 °C (78.8 °F) will also help in reducing neonatal hypothermia
- Other methods of warming infants:
  - Swaddle after drying
  - "Skin-to-skin" contact with mother
  - Polyurethane bags or wraps in infants with BWs less than 1500 g
  - Warming pads

Initial management—Once the infant is born:

- Dry the infant
- Clear the airway of secretions
- Provide warmth; place under radiant warmer
- Neonatal resuscitation if indicated

Newborn resuscitation

- Pediatrician or provider skilled in neonatal resuscitation should be present and equipment should be prepared prior to the birth of high-risk infants
- Preterm infants very likely will need at least some resuscitation, and they may develop complications from resuscitation more often than term infants

Indications for resuscitation

- Apnea or poor respiratory effort
- Cyanosis
- Bradycardia
- Poor muscle tone

Resuscitation steps

- Initial care includes providing warmth to the infant, clearing the airway, and drying and stimulating the infant
- Apneic or gasping infant with a heart rate < 100 beats/min (bpm):
  - Positive pressure ventilation (PPV) provided by bag-mask ventilation is initiated at a rate of 40–60 breaths/min
  - Chest compressions are required if the infant's heart rate remains < 60 bpm despite adequate ventilation for 30 s. Chest compressions must always be accompanied by PPV using 100% oxygen
  - Pulse oximetry is used to continuously monitor heart rate and oxygen saturation (SpO2)
  - Intubation or use of a laryngeal mask airway is needed if PPV is ineffective or prolonged, or chest compressions are being performed
- If the heart rate remains < 60 bpm despite adequate ventilation and chest compressions:
  - Intravenous administration of epinephrine is indicated (epinephrine can also be given via the endotracheal tube if vascular access is not available)
  - Cannulation of the umbilical vein is the quickest means of obtaining intravenous (IV) access in the newborn
- For infants with labored breathing or persistent cyanosis, and a heart rate ≥ 100 bpm:
  - Ensure the airway is optimally positioned and cleared of secretions; pulse oximetry is used to monitor SpO2
  - Supplemental oxygen is provided to targeted preductal SpO2
- Infants who require resuscitation are at risk of developing post-resuscitative complications
- After successful resuscitation, they require placement in a setting in which close monitoring and ongoing appropriate care can be provided

Withholding resuscitation

- Resuscitation efforts may be discontinued after 10 min of resuscitation if the neonate has demonstrated no signs of life (no heartbeat or no respiratory effort for greater than 10 min)
- Resuscitation can be withheld if it is legally acceptable and there is complete agreement among parents and care providers that the neonatal outcome is dismal

NEWBORN NURSERY CARE

Eye prophylaxis

- Ophthalmic erythromycin 0.5% ointment within 1 h after delivery
- Prevent *Neisseria gonorrhoeae* ophthalmia neonatorum

Hepatitis B prophylaxis

- Universal vaccination of newborns regardless of maternal hepatitis B virus surface antigen (HBsAg) status is recommended
- The first dose of the hepatitis B vaccine (HBV) should be given within 24 h of delivery (See Chap. 1 General Pediatrics)

Vitamin K

- Vitamin K 1 mg intramuscular (IM) injection in the first few hours after delivery prevents hemorrhagic disease of the newborn

Umbilical cord care

- In developed countries where aseptic care is routine in clamping and cutting of the umbilical cord, additional topical care beyond dry cord care is not needed to prevent omphalitis

Newborn screening

- All states in the USA require newborn screening for metabolic and genetic disorders
- Blood is collected for an initial screen between 24 and 48 h of life. Some states also require a second screen, which is usually collected between 7 and 14 days of age

Critical congenital heart defects screening

- Pulse oximetry cardiac screening for all newborns before discharge

Hearing loss

- Universal newborn hearing screening is recommended to detect infants with hearing loss

Feeding

- Breastfed infants:
  - Should be fed as soon as possible after delivery, preferably in the delivery room
  - Should receive at least 8–12 feeds per day during the newborn hospitalization
  - Rooming-in, skin-to-skin contact, frequent demand feedings in the early postpartum period, and lactation support increase the rate of successful breastfeeding
- Formula-fed infants
  - Healthy infants who are fed formula should be offered standard 19–20 kcal/oz. (20 kcal per 30 mL) iron-containing infant formula
  - Feeding on demand, but the duration between feedings should not exceed 4 h
  - The volume of feedings should be at least 0.5–1 oz. (15–30 mL) per feed during the first few days of life
- Pasteurized human donor milk may be available in some nurseries for the healthy breastfed newborn who may require supplementation
- Weight loss—term infants may lose up to 10% of their BW in the first few days of life and typically regain their BW by 10–14 days

Hypoglycemia

- Glucose screening—healthy, asymptomatic term infants born after an uncomplicated pregnancy and delivery are at low risk for significant hypoglycemia. As a result, blood glucose measurement is not routinely performed in these neonates
- Per American Academy of Pediatrics (AAP) guidelines, glucose monitoring should be performed for newborns with the following risk factors:
  - Preterm infants (infants of GA < 37 weeks)
  - Large for gestational age (LGA)
  - Small for gestational age (SGA)
  - Infants of diabetic mothers (IDM)
  - Post-term infants (GA > 42 weeks)

Hyperbilirubinemia

- Visual assessment is not accurate for estimating the degree of hyperbilirubinemia
- Use transcutaneous bilirubin or total serum bilirubin measurement
- Infants should be routinely assessed every 8–12 h and at discharge for the presence of jaundice
- Assess pre-discharge bilirubin screen and risk factors together for prediction of development or worsening of hyperbilirubinemia after discharge

24 h discharge criteria

- Full-term healthy infants between 37 and 41 weeks
- Normal spontaneous vaginal delivery
- Clinical course and physical examination at discharge have not revealed abnormalities
- Stable state at least 12 h before discharge with normal vital signs
- At least two successful consecutive feedings
- The infant has urinated regularly and passed at least one stool spontaneously
- Infant blood tests are available and have been reviewed, such as cord or infant blood type and direct Coombs test results, as clinically indicated
- Not at high risk to develop subsequent hyperbilirubinemia
- Newborn metabolic and hearing screenings have been completed

Timing of the first well-child visit after hospital discharge

- For infants with a birth hospitalization less than 48 h
  - An early follow-up visit is recommended within 48 h of discharge
- For infants with a birth hospitalization greater than 48 h
  - An initial well-child visit within 3–5 days after discharge is reasonable
  - Infants at high risk of developing worsening hyperbilirubinemia and breastfed infants should be seen by their pediatrician within 48 h of discharge

MATERNAL CONDITIONS

Premature Rupture of Membranes

Background

- Premature rupture of membranes (PROM) refers to a patient who is beyond 37 weeks gestation and has presented with rupture of membranes (ROM) prior to the onset of labor
- Preterm premature rupture of membranes (PPROM) is ROM prior to 37 weeks gestation
- Spontaneous preterm rupture of the membranes (SPROM) is ROM after or with the onset of labor occurring prior to 37 weeks gestation
- Prolonged ROM is any ROM that persists for more than 24 h and prior to the onset of labor

PROM at term (> 37 weeks gestation): Management

- Evaluate the mother by speculum examination
- Check fetal heart rate (FHR)
- Identify fetal presentation
- Most patients (90%) enter spontaneous labor within 24 h when they experience ROM at term. However, most obstetricians induce labor at this point. Evidence supports the idea that induction of labor, as opposed to expectant management, decreases the risk of chorioamnionitis without increasing the cesarean delivery rate

Preterm premature rupture of membranes (PPROM):

Risks

- Prematurity is the principal risk to the fetus
- The risk of infection increases with the duration of PPROM

Expectant management

- The immature fetus may benefit from expectant management, even if for a short period, to allow for administration of steroids and antibiotics

Indications for delivery

- In certain circumstances (e.g., chorioamnionitis, advanced labor, fetal distress, and placental abruption with nonreassuring fetal surveillance), immediate delivery of the fetus with PPROM is indicated
- If fetal lung maturity has been documented by either amniocentesis or collection of vaginal fluid, delivery should be facilitated

Medications during expectant management

- 48 h course of IV ampicillin and erythromycin followed by 5 days of amoxicillin and erythromycin is recommended during expectant management
- In the absence of chorioamnionitis, some obstetricians give tocolysis, even with active contractions after the steroid therapy is started. The use of tocolysis should be considered only when a clear clinical benefit exists, such as in transport of the mother to a tertiary institution with a newborn intensive care unit (NICU)
- Magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants

Chorioamnionitis

Background

- Inflammation of the fetal amnion and chorion membranes due to a bacterial infection

Clinical presentation

- Maternal fever (intrapartum temperature > 100.4 °F or > 37.8 °C) most frequently observed sign
- Significant maternal tachycardia (> 100 beats/min)
- Fetal tachycardia (> 160 beats/min)
- Purulent or foul-smelling amniotic fluid or vaginal discharge
- Uterine tenderness
- Maternal leukocytosis (total blood leukocyte count > 15,000 cells/μL in the absence of corticosteroid therapy)

Management

- Early delivery, supportive care, and antibiotic administration
- Pharmacotherapy for the mother includes:
  - Ampicillin and gentamicin
  - Clindamycin or metronidazole when endometritis is suspected
  - Vancomycin for penicillin-allergic patients
  - Penicillin G: Used exclusively for GBS intrapartum prophylaxis; if intraamniotic infection is suspected, antibiotic coverage should be broadened
- Pharmacotherapy for the neonate
  - Ampicillin and gentamicin
- Supportive care of the neonate with sepsis may include the following:
  - Warmth, monitoring of vital signs
  - Preparedness to perform a full resuscitation, including intubation and providing PPV
  - Treatment of hypovolemia, shock, and respiratory and/or metabolic acidosis
  - Surfactant replacement therapy
  - Glucose homeostasis
  - Assessment and treatment of thrombocytopenia and coagulopathy, if present

Preeclampsia

Defined as the presence of:

- Hypertension:
  - Systolic blood pressure (SBP) greater than or equal to 140 mm Hg or a diastolic blood pressure (DBP) greater than or equal to 90 mm Hg or higher, on two occasions at least 4 h apart in a previously normotensive patient, ***or***
  - SBP greater than or equal to 160 mm Hg or a DBP greater than or equal to 110 mm Hg or higher
- Proteinuria:
  - Proteinuria of ≥ 0.3 g in a 24-h urine specimen, a protein (mg/dL)/creatinine (mg/dL) ratio of ≥ 0.3, or a urine dipstick protein of 1+ (if a quantitative measurement is unavailable)

Preeclampsia with severe features is defined as the presence of one of the following symptoms or signs in the presence of preeclampsia:

- SBP of 160 mm Hg or higher or DBP of 110 mm Hg or higher, on two occasions at least 4 h apart while the patient is on bed rest (unless antihypertensive therapy has previously been initiated)
- Impaired hepatic function as indicated by abnormally elevated blood concentrations of liver enzymes (to double the normal concentration)
- Severe persistent upper quadrant or epigastric pain that does not respond to pharmacotherapy and is not accounted for by alternative diagnoses, or both
- Progressive renal insufficiency (serum creatinine concentration > 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- New onset cerebral or visual disturbances
- Pulmonary edema
- Thrombocytopenia (platelet count < 100,000/μL)

Eclampsia

- Defined as seizures that cannot be attributed to other causes in a woman with preeclampsia
- HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) may complicate severe preeclampsia

Management

- Delivery is the only cure for preeclampsia
- Patients with preeclampsia without severe features are often induced after 37 weeks gestation
- In patients with preeclampsia with severe features, induction of delivery should be considered after 34 weeks gestation. In these cases, the severity of disease must be weighed against the risks of infant prematurity. In the emergency setting, control of BP and seizures should be prioritized
- Medications used for BP control include the following:
  - Hydralazine
  - Labetalol
  - Nifedipine
  - Sodium nitroprusside (in severe hypertensive emergency refractory to other medications)
  - Magnesium sulfate is the first-line treatment for primary and recurrent eclamptic seizures

Diabetes Mellitus

Background

- Abnormal maternal glucose regulation occurs in 3–10% of pregnancies
- Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy
- GDM accounts for 90% of cases of DM in pregnancy

Risks of preexisting maternal DM on infants

- Growth restriction occurs with significant frequency in pregnancies in women with preexisting type 1 DM
- Double the risk of serious injury at birth, triple the likelihood of cesarean delivery, and quadruple the incidence of NICU admission
- Increased rate of miscarriage and birth defects in diabetic women with suboptimal glycemic control before conception
- A higher rate of congenital anomalies persists even with good glycemic control in the mother
- Anomalies involve the cardiovascular and CNS systems; abnormalities of the skeletal, genitourinary, and gastrointestinal (GI) systems are also seen

Management

- Insulin remains the standard medication for treatment of diabetes during pregnancy, but

the oral agents glyburide and metformin are increasingly being used
- Mothers should keep the fasting blood sugar value at 90–99 mg/dL, and keep 1-h, post-meal values at < 140 mg/dL
- Before diabetic women become pregnant, they should have a glycosylated hemoglobin (HbA1c) of < 6.5% and maintain the same during pregnancy
- The most common complication in a well controlled mother with DM is macrosomia

NEWBORN EXAMINATION

Apgar Score (Table 2.2)

- Dr. Virginia Apgar devised the Apgar score in 1952 as a simple and replicable method to quickly and summarily assess the health of newborn children immediately after birth
- The Apgar score alone cannot be considered to be evidence of or a consequence of asphyxia, does not predict individual neonatal mortality or neurologic outcome, and should not be used for that purpose
- Apgar score at 1 min and 5 min does not correlate well with long-term neurobehavioral sequelae

Table 2.2 Apgar score

Score	0	1	2
A—Activity	Absent	Some flexion of arms and legs	Active
P—Pulse (Heart rate)	Absent	< 100 beats/min	> 100 beats/min
G—Grimace (reflex irritability)	No response	Grimace	Cry or active withdrawal
A—Appearance (skin color)	Blue, pale	Acrocyanotic	Completely pink
R—Respiration	Absent	Slow and irregular; hypoventilation; weak cry	Good respiratory effort, crying

Apgar score is done at 1 min, 5 min routinely, and at 5-min intervals thereafter until 20 min for infants with a score less than 7

- Apgar score < 3 at 15 min has been associated with high mortality and severe neurologic sequelae

Newborn Crying

- Weak cry or high-pitched cry is abnormal
- Hoarseness can be caused by any process that affects the structure or function of the larynx
- Hoarse cry may indicate hypothyroidism or vocal cord paralysis

Temperature

- Persistent abnormal temperature in a normal temperature environment must be investigated
- Hypothermia: Look for environmental factors, sepsis, hypoglycemia, hypothyroidism, low Apgar scores (hypoxia), intracranial hemorrhage, drug withdrawal
- Hyperthermia: Look for environmental factors (overheating from incubators, radiant warmers or ambient environmental temperature; excessive bundling or swaddling), maternal fever, maternal epidural anesthesia, sepsis, adrenal hemorrhage, or CNS disorders

SKIN

- **Aplasia cutis congenita** (congenital absence of the skin):
  - Absence of a portion of skin in a localized or widespread area at birth
  - Most commonly (70%) manifests as a solitary defect on the scalp
  - Consider trisomy 13, especially if associated with midline defect
- **Acrocyanosis:** Cyanosis of hands and feet when exposed to colder temperature; this can be a normal finding
- **Generalized cyanosis:** Significant hypoxemia (e.g., cardiac or respiratory) or methemoglobinemia
- **Pallor:** Anemia or poor perfusion (e.g., placental abruption or placenta previa)

- **Cutis marmorata** (pale mottled skin): Cold environment, sepsis, or hypothermia
  - While cutis marmorata is a relatively benign disorder, persistent cutis marmorata is associated with Down (trisomy 21), Edward (trisomy 18), and Cornelia de Lange syndromes
  - Cutis marmorata may also indicate poor perfusion in infants developing sepsis. The mottled appearance of the skin in cutis marmorata usually disappears when the newborn is warmed
  - The syndrome usually resolves within weeks to months of its presentation
  - No formal treatment is necessary
- **Plethora** (very red skin): Polycythemia
- **Harlequin color change:** Cutaneous condition seen in newborn babies characterized by momentary red color changes of half the newborn, sharply demarcated at the body's midline
- **Harlequin ichthyosis:** Most severe form of autosomal recessive congenital ichthyosis that results in thickened keratin layer in fetal skin. The skin contains massive, diamond-shaped plates that are separated by deep cracks
- **Ecchymoses:** Usually due to birth trauma
- **Petechiae:** Scattered localized petechiae are common after delivery; however, extensive generalized petechiae must be investigated for thrombocytopenia, sepsis, and other causes

Subcutaneous Fat Necrosis of the Newborn (SCFN)

- Uncommon disorder characterized by firm, mobile, erythematous nodules and plaques over the trunk, arms, buttocks, thighs, and cheeks of full-term newborns
- Self-limited process that usually does not require treatment
- May be complicated by hypercalcemia and other metabolic abnormalities

Jaundice

- If present on the 1st day of life, the infant must be investigated for hemolytic anemia or sepsis

HEAD

Head Shape

- Head shape and symmetry may vary, depending on the intrauterine position, presentation at delivery, degree of molding, or the need for an instrument-assisted delivery
- Infants born by cesarean section often have a symmetrical, round head when compared to infants born vaginally whose head shape is often elongated in the occipital area with overriding sutures
- Molding is temporary overlapping of bones and must be distinguished from craniosynostosis. It typically resolves 2–3 days after birth

Fontanelles

- **Anterior fontanelle:** Diamond shaped, open, soft, and flat at birth; measures 4–6 cm at birth and usually closes at approximately 18 months of age
- **Posterior fontanelle:** Usually triangular, < 0.5 cm at birth and closes shortly after birth:
  - Hypothyroidism must be considered if posterior fontanelle is persistently opened
- **Bulging fontanelle** can be normal in a crying infant, but may be associated with hydrocephalus, birth injury, intracranial bleeding, or infection. It may be present as a late sign of increased intracranial pressure
- **Large fontanelles** may indicate hypothyroidism, hydrocephaly, in utero malnutrition, rickets, or a genetic disorder
- **Depressed anterior fontanelle** is a late sign of dehydration

Caput Succedaneum

- **Definition:** Diffuse subcutaneous edematous swelling of soft tissue of the scalp that may extend across the suture lines
- **Causes:** Secondary to the pressure of the uterus or vaginal wall
- **Outcome:** Usually resolves within 48–72 h

Cephalohematoma

Background
- Subperiosteal hemorrhage that is soft, fluctuant, cyst-like swelling with a well-defined outline
- Initially firm but becomes more fluctuant after 48 h
- Typically calcifies at the edges during resolution
- Cephalohematoma never extends across suture line

Causes
- Difficult or instrument-assisted delivery

Management
- Radiograph or computed tomography (CT) scan should be obtained if skull fracture is suspected
- Hemoglobin and bilirubin should be monitored
- Most cephalohematomas resolve within 2–3 weeks to several months

Subgaleal Hemorrhage

Background
- Serious but less common complication, usually associated with vacuum-assisted delivery
- Collection of blood between the aponeurosis and the periosteum
- Can extend to orbits and neck
- Usually secondary to rupture of emissary veins
- If massive, coagulopathy may be present

Management
- Progressive after birth but typically resolves within 2–3 weeks
- Monitor BP, hematocrit, bilirubin, and signs for hypovolemia, bleeding, and shock

Traumatic Epidural, Subdural, and Subarachnoid Hemorrhage

Risk factors
- Large head
- Prolonged labor in breech or precipitous delivery

Important
- Child abuse must be suspected in all infants with subdural hemorrhage after the immediate neonatal periods

Diagnosis
- Suspect subdural hemorrhage if megalocephaly, bulging fontanel, unexplained anemia and jaundice, or seizures
- CT scan and magnetic resonance imaging (MRI) are useful in the diagnosis

Skull Fractures

- **Linear fracture:** Linear fractures are benign and have excellent prognosis
- **Depressed fracture:** Ping-pong ball, usually not associated with loss of bone continuity; prognosis is good if neurological exam is normal
- **Basilar fracture:** Overall prognosis is guarded and there is significant risk of permanent sequelae

EYES

- **Red reflex examination:**
  - Dark spots in the red reflex, a blunted red reflex on one side, lack of a red reflex, and the presence of a white reflex are all indications for immediate ophthalmology referral
  - White pupillary reflex (leukocoria): Cataract, retinoblastoma, retinopathy of prematurity, retinal coloboma, Coats disease, persistent fetal vasculature
  - Cataract: Galactosemia, intrauterine infections (rubella); can be inherited as a dominant trait from an affected parent
- **Coloboma** (hole in the structure of the eye such as the lens, iris, retina, choroid, or optic disc)
  - CHARGE syndrome (Coloboma, Heart defect, Choanal atresia, Retarded growth and development, Genital abnormality, Ear abnormality), and trisomy 13 (Patau syndrome)
- **Brushfield spots:** Small white spots on the surface of the iris arranged in a concentric ring around the pupil; seen in healthy children but are far more common in patients with Down syndrome
- **Strabismus:** Persistent strabismus must be referred immediately; occasional eye deviation can be normal in the first 4 months of life
- **Eyelids:** Ptosis could be a sign of Horner syndrome or congenital myasthenia gravis. Check maternal history (for congenital myasthenia); check the arms and the clavicles
- **Subconjunctival hemorrhage:** Secondary to rupture of small blood vessels near the surface of the bulbar conjunctiva. Can occur normally during labor and delivery and resolves spontaneously over a period of time
- **Blue sclera:** Osteogenesis imperfecta or normal variant
- **Congenital glaucoma:** The classic triad of manifestations, any one of which should arouse suspicion of glaucoma in an infant or young child, includes epiphora, photophobia, and blepharospasm. The cornea is enlarged and becomes progressively cloudy. A corneoscleral junction more than 12 mm in diameter in the 1st year of life is highly suggestive of glaucoma

EARS

- **Malformed ears** and low set ears are associated with many syndromes, look for urogenital malformation
- **Preauricular pits and tags:** Renal ultrasound should be performed in any newborn with an ear anomaly accompanied by other dysmorphic features, family history of deafness, maternal history of gestational diabetes, or a defined syndrome

NOSE

- **Nasal stuffiness** after birth can be a sign of drug withdrawal
- **Choanal atresia** can be unilateral or bilateral (respiratory distress and cyanosis while feeding if bilateral)
- **Snuffles (rhinorrhea)** and saddle nose: Usually associated with syphilis
- **Flattened nasal bridge:** Can be a normal variant or associated with congenital syphilis, Down syndrome, or Williams syndrome

MOUTH

- **Epstein pearls:** Small, opaque whitish-yellow papules that are firm in consistency and are located on the mid-palatal raphe at the junction of the hard and soft palate (Fig. 2.1)
  - Represents keratin entrapment within the soft and hard palate
  - Common and benign finding

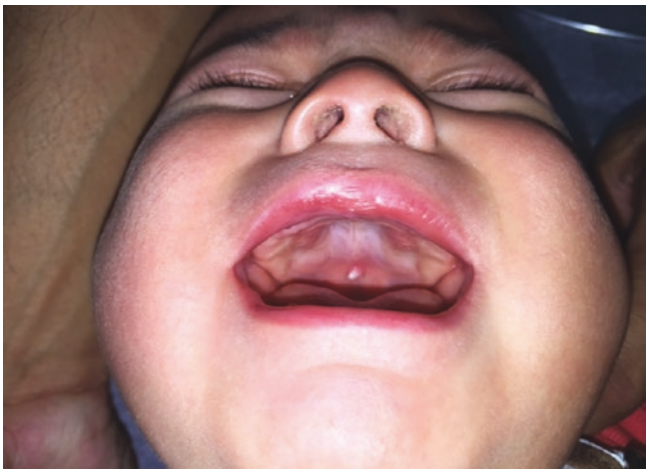


Fig. 2.1 Infant with Epstein pearl in the hard palate

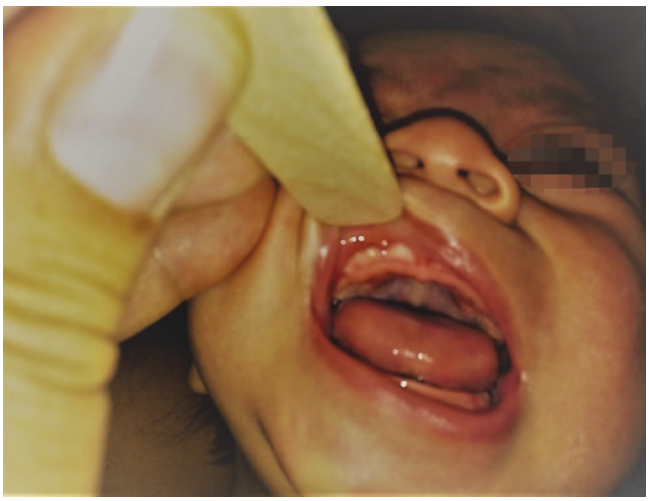


Fig. 2.2 Infant with Bohn nodules in the upper gums

- **Bohn nodules:** Grayish-white, firm nodules frequently present on the buccal or lingual aspects of the alveolar ridges (Fig. 2.2)
  - Exact etiology is unknown, but they are thought to arise from remnants of the dental lamina or from heterotopic salivary glands
  - Benign finding that will disappear with time
- **Ranula:** Translucent, firm papule or nodule found on the anterior floor of mouth, lateral to lingual frenulum
- **High arched palate:** Usually associated with syndromes
- **Pierre Robin sequence:** Triad of retrognathia or micrognathia, glossoptosis, and airway obstruction
- **Cleft lip and palate:** Can be hereditary or associated with syndromes
- **Macroglossia:** Can be congenital or acquired; associated with hypothyroidism, Beckwith-Wiedemann syndrome, Pompe disease, and Down syndrome

Natal teeth

- **Supernumerary:** Usually very loose and easy to remove with a little pinch
- **True milk teeth:** Usually hard and should not be removed (Fig. 2.3)

Ankyloglossia or tongue-tie

- Caused by a short frenulum on the underside of the tongue that prevents complete protrusion of the tongue
- Can interfere with breastfeeding and speech articulation
- Frenulotomy is recommended if interfering with feeding or speech

Fig. 2.3 Infant with two true milk lower central incisor teeth, hard to move

NECK

Brachial Plexus Injuries (BPI)

Background

- **Erb's palsy** (Duchenne-Erb palsy): Upper trunk nerve injury (C5 and C6, ±C7), due to traction on the upper trunk; most common form
- **Klumpke palsy:** Injury to the C8-T1 nerve roots; results in weakness of the hand muscles, absent grasp, and sometimes Horner syndrome
- Total brachial plexus injury involves both upper and lower roots
- Most patients have the least severe form of nerve injury (neuropraxia) and recover spontaneously or with supportive physical therapy

Classification

- Purely neurapraxic lesions
  - Stretching of nerve without disruption
  - These lesions generally are reversible and do not leave sequelae
- Axonotmetic lesions
  - Due to nerve fibers (axons) disruption with intact sheath
  - Cause degeneration of the axon distal to the injury
  - These injuries improve gradually over 4–6 months, depending on the level of the lesion
- Neurotmesis lesions
  - The most severe form
  - Involves disruption of the axon and myelin sheath (total severing, avulsion injury)
  - Muscle atrophy from a neurotmesis lesion begins 3–6 months after injury, and complete recovery is impossible (worst prognosis)

Clinical presentation

- Complete brachial plexus palsy (C5-T1)
  - Arm held limp at side
  - Deep tendon reflexes (DTRs) in the affected arm are absent
  - Moro response is asymmetrical, with no active abduction of the ipsilateral arm
  - Horner syndrome (i.e., miosis, ptosis, anhidrosis) may occur, a bad prognostic sign usually associated with avulsion injury
  - Respiratory distress and elevation of diaphragm may occur due to injury to phrenic nerve
- Erb's palsy (C5-C6, ±C7)
  - Arm adducted and internally rotated; elbow extended and the forearm pronated; wrist flexed and the hand in a fist (waiter tip position)
  - Absent Moro reflex, but grasp reflex is present on the affected side
  - In the 1st hours of life, the hand may appear flaccid, but strength soon returns
  - About 80% of patients with Erb's palsy will show complete recovery within the first 3 months, 90% recover by 12 months
- Klumpke palsy (C8-T1)
  - Rare
  - Absent grasp reflex on affected side
  - Supinated arm, elbow bent, wrist extended, and fingers flexed, "claw hand"
  - One-third of cases associated with Horner syndrome
  - Phrenic nerve injuries may be evident

Associated injuries

- The pediatrician must perform a careful examination of the infant with BPI to look for associated injuries
- The most common associated (not causative) injuries:
  - Clavicular and humeral fractures
  - Torticollis
  - Cephalohematoma
  - Facial nerve palsy
  - Diaphragmatic paralysis

Diagnosis

- Chest radiography: Look for clavicular fractures or elevation of diaphragm suggesting phrenic nerve injuries and root avulsion
- High-resolution MRI is the study of choice for evaluating brachial plexus injuries

- MRI is indicated for preoperative planning in severe cases requiring surgery

Management

- Rehabilitation must start immediately after the diagnosis. Treatment is directed towards preventing contractures:
  - Intermittent and partial immobilization: The arm can be fixed across the child's chest by pinning of his/her clothing to provide more comfort
  - Active and passive range of motion exercises
  - Dress the infant gently and avoid further traction on the arm
  - Wrist extension splint is necessary to maintain proper wrist alignment and to reduce the risk of progressive contractures
  - Assessments every 3–4 weeks are indicated
- Persistence of symptoms beyond 1 month of age suggests that the injury may require treatment
- Absence of full recovery by age of 3 months, signs of root avulsion (Horner syndrome, phrenic nerve involvement), total palsy, and Klumpke palsy are all indications for referral to orthopedics

CHEST

- Fracture of the clavicle is very common; crepitation usually found during examination
- Supernumerary nipple (polythelia) is fairly common and considered minor anomaly
- Pectus excavatum is a congenital depression of the sternum and is usually insignificant
- Widely spaced nipples are seen in Turner syndrome
- Breast hypertrophy and galactorrhea may be seen in both male and female infants (because of maternal hormones); engorgement may increase during the first few days but then usually resolves (Fig. 2.4)

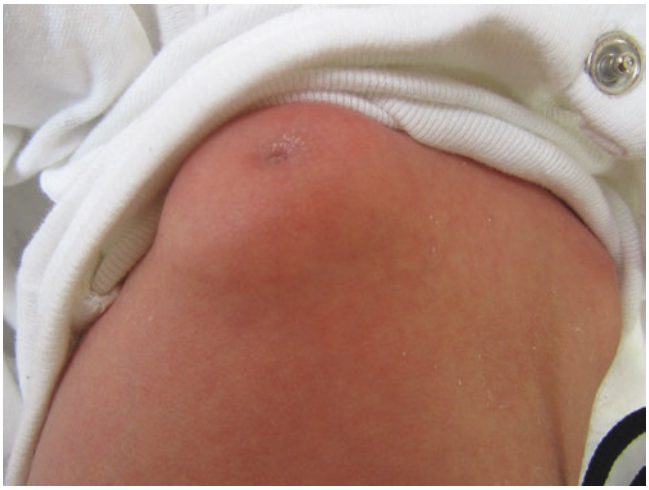


Fig. 2.4 Three-week-old infant with enlarged breast tissue, resolved spontaneously after several weeks

LUNG

Respiratory distress

- Normal respiratory rate is 40–60 breaths/min
- Respiratory rate persistently more than 60 breaths/min in the newborn period is abnormal
- Grunting, nasal flaring, retractions, and tachypnea may be transient in the first few hours after birth—transient tachypnea of the newborn (TTN). If it persists for more than 24 h, other causes must be explored

Unilateral movement of the chest

- Phrenic nerve palsy
- Diaphragmatic hernia

Cough

- Always abnormal in newborn
- Pneumonia must be considered

HEART

- **Point of maximal cardiac impulse (PMI):** Location is fourth to fifth intercostal space just medial to left mid-clavicular line
- If PMI is displaced, chest radiograph is recommended to rule out pneumothorax, dextrocardia, diaphragmatic hernia, or space-occupying lesion

- **Bradycardia:** HR < 100 bpm is abnormal. Look for sepsis, asphyxia, increased intracranial pressure, hypothyroidism, congenital heart disease, and heart block (as may be seen in infants born to mothers with systemic lupus erythematosus)
- **Tachycardia:** HR > 180 bpm. Look for fever, hypovolemia, anemia, tachyarrhythmia, hyperthyroidism, and drug withdrawal

Murmur

- Approximately 60% of infants will have a murmur auscultated in the newborn period
- Most murmurs in the neonatal period are benign. Benign murmurs are usually due to transient changes in the postnatal circulation (e.g., patent ductus arteriosus)
- 8% of murmurs at birth are associated with congenital heart disease
- Murmurs usually require workup if the following are present:
  - Persist after the first day of life
  - Presence of cyanosis
  - Evidence of poor perfusion
  - Poor feeding

Blood pressure

- SBP in term infants < 12 h usually between 60 and 90 mmHg
- BP in right arm and one leg must be determined; a pressure difference of more than 20 mmHg in favor of the arms may be considered evidence of coarctation of the aorta
- Absent/weaker pulse in the lower extremities is a red flag for coarctation of the aorta

ABDOMEN

Liver/Spleen

- Liver is normally palpated 1–2 cm below the right costal margin in the newborn
- Spleen is normally palpable not more than 1 cm below the left costal margin

Abdominal Masses

- Multicystic dysplastic kidney is the most common cause of an abdominal mass in the newborn period and is the most common cystic malformation of the kidney in infancy
- Subcapsular hematoma of the liver (traumatic delivery)

Abdominal Wall Defects

- **Umbilical hernia and diastasis recti**
  - Usually benign and self-limited conditions
  - Umbilical hernias are managed with observation, as these defects typically close by age 4 or 5 years (Fig. 2.5)
  - Any defects that persist beyond this age or the defect is larger than 2 cm should undergo surgical repair
- **Omphalocele**
  - Result of herniation of the intestine and other abdominal organs into the umbilical cord without returning into the abdominal cavity
  - The abdominal viscera are contained in a translucent sac, which is composed of amnion, Wharton jelly, and peritoneum
  - The umbilical vessels insert into the wall of the sac, and not the abdominal wall

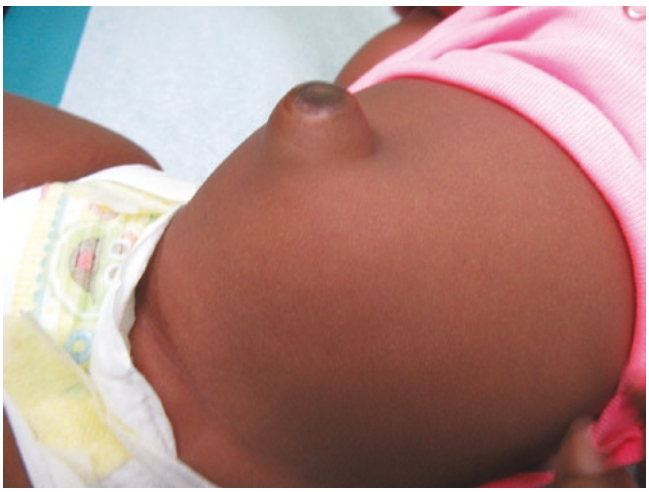


Fig. 2.5 Infant with a large umbilical hernia

  - Associated with syndromes and chromosomal abnormalities in > 50% of cases, including Beckwith-Wiedemann syndrome (omphalocele, macroglossia, organomegaly, hypoglycemia, and increased risk of childhood tumors such as Wilms tumor, neuroblastoma, and hepatoblastoma)
- **Gastroschisis**
  - Considered to be the result of a vascular accident of the omphalomesenteric artery, a failure of mesoderm formation, rupture of the amnion around the umbilical ring with herniation of the midgut, or abnormal involution of the right umbilical vein with body wall weakening
  - Full thickness defect in the abdominal wall with prolapse of the intestine through the defect
  - No covering membrane on the defect
  - Defect lies to the right of an intact umbilical cord
- **Prune belly syndrome (Eagle-Barrett syndrome)**
  - Caused by laxity of the abdominal musculature
  - Wrinkly folds of skin covering the abdomen
  - Associated with GI and genitourinary tract anomalies (obstructive uropathy) and pulmonary hypoplasia
  - Undescended testis in males
- **Urachal remnants**
  - The urachus is a structure that connects the dome of the bladder to the anterior abdominal wall at the level of the umbilicus
  - With a patent urachus, a complete communication between the bladder and umbilicus remains. Urine is noted to drain from the umbilicus
  - Remnants of this connection include a patent urachus, urachal sinus (free communication between the bladder and umbilicus), and urachal cyst
  - Umbilical polyps can be observed in association with a urachal remnant
- **Umbilical granuloma**
  - Granulation tissue may persist at the base of the umbilicus after cord separation
  - Surface of an umbilical granuloma may be smooth or irregular and is often pedunculated
  - The tissue is composed of fibroblasts and capillaries and can grow to more than 1 cm
  - Small granulomas may be treated adequately with applications of topical silver nitrate. Larger granulomas or those refractory to silver nitrate may require surgical resection
  - Umbilical granulomas must be differentiated from umbilical polyps, which do not respond to silver nitrate cauterization
- **Omphalomesenteric duct remnants**
  - Persistence of all or portions of the omphalomesenteric duct can result in fistulas, sinus tracts, cysts, congenital bands, and mucosal remnants. The most common remnant is a Meckel diverticulum
  - Patients with mucosal remnants can present with an umbilical polyp or an umbilical cyst
  - The condition should be suspected in cases of delayed separation of the cord or persistent, large, umbilical granulomas with associated drainage
- **Delayed separation of the umbilical cord**
  - The umbilical cord usually separates and sloughs by the end of the second postnatal week
  - Cord care involves keeping the area clean and dry
  - A marked delay in cord separation raises the suspicion of leukocyte adhesion deficiency (LAD), a rare disorder leading to defective neutrophil function
- **Single umbilical artery (SUA)**
  - The normal umbilical cord has one vein and two arteries
  - SUA occurs in up to 2% of all live-born infants

  - SUA is thought to result from either aplasia or atrophy of the second umbilical artery or from persistence of the normally transient early embryonic SUA
  - Associated structural or chromosomal anomalies are seen in 27% of infants with SUA, with renal malformations being the most common finding
  - A newborn with SUA should be examined thoroughly for dysmorphic features, abdominal masses, and the presence of heart disease
  - SUA is associated with an increased risk of chromosome abnormalities such as trisomy 13, trisomy 18, and triploidy

GENITALIA

Females

- Female infants have two orifices, one for the urethra just below the clitoris and the other for the vagina. The urethral orifice must be differentiated from the vagina
- Infants can have a creamy white to slightly blood-tinged discharge 2–3 days after birth, caused by withdrawal of maternal hormones
- Imperforate hymen can result in hydrometrocolpos, which usually presents as a bulging hymen especially with crying, or an abdominal mass

Males

Penis

- Term infant's penile length is 2.5–3.5 cm
- Micropenis: Penile length < 2.5 cm is abnormal (hormonal workup is needed). Infants should be observed for evidence of metabolic derangements
- Prepuce is usually adherent and should not be forcibly retracted
- **Chordae**: The skin on the underside of the penis may be tethered to the scrotum, called chordae; this may be associated with hypospadias
- **Hypospadias:** Defect of the urethra in a male infant that involves an abnormally placed urethral meatus. Instead of opening at the tip of the glans, the urethra opens anywhere along a line running from the tip along the ventral aspect of the shaft to the junction of the penis and the perineum
  - Infants with hypospadias should not be circumcised because the foreskin is often used during surgical repair
- **Epispadias:** Meatal opening is on the dorsal surface of the penis. It is less common than hypospadias
- **Mispositioned meatus:** May be associated with urethral or kidney abnormalities and may result in poor urinary stream

Testis

- Normally in the scrotum in term infants but may be palpated in the upper scrotum or in the inguinal canal
- **Cryptorchidism** occurs in 3–5% of term male infants
  - Undescended testicles may be true undescended testicles, ectopic testicles, or retractile testicles
- **Discoloration of the scrotum** may be present in a neonate born after breech presentation or may be caused by testicular torsion or hematoma
- **Testicular torsion** can occur in infancy and presents as an enlarged testicle with overlying discoloration of the scrotum

Ambiguous Genitalia (See Also Chap. 12 Endocrinology)

- Small penis, bifid scrotum, large clitoris, and pigmented fused vulva are signs of ambiguous genitalia

- Initial screening
  - Chromosomal analysis
  - Endocrine screening
  - Serum chemistries/electrolyte tests (possible CAH)
  - Androgen-receptor levels
  - 5-Alpha reductase type II level
  - Abdominal ultrasound to evaluate for the presence of ovaries/uterus vs. testicles
  - Genetic and endocrinology consultations

Anus

- The anus should be examined carefully to confirm it is not just a fistula
- Presence of meconium does not rule out imperforate anus; meconium may pass from the fistula
- Position of the anus should be determined
- Mild mislocation of the anus may be associated with constipation later in life
- Meconium usually passes in the first 24 h of birth and 99% of term infants will pass meconium within the first 48 h
- Impaction of meconium that causes intestinal obstruction is often associated with cystic fibrosis (CF)

BACK

Sacral dimple

- A pilonidal sinus (sacral dimple) may be present at the base of the spine between the buttocks
  - Typically, benign
  - Rarely, a true sinus tract associated with a myelomeningocele may be present
  - May be associated with a tethered cord
- Abnormal pigmentation, overlying hemangioma, pigmented nevus, or a hair tuft over the lower spine may be associated with vertebral anomalies
- Indication for ultrasound or MRI
  - Multiple dimples
  - Dimple diameter more than 5 mm
  - Dimple > 2.5 cm above the anus (the higher the lesion, the higher the risk)
  - Dimple outside the sacrococcygeal region
  - Marked by a tuft of hair, skin discoloration, or skin tag
  - Base of the dimple cannot be visualized
- Indications for referral to neurosurgery
  - Abnormal ultrasound or MRI, e.g., occult spinal dysraphism; split cord malformation, dermal sinus tract, tethered spinal cord, and intraspinal lipoma
  - Other associated cutaneous findings, e.g., hypertrichosis and hemangioma
  - Abnormal neurologic examination

EXTREMITIES

Developmental dysplasia of the hip (DDH)

- Ortolani and Barlow tests (See also Chap. 13 Orthopedics) must be performed for all newborns before discharge from the newborn nursery

Hemihypertrophy

- Wilms tumor occurs in association with either isolated hemihypertrophy of the extremities or Beckwith-Wiedemann syndrome

Polydactyly

- Ulnar or postaxial polydactyly
  - The most common and usually isolated condition
  - Postaxial polydactyly more common than pre-axial polydactyly
  - Usually autosomal dominant with incomplete penetrance
- Radial or preaxial polydactyly
  - Usually syndromic and associated with other anomalies

Assessment of gestational age (Table 2.3)

Table 2.3 Gestational age ranges according to the physical characteristics of newborn and maturity

Body parts	Characteristics	Weeks of gestation range
Vernix (waxy or cheese-like white substance found coating the skin of newborn babies)	Coat the entire body	< 38 weeks
	Less coated areas	38–39 weeks
	Scant	40–41 weeks
	No vernix	> 42 weeks
Lanugo (very fine, soft, unpigmented, downy hair covers the body of a newborn)	Covers most of the body	< 32 weeks
	Disappears from face	33–37 weeks
	Present on shoulders only	38–41 weeks
	None present	≥ 42 weeks
Testes	Palpable in inguinal canal	< 36 weeks
	Palpable in upper scrotum	36–39 weeks
	Palpable in lower scrotum	≥ 40 weeks
Scrotum	Few rugae	< 36 weeks
	More rugae	36–39 weeks
	Rugae all over the scrotum	40–41 weeks
	Pendulous scrotum	≥ 42 weeks
Labia and clitoris	Prominent clitoris and labia minora	Preterm
	Labia majora is prominent	Full-term
Sole creases	No anterior sole creases	< 32 weeks
	1–2 anterior creases	32–33 weeks
	2–3 anterior creases	34–35 weeks
	2/3 of the anterior sole with creases	36–37 weeks
	Heel creases present	38–41 weeks
	Deeper creases over entire sole	≥ 42 weeks

NEONATAL CONDITIONS

Intrauterine Growth Retardation (IUGR)

Definition

- IUGR, which is defined as less than 10% of predicted fetal weight for GA, may result in significant fetal morbidity and mortality
- Second leading cause of perinatal mortality

Causes

- Fetal factors:
  - Chromosomal abnormalities (aneuploidy)
  - Multifactorial congenital malformations—cardiovascular abnormalities, renal agenesis
  - Multiple gestation
  - Infections: Congenital cytomegalovirus, toxoplasmosis, herpes simplex virus (HSV), rubella
  - Aberrant genomic imprinting—uniparental disomy
- Maternal factors
  - Chronic diseases—hypertension, chronic renal disease, systemic lupus erythematosus, DM
  - Preeclampsia early in gestation
  - Smoking, drugs, and alcohol
  - Constitutionally small mother
  - Malnutrition
- Placental factors
  - Placental infarction
  - Small placenta
  - Chronic vascular disease
  - Uteroplacental insufficiency

Symmetrical (proportional) vs. asymmetrical (relative head sparing) IUGR

- **Symmetrical IUGR** results from an early fetal insult caused by chemical exposure (e.g., nicotine from cigarette smoking), viral infection, or inherent developmental abnormalities caused by aneuploidy
- **Asymmetrical IUGR** is likely to result from uteroplacental insufficiency

Diagnosis

- Although no single biometric or Doppler measurement is completely accurate for helping make or exclude the diagnosis of growth restriction, screening for IUGR is important to identify at-risk fetuses

Multiple Births

Definition

- Multiple births occur when multiple fetuses are carried during a pregnancy with the subsequent delivery of multiple neonates

Types

- **Dizygotic twins** develop when two ova are fertilized; dizygotic twins have separate amnions, chorions, and placentas
- **Monozygotic twins** develop when a single fertilized ovum splits after conception. An early splitting (i.e., within 2–3 days after fertilization) of monozygotic twins produces separate chorions and amnions (dichorionic diamniotic). Monochorionic monoamniotic twins occur when the split takes place after the ninth day after fertilization. Cleavage of the fertilized ovum between days 4 and 8 of fertilization results in monochorionic diamniotic twins

Associated complications

- Premature delivery
- Malpresentation
- Congenital abnormalities
- Umbilical cord compression and cord entanglement
- Placental abruption
- Twin-twin transfusion syndrome
- Fetal growth restriction
- Conjoined twins
  - Occur only in monoamniotic, monochorionic twins
  - Occur in 1/50,000 births

Infant of Diabetic Mother (IDM)

Background

- About 3–10% of pregnancies are affected by abnormal glucose regulation and control. Of these cases, 80–88% are related to abnormal glucose control of pregnancy or gestational DM
- Hyperglycemia during pregnancy causes fetal hyperglycemia and fetal hyperinsulinemia
- Fetal congenital malformations are most common when maternal glucose control has been poor during the first trimester of pregnancy
- Preconceptional glycemic control in women with diabetes cannot be overstated
- Maternal hyperglycemia during late gestation is more likely to lead to fetal macrosomia, hypoxia, polycythemia, and cardiomegaly with outflow tract obstruction

Complications

- Fetal macrosomia
  - Weight > 90th percentile for GA or > 4000 g in the term infant occurs in 15–45% of diabetic pregnancies
  - Most commonly observed as a consequence of maternal hyperglycemia and fetal hyperinsulinemia
  - Infant may appear puffy, fat, ruddy, and often hypotonic
  - LGA infants should be routinely screened for hypoglycemia
- Impaired fetal growth
  - Infants whose BW is below the tenth percentile are considered SGA
  - Impaired fetal growth may occur in as many as 20% of diabetic pregnancies
  - Maternal renovascular disease is a common cause of impaired fetal growth in pregnancies complicated by maternal diabetes
  - Perinatal asphyxia is more common in infants with impaired fetal growth

- Pulmonary disease
  - IDM are at increased risk of **respiratory distress syndrome** that may present within the first few hours after birth with tachypnea, nasal flaring, intercostal retractions, and hypoxia
  - Transient tachypnea of the newborn
  - **Persistent pulmonary hypertension of newborn** secondary to polycythemia may occur
- Metabolic and electrolyte abnormalities
  - Hypoglycemia is caused by hyperinsulinemia due to hyperplasia of fetal pancreatic beta cells consequent to maternal-fetal hyperglycemia
  - Hypoglycemia may present within the first few hours of life and may persist for as long as a week
  - Infant may present with no symptoms
  - Jitteriness, irritability, apathy, poor feeding, high pitched or weak cry, hypotonia, or frank seizure activity may occur
- Hypocalcemia or hypomagnesemia
  - Symptoms may include jitteriness or seizure activity
  - Hypocalcemia (levels < 7 mg/dL) is believed to be associated with a delay in parathyroid hormone synthesis after birth
- Iron deficiency
  - 5% of all IDMs demonstrate abnormalities of iron metabolism at birth
  - Iron deficiency increases the infant's risk for neurodevelopmental abnormalities
- Polycythemia
  - Caused by increased erythropoiesis triggered by chronic fetal hypoxia
  - Clinically presents as "ruddy" appearance, sluggish capillary refill, or respiratory distress
  - Hyperviscosity due to polycythemia increases the risk for stroke, seizure, necrotizing enterocolitis, and renal vein thrombosis
- Hyperbilirubinemia
  - Common, especially in association with polycythemia
- Thrombocytopenia
- Cardiovascular anomalies
  - Cardiomyopathy with ventricular hypertrophy and outflow tract obstruction may occur in as many as 30% of IDMs
    - Cardiomyopathy may be associated with congestive failure with a weakly functioning myocardium or may be related to a hypertrophic myocardium with significant septal hypertrophy and outflow tract obstruction
  - Echocardiography is indicated if cardiomegaly or hypoperfusion are present
  - Increased risk of congenital heart defects, including (most commonly) ventricular septal defect (VSD) and transposition of the great arteries (TGA)
- Congenital malformations
  - CNS malformations are 16 times more likely in IDMs
    - Risk of anencephaly is 13 times higher
    - Risk of spina bifida is 20 times higher
  - Sacral agenesis; the risk of caudal dysplasia is up to 600 times higher in IDM
  - Increased risk of renal abnormalities—hydronephrosis, renal agenesis, and ureteral duplication
  - Increased risk of GI abnormalities—small left colon syndrome, and duodenal or anorectal atresia

Management of Hypoglycemia

- Screening policy for hypoglycemia after birth is necessary to detect hypoglycemia
- Initial feed within 1 h; screen glucose within 30 min
- Asymptomatic infant; birth—4 h of age:
  - If initial blood glucose value is < 25 mg/dL
  - Refeed and check blood glucose in 1 h
  - If blood glucose is still < 25 mg/dL, immediate IV with 2 mL/kg infusion of 10% dextrose followed by continuous infusion of dextrose at an infusion rate of 5–8 mg/kg/min

    - Failure to start maintenance dextrose infusion may result in rebound hypoglycemia as a result of heightened pancreatic insulin release triggered by the glucose infusion
    - Once the infant's glucose levels have been stable for 12 h, IV glucose may be tapered by 1–2 mg/kg/min
    - Achieve plasma glucose of 45–50 mg/dL
  - If blood glucose level is 25–40 mg/dL:
    - Refeed; provide IV dextrose as needed
- **Asymptomatic infant; 4–24 h of age:**
  - Continue feeds every 2–3 h
  - If blood glucose is < 35 mg/dL:
    - Refeed and check blood glucose in 1 h
    - If blood glucose is still < 35 mg/dL, immediate IV therapy with 2 mL/kg infusion of 10% dextrose followed by continuous infusion of dextrose at an infusion rate of 5–8 mg/kg/min
  - If blood glucose is 35–45 mg/dL, refeed; provide IV dextrose as needed
  - Provide IV dextrose if infant develops symptoms of hypoglycemia

Hyperbilirubinemia

- Jaundice occurs in approximately 60% of neonates born yearly in the USA
- Most common condition that requires medical attention and hospital readmission in newborns

Pathophysiology

- Hemolysis of RBCs→hemoglobin is released
- Biliverdin is formed from heme through the action of heme oxygenase
- Biliverdin reductase reduces biliverdin to unconjugated (indirect) bilirubin
- **Unconjugated bilirubin** binds to albumin and is transported to the liver
- **Unconjugated bilirubin** can become unbound if albumin is saturated or if bilirubin is displaced from albumin by medications (e.g., sulfisoxazole, streptomycin, chloramphenicol, ceftriaxone, ibuprofen, salicylates)
- **Unbound unconjugated bilirubin** can cross the blood-brain barrier and is toxic to the CNS
- Once unconjugated bilirubin reaches the liver, it is conjugated by uridine diphosphate glucuronosyl transferase (**UGT1A1**)
- **Hepatic UGT1A1** increases dramatically in the first few weeks after birth
- At 30–40 weeks gestation, UGT1A1 values are approximately 1% of adult values, rising to adult concentrations by **14 weeks of age**
- Conjugated (direct) bilirubin is excreted into the intestine via the gallbladder and bile duct
- Bacteria in the intestine can deconjugate bilirubin, allowing it to be reabsorbed into the blood. The rest of the bilirubin is excreted with the stool

Physiologic Jaundice

Background

- Unconjugated hyperbilirubinemia that occurs after the first postnatal day
  - Jaundice that is visible during the first day of life is pathologic
  - Infants who present with jaundice after 3–4 days of life may also require closer scrutiny and monitoring
  - In infants with severe jaundice or jaundice that continues beyond the first 1–2 weeks of life:
    - Check for galactosemia and congenital hypothyroidism in newborn metabolic screen results
    - Explore family history
    - Evaluate infant's weight curve
    - Elicit mother's impressions of the adequacy of breastfeeding
    - Assess stool color
- It can last up to 1 week
- **Total serum bilirubin (TSB)** concentration peaks in the first 3–5 postnatal days in term infants
- A decline to adult values over the next several weeks

- TSB concentrations vary greatly in infants, depending on race, type of feeding, and genetic factors

Physiologic jaundice occurs in infants for a number of reasons:

- Increased breakdown of fetal erythrocytes due to:
  - Shortened lifespan of fetal erythrocytes (70–90 days)
  - Higher erythrocyte mass in neonates
- Hepatic excretory capacity is low because of:
  - Low concentrations of the binding protein ligandin in the hepatocytes
  - Low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation)
  - Thus, neonates have a high rate of bilirubin production and an impaired ability to extract bilirubin from the body

Clinical presentation

- Jaundice
- The TSB concentration peaks at approximately 5.5 mg/dL (94.1 μmol/L) by the third postnatal day in white and African American infants
- By 96 h of age, 95% of infants have TSB concentrations of < 17 mg/dL
- Bilirubinemia > 17 mg/dL is not physiologic

Risk factors for development of severe hyperbilirubinemia in newborns > 35 weeks GA

- Jaundice observed in the first 24 h of age
- Predischarge TSB or transcutaneous bilirubin in the high-risk zone
- Blood group incompatibility (ABO or Rh) with positive direct antiglobulin test; other known hemolytic disease such as glucose-6-phosphate dehydrogenase deficiency
- GA of 35–36 weeks
- Previous sibling requiring phototherapy
- Cephalohematoma or significant bruising
- Poor feeding
- Exclusive breastfeeding
- East Asian race (defined by mother's description) or Mediterranean descent
- Jaundice observed before discharge
- Macrosomic infant of a diabetic mother
- Male gender

Early Onset Breastfeeding Jaundice

Background

- Early onset breastfeeding jaundice (manifests in the first 3 days of life) is the most common cause of unconjugated hyperbilirubinemia

Causes

- Breastfeeding exaggerates physiologic jaundice in the first postnatal week because of caloric deprivation, leading to an increase in enterohepatic circulation
- Mild dehydration and delayed passage of meconium also plays roles

Prevention

- Successful breastfeeding decreases the risk of hyperbilirubinemia
- Infants need to be fed at least 8–12 times in the first few days after birth to help improve the mother's milk supply
- The best way to judge successful breastfeeding is to monitor infant urine output, stool output, and weight
- Newborns should have four to six wet diapers and three to four yellow, seedy stools per day by the fourth day after birth
- Breastfed infants should lose no more than 10% of their body weight by the third or fourth postnatal day
- Formula supplementation may be necessary if the infant has significant weight loss, poor urine output, poor caloric intake, or delayed stooling

- Water and dextrose solutions should not be used to supplement breastfeeding because they do not prevent hyperbilirubinemia and may lead to hyponatremia

Late Onset Breast Milk Jaundice

Background

- Thought to be a normal exaggeration of physiologic jaundice in human milk fed infants
- Indirect hyperbilirubinemia that develops in an otherwise healthy breastfed newborns after the first 4–7 days of life and may persist for 6–12 weeks
- Exact mechanism is not entirely clear
- It is suggested that beta-glucuronidases and non-esterified fatty acids in the human milk inhibit enzymes that conjugate bilirubin in the liver

Management

- Breastfeeding should be continued and parents reassured
- Ensure there are no other causes of prolonged hyperbilirubinemia (e.g., galactosemia, hypothyroidism, urinary tract infection (UTI), hereditary spherocytosis)
- If serum bilirubin levels continue to rise or > 20 mg/dL, breastfeeding can be discontinued for 48 h to observe whether a decrease in TSB concentration occurs. Phototherapy may be considered:
  - During this time, the mother should continue to express milk to maintain her supply and supplement the infant with formula
  - TSB concentrations usually peak between 12 and 20 mg/dL (205.2 and 342.1 μmol/L) and should decrease by 3 mg/dL (51.3 μmol/L) per day. If this decrease occurs, breastfeeding should be restarted
  - Phototherapy, if needed, can be administered with standard phototherapy units and biliblankets

Jaundice in Premature Infants

- Hyperbilirubinemia is more common and more severe in preterm infants and lasts longer
- Sick preterm newborns are more likely to have a delay in initiating enteral nutrition, resulting in an increase in enterohepatic circulation
- Kernicterus is extremely uncommon; however, kernicterus does occur at lower TSB concentrations, even without acute neurologic signs
- TSB values as low as 10–14 mg/dL (171.0–239.5 μmol/L) have resulted in milder forms of bilirubin-induced neurologic dysfunction in preterm infants
- Initiation of phototherapy according to the weight of infants and associated complications is paramount (Table 2.4) [2]

Table 2.4 Suggested use of phototherapy and exchange transfusion in preterm infants < 35 weeks gestational age[b]

	Phototherapy	Exchange transfusion
Gestational age (wk)	Initiate phototherapy total serum bilirubin[a] (mg dl^{-1})	Total serum bilirubin (mg dl^{-1})
< 28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18
34 0/7–34 6/7	12–14	17–19

[a]Use the lower range of the listed total serum bilirubin (TSB) levels for infants at greater risk for bilirubin toxicity (e.g., lower gestational age, serum albumin levels < 2.5 g/dL, clinically unstable infants). Recommendations for exchange transfusion apply to infants who are receiving intensive phototherapy but whose TSB levels continue to increase to the levels listed. For all infants, an exchange transfusion is recommended if the infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonus, high-pitched cry)

[b]From Maisels et al. [2], with permission

Unconjugated Hyperbilirubinemia

Causes

- Increased bilirubin production
- Deficiency of hepatic uptake
- Increased enterohepatic circulation
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency; more common in African American
- Blood group incompatibility
- Structural defects in erythrocytes
- Impaired conjugation of bilirubin

Gilbert syndrome

- Autosomal recessive condition in which UGT1A1 activity decreases mildly in hepatocytes, typically resulting in a benign unconjugated hyperbilirubinemia
- The likelihood of severe hyperbilirubinemia is increased if the infant also has G6PD deficiency

Crigler-Najjar syndrome type 1

- Autosomal recessive
- Severe deficiency of UGT1A1 results in intense jaundice in the first days of life and persists thereafter. Bilirubin encephalopathy develops in the first few days or month after birth

Crigler-Najjar syndrome type 2

- Autosomal dominant
- Bilirubin levels are generally < 20 mg/dL
- The incidence of bilirubin encephalopathy is low.

Conjugated Hyperbilirubinemia (See Also Chap. 22 Gastroenterology)

Background

- Conjugated bilirubin concentration greater than 1 mg/dL when the TSB concentration is < 5 mg/dL (85.6 μmol/L) ***or***
- Conjugated bilirubin level > 20% of the TSB if the total is > 5 mg/dL

Causes

- Biliary atresia
- Thyroid abnormalities
- Galactosemia
- Alagille syndrome
- Choledochal cyst
- Viral infections, e.g., cytomegalovirus (CMV), human immunodeficiency virus (HIV)
- Bacterial infections (UTI, syphilis); sepsis
- Idiopathic neonatal hepatitis
- Prolonged parenteral nutrition

Kernicterus

Background

- Kernicterus is brain injury caused by unconjugated bilirubin deposition in basal ganglia and brain stem nuclei
- Bilirubin can cross the blood-brain barrier and enter the brain tissue if it is unconjugated and unbound to albumin, or if there is damage to the blood-brain barrier
- Acute bilirubin toxicity may occur in a term infant if there are no signs of hemolysis and the TSB concentration is greater than 25 mg/dL
- Physicians should be concerned if the TSB concentration is above 20 mg/dL in a term infant who has hemolysis

Clinical presentation

- Bilirubin-induced neurologic dysfunction (BIND) is the term applied to the spectrum of neurologic abnormalities associated with hyperbilirubinemia, approximately 15% of babies with BIND have no neurologic signs
- Clinical features have been well described and can be divided into 3 stages:
- **Phase 1** (first few days of life):
  - Decreased alertness
  - Hypotonia
  - Poor feeding, poor suck

- A high index of suspicion of possible BIND at this stage that leads to prompt intervention can halt the progression of the illness, significantly minimizing long-term sequelae
  - Of note, seizure is not typically associated with acute bilirubin encephalopathy
- **Phase 2** (variable onset and duration):
  - Hypertonia of the extensor muscles is a typical sign. Patients present clinically with retrocollis (backward arching of the neck), opisthotonus (backward arching of the back), or both. Infants who progress to this phase develop long-term neurologic deficits
- **Phase 3** (infants aged > 1 wk): Hypotonia is a typical sign

Chronic Bilirubin Encephalopathy

- Clinical features evolve slowly over the first several years of life in the affected infant
- The clinical features can be divided into phases:
  - First phase occurs in the first year of life: Hypotonia, hyperreflexia, and delayed acquisition of motor milestones
  - Tonic neck reflex can be observed
- Extrapyramidal abnormalities: Athetosis is the most common movement disorder, although chorea can also occur
  - Upper extremities are usually more affected than the lower ones; bulbar functions can also be impacted
- Visual abnormalities:
  - Ocular movements are affected, most commonly resulting in upward gaze
  - Horizontal gaze abnormalities
  - Gaze palsies
- Auditory abnormalities:
  - High frequency hearing loss
  - Delayed language acquisition
- Abnormalities of dentition: Dental enamel hypoplasia
- Cognitive function is relatively spared, but minor intellectual deficits can also occur

ABO and Rh Incompatibility (See Chap. 10 Hematology/Oncology)

- ABO incompatibility may occur if the mother's blood type is O and the infant's blood type is A or B
- Infants should be assessed for jaundice at a minimum of every 8–12 h after birth; earlier assessment is indicated if cord bilirubin is > 1.5 mg/dL

Transcutaneous Bilirubin Devices

- Newer devices used to detect transcutaneous bilirubin (TcB) have been shown to correlate well with TSB
  - Important to note that TcB assessments and clinical examination are unreliable after phototherapy
- Once TcB or TSB has been measured, the result should be interpreted based on the nomogram
  - The value should be plotted on the nomogram to assess the risk level and whether or not treatment is indicated
- AAP Subcommittee on Hyperbilirubinemia has recommended assessing TSB or TcB on all newborns before discharge [3]

Management of Hyperbilirubinemia

Feeding

- More frequent feeding (breastfeeding or bottle feed) every 2–3 h

Phototherapy

- Phototherapy works by converting bilirubin into a water-soluble compound, lumirubin, which is excreted in the urine or bile
- When bilirubin decreases to 13–14 mg/dL, discontinue phototherapy
- Consider exchange transfusion if the TSB is not decreasing or is moving closer to the level for exchange transfusion

- Depending on the cause of hyperbilirubinemia, measuring TSB 24 h after discharge to check for rebound is an option

Complications of phototherapy

- Insensible water loss (increase fluid intake or the volume and frequency of feeding)
- Phototherapy may be associated with loose stool
- Retinal damage (covering the eye is routine during phototherapy)

Treatment of hyperbilirubinemia if bilirubin level is not decreasing

- Intravenous immunoglobulin
- Exchange transfusion

Hemorrhagic Disease of the Newborn

Background

- Also referred to as vitamin K deficiency bleeding
  - Transient deficiency in vitamin K-dependent factors
- Presents in three forms:
  - **Early** (first 24 h): Associated with maternal use of drugs such as anticoagulants, barbiturates, carbamazepine, phenytoin, some cephalosporins, rifampin
  - **Classic** (2–7 days of life): Associated with no vitamin K prophylaxis at birth
  - **Late** (after 1 week of age): Occurs in exclusively breastfed infants who have not received adequate vitamin K prophylaxis, and with vitamin K malabsorption, e.g., neonatal hepatitis, biliary atresia

Clinical presentation

- Bleeding can occur anywhere, e.g., GI, nasal, subgaleal, intracranial, circumcision bleeding, following cord separation, after phlebotomy

Diagnosis

- Elevated PT due to low vitamin K

Treatment

- Treat with 1 mg IV vitamin K ± fresh frozen plaza (FFP)

Prevention

- 1 mg vitamin K IM administration after birth

Respiratory Distress Syndrome (RDS) (aka Hyaline Membrane Disease)

Background

- The most common cause of respiratory failure in the newborn
- Occurs almost exclusively in premature infants
- The incidence and severity of RDS are related inversely to the GA of the newborn infant
- RDS develops in premature infants because of impaired surfactant synthesis and secretion leading to lung atelectasis
- RDS does not occur in all preterm babies
- Surfactant protein (SP) deficiency occurs in a small group of term infants with severe respiratory distress that leads to intractable respiratory failure and death
  - SP-B deficiency is the most common form and occurs as an autosomal recessive trait

Surfactant is stored in type II alveolar cells and composed of

- Dipalmitoyl phosphatidylcholine
- Phosphatidylglycerol
- Apoproteins (SP-A, B, C, and D)
- Cholesterol

Risk factors

- Prematurity
- Maternal DM
- C-section
- Asphyxia
- Male gender
- Hypothermia
- Multiple gestations
- Family history of a sibling who developed RDS

Factors that decrease the risk of RDS

- Premature rupture of membranes
- Maternal hypertension
- Sub-acute placental rupture
- Maternal use of narcotics

Clinical presentation

- Same as that seen in other conditions that cause respiratory distress
- Tachypnea usually > 60 breaths/min
- Expiratory grunting (from partial closure of glottis)
- Subcostal and intercostal retractions
- Cyanosis
- Nasal flaring
- Extremely premature neonates may develop apnea and/or hypothermia

Diagnosis

- Chest radiograph (Fig. 2.6)
  - Bilateral, diffuse, reticular granular, or ground glass appearance
  - Diffuse atelectasis and air bronchograms (prominent air bronchograms represent aerated bronchioles superimposed on a background of collapsed alveoli)

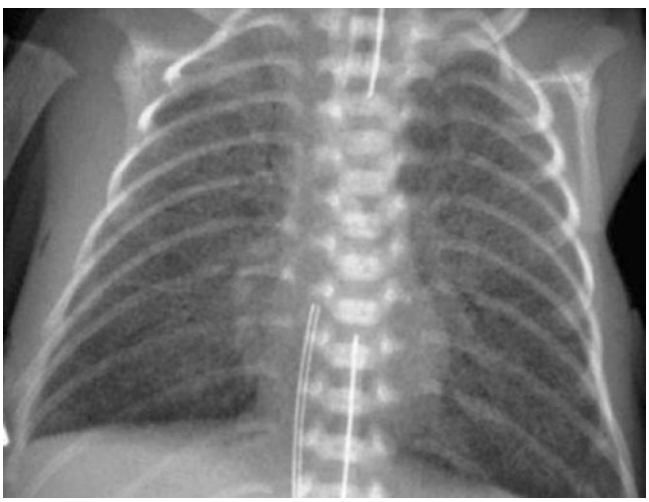


Fig. 2.6 Chest radiograph of premature newborn shows a bilateral and symmetrical diffuse ground glass lung appearance with a hyperinflated thorax (due to intubation). Without intubation, the thorax typically has a low volume. In some patients, air-bronchograms can be seen. The patient has venous and arterial umbilical catheters

  - Poor lung expansion
  - The appearance of GBS pneumonia on chest radiograph can be identical to that of RDS
- Blood gas
  - Hypoxia
  - Metabolic acidosis
  - Hypercarbia
- Fetal lung test for maturity prediction
  - Lecithin-to-sphingomyelin ratio ***and/or***
  - Testing for the presence of phosphatidylglycerol in amniotic fluid obtained by amniocentesis

Management

- Prenatal administration of steroids (betamethasone)
- Maintain core temperature
- Nasal continuous positive airway pressure (CPAP) is often used for initial stabilization in spontaneously breathing premature infants immediately after birth
- Intubation and mechanical ventilation (MV) in infants who do not respond to noninvasive ventilation strategies and surfactant therapy
- Surfactant prophylaxis may be considered in infants < 27 weeks gestation
- Prophylactic surfactant may be considered for neonates > 26 weeks but < 30 weeks gestation if intubation is required or if the mother has not received any prenatal steroids
- Many institutions practice only rescue surfactant
- When possible, duration of MV should be shortened by early extubation to CPAP after surfactant administration, provided the newborn is otherwise stable
- IV fluids if respiratory status is not stable: 10% glucose in the first 24 h
- Parenteral nutrition should be provided to very preterm infants
- Treat with antibiotics until sepsis is ruled out
- Cardiac causes should be considered in worsening cases despite appropriate therapy

Prenatal steroids

- Decreases the incidence and severity of RDS
- Usually given to women at 24–34 weeks gestation with high risk for preterm birth, e.g., premature rupture of membrane

Transient Tachypnea of the Newborn (TTN)

Background

- TTN is a common, relatively benign self-limited disease in newborns
- Infants with TTN present within the first few hours of life with tachypnea, increased oxygen requirement, and arterial blood gases (ABGs) that do not reflect carbon dioxide retention
- TTN is the result of a delay in clearance of fetal lung fluid by the lymphatics and pulmonary circulation, with resultant transient pulmonary edema
- Most common in infants delivered between 37 and 42 weeks gestation
- Common with C-section delivery in the absence of labor
- Other risk factors are male sex; perinatal asphyxia; umbilical cord prolapse; and maternal complications such as asthma, diabetes, and anesthesia and analgesia during labor

Clinical presentation

- Signs of respiratory distress (e.g., tachypnea, nasal flaring, grunting, retractions, cyanosis in extreme cases) become evident shortly after birth
- The disorder is transient with resolution usually occurring within 72 h after birth
- Extreme cases may exhibit cyanosis
- Prolonged course > 72 h or clinical deterioration may suggest other diagnosis

Diagnosis

- Chest radiograph:
  - Hyperinflation
  - Prominent perihilar vascular markings, which correlates with the engorgement of the lymphatic system with retained lung fluid
  - Fluid in the fissures
  - Small pleural effusions may also be present

Treatment

- Supportive care
- Supplemental oxygen may be required
- Antibiotics may be considered until sepsis has been ruled out
- Provide IV hydration and nutrition

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Background

- PPHN is defined as the failure of the normal circulatory transition that occurs after birth
  - Syndrome characterized by marked pulmonary hypertension that causes hypoxemia secondary to right-to-left shunting of blood at the foramen ovale and ductus arteriosus
- Most often recognized in term or near-term neonates but can also occur in preterm infants
- Selective serotonin reuptake inhibitors (SSRIs), commonly prescribed antidepressants, have been reported to be associated with PPHN, especially during the third trimester of pregnancy
- Genetic factors may increase susceptibility to pulmonary hypertension, e.g., polymorphisms of the carbamoyl phosphate synthase gene and urea cycle enzyme genes
- Higher frequency in babies with Down syndrome

Etiology and common associated conditions

- Idiopathic
- RDS
- Polycythemia
- Hypoglycemia

- Meconium aspiration
- GBS pneumonia
- Sepsis
- Diaphragmatic hernia
- Pulmonary hypoplasia
- IDM
- Down syndrome

Clinical presentation

- Usually symptoms appear in the first 24 h
- Tachypnea
- Cyanosis
- Respiratory distress (grunting, flaring, retraction, tachycardia)
- Profound and often labile hypoxemia
- Preductal and postductal oxygen saturation gradient difference of at least 10% (with preductal saturations being higher)
- Loud, single second heart sound (S2)
- A harsh systolic murmur secondary to tricuspid regurgitation may be heard
- Systemic hypotension, shock, and evidence of poor perfusion may occur

Diagnosis

- Hypoxemia is universal and poorly responsive to 100% oxygen
- Differential cyanosis: Higher oxygen saturation in preductal blood (right radial artery) than that obtained from tibial arteries (postductal)
- Echocardiography is essential for distinguishing congenital heart disease from PPHN, which is a diagnosis of exclusion
  - Right ventricular hypertrophy
  - Bowing of the interventricular septum into the left ventricle
  - Tricuspid regurgitation
  - Right-to-left or bidirectional shunting at the patent foramen ovale and/or patent ductus arteriosus

Management

- Treatment of the underlying cause is the most important step
- Minimize stimulation
- Maintain a normal body temperature and correct electrolytes, glucose abnormalities and metabolic acidosis
- Maintain adequate systemic BP
- MV; avoid hyperventilation
- Inhaled nitric oxide
- Extracorporeal membrane oxygenation (ECMO)

Meconium Aspiration Syndrome (MAS)

Background

- Meconium aspiration is one of the most common etiologies of respiratory failure in newborns
- Because meconium is rarely found in the amniotic fluid prior to 34 weeks gestation, meconium aspiration primarily affects infants born at term and post-term

Factors that increase the risk of meconium aspiration

- Placental insufficiency
- Maternal hypertension
- Preeclampsia
- Oligohydramnios
- Maternal drug abuse, especially of tobacco and cocaine
- Maternal infection/chorioamnionitis
- Fetal hypoxia and acidosis

Clinical presentation

- Cyanosis
- Nasal flaring
- End-expiratory grunting
- Intercostal retractions
- Tachypnea
- Barrel chest in the presence of air trapping
- Auscultated rales and rhonchi (in some cases)
- Yellow-green staining of fingernails, umbilical cord, and skin may be observed

Diagnosis

- Chest radiograph
  - Air trapping and hyperexpansion from airway obstruction
  - Diffuse chemical pneumonitis (streaky, linear, or patchy infiltrates)
  - Acute atelectasis
  - Pneumomediastinum and other air leak syndromes

Prevention of MAS

- AAP recommendations
  - If the infant is not vigorous (defined as depressed respiratory effort, poor muscle tone, and/or heart rate < 100 beats/min): Place the infant on a radiant warmer, clear the secretions with a bulb syringe, and proceed with the normal steps of newborn resuscitation (i.e., warming, repositioning the head, drying, and stimulating). If after these initial steps the infant is still apneic or the heart rate is < 100 beats bpm, administer PPV to minimize the delay in initiating ventilation
  - If the infant is vigorous (defined as normal respiratory effort, normal muscle tone, and heart rate > 100 beats/min): Do not electively intubate. Clear secretions and meconium from the mouth and nose with a bulb syringe and proceed with the normal steps of neonatal resuscitation
  - Resuscitation should follow the same principles as for infants born through clear amniotic fluid

Management

- Oxygen therapy
- Surfactant therapy commonly used
- Noninvasive or invasive MV
- Supportive care—Maintain fluid and electrolyte balance; maintain normal BP
- Inhaled nitric oxide
- ECMO if infant unresponsive to medical management

Pneumothorax and Pneumomediastinum

Background

- Pneumothorax refers to the presence of air or gas in the pleural cavity between the visceral and parietal pleura
- Pneumomediastinum is air in the mediastinum that may be confused with pneumothorax
- Pneumothorax may be iatrogenic or spontaneous
- Factors associated with pneumothorax:
  - Overly vigorous resuscitation at birth
  - RDS
  - MAS
  - Pneumonia
  - Pulmonary hypoplasia
  - Assisted ventilation

Clinical presentation

- Depends on the severity and size of the pneumothorax
- Tension pneumothorax:
  - Cyanosis
  - Hypoxemia
  - Tachypnea
  - Sudden decrease in heart rate
  - Hypotension
  - Narrowed pulse pressure
  - Decreased breath sounds on the affected side
  - Shift of the maximal cardiac impulse away from the affected side

Chest radiograph

- Shift of mediastinum away from the side of pneumothorax
- Depressed diaphragm
- Displacement of the lung to the opposite side

Management

- Symptomatic tension pneumothorax is an emergency

  - Transillumination of the chest is useful for immediate diagnosis
  - Limited time for chest radiograph confirmation
- If the patient is deteriorating rapidly:
  - A 22–24-gauge needle or angiocath can be inserted for aspiration (thoracentesis). The site of puncture should be at the second or third intercostal space along the midclavicular line
  - Thoracostomy or chest tube placement may be needed
- Asymptomatic pneumothorax: 100% oxygen administration for 8–12 h may be considered. The rate of resolution of spontaneous pneumothoraces is not improved with oxygen supplementation. Because of concerns regarding the risks of hyperoxia, we do not routinely administer supplemental oxygen above the concentration needed to maintain adequate saturation.

Neonatal Sepsis

Background

- Neonatal sepsis may be categorized as early onset or late onset
- Newborns with **early onset sepsis** (< 72 h): 85% present within 24 h, 5% present at 24–48 h, and a smaller percentage present within 48–72 h. Onset is most rapid in premature neonates
- **Late onset sepsis** occurs at > 72 h–28 days of life and is acquired from the caregiving environment
- The microorganisms most commonly associated with early onset infection include the following:
  - GBS
  - *Escherichia coli*
  - Coagulase-negative *Staphylococcus*
  - *Staphylococcus aureus*
  - *Haemophilus influenzae*
  - *Listeria monocytogenes*
  - Enterococci
  - *Haemophili* and other Gram-negatives (*Klebsiella, Enterobacter, Citrobacter, Acinetobacter, Pseudomonas*)
- The microorganisms most commonly associated with late onset infection include the following:
  - Coagulase-negative *Staphylococcus*
  - *S. aureus*
  - *E. coli, Klebsiella,* enterococci, *Pseudomonas, Serratia*
  - *Candida*
  - GBS

Risk factors

- Maternal GBS status
- Premature ROM
- Prolonged ROM
- Maternal fever
- Maternal UTI
- Prematurity
- Chorioamnionitis
- Low BW
- Male gender
- Intrapartum or postpartum instrumentation

Initial clinical presentations of infection

- In newborns, signs of infection are nonspecific and can be subtle or dramatic (Table 2.5)

Common clinical manifestation of bacterial sepsis

- Pneumonia
- Meningitis
- Bacteremia
- Osteomyelitis
- UTIs

Investigations

- Cultures (blood, urine, cerebrospinal fluid)
- CBC and differential (normal count does not rule out sepsis)
  - Neutropenia, especially an absolute neutrophil count < 1800 cells/mcL
  - Immature-to-total (I/T) neutrophil ratio > 0.15 in the first 24 h of life is suggestive of sepsis
  - Thrombocytopenia
- C-reactive protein (CRP)
- Procalcitonin
- Coagulation studies

Table 2.5 Initial clinical presentations of infection in newborn infants

System	Possible clinical presentation of neonatal sepsis
General	Temperature instability
	Hypoglycemia
	Poor feeding
Respiratory	Apnea
	Tachypnea, nasal flaring, grunting, retractions
	Cyanosis
Cardiovascular	Pallor, mottling, cold, clammy skin
	Tachycardia, bradycardia, hypotension
	Delayed capillary refill
Gastrointestinal	Vomiting (bilious or nonbilious)
	Abdominal distension
Central nervous system	Seizures
	Tremor
	Abnormal reflexes
	Irregular respiration
	Full fontanel
	High-pitched cry
Hematologic system	Pallor, jaundice
	Thrombocytopenia, bleeding, petechiae, purpura
Renal	Oliguria
Others	Leukocytosis or leukopenia
	Elevated immature WBCs, e.g., bands
	Elevated C-reactive protein
	DIC
	Lactic acidosis
	Hypoxemia

WBCs white blood cells, *DIC* disseminated intravascular coagulation

- Lumbar puncture is warranted for early- and late onset sepsis
- HSV PCR testing in suspected cases
- Chest radiograph
- MRI may be needed late in the course of complex neonatal meningitis to document obstructive hydrocephalus
- Head ultrasonography in neonates with meningitis may reveal evidence of ventriculitis, abnormal parenchymal echogenicity, extracellular fluid, and chronic changes
- Serially, head ultrasonography can reveal the progression of complications

Management

- When neonatal sepsis is suspected, treatment should be initiated immediately because of the neonate's relative immunosuppression
- Begin antibiotics as soon as diagnostic tests are performed
  - Early onset sepsis: Ampicillin and gentamicin
- An infant with temperature instability needs thermoregulatory support with a radiant warmer or incubator

Medications

- The antibiotics commonly used to treat neonatal sepsis include:
  - Ampicillin and gentamicin for early onset sepsis
  - Nafcillin/vancomycin and gentamicin/cephalosporins for late onset sepsis (antibiotic coverage should be directed at organisms implicated in hospital-acquired infections)
- The choice of antibiotic agents should be based on the specific organisms associated with sepsis

Group B Streptococcal Infection in Neonates

Background

- GBS, also known as *Streptococcus agalactiae*, is best known as a cause of postpartum infection and as the most common cause of neonatal sepsis
- Neonates can acquire the organism vertically in utero or from the maternal genital tract during delivery
  - Although the transmission rate from mothers colonized with *S. agalactiae* to neonates delivered vaginally is approximately 50%, only 1–2% of colonized neonates go on to develop invasive GBS disease
- Preterm neonates have higher rates of GBS late onset disease
- Early onset GBS sepsis often presents within 24 h of delivery but can become apparent up to 7 days postpartum
- Late onset GBS sepsis is defined as infection that presents between 1 week postpartum and age 3 months

- Optimal timing of maternal GBS screening is between 35 and 37 weeks gestation
- Adequate treatment of maternal GBS infection does not rule out GBS infection in infants

Indication of intrapartum GBS prophylaxis

- Previous infant with invasive GBS disease
- GBS bacteriuria during any trimester of the current pregnancy
- Positive GBS vaginal-rectal screening culture in late gestation during current pregnancy
  - Intrapartum antibiotic prophylaxis is not indicated in the two above circumstances if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes
- Unknown GBS status at the onset of labor (culture is not done, incomplete, or results unknown) and any of the following:
  - Delivery at < 37 weeks gestation
  - Amniotic membrane rupture ≥ 18 h
  - Intrapartum temperature ≥ 100.4 °F (≥ 38.0 °C)
  - Intrapartum nucleic acid amplification test (NAAT) positive for GBS

Secondary prevention of early onset GBS disease among newborns

- If no GBS prophylaxis was needed, the infant should be managed with routine newborn care
- Full diagnostic evaluation and antibiotic therapy if any signs of neonatal sepsis at any time
- Blood culture, CBC with differential at birth (limited evaluation), and antibiotic therapy if chorioamnionitis
- If intrapartum antibiotic prophylaxis (IAP) was not given ≥ 4 h before delivery and infant < 37 weeks gestation, or duration of rupture of membrane is ≥ 18 h, do a limited evaluation and observe for at least 48 h or more in the hospital
- If IAP was not given ≥ 4 h before delivery, infant > 37 weeks gestation and duration of rupture of membrane < 18 h, observe for at least 48 h or more in the hospital
- If the mother received IAP > 4 h before delivery and the infant is > 37 weeks and asymptomatic, provide routine clinical care

Clinical presentation

- Early onset GBS infection manifests with bacteremia, sepsis, pneumonia, and meningitis
  - Most infants present early in the first 8–12 h
  - Respiratory distress (tachypnea, grunting, and retractions)
  - Cyanosis, apnea, poor perfusion, hypotension, and signs of sepsis can rapidly develop
  - Shock
  - Death can occur
- Late onset GBS infection presents as:
  - Meningitis
  - Occult bacteremia
  - Focal infections such as osteomyelitis or arthritis, facial cellulitis, submandibular cellulitis, or cellulitis-adenitis in other regions

Diagnosis

- Leukopenia or leukocytosis
- Bandemia
- Thrombocytopenia
- Abnormal PT and PTT
- Chest radiograph may show signs of pneumonia
- Abnormal CSF studies in cases of meningitis (See also Chap. 9 Infectious Diseases)

Treatment

- Ampicillin and gentamicin are used empirically for treatment of GBS disease and substituted with penicillin once the organism is cultured from a sterile site
- Pneumonia and septicemia usually require treatment for 10–14 days
- Meningitis usually treated for 14–21 days

Prevention guidelines

- The drug of choice for intrapartum prophylaxis remains intravenous penicillin, with ampicillin as an acceptable alternative.

- Both agents are given every 4 h until delivery, with at least one dose administered 4 h before birth.
- Well-appearing infants whose mothers received adequate intrapartum prophylaxis should be observed for at least 48 h. No diagnostic testing required.
- Well-appearing infants > 37 weeks gestation and none/inadequate maternal prophylaxis with rupture of membranes < 18 h before delivery should be observed for 48 h. No diagnostic testing required.
- Well-appearing infants with none/inadequate maternal prophylaxis and either < 37 weeks gestation or rupture of membranes > 18 h before delivery should have limited evaluation (blood culture, CBC with diff and platelets at birth or 6–12 h) and be observed for 48 h.

Congenital Toxoplasmosis

Background

- Risk of transmission exists with primary infection but not if the infection is acquired before conception
- Infection in the first trimester is less frequent but results in more severe disease, including fetal death in utero or severe CNS involvement, such as cerebral calcifications and hydrocephalus
- Infection in the third trimester is more frequent, and the infant appears normal at birth, but the symptoms may appear later in life, e.g., chorioretinitis
- Treatment during pregnancy has been shown to reduce the rate of transmission and seems to reduce serious neurological sequelae

Clinical presentation

- Classic triad
  - Chorioretinitis (Fig. 2.7)
  - Hydrocephalus
  - Intracranial calcifications
- Hydrops fetalis and death
- IUGR

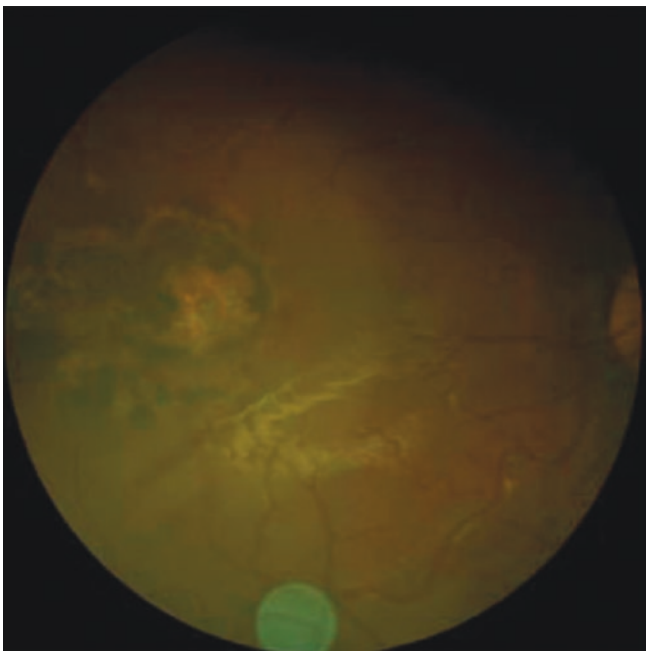


Fig. 2.7 Chorioretinal scar of the right eye, due to toxoplasmosis. (Courtesy of Violeta Radenovich MD MPH, Children's Eye Center, Department of Ophthalmology, Texas Tech University, El Paso, Texas)

- Thrombocytopenia
- Prematurity
- Cytopenias
- Jaundice
- Maculopapular rash
- Visual and learning disabilities

Important

- Approximately, 75% of congenitally infected infants are asymptomatic at birth, but up to 85% of children will develop visual and learning disabilities later in life if they are not treated in infancy

Treatment

- Pyrimethamine and sulfadiazine for 1 year

Congenital Syphilis

Background

- Congenital syphilis is more likely to occur with maternal primary or secondary syphilis, if maternal disease is of unknown duration or

untreated, if < 4 weeks have elapsed between treatment and delivery, or if maternal plasma nontreponemal titer (VDRL or RPR) is > 1:16 after therapy or delivery
  - The transmission rate approaches 90% if the mother has untreated primary or secondary syphilis
- Fetal infection can develop at any time during gestation

Clinical presentation
- Asymptomatic: 60% of infants born with congenital syphilis are asymptomatic at birth
- Hepatomegaly: The most common physical finding, reported in almost 100%, usually with abnormal liver function
- Signs of congenital syphilis are nonspecific and include:
  - Prematurity and low BW
  - Hepatomegaly with or without splenomegaly
  - Hutchinson teeth, skeletal abnormalities, e.g., periostitis or osteitis
  - Generalized lymphadenopathy
  - Maculopapular rash—also vesicular rash and bullae—may develop. These lesions are highly contagious
  - Rhinitis ("snuffles"). Nasal secretions are highly contagious
  - Thrombocytopenia
  - Coombs negative hemolytic anemia with hydrops
- Abnormal CSF examination is seen in half of symptomatic infants but can also be found in 10% of those who are asymptomatic

Diagnosis
- Nontreponemal serology screening tests: RPR and VDRL are the best screening tools
- A fourfold or greater rise in titer in the infant compared to the mother signifies probable active disease
- Fourfold increase in titer following therapy suggests reinfection or relapse and necessitates reevaluation

Treponema-specific tests
- *Treponema pallidum* immobilization, fluorescent treponemal antibody absorption (FTA-ABS), and *T. pallidum* particle agglutination (TPPA) are used to confirm a positive nontreponemal serology screening test
- These test findings become positive soon after infection and typically remain positive for life, despite adequate treatment
- These test results do not correlate with disease activity and are not quantified

Management
- Treat congenital infection, either proven or presumed, with 10–14 days of aqueous crystalline penicillin G or penicillin G procaine
- Aqueous crystalline penicillin G is recommended if congenital syphilis is proved or is highly suspected
- Base dosage on chronological, not gestational, age
- The recommended dosage of aqueous crystalline penicillin G is 50,000 U/kg IV every 12 h (1 week or younger), then every 8 h for infants older than 1 week for a total of 10 days of therapy
- The dose for penicillin G procaine is 50,000 U/kg IM as a single daily dose for 10 days

Infection is suspected with the following:
- Physical or radiographic evidence of active disease
- Serum quantitative nontreponemal titer at least four times greater than the maternal titer
- Reactive CSF VDRL test result or abnormal CSF cell count and/or protein levels
- Positive IgM FTA-ABS test findings
- Positive dark-field microscopy findings or positive findings when staining for treponemes in placenta or umbilical cord

Failure to Pass Meconium in the First 48 h of Life

Background

- 97% of term infants and 76% of premature infants pass a stool in the first 24 h of life
- Almost every infant will have passed meconium by 36 h (99.8%) of age. 99% of premature infants pass a stool by 48 h

Differential diagnosis

- Constipation
- Anorectal anomalies (imperforate anus)
- Meconium plug
- Meconium ileus
- Hirschsprung disease
- Ileal atresia
- Incarcerated hernia
- Malrotation

Meconium Plug Syndrome

Background

- A transient form of distal colonic or rectal obstruction suspected to be related to transient decrease in intestinal motility
- Meconium plug syndrome is the most common form of functional distal obstruction in newborns
- More common in infants of diabetic mothers
- Usually occurs in the lower colon or anorectal region

Common associated conditions

- Small left colon syndrome
- Magnesium sulfate therapy for preeclampsia
- Maternal drug abuse
- CF
- Hypothyroidism
- Hirschsprung disease

Clinical presentation

- Failure to pass meconium in the first 24–48 h
- Relieved by passage of meconium plugs

Management

- Plain radiograph for any newborn who did not pass stool within the first 48 h of life
- Hyperosmolar Gastrografin enemas are considered the initial diagnostic procedure and are often therapeutic in patients with meconium plug syndrome
- Rectal biopsy should be considered in all these infants because of the high risk of Hirschsprung disease (up to 38%)

Meconium Ileus

Background

- Meconium ileus represents obstruction of the small bowel caused by accumulation of sticky and inspissated intraluminal meconium
- The third most common cause of neonatal small bowel obstruction
- Accounts for about 30% of cases of intestinal obstruction in newborns
- Meconium ileus occurs in 10–20% of patients with CF
  - In most cases, this results from intestinal and pancreatic dysfunction associated with CF
  - However, not all patients with meconium ileus have CF

Clinical presentation

- Abdominal distention, delayed passage of meconium, and bilious emesis
- Sometimes the impacted meconium can be palpated
- Massive distention, abdominal tenderness, or abdominal erythema indicates the presence of complications such as volvulus, intestinal necrosis, perforation, and meconium peritonitis

Diagnosis

- Abdominal radiographs: May reveal signs of either small or large bowel obstruction (distended bowel, few air-fluid levels, and in the

right lower abdomen), meconium mixed with air "soap bubble," which has a ground-glass appearance on plain film
- The presence of calcifications, free air, or very large air-fluid levels suggests complications
- The small bowel is of narrow caliber below the plug and dilated above the plug
- Sweat test or genetic testing for all infants with meconium ileus because of high risk of CF

Management
- Simple meconium ileus may be successfully treated by administration of a diatrizoate meglumine (Gastrografin) enema and IV fluids; the success rate is 16–50%
- If the Gastrografin enema is unsuccessful, operative evacuation of the obstructing meconium by irrigation will be necessary
- Complications such as atresia, perforation, and meconium peritonitis always require immediate surgery, including resection, intestinal anastomosis, and ileostomy

Necrotizing Enterocolitis (NEC)

Background
- NEC is the most common GI medical/surgical emergency occurring in preterm neonates
- Acute inflammatory disease with variable damage to the intestinal tract, ranging from mucosal injury to full-thickness necrosis and perforation
- NEC affects close to 10% of infants who weigh less than 1500 g, with mortality rates of 50% or more, depending on severity
- It can also be observed in term and near-term babies
- The main cause of NEC is still unclear, but the risk is higher in premature infants

Clinical presentation
- Feeding intolerance
- Delayed gastric emptying, high gastric residuals
- Abdominal distention, abdominal tenderness, or both
- Ileus/decreased bowel sounds
- Abdominal wall erythema (advanced stages)
- Hematochezia
- Apnea, bradycardia
- Labile body temperature
- Lethargy
- Decreased peripheral perfusion
- Shock (in advanced stages)
- Cardiovascular collapse
- Bleeding diathesis (consumption coagulopathy)

Diagnosis
- Abdominal radiograph
  - The mainstay of diagnostic imaging is abdominal radiography; radiographic appearance of NEC depends on severity
  - Abnormal gas pattern
  - Dilated loops
  - Thickened bowel walls (suggesting edema/inflammation)
  - Pneumatosis intestinalis (intramural air bubbles) is a radiologic sign pathognomonic of NEC
  - Abdominal free air is ominous and usually requires emergency surgical intervention
  - Portal gas represents air present in the portal venous system. Its presence is considered to be a poor prognostic sign

Laboratory studies
- Hyponatremia
- Metabolic acidosis
- Thrombocytopenia
- Leukopenia or leukocytosis with left shift
- Neutropenia
- Prolonged PT and activated PTT (aPTT), decreasing fibrinogen, rising fibrin split products (in cases of consumption coagulopathy)

Management
- Nothing by mouth and IV fluids
- Rapid nasogastric decompression
- Start IV antibiotics after cultures are taken:

  - Frequently used regimen is ampicillin, aminoglycoside (e.g., gentamicin) or third-generation cephalosporin (cefotaxime), piperacillin and tazobactam, and clindamycin or metronidazole
  - Vancomycin should be included if *Staphylococcus* coverage is deemed appropriate
  - Medical management usually continues for 10–14 days with parenteral nutrition provided during that time
- Consult with a pediatric surgeon at the earliest suspicion of developing NEC

Indication for surgery
- Intestinal perforation with free air in the peritoneal space
- Peritoneal tap showing feces or pus
- Deteriorating clinical condition despite medical treatment
- Compartment syndrome

Note: Patients who are extremely small and ill may not have the stability to tolerate laparotomy. If free air develops in such a patient, one may consider inserting a peritoneal drain under local anesthesia in the NICU.

Congenital Diaphragmatic Hernia (CDH)

Background
- Herniation of abdominal viscera into the thoracic cavity through a defect in the diaphragm
- There is a variable degree of pulmonary hypoplasia associated with a decrease in cross-sectional area of the pulmonary vasculature and alterations of the surfactant system
- Approximately 85% are left-sided
- Approximately 50–60% are diagnosed antenatally

Clinical presentation
- Respiratory distress, tachypnea, grunting, retraction, and cyanosis
  - Respiratory distress and cyanosis in the first minutes or hours of life, although a later presentation is possible
  - The respiratory distress can be severe and may be associated with circulatory insufficiency, requiring aggressive resuscitative measures
- Scaphoid abdomen
- Increased chest wall diameter
- Heart sounds may be shifted to the right in patients with left-sided CDH
- Bowel sounds may be heard in the chest with a decrease in breath sounds bilaterally
- Associated anomalies: Dysmorphisms such as craniofacial abnormalities, extremity abnormalities, or spinal dysraphism may suggest syndromic congenital diaphragmatic hernia

Laboratory tests
- ABG measurements to assess for pH, PCO2, and PaO2
- Chromosome studies, including microarray analysis, if associated anomalies
- Levels of serum electrolytes, ionized calcium, and glucose
- Continuous pulse oximetry is valuable in the diagnosis and management of PPHN

Imaging studies
- Chest radiography to confirm diagnosis of CDH and to rule out pneumothorax
- Cardiac and renal ultrasonography to rule out associated anomalies
- Cranial sonography when an infant is considered for ECMO
  - Prognosis is worse if ECMO is required

Delivery room management
- Avoiding mask ventilation and immediately intubating the trachea

- Endotracheal intubation and MV: Required in infants with severe CDH who present in the first hours of life

Management

- Placement of a sump/Replogle tube and connecting it to continuous suction to prevent bowel distention and further lung compression
- Avoiding high peak inspiratory pressures with MV; synchronizing ventilation with the infant's respiratory effort
- Continuous monitoring of oxygenation, BP, and perfusion
- Maintaining glucose and ionized calcium concentrations within reference range
- Vasoactive agents (e.g., dopamine, dobutamine, milrinone) as needed
- Echocardiogram is a critically important imaging study, and it guides therapeutic decision by measuring pulmonary and systemic artery pressure
- Surgical correction

Hypoxic Ischemic Encephalopathy (HIE)

Background

- Perinatal asphyxia, more appropriately known as hypoxic-ischemic encephalopathy (HIE), is characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia
- Birth asphyxia causes 23% of all neonatal deaths worldwide

Pathogenesis

- Brain hypoxia and ischemia due to systemic hypoxemia, reduced cerebral blood flow, or both are the primary physiological processes that lead to hypoxic-ischemic encephalopathy
- Excitatory amino acid (EAA) receptor overactivation plays a critical role in the pathogenesis of neonatal hypoxia-ischemia
- During cerebral hypoxia-ischemia, the uptake of glutamate, which is the major excitatory neurotransmitter of the mammalian brain is impaired
- Accumulation of Na^+ coupled with the failure of energy-dependent enzymes such as Na^+/K^+-ATPase leads to rapid cytotoxic edema and necrotic cell death

Diagnosis

- Profound metabolic or mixed acidemia (pH < 7) in an umbilical artery blood sample, if it was obtained
- Persistence of an Apgar score of 0–3 for longer than 5 min
- Neonatal neurologic sequelae (e.g., seizures, coma, hypotonia)
- Multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines)

Clinical presentation

- Mild hypoxic-ischemic encephalopathy
  - Muscle tone may be slightly increased, and deep tendon reflexes may be brisk during the first few days
  - Poor feeding, irritability, excessive crying or sleepiness may be observed
  - The neurologic examination findings normalize by 3–4 days of life
- Moderately severe hypoxic-ischemic encephalopathy
  - The infant is lethargic, with significant hypotonia and diminished deep tendon reflexes
  - The grasp, Moro, and suck reflexes may be sluggish or absent
  - The infant may experience occasional periods of apnea
  - Seizures may occur within the first 24 h of life
  - Full recovery within 1–2 weeks is possible and is associated with a better long-term outcome
- Severe hypoxic-ischemic encephalopathy
  - Stupor or coma is typical. The infant may not respond to any physical stimulus

  - Breathing may be irregular, and the infant often requires ventilatory support
  - Generalized hypotonia and depressed deep tendon reflexes are common
  - Neonatal reflexes (e.g., sucking, swallowing, grasping, Moro) are absent
  - Skewed deviation of the eyes, nystagmus, bobbing, and loss of "doll's eye" (i.e., conjugate) movements
  - Pupils may be dilated, fixed, or poorly reactive to light
  - Seizures
  - Irregularities of heart rate and BP are common during the period of reperfusion injury
  - Death from cardiorespiratory failure

Laboratory studies

- Serum electrolyte levels, renal, liver, and cardiac function study
- Coagulation system—includes PT, PTT, and fibrinogen levels
- ABG—Blood gas monitoring is used to assess acid base status and to avoid hyperoxia and hypoxia, as well as hypercapnia and hypocapnia

Imaging studies

- Head imaging study, e.g., MRI of the brain or cranial ultrasonography
- Electrocardiogram (ECG)
- Electroencephalogram (EEG)
- Hearing test
- Retinal and ophthalmic examination

Management

- Fluid and ventilation management
- Treatment of seizures
- Hypothermia therapy (selective brain cooling or total body hypothermia)
  - Extensive experimental data suggest that mild hypothermia (3°–4°C below baseline temperature) applied no later than 6 h following injury is neuroprotective

Intraventricular Hemorrhage (IVH) and Leukomalacia

Background

- A predominant disorder of preterm infants
- Originates in the periventricular subependymal germinal matrix with subsequent entrance of blood into the ventricular system

Risk factors

- Extreme prematurity
- Hypoxic-ischemic insult
- Coagulopathy
- Respiratory disturbances—hypercarbia, hypocarbia, pneumothorax, hypoxemia, rapid alterations in blood gases
- Rapid volume expansion
- Sudden elevation of arterial BP

Classification of IVH

- Grade I: Hemorrhage is confined to the germinal matrix
- Grade II: IVH without ventricular dilatation
- Grade III: IVH with ventricular dilatation
- Grade IV: Intraparenchymal hemorrhage

Clinical presentation

- Sudden drop in hematocrit level
- Apnea
- Bradycardia
- Acidosis
- Seizures
- Change in muscle tone
- Catastrophic syndrome (rapid onset stupor, coma, respiratory abnormalities, seizures, decerebrate posturing, fixed pupil to light, flaccid quadriparesis)

Diagnosis

- Ultrasonography is the study of choice
- All infants younger than 30 weeks gestation should be screened by cranial ultrasonography at 7–14 days postnatal life and at 36–40 weeks postmenstrual age. Instead of a

cranial ultrasound, some institutions prefer to obtain a brain MRI at term corrected age
- Serial ultrasonography is indicated weekly to follow for progression of hemorrhage and the development of post-hemorrhagic hydrocephalus

Complication
- Obstructive hydrocephalus
- Nonobstructive hydrocephalus
- Developmental impairment
- Cerebral palsy
- Seizures

Prognosis
- Grade I and grade II hemorrhage: Neurodevelopmental prognosis is excellent
- Grade IV (severe with either periventricular hemorrhagic (PVH) infarction and/or periventricular leukomalacia): Mortality approaches 80%. A 90% incidence of severe neurological sequelae including cognitive and motor disturbances

Prevention
- Use of antenatal steroids
- Avoid hypoxia-ischemia
- Avoid large and rapid fluctuation of BP
- Avoid rapid infusion of volume expanders
- Correct acid base abnormalities
- Correct coagulation abnormalities
- Gentle handling of preterm babies

Teratogens (Table 2.6)

Table 2.6 Teratogens

Drug name	Effect on fetus
Phenytoin	Broad, low nasal bridge
	Midface hypoplasia and epicanthal fold
	Distal digital or nail hypoplasia
	Wide spaced eyes (hypertelorism)
	Intellectual disability
	IUGR
	Cardiovascular abnormalities
	Bleeding (vitamin K deficiency)
Valproic acid	Neural tube defect (spina bifida)
	Cardiac, renal, and limb anomalies
Carbamazepine (CBZ)	Orofacial clefts
Warfarin	Bone stippling
	Facial anomalies
	Fetal bleeding and death
Lithium	Ebstein anomalies
	Hypothyroidism
	Nephrogenic diabetes insipidus
	Macrosomia
Cocaine	Limb defect or reduction
	Intracranial hemorrhage
	Leukomalacia
	Nonduodenal intestinal atresia
	Gastroschisis (most likely due to disruption of omphalomesenteric artery)
Marijuana	No specific feature to identify because of possible poly-drug abuse
	Irritability
	Tremulousness
	Abnormal response to visual stimuli
Cigarette smoking	Low birth weight for gestational age
Danazol	Virilization
Tetracycline	Retarded skeletal growth, pigmentation of teeth, hypoplasia of enamel, cataract, limb malformations

Fetal Alcohol Syndrome

Background
- Adverse fetal, neonatal, and pediatric effects occur with maternal alcohol consumption during pregnancy
- The greater the intake of alcohol, the more severe the signs
- No safe amount of alcohol during pregnancy has yet been determined

Clinical presentation
- Small for GA
- Short palpebral fissures (< 10% for age)
- Epicanthal folds
- Micrognathia
- Midface hypoplasia
- Microphthalmia
- Smooth philtrum
- Thin upper lip
- Microcephaly
- Irritability in infancy
- Intellectual impairment (mild to moderate intellectual disability)

- Cognitive impairment
- Hyperactivity in childhood or attention-deficit/hyperactivity disorder (ADHD)
- Skeletal abnormalities, e.g., radioulnar synostosis
- Hearing and visual abnormalities, e.g., deafness and strabismus

PEARLS AND PITFALLS

- It is important to recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
- Infants < 38 weeks gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.
- All bilirubin levels should be interpreted according to the infant's age in hours. A systematic assessment for the risk of severe hyperbilirubinemia should be performed on all infants before discharge.
- The most common bacterial pathogen for early onset sepsis is GBS, followed by *E. coli.*
- HSV PCR testing in the asymptomatic newborn should be delayed for 24–48 h after birth in order to differentiate viral replication in the newborn from transient colonization of the newborn at birth.
- The congenital infection most commonly associated with hydrops fetalis is parvovirus B19.
- The most common cause of respiratory distress in the term newborn is transient tachypnea of the newborn (TTN). This is a self-limited disorder and usually resolves within 48 h.
- Nonvigorous newborns with meconium-stained amniotic fluid *do not* require routine intubation and tracheal suctioning. However, meconium-stained amniotic fluid is a perinatal risk factor that requires the presence of one resuscitation team member with full resuscitation skills, including endotracheal intubation.
- The most common form of esophageal atresia and tracheo-esophageal fistula is esophageal atresia with a distal fistula (88% of cases), where the upper esophagus ends in a blind pouch and the trachea is connected by a fistula to the distal esophagus.
- Approximately 85% of congenital diaphragmatic hernias (CDH) are left sided; in these patients, there can be herniation of the small or large bowel and other solid intra-abdominal organs. Patients with CDH who require ECMO have worse prognosis than those who do not require ECMO.
- In newborns who present with bilious vomiting, one of the most important diagnoses to exclude is malrotation with or without volvulus.
- Infants with volvulus constitute a surgical emergency and require prompt medical and surgical intervention. Up to 80% of affected patients receive a diagnosis during the neonatal period, with 50% presenting in the first week after birth. If not recognized in a timely fashion, volvulus can lead to catastrophic loss of bowel with resultant lifelong disability and even death.
- Gastroschisis presents as a full thickness defect in the abdominal wall with prolapse of the intestine through the defect. There is no covering membrane, and the defect lies to the right side of an intact umbilical cord.
- In omphalocele, the defect is midline and the prolapsed organs are always covered with a protective membrane consisting of amnion on the outer surface, peritoneum on the inner surface, and Wharton jelly in between.
- Omphaloceles contain a variable amount of intestine, often parts of the liver, and occasionally other organs.
- There is no evident genetic cause for gastroschisis; associated intestinal atresias may be present. In contrast, omphaloceles are associated with syndromes and chromosomal

abnormalities in over 50% of cases, including Beckwith-Wiedemann syndrome (omphalocele, macroglossia, organomegaly, hypoglycemia, and increased risk for childhood tumors such as Wilms tumor, neuroblastoma, and hepatoblastoma).

References

1. Fernandes CJ. Neonatal resuscitation in the delivery room. In: Post TW, editor. UpToDate. Waltham: UpToDate. http://www.uptodate.com. Accessed 13 Jan 2019.
2. Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol. 2012;32:660–4.
3. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297–316.

Suggested Reading

Barnes-Powell LL. Infants of diabetic mothers: the effects of hyperglycemia on the fetus and neonate. Neonatal Netw. 2007;26:283–90.

Campbel DE. Neonatology for primary care. Elk Grove Village: American Academy of Pediatrics; 2015.

Gornall AS, Kurinczuk JJ, Konje JC. Antenatal detection of a single umbilical artery: does it matter? Prenat Diagn. 2003;23:117–23.

Hibbs AM, Black D, Palermo L, Cnaan A, Luan X, Truog WE, et al. Accounting for multiple births in neonatal and perinatal trials: systematic review and case study. J Pediatr. 2010;156:202–8.

Laptook A, Tyson J, Shankaran S, McDonald S, Ehrenkranz R, Fanaroff A, National Institute of Child Health and Human Development Neonatal Research Network, et al. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics. 2008;122:491–9.

Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA, et al. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2002;58:1726–38.

Norton ME, Scoutt LM, Feldstein VA, editors. Callen's ultrasonography in obstetrics and gynecology. 6th ed. Philadelphia: Elsevier; 2017.

Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, et al. Part 13: neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132(18 Suppl 2):S543–60.

Adolescent Medicine

3

Jessica Addison

PHYSIOLOGICAL CHANGES AND DEVELOPMENT DURING ADOLESCENCE

Puberty Sequence in Girls

- Puberty for girls generally lasts an average of 4 years (1.5–8 years)

Thelarche: Appearance of breast tissue

- Enlargement of the breast is the earliest sign of puberty
- Mean age 9.7 years (7.8–11.6 years) in Caucasian girls
- Mean age 8.8 years (6.1–10.1 years) in African-American girls

Pubarche: The appearance of pubic hair; first appearance of axillary hair, apocrine body odor, and acne

Peak height velocity

- Occurs about 6 months prior to menarche
- Occurs at a mean age of 11.5 years in girls
- Approximately 8.3 cm/year

Menarche: Time of first menstrual bleeding

- Menarche usually starts 2–3 years after breast development
- The first menstrual bleed is often not associated with ovulation
- Girls who develop earlier (or later) than their peers in school may face psychological challenges

Puberty Sequence in Boys

- Puberty in boys usually lasts an average of 3 years (2–5 years)

Increase in testicular volume

- Enlargement of the testicles is the earliest sign of puberty
- The mean age is 11.4 years (9.5–13.5 years)
- Expected growth: Volume ≥ 4 mL and length ≥ 2.5 cm

Penile growth

- Growth in length rather than width. Pubic hair is getting darker and coarser

Pubarche

- Appearance of axillary hair, apocrine body odor, acne, and voice changes

Peak height velocity

- Occurs at a mean age of 13.5 years in boys
- Is approximately 9.5 cm/year

J. Addison (✉)
Division of Adolescent/Young Adult Medicine, Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: Jessica.Addison@childrens.harvard.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_3

Table 3.1 Tanner staging [1, 2]

Stage	Pubic hair	Male genitalia	Female breasts
1	No pubic hair	No signs of puberty testicular volume < 4 mL	No breast tissue
2	Sparse hair that are straight and lack pigment	Enlargement of the scrotum and testes. Reddening of scrotum	Breast tissue formation (breast bud) Widening of areola
3	Coarse, dark, curly hair	Elongation of penis	Continued enlargement of breast and areola with no separation of contour
4	Pubic hair dense, curly, pigmented (does not reach medial thigh)	Continued growth of testes and penis	Areola and nipple project above breast tissue (secondary mound)
5	Adult hair growth Pubic hair spreads to the medial thigh	Testicular volume > 20mL	Adult pattern

Skeletal growth

- The growth spurt in girls occurs earlier than in boys, sexual maturity rating (SMR) II–III for girls vs. SMR IV for boys
- Girls reach their final height earlier than boys (average 16 years for girls vs. 18 years for boys)

Tanner staging (Table 3.1) [1, 2]

Hematological changes

- In boys, blood volume, red blood cell (RBC) mass, hemoglobin, and hematocrit all increase during puberty under the effect of testosterone (this is not the case with girls)

Risks and conditions associated with death during adolescence

- Unintentional injuries such as motor vehicle accidents are the leading causes of adolescent morbidity and mortality
- Suicide is the second leading cause of death among adolescents
- Most of the adolescent's medical care is received in the emergency department

Reasons for hospitalizations

- Number 1: Pregnancy
- Number 2: Mental disorders
- Number 3: Injuries

Common problems

- Pregnancy
- Acne
- Smoking and illicit drugs
- Obesity
- Gynecomastia
- Mental health

***Cognitive development* [3]**

- Early adolescence (10–13 years old): Concrete thinking, egocentrism, and impulsive behavior
- Middle adolescence (14–16 years old): Abstract thinking
- Late adolescence (17–21 years old): Becoming a separate entity from family

Identity development

- Early: Privacy, self-exploration, testing authority, and lack of impulse control
- Middle: Feelings of omnipotence, immortality, and engaging in risk-taking behavior
- Late: Rational and realistic conscience with the ability to delay gratification, to compromise, and to set limits

Management of poor self-image

- Perception of self is shaped by personal goals, life experiences, ethnicity, religion, and sexual identity
- Risk factors for poor self-image: Neglect and abuse, mental health problems, poverty, witnessing or experiencing trauma
- Signs of poor self-esteem/self-image: Mood changes, poor school performance, substance abuse, risk-taking behaviors
- Management: Family support and acceptance, focusing on individual strengths, emphasizing

that adolescence is a time of self-growth and discovery and that they are not alone

***Psychological separation from the family and peer group relationships* [3]**

- Separation occurs during late adolescence and shapes personal development but can also be linked to start of risk-taking behaviors
- Peer group development
  - Early (10–13 years old): Dependent on friends, nonromantic relationships
  - Middle (14–16 years old): Peer group most powerful, includes romantic relationships, involvement with clubs, team sports, gangs, and other groups of interest
  - Late (17–21 years old): Peer group values become less important, separate identity from parents, more time spent in a relationship with one individual

Family influence on adolescent behavior

- Parents' behavior significantly influences the behavior of their children
- If parents are viewed in a positive way and exhibit high self-esteem, their child is more likely to model them
- If a parent is viewed in a negative way, the child may mimic negative attitude and generalize it to the rest of society
- Support from parents helps develop positive bonds with the adolescent, which hinders the formation of deviant behaviors

Sexuality

- It is important to normalize sexual behavior (e.g., sexual intercourse, masturbation), sexual identity and exploration
  - Adolescents are at increased risk for sexually transmitted infections and pregnancy, so counseling regarding safe sex practices is recommended at all visits
- Open, honest communication regarding sexuality between adolescents and their parents is strongly encouraged
- Discussing sexuality will not cause adolescents to become sexually active if they have not started already

Emancipation and Healthcare Decisions [4]

Emancipated minors

- Process where a minor (< 18 years of age) is legally declared an adult
- Examples of an emancipated minor include those who are married, active member of military, moved from the parental home and paying their own bills, and being a parent

Mature minor doctrine

- Allows minor to consent to routine, nonemergency care, especially when the risk of treatment is considered to be low
- Must be able to understand the risks and benefits of treatment plan and be able to provide the same level of consent as an adult
- Many states allow minors to seek help for pregnancy, contraception, substance abuse, sexually transmitted disease (STD), and mental health issues without parental consent

Best approach in difficult cases

- Encourage the minor to agree to bring the parents or guardian into decision-making process, with the physician acting as a facilitator

Adolescent Routine Health Visit

Interview

- Allow adolescents to become autonomous, involve the parents only as much as the adolescent wishes
- Interview the adolescent alone and in a confidential manner when discussing drugs, contraception, STDs, and mental health. Confidentiality can be broken if it appears the adolescent is a harm to themselves or others (e.g., actively suicidal)

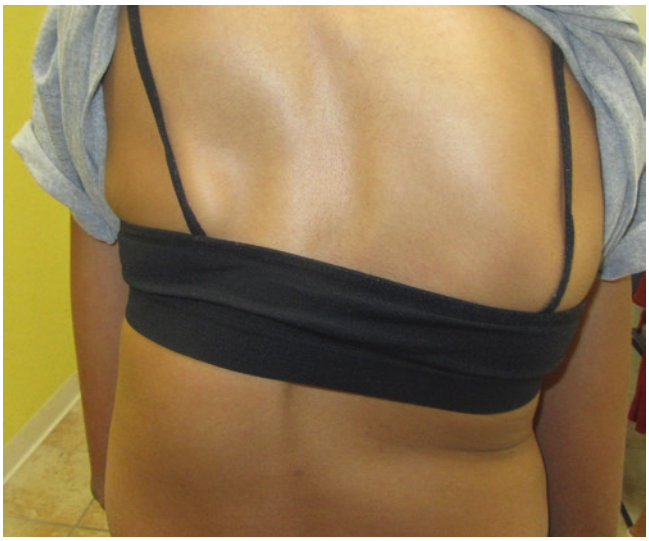


Fig. 3.1 An adolescent female with severe thoracolumbar scoliosis

- Ask about peer and family relationships, depression, sexual relationships, substance abuse, and eating disorders

Physical examination

- Hearing and vision
- Blood pressure
- Scoliosis: Current evidence is insufficient to recommend screening for scoliosis in adolescents < 18 years of age and that the balance of benefits and harms of screening for adolescent idiopathic scoliosis cannot be determined [5] (Fig. 3.1)
- Visual breast examination
- Pelvic examination
  - Indications for pelvic exam in an adolescent: Persistent vaginal discharge, dysmenorrhea refractory to medical management, amenorrhea, abnormal vaginal bleeding, lower abdominal pain. Routine cervical screening at age 21
- External genital exam to evaluate for masses, hernia, varicocele, hydrocele, appropriate size of testes, or other pathology. Vaginal exam to evaluate for cysts, abnormal discharge, genital warts, irritation, clitoromegaly, or other pathology
- Calculate body mass index (BMI)

Laboratory

- Annual screening for chlamydia and gonorrhea infection in all sexually active women < 25 years of age
- Screening for chlamydia in sexually active adolescent men should be considered in clinical settings where there is a high prevalence
- Universal cholesterol for youth 9–11 years old; a second screening for youth between 17 and 21 years old or those with a family history of early cardiovascular disease
- Consider obtaining a complete blood count (CBC) in adolescent females starting at age 12 if risk factors are identified for anemia (history of poor dietary iron intake, heavy menstrual blood loss)
- Screening for HIV infection should be performed, at least once for all patients between 15 and 18 years old

Immunization

- At 11–12 years, give Tdap vaccine (against tetanus, diphtheria, and pertussis), meningococcal conjugate vaccine (MCV4), and human papilloma virus (HPV) vaccine; 3-dose series if started after the age of 15 years old, 2-dose series if started before that age
- At 16 years, give a booster dose of MCV and consider Bexsero (2 doses 1 month apart) or Trumenba (2 doses 6 months apart) for healthy adolescents

Anticipatory guidance

- Promote injury prevention
- Seat belt use all the time
- Alcohol/substance abuse
- Helmet use
- Weapon safety
- Exercise preparedness to prevent injury
- Risky behaviors
- Indication for intervention in cases of obesity (Table 3.2)
- Screen for eating disorder behaviors

Table 3.2 Indication for intervention in cases of obesity

BMI* ≥ 95th percentile
Or
BMI between 85th and 95th percentile *and*
Family history of premature heart disease, obesity, HTN*, or DM*
HTN
Cholesterol > 200 mg/dL
Increase of ≥ 2 points in BMI in 12 months
Adolescent is concerned about his or her weight

**BMI* body mass index, *HTN* hypertension, *DM* diabetes mellitus

BEHAVIORAL HEALTHCARE

General

- It is important to take a developmentally appropriate psychosocial history during each interaction with an adolescent

Adherence

- Factors that negatively affects adolescents' adherence to medical regimens: Mental health issues, peer influence, family stressors, cognitive change (e.g., concrete to abstract thinking), poor access to healthcare, independence from family (e.g., now making their own decisions)
- Factors that positively affect adolescents' adherence to medical regimens: Positive family relationships, self-control, treatment with immediate benefits, positive patient–clinician relationship

Risk-taking

- Factors associated with risk taking behaviors: Peer influence, mental health issues, family stressors, adversity and stress, neuropsychological changes (brain development)

Violence

- There is a high occurrence of sexual assault in the adolescent population, which has negative medical, social, and psychological consequences
- All adolescents should be screened for sexual victimization
- Teaching adolescents to listen and communicate with one another in an effort to develop empathy and understanding can assist in conflict resolution
- Opportunities to discuss conflict/anger with adults or peers offer alternative perspectives and can result in calm, rational decision-making instead of impulsivity and violence

Stress

- Can manifest in a variety of ways in adolescents: Clinical symptoms (e.g., abdominal pain, headache), mood changes (e.g., depression), poor school performance, sleep disturbance, and behavioral changes

SUBSTANCE ABUSE (TABLE 3.3) [6]

- American Academy of Pediatrics (AAP) recommends annual substance use screening of all adolescents, starting at 9 years of age, and use of brief intervention techniques

Background

- Marijuana, alcohol, and tobacco are the most commonly used substances during adolescence
- Mean age of smoking is 12 years, and 12.6 years for alcohol consumption
- The earlier an adolescent begins using substances, the greater the risk of developing substance use problems as an adult. Boys have a lower age of smoking initiation compared to girls.

Stages of drug/alcohol abuse

- Abuse
  - Substance use resulting in failure to meet obligations (e.g., school or work)
  - Using substance in situations that can cause harm (e.g., driving a car)
  - Continued use despite having negative effects on interpersonal relationships

Table 3.3 Substance abuse, intoxications, and means of administration [6]

Substance abuse	Consequence and intoxications	Means of administration
Alcohol	Euphoria, grogginess, talkativeness, impaired short-term memory, diuresis, gastritis, hypothermia, decreased coordination, road crashes, respiratory depression, transaminitis, pancreatitis, gastrointestinal symptoms	Drinking
Marijuana	Euphoria, poor performance of tasks requiring divided attention, loss of critical judgment, distortion of time perception, road crashes, injected conjunctiva, tachycardia, dry mouth, respiratory symptoms (worsening of asthma)	Smoking
Opioids	Euphoria, diminution of pain, flushing of skin, pinpoint pupils, tracks (skin lesions follow large veins), skin abscesses (use of unsterile needles), loss of libido, increased risk of STDs (e.g., HIV), constipation, endocarditis, cerebral micro-abscesses, respiratory depression, coma, death	Injected (IV/SC), snorted/sniffed, or smoked
Amphetamine	Increased physical activity, rapid and/or irregular heart rate, increased blood pressure, decreased appetite, psychosis, violence, increased risk of STDs, withdrawal syndrome or crash phase (depression, agitation, craving for more drug), limited interest in the environment, anhedonia	Ingested orally, smoking, injection, mucosal absorption
Hallucinogen—(LSD)	Delusional ideation, altered changes in vision and hearing, body distortion, distortion of time, suspiciousness, toxic psychosis, dizziness, dilated pupil, nausea, flushing, decreased temperature, tachycardia (not addictive)	Drinking (liquid or tablets)
Hallucinogen—MDMA ("X," ecstasy)	Euphoria, heightened sensual awareness, increased psychic and emotional energy, nausea, jaw clenching, teeth grinding, blurred vision, anxiety, panic attacks, and psychosis	Drinking (tablets or capsules)
Hallucinogen—PCP	Euphoria, nystagmus, ataxia, emotional lability, shallow breathing, flushing, generalized numbness of extremities, loss of motor coordination, bizarre distortion of body image, panic reactions, disorientation, hypersalivation, abusive language, seizures, cardiac arrhythmias, death (dose-related)	Drinking (tablets, liquids, or powder), e.g., angel dust and peace pill
Cocaine	Euphoria, increased motor activity, decreased fatigability, pupillary dilatation, tachycardia, hypertension, anxiety, psychosis (Snorting cocaine: loss of sense of smell, nosebleeds, chronic rhinorrhea, destruction of nasal septum)	Smoking, snorting, injection
Inhalants	Euphoria, slurred speech, decreased coordination, dizziness, violent excitement, brain damage, coma from prolonged use. Death from cerebral edema, pulmonary edema, or myocardial involvement	Inhalation, e.g., toluene found in paint thinners and removers

STD sexually transmitted disease, *IV* intravenous, *SC* subcutaneous, *LSD* lysergic acid diethylamide, *MDMA* 3,4-methylenedioxy-methamphetamine, *PCP* phencyclidine

- Tolerance
  - No longer responds to the same amount of substance
  - Needs increased amounts of substance to achieve intoxication or desired effect
- Dependence
  - Can only function normally when on substance and experiences withdrawal symptoms if off drug
- Addiction
  - No longer for pleasure, physical and psychological need to use substance
  - Continues to use drug despite negative consequences

Tobacco

- Tobacco use by adolescents can become a serious drug addiction

- Adolescents underestimate the addictive nature of cigarettes
- There has been an increase in e-cigarette use in adolescents, which can serve as a gateway drug to traditional cigarette smoking
- Systemic effects of tobacco
  - Cardiovascular disease
  - Cancers
  - Diminished bone density
  - Pulmonary effects (worsening asthma)
  - Gastrointestinal effects (gastroesophageal reflux)
  - Reproductive effects (pregnancy)
- Assess adolescents' willingness to quit smoking at each clinical encounter
- Tailor counseling around helping adolescents identify their own benefits and barriers to quitting
- Nicotine replacement therapies are available over the counter for those > 18 years of age and by prescription for adolescents < 18 years
- Bupropion or varenicline can be considered for treatment of adolescents with moderate to severe nicotine addiction
- School and community support program
  - Mobile phone–based programs
  - Proactive community-wide telephone support combined with patient education materials
- E-cigarettes counselling
  - AAP recommends screening all family members for e-cigarette use, counsel all children and youth about the potential harms of e-cigarettes, and promote family strategies to avoid exposure to e-cigarettes, including banning their use from the household and car

Alcohol

- Alcohol use is common during adolescence, and initiation at an early age is associated with future alcohol-related problems and substance abuse
- Alcohol use contributes to the leading causes of adolescent death (e.g., motor vehicle accidents and suicide)
- Psychiatric conditions (anxiety and depression) often occur with alcohol use

Marijuana

- Can have permanent negative effects on the developing adolescent brain
- Most common illicit drug used by adolescents
- Adverse psychosocial outcomes: Poor school performance, impaired peer and family relationships, mood changes, and impaired memory

Opioids

- Physiologic consequences: Hypotonia, respiratory failure, hypotension, miosis, coma
- Acute overdose management: Airway, breathing, and circulation (ABCs), naloxone IV

Amphetamines

- Nonmedical use of prescription amphetamine is increasing among adolescents
- Antipsychotics and/or benzodiazepines are used in cases of acute intoxication for agitation management

Hallucinogens

- Adverse effects from chronic use: Psychosis, depression, and personality changes
- Hallucinogen use should be on differential diagnosis in an adolescent presenting with new-onset psychosis
- Treatment of acute intoxication/overdose is supportive, preferably in a calm environment

Cocaine

- Signs of cocaine intoxication: Hypertension, hyper-alertness, tachycardia, dilated pupils, hyperactive reflexes
- Management and treatment of cocaine overdose: Respiratory, renal (rhabdomyolysis), cardiovascular (electrocardiographic, cardiac enzymes) support and monitoring

Inhalants

- Used by inhaling from a plastic bag ("bagging") or by inhaling through a cloth saturated with substance ("huffing")

- Products used as inhalant substances: Toluene (found in spray paint), cleaning fluids, rubber cement, and permanent markers
- Inhalant abuse is a significant risk of "sudden sniffing death syndrome" → cardiac arrest
- Sudden death may occur in all inhalant users, including those experimenting with inhalant abuse for the first time.
- Treatment is supportive and includes respiratory and circulatory support

Over-the-counter and prescription medicine

- Commonly abused over-the-counter medications: Cold medicines (pseudoephedrine), cough medicines (dextromethorphan), analgesics (acetaminophen)
- Commonly abused prescription medications: Stimulants, opioids, sedatives, anxiolytics
- Risk factors for abuse of over-the-counter and prescription medicine
  - Family history of substance abuse problems, history of or current substance use, peer pressure, easy access to prescription drugs (personal prescription or family member has prescription), lack of knowledge regarding potential harm

Anabolic steroids

- Can be taken as an oral or injectable agent
- Adverse effects: Psychiatric (mood changes), cardiovascular (hypertension), endocrine (premature epiphyseal closure, testicular atrophy), dermatologic (acne)

Red flags of substance abuse

- Behavioral problems
- School failure
- Emotional distress
- Absent or hostile communication
- Risky behaviors
- New disinterest in sports

Indications of substance abuse screening

- Unexplained accidents
- Trauma
- Psychiatric symptoms
- School failure or deterioration
- Increased school absence
- Suicide attempt
- Altered mental status

Consent for drug testing

- Drug testing of older competent adolescent should be voluntary

EATING DISORDERS

Introduction

- Eating disorders are serious mental health conditions in children, adolescents, and young adults
- These disorders can cause significant morbidity and mortality, as well as devastating effects on the child's psychosocial development, family dynamics, and education
- Anorexia nervosa has the highest fatality rate of any mental health disorder

Suspicious behaviors

- Assumption of a vegan, vegetarian, low fat, or "healthier" diet, scrutiny of ingredient lists
- Initiation of precise calorie counting or weighing one's self several times daily
- Taking smaller portions or taking a longer period of time to eat
- Increasing the duration and intensity of exercise in an attempt to utilize more energy
- Avoiding eating with family and friends or hiding food during social meals
- Signs of purging activity include frequent trips to the bathroom after meals
- Discovery of empty containers of diet pills or laxatives
- Extra layers of clothing to cover up signs of emaciation and to retain body heat

Indication of hospitalization of patients with eating disorders

- Weight < 75% of ideal body weight for age, gender, and stature
- Acute weight decline and refusal of food
- Hypothermia
- Hypotension

- Bradycardia
- Arrhythmia
- Syncope
- Suicidal risks
- Electrolyte disturbance
- Failure to respond to outpatient treatment

Anorexia Nervosa

Background

- Anorexia is divided into two subtypes: Binge/purging and restrictive
- Anorexia nervosa is a potentially life-threatening eating disorder characterized by the inability or refusal to maintain a minimally normal weight, a devastating fear of weight gain, relentless dietary habits that prevent weight gain, and a disturbance in the way in which body weight and shape are perceived
- Individuals usually involved in ballet or sports, e.g., gymnastics, wrestling, running marathons

Clinical presentation (Table 3.4)

- Hypotension, bradycardia, and hypothermia
- Dry skin
- Lanugo-like body hair
- Thinning hair
- Swelling of the parotid and submandibular glands
- Atrophy of the breasts
- Patients with purging behavior may have calluses to the dorsum of their dominant hand and dental enamel erosion
- Loss of muscle mass
- Low blood glucose (impaired insulin clearance)
- Low parathyroid hormone levels
- Elevated liver function
- Low white blood cell (WBC) count

Laboratory

- CBC
- TSH
- ALT

Table 3.4 Diagnostic criteria for anorexia nervosa

Criterion	DSM-V
Body weight	Restriction of energy intake relative to requirements leading to a markedly low body weight (less than minimally expected for age and height)
Fear of weight gain	Intense fear of gaining weight or becoming fat, although underweight, or persistent behavior to avoid weight gain, although at a markedly low weight
Body image	Disturbance in the way one's body weight or shape is experienced; denial of the seriousness of low body weight; undue influence of body weight or shape on self-evaluation

DSM-V Diagnostic and Statistical Manual of Mental Disorders-V

- EKG
- Metabolic panel
- Urinalysis
- Pregnancy test (in females of childbearing age)

Complications of anorexia nervosa [7]

- Gastrointestinal
  - Gastric dilatation and rupture, delayed gastric emptying, decreased intestinal motility, elevated liver aminotransferase concentrations, elevated serum amylase concentrations, superior mesenteric artery syndrome
- Cardiovascular
  - Decreased left ventricular forces, prolonged QT interval corrected for heart rate, increased vagal tone, pericardial effusion, congestive heart failure
- Hematologic
  - Anemia, leukopenia, thrombocytopenia
- Endocrine and metabolic
  - Low bone density, euthyroid sick syndrome, amenorrhea, refeeding syndrome, electrolyte disturbances, decreased serum testosterone or estradiol, hypercholesterolemia, hypercortisolism
- Renal
  - Increased blood urea nitrogen, calculi formation
- Neurological
  - Pseudo-cortical atrophy, enlarged ventricles

Management

- The process of refeeding must be undertaken slowly, with modest increases in metabolic demands, in order to avoid refeeding syndrome
- Refeeding syndrome: As the adolescent's caloric intake increases, low levels of serum phosphorus can lead to:
  - Rhabdomyolysis
  - Decreased cardiac motility, cardiomyopathy
  - Respiratory and cardiac failure
  - Edema, hemolysis, acute tubular necrosis
  - Seizures and delirium
  - Dangerous fluctuations in potassium, sodium, and magnesium levels
- A nutritionist or dietitian should be an integral part of the refeeding
- Psychological therapy, e.g.:
  - Individual therapy (insight-oriented)
  - Cognitive analytic therapy
  - Cognitive behavioral therapy
  - Family-based therapy

Bulimia

Background

- Bulimia is divided into two subtypes: Purging and non-purging
- Binge eating is seen in both subtypes
- The purging subtype describes an individual who engages regularly in self-induced vomiting or misuse of laxatives, diuretics, or enemas
- The non-purging subtype describes an individual who uses other inappropriate compensatory behaviors, such as excessive exercise or fasting to burn calories
- It is important to note that patients who have bulimia often are not low weight and thus may easily hide their eating disorder

Clinical presentation (Table 3.5)

- Fatigue
- Bloating
- Irregular menses
- Throat pain
- Bilateral parotid gland swelling
- Calluses on the dorsum of the fingers and loss of tooth enamel from acidic vomit
- Aspiration pneumonia
- Metabolic alkalosis
- Elevated serum amylase

Table 3.5 Diagnostic criteria for bulimia

Criterion	DSM-V
Binge eating	Eating an amount of food in a discrete period of time (2 h) that is definitely larger than most people would eat
Compensatory behavior	Recurrent inappropriate compensatory behavior in order to prevent weight gain such as self-induced vomiting, misuse of laxatives, diuretics, enemas, other medications, fasting, or excessive exercise
Frequency of above behaviors	Binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months
Self-evaluation	Unduly influenced by body shape and weight
Relation to anorexia nervosa	The disturbance does not occur exclusively during episodes of anorexia nervosa

DSM-V Diagnostic and Statistical Manual of Mental Disorders-V

Management

- Psychological therapy
- Management of associated conditions, e.g., obsessive, compulsive, or affective disorders
- Pharmacological therapy: Consider selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine

FEMALE BREAST MASSES

Introduction

- Estrogen is the most important factor in breast development.
- Asymmetrical growth of breasts where one is slightly bigger than the other is normal.

- The most common breast masses are solitary cysts, fibrocystic changes, and fibroadenoma
- Breast cancer in adolescence is extremely rare
- Family history is extremely important

Solitary cyst [8]

- It is a benign breast mass
- > 50% of cases resolve spontaneously in 2–3 months
- Follow up with serial exams
- Breast ultrasound if cannot differentiate between cystic and solid mass by physical examination
- Pain is commonly associated with solitary cystic masses
- Nonsteroidal anti-inflammatory drug (NSAID) can be used for pain
- Oral contraceptives may reduce the frequency and duration

Fibroadenoma [8]

- Fibroadenoma is the most common breast mass that usually presents as a single breast mass in young women
- Discrete solitary breast mass of 2–3 cm located in the upper outer quadrant in majority of cases
- Fibroadenoma is usually smooth, mobile, nontender, and rubbery in consistency
- They have no malignant potential

Cystosarcoma phyllode

- Rare, rapidly growing lesion with a small risk of becoming malignant

Intraductal papilloma

- Benign, slow-growing tumor located under the areola
- It may present with a serous or bloody discharge

Indication for surgical intervention

- Persistence of a mass or enlargement over three menstrual cycles
- Ultrasound can be used for screening (mammography not used for adolescents)

AMENORRHEA

Primary amenorrhea

- Absence of menarche by 15 years old

Secondary amenorrhea

- Loss of menses for > 3 consecutive months after previous regular cycles
- Loss of menses for 6 months in those with previously irregular cycles

Causes of amenorrhea (Fig. 3.2) [9]

- Pregnancy is the most common cause of secondary amenorrhea
- Central (hypothalamic or pituitary).
- Ovarian or anatomic (uterus, cervix, vagina, imperforate hymen)
- Polycystic ovarian syndrome (PCOS)
- Prolactinoma, thyroid dysfunction, weight loss (anorexia)

Clinical approach to an adolescent with secondary amenorrhea

- Perform history and physical and review medications (are they on contraception?)
- Assess estrogen status with progesterone challenge
- Labs and imaging:
  - Pregnancy test
  - Luteinizing hormone (LH)
  - Follicle-stimulating hormone (FSH) (if elevated, consider premature ovarian insufficiency and consider karyotype to rule out Turner syndrome)
  - Thyroid-stimulating hormone (TSH)
  - Prolactin (if elevated, consider brain magnetic resonance imaging (MRI) to rule out prolactinoma)
  - Assess for biochemical signs of hyperandrogenism

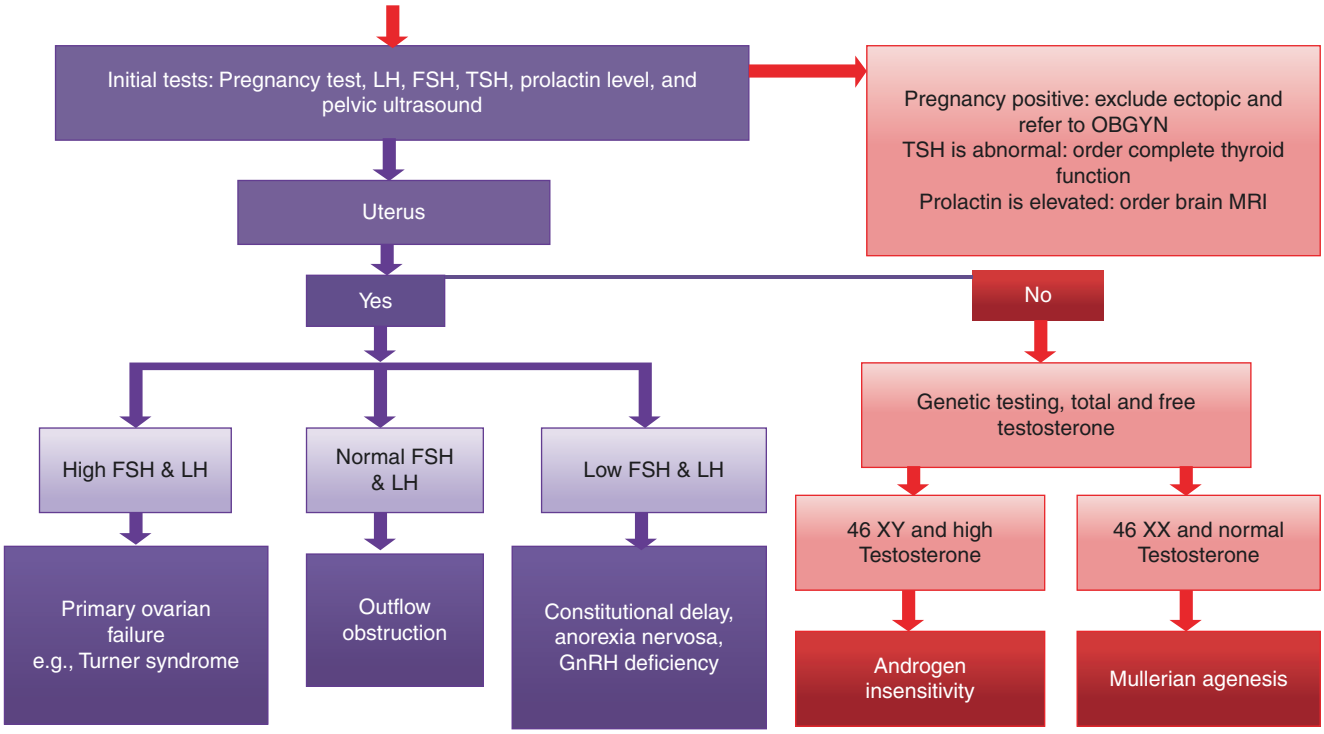


Fig. 3.2 Approach to the adolescent with primary amenorrhea. *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *TSH* thyroid-stimulating hormone. *MRI* magnetic resonance imaging, *GnRH* gonadotropin-releasing hormone [9]

- Free and total testosterone (if elevated, consider PCOS)
- 17 hydroxyprogesterone (if elevated, consider late-onset congenital adrenal hyperplasia)
- DHEA-S (if elevated > 500 μ/dL, obtain abdominal MRI or computed tomography [CT] scan)

- Consider pelvic ultrasound to evaluate for anatomic abnormality

Polycystic Ovarian Syndrome (PCOS)

- Characterized by oligo-/anovulatory cycle and hyperandrogenism (clinical and/or biochemical)
- Increased risk for metabolic abnormalities (insulin resistance and hyperlipidemia)
- Pharmacologic treatment: Combined hormonal contraceptives, cyclic progestins (induces withdrawal bleed), metformin (lowers insulin levels and decreases steroid hormone production by ovaries)

Dysmenorrhea

Background

- Leading cause of school absenteeism in female adolescents
  - Due in most cases to prostaglandin production before menses, which causes vasoconstriction and muscular contractions

Clinical presentation

- Abdominal pain and cramps

Differential diagnosis

- Anatomic abnormality
- Pelvic inflammatory disease (PID)
- Endometriosis
- Psychosocial (e.g., trauma, stress)

Management

- Ibuprofen, naproxen
- Contraceptives are very effective in reducing or eliminating dysmenorrhea

Dysfunctional Uterine Bleeding

- The most common cause of excessive bleeding that requires hospitalization in adolescence
- During the first 2 years after menarche, menstrual cycles are typically anovulatory, which can result in irregular bleeding
- Abnormal bleeding at the time of menarche may be the first sign of a bleeding disorder, e.g., Von Willebrand disease
- Lacerations of vagina, hymenal tear, and foreign bodies may present with vaginal bleeding
- Differential diagnosis of dysfunctional uterine bleeding:
  - Vaginal adenocarcinoma in girls because their mothers received diethylstilbestrol (DES)
  - Thyroid dysfunction, hyperprolactinemia, hypothalamic dysfunction
  - Bleeding disorder
  - Anovulatory cycles
  - Structural lesions, cervical polyps
  - Endometrial diseases, e.g., endometritis
  - STDs

Imperforate Hymen (Fig. 3.3) [10]

- Common obstructive lesions of the female genital tract
- Associated with amenorrhea, cyclic pelvic pain, and accumulation of blood in the vagina (hematocolpos)
- Treatment: Surgical correction

Labial Adhesions

- Clinical symptoms: Asymptomatic, urinary symptoms, vaginal symptoms (pain, discharge, and infection)
- Management: Topical estrogen or estradiol; consider surgery if no response to medical management

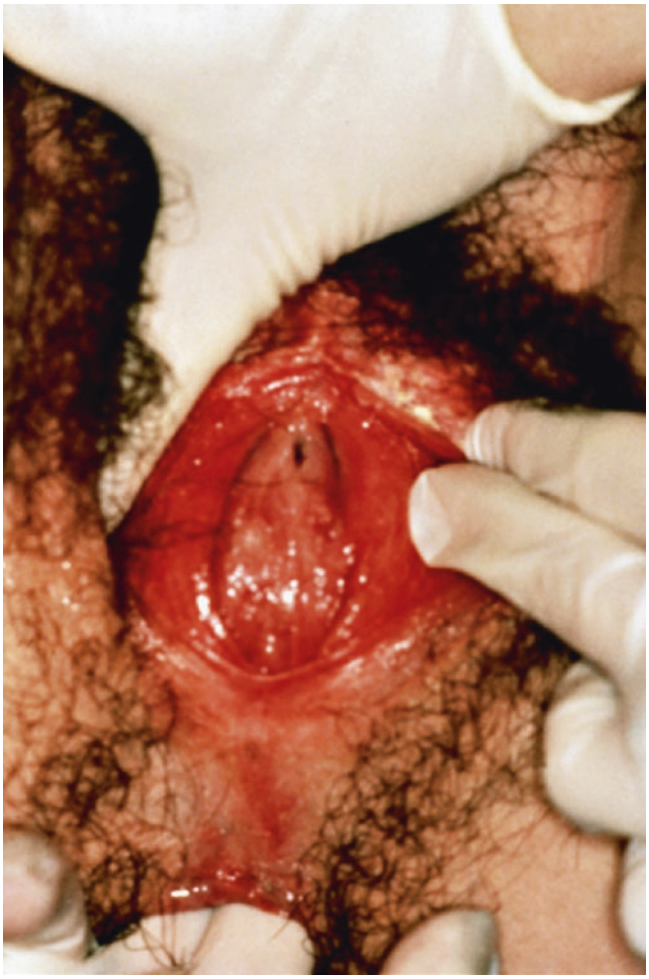


Fig. 3.3 Imperforate hymen. (From Emans and Laufer [10], with permission)

Ovarian Torsion

- **Clinical symptoms**
  - Sudden onset of unilateral pelvic pain that worsens over hours, adnexal mass, nausea, and vomiting. Fever may occur as the ovary becomes necrotic
- **Diagnosis**
  - Ultrasonography with color Doppler analysis is the method of choice for the evaluation of adnexal torsion
- **Treatment**
  - Immediate gynecologic consultation and subsequent laparoscopy are critical

Ovarian Cyst

- Presents with lower abdominal pain
- Evaluation
  - History (menstrual history) and physical
  - Labs: Pregnancy test, CBC (in setting of heavy menstrual bleeding), STI testing
  - Ultrasound: Adnexal mass and fluid in the pelvis suggest a ruptured ovarian cyst but is not diagnostic
- Treatment is observational vs. surgical (if hemodynamically unstable or large cyst)

Gynecomastia (Fig. 3.4)

- Occurs in 50% of boys between 10 and 16 years
- The area may be tender and asymmetric
- Most gynecomastia resolves spontaneously
- Benign pubertal gynecomastia is usually < 4 cm and does not need any specific workup or therapy
- Large breast similar to female breast SMR II–III or more is unlikely to resolve spontaneously and may require surgery

Rare causes of gynecomastia

- Klinefelter syndrome
- Tumor of testicular, adrenal, or pituitary glands
- Anabolic steroids
- Frequent marijuana use

Scrotal Masses

- Neoplasm usually presents as a painless mass that may be discovered accidentally by self-examination
- May present with pain if hemorrhage or necrosis occurs
- Back pain if retroperitoneal lymph node is present
- 95% of testicular tumors are germ cell in origin, e.g., seminoma, embryonal carcinoma, teratoma, and choriocarcinoma. Other 5% are of stromal tissue origin
- Human chorionic gonadotropin (HCG) is elevated in choriocarcinoma
- α-Fetoprotein is elevated in a yolk sac tumor and embryonal carcinoma
- Most seminomas do not produce any markers
- Investigation includes testicular ultrasonography and CT scan of the chest and abdomen
- Treatment includes orchiectomy, peritoneal lymph node dissection, radiation therapy, and chemotherapy, depending on staging

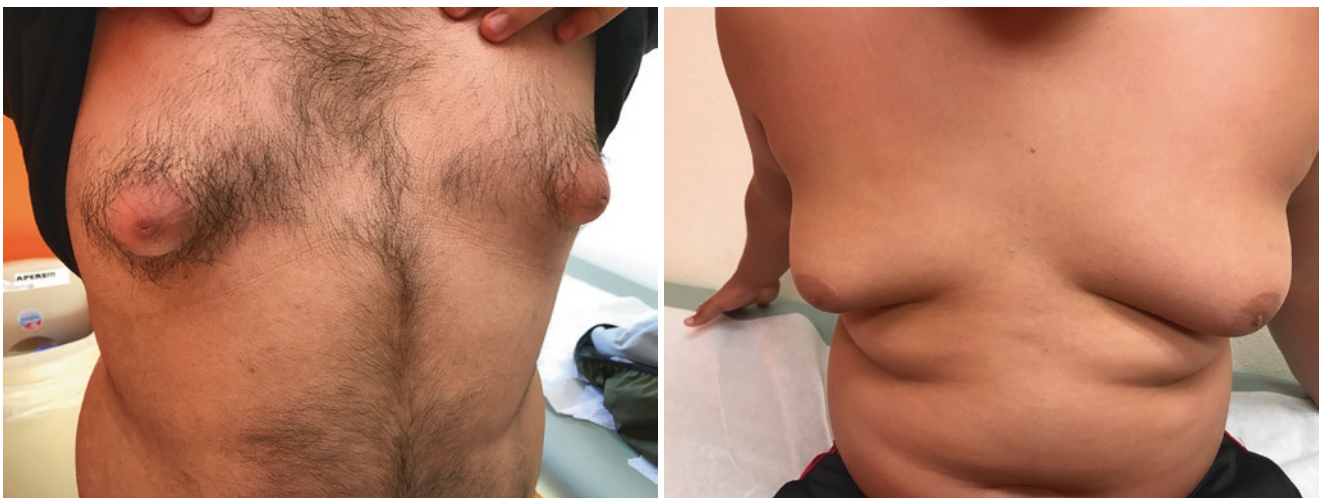


Fig. 3.4 Male adolescents with different degrees of gynecomastia

Contraception

Background

- Providing adolescents with accurate information about contraception is important. The choice of contraceptive method is a complex decision and healthcare providers should create a supportive, nonjudgmental, and confidential environment
- The discussion should be patient-centered when providing contraceptive counseling
- Topics such as: goals of using contraception, safety in relationship (e.g, intimate partner violence, coercion), and reproductive health (e.g, STI prevention) should be discussed with the adolescents

Contraceptive Methods

- Abstinence
- IUD
- Implants
- Injectable depot medroxyprogesterone acetate
- Contraceptive Patch
- Contraceptive pills (Progestin-only and combined hormonal oral contraceptives)
- Contraceptive vaginal ring
- Female condom
- Male condom
- Diaphragm—prevents pregnancy by acting as a barrier to the passage of semen into the cervix
- Cervical cap—acts as a mechanical barrier to sperm migration into the cervical canal and as a chemical agent with the use of spermicide
- Spermicidal agent

Absolute contraindication for combined hormonal oral contraceptive [11]

- Migraine with aura
- < 21 days postpartum
- Abnormal vaginal bleeding of unknown cause
- Estrogen-dependent tumor
- Liver disease
- Thromboembolic disease
- Cerebral events
- Hypertension (systolic > 160 or diastolic > 100)
- Smoking (> 35 years of age)
- Known or suspected pregnancy

Relative contraindication of oral contraceptive

- Tobacco use
- Diabetes mellitus
- Seizures
- Migraine
- Hypertension

Emergency contraception

- Levonorgestrel (Plan B) is available over the counter or by prescription with no age restriction
- Ulipristal acetate (Ella) is available by prescription with no age restriction
- Most effective if used as soon as possible but also up to 120 h after unprotected intercourse

SEXUALLY TRANSMITTED DISEASE IN ADOLESCENTS

Neisseria gonorrhoeae

Background

- Most men are symptomatic
- Female may present with PID

Clinical presentation in females

- Vaginal discharge
- Dysuria
- Intermenstrual bleeding
- Lower abdominal pain: Most consistent symptom of PID
- Right upper quadrant pain from perihepatitis (Fitz-Hugh–Curtis syndrome)

Clinical presentation in males

- Burning upon urination and a serous discharge; a few days later, the discharge usually becomes more profuse, purulent, and sometimes tinged with blood
- Acute epididymitis

- Rectal infection: May present with pain, pruritus, discharge, or tenesmus

Disseminated gonococcal infection

- Arthritis dermatitis syndrome is the most classic presentation
- Migratory polyarthralgia, especially of the knees, elbows, and more distal joints
- Septic arthritis; the knee is the most common site of purulent gonococcal arthritis
- Skin rash (may involve the palms and soles)
- The dermatitis consists of lesions, varying from maculopapular to pustular lesions, that can be painful
- Fever is common
- Gonococcal endocarditis is rare (more common in men than in women)

Diagnosis

- Nucleic acid amplification tests (NAATs) are highly sensitive and specific diagnostic tests for *Chlamydia trachomatis* and *N. gonorrhoeae* infections and can be used with endocervical, vaginal, urethral, and urine specimens (Table 3.6)

Treatment [12]

- Uncomplicated gonorrhea
  - Ceftriaxone 250 mg intramuscular (IM) as a single dose and azithromycin 1 g orally as a single dose (treatment for *C. trachomatis*)

Table 3.6 Differential diagnosis and treatment of genital ulcers

Syphilis	Chancroid	Lymphogranuloma venereum
Clinical findings		
Treponema pallidum Chancre; painless ulcer palmar rash	*Haemophilus ducreyi* Painful genital ulcers	*Chlamydia trachomatis serovars* Self-limited genital papules or ulcers followed by painful inguinal and/or femoral lymphadenopathy
Mucocutaneous lesions	Tender, suppurative inguinal lymphadenopathy	Commonly seen on coronal sulcus, prepuce, glans, and scrotum
Lymphadenopathy. Cardiac, ophthalmic, auditory abnormalities (gummatous lesions). Late latent syphilis		Posterior vaginal wall, vulva
Diagnostic labs and evaluation		
Dark-field examinations to detect *T. pallidum* A diagnosis requires use of a nontreponemal (VDRL or RPR) and a treponemal test (FTA-ABS] or TP-PA) RPR or VDRL correlate with disease activity. A fourfold change in titer is considered clinically significant	No evidence of *T. pallidum* infection by dark-field examination	Clinical diagnosis based on symptomatology and the exclusion of other etiologies
CSF VDRL if neurosyphilis suspected	Negative syphilis serologic test HSV PCR or HSV culture is negative	
Treatment		
Primary, secondary, early latent: Benzathine penicillin G 2.4 million units × 1 IM **Alternative regimen only if nonpregnant and penicillin allergy:** Doxycycline 100 mg PO BID × 14 days	Azithromycin 1 g PO × 1 *or* Ceftriaxone 250 mg IM × 1 *or* Ciprofloxacin 500 mg PO BID × 3 days *or* Erythromycin base 500 mg PO TID × 7 days	Doxycycline 100 mg PO BID for 21 days
Late latent or latent of unknown duration: Benzathine penicillin G 2.4 million units IM q week for latent syphilis		Erythromycin base 500 mg PO QID for 21 days
Neurosyphilis Aqueous crystalline penicillin G 3–4 million units IV every 4 h × 10–14 days for neurosyphilis		

RPR rapid plasma reagin, *VDRL* venereal disease research laboratory, *FTA-ABS* fluorescent treponemal antibody absorption test, *CSF* cerebrospinal fluid, *PO* by mouth, *HSV* herpes simplex virus, *IM* intramuscular, *BID* twice a day, TID three times a day, QID four times a day

OR
  - Doxycycline 100 mg orally twice daily for 7 days
- Disseminated gonococcal infection
  - Ceftriaxone 1 gm intravenous (IV)/IM q 24 h and azithromycin 1 g orally as a single dose
  - Cefotaxime 1 g IV q 8 h or ceftizoxime 2 g IV every 8 h for 7 days and azithromycin 1 g orally as a single dose

Chlamydia trachomatis

Men
- Urethral discharge
- Asymptomatic infection is common
- Absence of Gram-negative intracellular diplococci in a urethral smear
- Presence of ≥ 5 WBCs/oil field is highly sensitive and specific for urethritis

Females
- Mucopurulent cervicitis
- Often asymptomatic
- May have discharge or bleeding after intercourse

Diagnosis
- Nucleic acid amplification tests (NAATs)

Treatment
- Azithromycin 1 g orally as a single dose *or* doxycycline 100 mg orally twice daily for 7 days (in cases of azithromycin allergy)

Pelvic Inflammatory Disease

Background
- Most commonly due to untreated cervicitis
- PID increases the risk of ectopic pregnancy; infertility is a common complication of chlamydial infection
- Untreated cervicitis can progress to an ascending genital tract infection (salpingo-oophoritis or PID)
- *C. trachomatis* and *N. gonorrhoeae* are the most commonly associated organisms
- The highest rates of chlamydial/gonorrheal infections occur among adolescent females 14–24 years of age [13]
- Most infected individuals are asymptomatic, especially females with chlamydial infections
- Other organisms can cause PID: Anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae, Streptococcus agalactiae*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and enteric Gram-negative rods

Clinical presentation
- Abdominal pain
- Symptoms more intense during menses
- Abdominal tenderness (occasionally with rebound tenderness)
- Adnexal tenderness
- Cervical motion tenderness
- Elevated temperature
- Mucopurulent cervical discharge

Diagnosis
- Definitive diagnosis by endometrial biopsy or laparoscopy

Clinical diagnostic criteria
- At least *one* of the following:
  - Cervical motion tenderness
  - Uterine tenderness
  - Adnexal tenderness

One or more of the following additional criteria in conjunction with at least one minimum clinical criterion can support diagnosis:
- Elevated WBC count
- Fever
- Elevated erythrocyte sedimentation rate or C-reactive protein concentration
- Mucopurulent cervical discharge
- Cervical friability

- Evidence of positive gonococcal or chlamydial infection
- Pelvic ultrasonography may demonstrate:
  - Fluid in the cul-de-sac
  - Thickened fallopian tubes
  - Tubo-ovarian abscess

Treatment [12]

- Outpatient treatment
  - Ceftriaxone 250 mg IM × 1 *plus* Doxycycline 100 mg orally twice daily × 14 days *with or without* Metronidazole 500 mg orally twice daily for 14 days
- Inpatient
  - Cefoxitin 2 g IV every 6 hours *plus* doxycycline 100 mg orally twice daily for 14 days

or

  - IV clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV/IM loading dose (2 mg/kg), followed by a maintenance dose (1.5 mg/kg) every 8 hours

Trichomoniasis

- Trichomoniasis is due to the protozoa *Trichomonas vaginalis* (Table 3.7)
- Most men are asymptomatic
- Most women will present with malodorous yellow-green thin and frothy discharge with vulvovaginal itching, burning, or soreness
- Strawberry cervix describes a diffuse or patchy macular erythematous lesion of the cervix
- Flagellated pyriform protozoa or trichomonads on saline wet mount is diagnostic
- Treatment should be instituted immediately and, whenever possible, in conjunction with all sexual partners
- Metronidazole and tinidazole are US Food and Drug Administration (FDA) approved
- Pregnant women with symptoms can be treated with metronidazole as well

Human Papillomavirus (HPV)

- HPV type 6 or 11 usually causes visible wart
- Besides the genital area, HPV type 6 or 11 can produce warts in conjunctival, nasal, oral, and laryngeal areas
- HPV 16, 18, 31, 33, and 35 are associated with cervical neoplasia, also neoplasm of penis, anus, and vulva
- Treatment of external genital warts
  - Podofilox 0.5% solution or gel
  - Imiquimod 5% cream
  - Cryotherapy
  - Surgical removal
- Note: C-section is not an indication because of genital warts; however, C-section may be indicated if the genital wart obstructs the pelvic outlet

Table 3.7 Differential diagnosis of infections with vaginal discharge

Bacterial vaginosis	Trichomoniasis	Vulvovaginal candidiasis
Gardnerella vaginalis	*Trichomonas vaginalis*	*Candida albicans*
Homogenous, white, fishy odor, noninflammatory discharge that smoothly covered the vaginal wall	Malodorous yellow-green thin and frothy discharge	Thin and watery, or thick and white (like cottage cheese) discharge
Vulvar irritation is less common	Vulvar itching, vulvar soreness and irritation	Vulvar itching, vulvar soreness and irritation
pH of vaginal fluid >4.5	pH of vaginal fluid >4.5	pH of vaginal fluid <4.5
Clue cells	Flagellated pyriform protozoa	Fungal cells
Metronidazole	Metronidazole	Antifungal topical cream *or* fluconazole 150 mg oral tablet ×1

Human Immunodeficiency Virus (HIV)

Indication of HIV testing

- Routine screening once between 15 and 18 years of age for all adolescents (https://www.aap.org/en-us/Documents/periodicity_schedule.pdf)
- All who seek evaluation and treatment for STDs
- Adolescents with high-risk behaviors
- Unexplained enlargement of the parotid glands
- Adolescent with oral thrush
- Adolescent with acute retroviral syndrome; fever, malaise, lymphadenopathy, and skin rash

HIV testing

- HIV-1 and HIV-2 antigen/antibody immunoassay
- If there is suspicion for early infection in setting of an initial negative antigen/antibody immunoassay test, an HIV-1 nucleic acid test should be performed

Herpes Simplex

- Genital herpes is HSV-2
- Painful itchy lesions with multiple vesicles
- Diagnosis: Isolation of HSV in cell culture is preferred, serology testing for herpes immunoglobulin G (IgG)
- Treatment: Acyclovir, famciclovir, valacyclovir

Pediculosis

- Lice can be sexually transmitted and must be included in the differential for an adolescent presenting with persistent pruritus or nits
- Pediculosis usually presents with itching
- *Phthirus pubis* (crab louse)
- Existing lice and nits can be seen in pubic hair, on the body and on scalp
- Treatment is permethrin 1% topical liquid

Scabies

- Caused by *Sarcoptes scabiei*
- Presents with intense itching
- Burrows in the webs of the fingers and toes
- Treatment is permethrin 5% cream
- Ivermectin 200 μ/kg orally, repeat in 2 weeks

Vaccines Prevent STDs

- Hepatitis A
  - Single IM dose of immunoglobulin after exposure with a person with hepatitis A infection (sexual contact or sharing IV drugs) if unvaccinated
  - Hepatitis A vaccine is recommended after exposure
- Hepatitis B
  - Give hepatitis B immunoglobulin and hepatitis B vaccine after exposure (sexual contact or sharing IV drugs) with a person with hepatitis B if unvaccinated
  - Hepatitis B vaccination is recommended
- HPV
  - 9-valent human papillomavirus virus vaccine (Gardasil-9) protects against HPV type 6, 11, 16, 18, 31, 33, 45, 52, and 58
  - Given in 3-dose series—0, 2, 6 months for ages 15–26 years
  - Given in 2-dose series—0 and 6–12 months after initial shot for ages 9–14 years

PEARLS AND PITFALLS

- Always consider pregnancy in the differential for an adolescent female with irregular or missed periods.

- When interviewing adolescents, perform a history, physical exam, and psychosocial screening in a confidential manner.
- The American College of Obstetrics and Gynecology recommends that cervical cytology not be obtained until the age of 21, regardless of age of sexual debut, number of lifetime partners, or history of sexually transmitted infection. Exceptions to this rule are HIV-positive adolescents who should receive a cervical cytology test at the time of initial diagnosis of HIV [14].
- The majority of adolescent deaths are due to unintentional injuries (motor vehicle accidents), suicide, and homicide, which are often associated with substance abuse.
- Eating disorders are commonly thought to occur only in women. However, approximately one in three people struggling with an eating disorder is male.
- Routine screening for STIs is important because the majority of gonorrhea and chlamydia infections are asymptomatic.

Acknowledgments The author gratefully acknowledges the contribution of Marwa Abdou, MD, Department of Pediatrics, Texas Tech University Health Center, El Paso, Texas, USA, to the 1st edition of this chapter, many of which have been incorporated into this edition as well.

References

1. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45(239):13–23.
2. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291–303.
3. Sherer S, Radzik M. Psychosocial development in normal adolescents and young adults. In: Rickert V, Joffe A, Gordon C, Callhan T, Katzman D, Neinstein L, editors. Neinstein's adolescent and young adult health care: a practical guide. 6th ed. Philadelphia: Wolters Kluwer; 2016. p. 38–41.
4. Boonstra H, Nash E. Special analysis. Minors and the right to consent to health care. Guttmacher Rep Public Policy. 2000;3(4):4–8. https://www.guttmacher.org/sites/default/files/pdfs/pubs/tgr/03/4/gr030404.pdf. Accessed 17 Nov 2018.
5. Grossman DC, Curry SJ, Owens DK, et al. Screening for adolescent idiopathic scoliosis. JAMA. 2018;319(2):165. https://doi.org/10.1001/jama.2017.19342.
6. Stager M. Substance abuse. In: Kliegman RM, Behrman RE, Schor NF, Stanton BF, Geme JW, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011. p. 671–85.
7. Campbell K, Peebles R. Eating disorders in children and adolescents: state of the art review. Pediatrics. 2014;134(3):582–92.
8. Fallat ME, Ignacio RC. Breast disorders in children and adolescents. J Pediatr Adolesc Gynecol. 2008;21(6):311–6.
9. Klein DA, Poth MA. Amenorrhea: an approach to diagnosis and management. Am Fam Physician. 2013;87(11):781–8.
10. Emans SJ, Laufer MR. Emans, Laufer, Goldstein's pediatric and adolescent gynecology. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2012.
11. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep. 2016;65(3):1–103. https://www.cdc.gov/mmwr/volumes/65/rr/rr6503a1.htm. Accessed 17 Nov 2018
12. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(RR-3):1–137. https://www.cdc.gov/

std/tg2015/tg-2015-print.pdf. Accessed 17 Nov 2018.
13. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2016. Atlanta: U.S. Department of Health and Human Services; 2017. https://www.cdc.gov/std/stats16/CDC_2016_STDS_Report-for508WebSep21_2017_1644.pdf. Accessed 17 Nov 2018
14. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012;62(3):147–72.

Suggested Reading

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.

Rosen D, The Committee on Adolescence. Clinical report-identification and management of eating disorders in children and adolescents. Pediatrics. 2010;126:1240.

Work Group on Eating Disorders. Practice guideline for the treatment of patients with eating disorders. 3rd ed. Arlington: American Psychiatric Association; 2006.

Workowski KA, Bolan G. CDC sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(3):1–140.

Genetic Disorders

4

Golder N. Wilson, Osama I. Naga, and Vijay S. Tonk

GENETICS AND DYSMORPHOLOGY: BASIC FACTS

Medical genetics

- The human genome contains 6 billion A, G, C, and T nucleotides in each diploid cell, packaged into 22 paired autosomes and 2 (XX or XY) sex chromosomes, totaling 46 chromosomes
- Humans have ~23,000 genes, stretches of DNA on chromosomes that encode RNA and protein (1.5% of our genome)

Dysmorphology (*dys* = abnormal or painful)

- The study of birth defects (altered structure or morphology) produced by abnormal embryogenesis

Teratology (*terata* = monstrosities)

- Refers more specifically to anomalies produced by physico-chemical agents during pregnancy

Major anomalies

- Produced during organogenesis and involve single organs or regions (e.g., cleft palate, congenital heart defects, hypospadias)
- Major anomaly combinations can represent a syndrome, association, or sequence
  - Syndromes: Distinctive patterns of major and minor anomalies
  - Associations: Mostly major anomalies conjoined more frequently than expected by chance
  - Sequences: Several anomalies arising from a single embryogenetic defect
- Syndromes usually follow chromosomal or Mendelian inheritance; single defects, multifactorial determination

Minor anomalies

- Distinguished from major anomalies by lack of cosmetic or functional significance; produced during phenogenesis (e.g., hypertelorism/widespaced eyes, single palmar crease)
- Minor anomalies distinguish syndromes from single birth defects (isolated congenital anomalies)

Chromosomal Inheritance

Background

- Normal chromosomal inheritance involves the segregation of 22 plus X or Y chromosomes into gametes and their reunion in the fertilized egg as 46,XX or 46,XY zygotes

The original version of this chapter was revised. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-21267-4_34

G. N. Wilson (✉)
Department of Pediatrics, Texas Tech University Health Sciences Center and KinderGenome Medical Genetics, Dallas, TX, USA
e-mail: golder.wilson@ttuhsc.edu

O. I. Naga
Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, USA

V. S. Tonk
Department of Pediatrics, Texas Tech University Health Sciences Center, Lubbock, TX, USA

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_4

- Abnormal chromosomal inheritance produces extra (duplicated), missing (deleted), or rearranged (translocation) chromosomes in gametes through abnormal meiotic division:
  - Extra or missing (unbalanced) chromosome material: Birth defects and intellectual disability (ID)
  - Balanced rearrangements (e.g., translocations): Normal appearance with abnormal gametes/offspring

Partial aneuploidies, microduplications, and microdeletions [1]

- Partial aneuploidy: Partial duplication or deletion of chromosome regions
- Extra or missing material can involve the short (p) or long (q) chromosome arms
- Fluorescent *in situ* hybridization (FISH) and microarray analysis define submicroscopic (microdeletions) of 4p (Wolf-Hirschhorn) or 7p (Williams) syndromes
- Microduplications of 11p (Beckwith-Wiedemann) or 7p (Williams) also cause syndromes

Translocations

- Translocations involve rearranged chromosomes due to breakage and recombination
- Robertsonian translocations (end-to-end joining of short-armed chromosomes 13–15, 21–22) produce Patau or Down syndromes by transmitting attached 13 or 21 chromosome regions
- Reciprocal translocations (produced by exchange of chromosome material) can undergo unbalanced segregation, the extra/missing material causing miscarriage or birth defects in offspring

Ostensibly normal individuals

- A risk for non-disjunction in oocytes that increases with age
- Ostensibly normal individuals may have unrecognized chromosome mosaicism that passes abnormal chromosomes to offspring (e.g., 46XX/45,X mosaicism producing 45,X Turner syndrome)

Autosomal Dominant (AD) Inheritance

Background

- Every gene on the paired chromosomes 1–22 (autosomes) has two copies or alleles, each parent contributing one gene copy
- AD inheritance occurs when one gene copy (allele) has a variant DNA sequence (mutation) that produces disease
- Dominantly inherited diseases have a 50% chance that the abnormal allele will be passed to each offspring
- Affected individuals have a 50% risk that their disorder will recur in each offspring (50%) recurrence risk

Usual characteristics of genetic transmission for AD diseases (Fig. 4.1)

- Both sexes are equally affected
- Both sexes can transmit to offspring
- No generation is skipped, producing a vertical pattern of affected individuals in pedigrees
- Every affected child has a parent with the disorder

Exceptions to autosomal dominant inheritance

- Variable or sex-limited expression, incomplete penetrance:
  - Variable expression (affected individuals have variable symptoms and severity)
  - Incomplete penetrance (individuals with the abnormal allele have no symptoms)

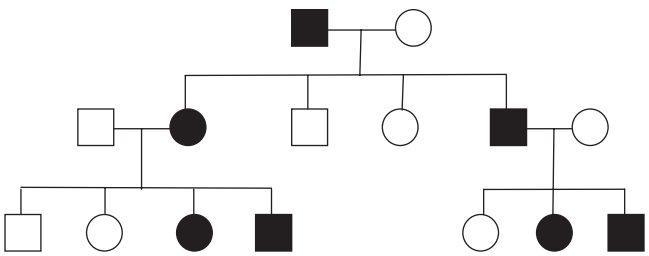


Fig. 4.1 Autosomal dominant pedigree. Note the square symbols for males, circles for females, connecting lines between spouses and offspring, filled symbols for affected individuals

- New (*de novo*) mutations
  - Affected offspring to unaffected parents suggests a new mutation or germ-line mosaicism (*below*)
- Germ-line mosaicism
  - Unaffected parents can have mutations in germ-line cells (oogonia or spermatogonia)
  - Usual recurrence risks for unaffected parents with germ-line mosaicism are 5–10% for each offspring
  - Affected children of these parents will have the usual 50% recurrence risk for each offspring
  - Germ-line mosaicism is more frequent in certain AD disorders like osteogenesis imperfecta
- Somatic mutations
  - Occur in a somatic cell and affect only that cell and its progeny
  - Examples include segmental neurofibromatosis, skin, and other cancers

Examples of AD diseases

- Osteogenesis imperfecta
- Neurofibromatosis
- AD polycystic kidney disease
- Achondroplasia

Autosomal Recessive (AR) Inheritance

Background

- AR inheritance occurs when an abnormal gene copy (allele) on an autosome recedes or hides behind its normal partner, producing disease only when both alleles are abnormal
- Parents of children with AR disorders will typically have one normal and one abnormal gene copy, their single abnormal allele making them a "carrier" of disease rather than being affected by it
- Offspring will receive one or the other gene copy such that they have:
  - A 25% chance to have two normal copies (normal individual)
  - A 50% chance to have one normal and one abnormal copy (carrier individual)
  - A 25% chance to have two abnormal alleles (affected individual)

Usual characteristics of genetic transmission in AR cases (Fig. 4.2)

- Males and females are equally affected
- Males and females can each transmit copies of the mutated gene
- Males and females affected with AR diseases have mutations in both gene copies
- Males and females who have one copy of the mutant autosomal gene are called carriers
- Parents who have a previous affected child must be carriers
- Parents who are both carriers have a risk of one-fourth or 25% for each offspring to be affected
- All offspring of affected individuals will be carriers
- Affected individuals can have affected offspring only if their spouse is also a carrier
- The chance for a spouse to have the same AR disease is equal to twice the square root of disease prevalence (per the Hardy-Weinberg law)
- The chance for a spouse to be a carrier increases greatly if the couple has common ancestry
- Relatedness or consanguinity increases the risk of having offspring with AR disorders

Exceptions to AR inheritance

- Uniparental disomy
  - Rare cases of AR disease can occur when a carrier parent transmits both autosomes containing the abnormal gene copy to a child
  - The recurrence risk will then be negligible for future affected children rather than 25%

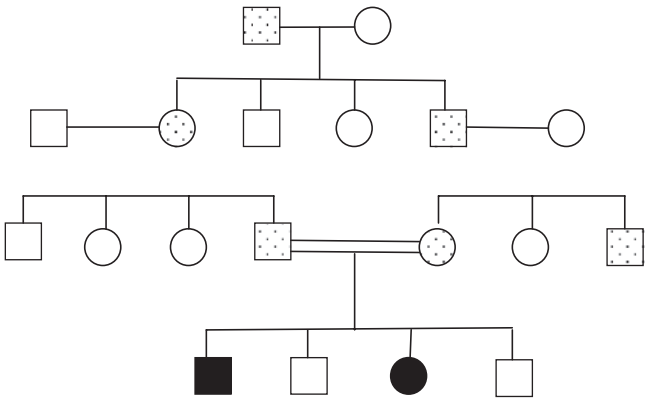


Fig. 4.2 Autosomal recessive pedigree with parental consanguinity. *Dots within symbols* for carriers, *filled symbols* for affected individuals

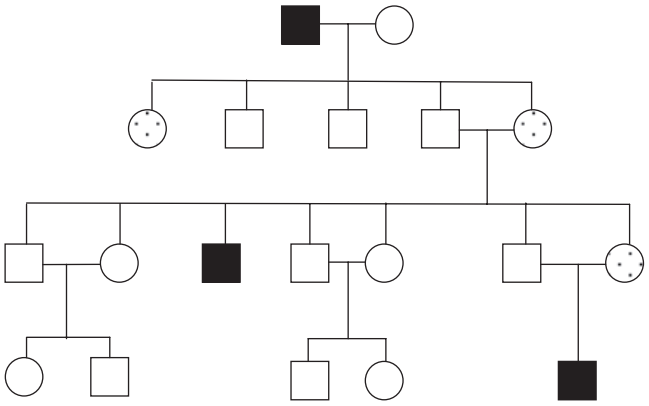


Fig. 4.3 X-linked recessive pedigree. *Dots within symbols for* carriers, *filled symbols* for affected individuals

- New mutation
  - A new mutation altering the normal gene copy in an offspring receiving an abnormal allele from a carrier parent may cause AR disease
  - The recurrence risk will then be negligible for future affected children, rather than 25%

Examples of AR diseases

- Cystic fibrosis
- Spinal muscular atrophies
- AR polycystic kidney disease
- Diastrophic dwarfism

X-Linked Inheritance

Background

- Genes on the X chromosome are paired in XX females but mostly single (hemizygous) in XY males
- X-linked recessive inheritance occurs when the single X chromosome gene copy of a male is abnormal, most often when the mother is a carrier with one normal and one abnormal X chromosome allele
- Males with X-linked recessive disorders can also occur through new mutation, comprising one-third of the first affected males in families according to Haldane's law
- X-linked dominant inheritance occurs when the abnormal X chromosome gene copy in females dominates over its partner allele to cause disease
- X-linked dominant disorders are often lethal in affected males because their only X chromosome allele is abnormal
- X-linked dominant disorders can have odd ratios of affected children due to miscarriage of affected males

Usual characteristics of genetic transmission in X-linked recessive cases (Fig. 4.3)

- Males are more commonly and more severely affected than females
- Female carriers are generally unaffected or affected more mildly than males
- Female carriers have equal chances to transmit their normal or altered X chromosome, giving:
  - 25% risk for an affected son
  - 25% risk for a carrier daughter
  - 25% chance for an unaffected son
  - 25% chance for a non-carrier daughter
- Affected males have:
  - 100% chance each daughter will be a carrier
  - 0% chance their sons will be affected because their Y chromosome must be transmitted to sons
- Male-to-male transmission therefore excludes X-linkage

- X-linked dominant diseases manifest in both sexes, with males being more severely affected

Examples of X-linked recessive diseases
- Hemophilia A
- Duchenne and Becker muscular dystrophy
- Hunter syndrome
- Fabry disease

Examples of X-linked dominant diseases
- X-linked hypophosphatemia
- Incontinentia pigmenti
- Rett syndrome
- Most cases of Alport syndrome

Multifactorial Determination

Background
- Multifactorial determination (not inheritance because environmental factors are involved) applies to common diseases like diabetes, coronary artery disease, asthma, and most isolated birth defects like cleft palate
- Predisposition includes gene combinations (polygenic inheritance) and pre-/postnatal environmental factors
- Risks for multifactorial diseases are empirical and approximate because all factors are never defined
- Multifactorial determination often exhibits sex predilection due to hormonal or other factors

Multifactorial determination characteristics
- ***Example 1:*** Hip dysplasia is nine times more common in females than in males
  - Unlike the fixed ratios of Mendelian inheritance, recurrence risks for multifactorial disorders increase with
    - The number of affected family members
    - Affliction of the atypical sex
    - Severity of the condition
  - General recurrence risks for parents with a first child affected are on the order of 3–5%
  - Diagnosis of additional family members indicates that additional genetic factors are present with increased risk
- ***Example 2:*** Risk for parents with type I diabetes to have an affected child:
  - About 6% if only the father is affected (atypical sex)
  - About 4% if only the mother is affected (more commonly affected sex)
  - About 10–25% if both parents have type I diabetes (two affected primary relatives)
- ***Example 3:*** Risk for an average couple to have a child with cleft palate:
  - About 1 in 600 before having children
  - About 2–5% if their first child has cleft palate (one relative with disease)
  - About 10–12% if two children or a first child and other relatives have clefts (more relatives affected)
  - Even higher if affected relatives have large bilateral clefts (more severe disease)
- ***Example 4:*** Risks for parents with a neural tube defect (spina bifida, anencephaly) to have an affected child:
  - About 0.1% if neither parent is affected (the general population prevalence depending on ethnicity)
  - About 2% if mother is affected (typically affected sex)
  - About 5% if father is affected (atypical sex)
  - Increased with low folic acid levels during pregnancy, the reason for routine folate supplementation
- ***Example 5:*** Risks for parents to have a child with autism:
  - About 1% (the general population prevalence)
  - About 5% for the next child if a son has autism (typically affected sex)
  - About 10% for the next child if a daughter has autism (atypical sex)
  - Increase with autism severity (e.g., autism with ID versus high-functioning autism spectrum disorder)

Mitochondrial Inheritance

Background

- Mitochondria
  - Have the only genetic material outside of the nucleus
  - Are transmitted to zygotes only from eggs (Fig. 4.4) and not sperm (maternal inheritance)
  - Convert oxygen to biochemical energy (ATP) through four respiratory chain complexes
- Mitochondrial diseases
  - Impact energy-dependent tissues: Brain, sensory/peripheral nerves, muscle, heart, bowel
  - Are rarely transmitted by fathers since sperm have few mitochondria

Examples of mitochondrial disease

- Leigh disease
- Kearns-Sayre syndrome
- LHON (Leber hereditary optic neuropathy)
- MELAS (mitochondrial encephalopathy with stroke-like episodes and lactic acidosis)
- MERRF (myoclonic epilepsy and red ragged fibers disease)

Genetic anticipation

- Genetic anticipation occurs when a disorder becomes more severe in subsequent generations
- Examples include disorders caused by expanded triplet repeats such as fragile X syndrome, Huntington chorea, and myotonic dystrophy

Genomic Imprinting

Imprinting characteristics

- Gene expression and clinical symptoms depend on whether the affected gene is transmitted from the mother or the father
- Uniparental disomy occurs if segments or entire copies of a chromosome come from one parent rather than usual biparental contribution
- Uniparental heterodisomy refers to inheritance of both chromosome copies from one parent, while uniparental isodisomy refers to inheritance of two copies of one parental chromosome

Examples of genomic imprinting

- Prader-Willi syndrome and Angelman syndrome
- Diagnosis of all cases can be achieved by analysis of 15q11 DNA to define biparental (normal result), maternal (Prader-Willi syndrome), or paternal (Angelman) methylation patterns

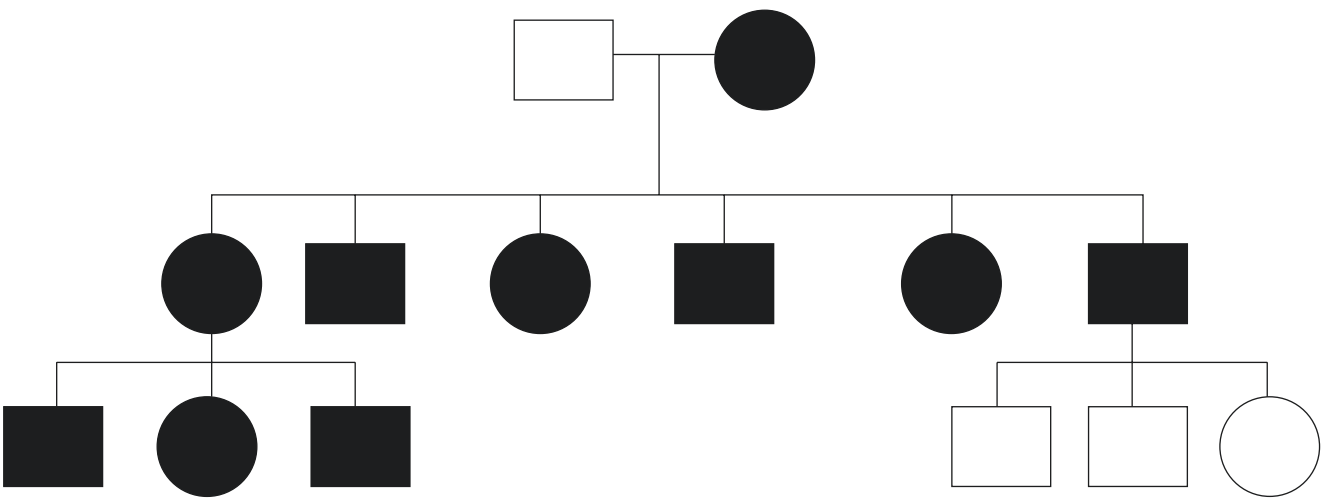


Fig. 4.4 Pedigree of a mitochondrial disorder showing maternal inheritance

GENETIC TESTING [1]

Phenotypic Testing

- A variety of anatomic and tissue traits were observed including the Kayser-Fleischer rings in Wilson disease, the ragged red muscle fibers in certain mitochondrial disorders, and the excess liver glycogen in glycogen storage diseases
- Specific measurements and physical findings helped with genetic diagnosis, including:
  - Disproportionate short stature in achondroplasia
  - Extended wing span and long fingers in Marfan syndrome

Metabolic Testing

- As biochemical pathways were defined, chemical reactions were developed to measure abnormal levels of metabolites—e.g., the red/purple color of urine in those with porphyrins
- Chromatographic and then mass spectrometric methods for defining excess metabolites were developed, focusing subsequent enzyme and DNA analysis (see also Chap. 5 Metabolic Disorders)

Chromosome Analysis or Karyotyping

- The chromosomes are examined for extra or missing regions (bands) and aberrations reported using specific nomenclature—chromosome number, sex chromosomes, p for short arm, q for long arm, and numbers for altered bands proceeding from the chromosome center (centromere)
- Entire extra chromosomes are reported as 47,XX,+13 for a female with trisomy 13/Patau syndrome, 47,XY,+21 for a male with trisomy 21/Down syndrome, and 47,XXY for a male with Klinefelter syndrome
- Monosomies are similarly reported as 45,X for usual Turner syndrome but are lethal unless mosaicism (mixture of cells with normal and aberrant chromosomes) is present
- Mosaicism is reported using a slash, e.g., 46,XX/45,XX-21 for monosomy 21 mosaicism
- Translocations can involve reciprocal exchange through breakage and exchange of two chromosome regions (e.g., 46,XX,t[9q;22q])] or joining of short-armed acrocentric chromosomes (e.g., 45,XY,t[14:21])

Molecular Cytogenetics: Fluorescent *In Situ* Hybridization (FISH)

- Specific FISH tests involve use of differently colored test and control probes to highlight particular loci in chromosome spreads
- For example, a test red probe for the 22q11 region that gave a signal only on one of the two chromosomes 22 in metaphase spreads would be diagnostic of the DiGeorge/velocardiofacial/22q11 deletion, provided the control green probe directed to the unaffected 22 terminus gave signals on both chromosomes 22 in all spreads

DNA Testing: Microarray Analysis (aCGH or CMA)

- Examines every region of every chromosome and reports extra or missing DNA pieces using coordinates established by the human genome project
- Microarray analysis can find any chromosome dosage alteration, from trisomies like 47,XX,+13 to small deletions like that of 22q11, but not balanced translocations that involve rearrangement without duplication or deletion of DNA

DNA Testing: DNA Sequencing

- *Single gene sequencing*: Delineates the nucleotide sequence of genes and defines alterations (mutations) that cause disease. Example:
  - Diagnosis of sickle trait (one mutated beta-globin gene copy), normal, or sickle cell individuals at the DNA level enabled prenatal testing using fetal tissues
- *Gene panel sequencing*: Sequencing of multiple genes associated with a type of disease Example:
  - Sequencing of > 40 genes known to cause epilepsy or > 20 known to cause cardiomyopathy
- *Genome sequencing (genomics)*: Sequencing of all human genes or DNA. Example:
  - Whole exome sequencing (WES) looks at protein-coding regions (exons of genes), focusing on DNA variants that cause rather than associate with disease (e.g., mutations causing sickle cell or CF)
  - Together, microarray and genomic sequencing constitute a new approach called genomics, where the genetic focus on one gene is expanded to the entire genome

Clinical Applications of Genetic Testing (Table 4.1)

Postnatal genetic testing based on symptoms

- *Traditional medical testing is guided by clinical symptoms and the resulting differential diagnosis*
- *Indications for chromosome testing, now using microarray analysis as a first line test, include:*
  - Symptoms like ID or autism
  - Dysmorphology and/or multiple clinical anomalies, particularly with growth delays
  - History of recurrent pregnancy loss
  - Risk for a chromosome disorder based on family history
  - Availability of tissue from postmortem or biopsy that supports DNA analysis only
- Indications for a regular karyotype in addition to microarray analysis are:
  - Normal individual with recurrent pregnancy loss, recognizing the possibility of a balanced translocation/rearrangement
  - Patients with extra chromosome material that could derive from trisomy or translocation, such as 46,XX,t(14;21) translocation versus 47,XX,+21 Down syndrome—microarray will only detect the extra 21 material, not whether it is present as translocation or free-standing chromosome 21
  - Individuals with multiple CNVs (copy number variations) or indeterminate results by microarray that suggest complex chromosome rearrangements or mosaicism
- Indications for DNA testing based on symptoms:
  - Suspicion of a Mendelian disorder based on symptoms or family history (including suspected inborn errors of metabolism where DNA testing can replace enzyme or metabolite analysis)
  - Presence of a diagnostic category (e.g., epilepsy) that has gene panel testing
  - Physician or patient preference for genome sequencing to detect symptom-related and other detrimental mutations

Presymptomatic genetic testing

- Test for genetic diseases and predispositions before symptoms
- Complex consent is required
- May affect potential employment or cause insurance discrimination
- Example:
  - Presymptomatic diagnosis of Huntington chorea in a young person with its prediction of middle-age dementia may cause depression and suicidal ideation

Table 4.1 Summary of genetic testing strategies

Strategy	Sample	Genetic test
Newborn—abnormal metabolic screen		
Follow-up screen	Blood spot	Confirm altered metabolite
Definitive diagnosis	Blood/cheek swab	Enzyme/DNA to confirm inborn error
Future screen	Cheek swab	WES for all Mendelian diseases
Newborn—specific chromosome disorder suspected		
Rapid screen	Blood	Rapid FISH for trisomies 13, 18, 21, monosomy X
Definitive Dx	Blood	Routine karyotype and microarray analysis
Newborn with heart defect like tetralogy of Fallot		
Rapid screen	Blood	FISH for deletion 22[a]
Definitive Dx	Blood	Routine karyotype and microarray analysis
Child with delays, autistic behaviors		
PE—normal male	Blood	Microarray, fragile X DNA analysis
PE—normal female	Blood	Microarray analysis
PE—specific syndrome	Blood/cheek swab	Targeted DNA test or panel (e.g., for Noonan syndrome)
PE—birth defects, dysmorphology	Blood/cheek swab	Routine karyotype and microarray analysis[b]
Pregnancy, child with family history, age, or other risks for genetic disorder (e.g., abnormal fetal ultrasound)		
Parent carrier testing	Blood	Routine karyotype if child has translocation Targeted DNA test for known disorder (e.g., CF)
Presymptomatic Dx	Blood	Targeted DNA test for at-risk disorder (e.g., fragile X)
Prenatal Dx: PGD	Embryonic cells	Targeted DNA test on embryos obtained by IVF
Prenatal Dx: NIPT	Fetal cells in maternal blood	DNA dosage screens for common trisomies[c]
Prenatal Dx: CVS/amniocentesis	Chorion/amnion cells	Routine karyotype, FISH for deletion 22, targeted DNA test
Individuals or pregnancies with no genetic risks		
Genomic screening	Blood, embryonic, fetal samples	Combined whole exome sequencing and microarray analysis to detection any genetic disease[c]

CF cystic fibrosis, *CVS* chorionic villus sampling, *Dx* diagnosis, *FISH* fluorescence *in situ* hybridization, *IVF* in vitro fertilization, *NIPT* noninterventional prenatal testing, *PE* physical exam, *PGD* preimplantation genetic diagnosis, *WES* whole exome sequencing

[a]Some recommend microarray analysis for any child with a heart defect

[b]Increasing use of whole exome sequencing as first-line test since improved technology defines DNA dosage as well as sequence change

[c]Future detection of all chromosome or Mendelian disorders is feasible but not yet practical

Genetic screening

- Universal newborn metabolic screening has improved clinical outcomes
- Screening particular ethnic groups, e.g.:
  - Cystic fibrosis (CF) in Caucasians
  - Sickle cell anemia in African-Americans
  - Several disorders like Tay-Sachs among people of eastern European (Ashkenazi) Jewish descent

Preconception screening

- Preconception counseling
  - Crucial for pregnancy risks and maternal-child health
  - Ability to screen over 200 disorders is now available
  - Example
    - Women over 35 with increased risks for chromosome disorders

Preimplantation genetic diagnosis (PGD)

- Used for in vitro fertilization (IVF) for those with infertility
- Single cells are removed from the resulting embryos to determine presence of normal or abnormal chromosomes or genes
- Detection of single embryonic cells with mutant alleles before implantation

Noninvasive pregnancy testing (NIPT)

- Uses fetal cells that enter the maternal bloodstream early in pregnancy
- DNA from these cells can be distinguished from maternal DNA when there are chromosome aberrations such as the extra chromosome 21 in Down syndrome
- Detection of fetal Down syndrome and other trisomies can be achieved in maternal blood samples as early as 10 weeks of pregnancy
- NIPT currently has significant error rates, so abnormal results should be confirmed by standard prenatal diagnosis [2]

Prenatal diagnosis based on maternal blood screening

- Combination of fetal ultrasonography, maternal blood and serum testing, and invasive sampling of fetal cells for genetic testing
- Measures the levels of fetal proteins like alpha-fetoprotein in maternal serum (MSAFP) and/or amniotic fluid (amniotic AFP)
- **Clinical significance**
  - Elevated levels of MSAFP indicate leakage of fetal fluid into the amniotic cavity through birth defects like anencephaly/spina bifida, gastroschisis/ruptured omphalocele, or urologic disorders causing fetal proteinuria
  - Low levels of MSAFP indicate lower fetal weight and growth delay, common in chromosome disorders like trisomy 13/18 and somewhat in trisomy 21

Traditional Prenatal Diagnosis

Amniocentesis

- Needle aspiration of amniotic fluid at 12–16 weeks of pregnancy
- Less than 0.1% risk for miscarriage when performed with ultrasound guidance to avoid fetal tissue damage
- Amniotic fluid can be used to measure levels of fetal proteins like AFP or maternofetal hormones as in the triple test on maternal serum

Chorionic villus sampling (CVS)

- Earlier diagnosis in pregnancy
- Using catheters to aspirate cells from the fetal portion of the early placenta (chorion) at 10–12 weeks of pregnancy
- CVS has higher risks for miscarriage (1–2%) than amniocentesis
- Traditional prenatal diagnosis by CVS or mid-trimester amniocentesis can be performed

only with specific diagnosis in mind, e.g., a prior child with phenylketonuria or Down syndrome rather than nonspecific ID

Indications for prenatal diagnosis are:

- Prior child with chromosome aberration
- Maternal age over 35, the risk of common trisomies like Down syndrome reaching about 1% compared to less than 1 in 1000 before age 30
- Parent with translocation that confers significant risks for fetal trisomy
- Recurrent pregnancy loss with no obvious cause or parental genetic disorder may justify low-risk amniocentesis in a premium pregnancy

EXAMPLES OF CHROMOSOME DISORDERS: AUTOSOMAL ANEUPLOIDIES

Examples of syndromes and associations are presented with sections comprising Background (describing prevalence, diagnostic tests, inheritance), Abnormalities (major and minor if warranted), and Health Supervision/Preventive Care (for more common disorders). Data for these entries are taken from textbooks [3, 4], specific references as listed, and information available to all at specific sites [5] or the general Internet.

Down Syndrome (Fig. 4.5)

Background

- Prevalence of 1 in 660 newborns with trisomy 21 nondisjunction (comprising 94% of cases)
- Similar prevalence in males, females, and in different ethnic groups relative to maternal age
- Microarray analysis or routine karyotype will show extra material from chromosome 21
- If trisomy 21 is found by microarray analysis, a routine karyotype must be performed to distinguish trisomy (e.g., 47,XY,+21) from translocation (e.g., 46,XY,t[14:21])
- Finding a translocation mandates testing of the parents to decide if it was inherited or arose *de novo*
- Robertsonian translocations that join two short-armed or acrocentric chromosomes (chromosomes 13–15, 21–22) to form one chromosome occurs in 3.3% of cases
- Mosaicism, e.g., 46,XX/47,XX,+21, also requires a karyotype and occurs in 2.4% of cases
- Risks for a first affect child with trisomy 21 are 1 in 1500 for mothers aged 15–29, 1 in 800 for ages 30–34, 1 in 270 for ages 35–39, 1 in 100 for ages 40–44, and 1 in 50 for over 45
- Parental recurrence risk for trisomy 21 after birth of an affected child is 1% plus the maternal age-related risk
- Risk of recurrence in Robertsonian translocation
  - If the mother is a 14:21 translocation carrier (45,XX,t[14:21]), her recurrence risk is 15% for translocation Down syndrome at mid-pregnancy (by amniocentesis) and 10% at birth
  - If the mother has a 21;21 translocation, her recurrence risk approaches 100%
- Median survival increased from 25 to 49 years, cardiac defects mainly responsible
- Dementia and Alzheimer disease are more common and of earlier onset in adults with Down syndrome

Clinical findings in the newborn

- Flat facial profile
- Hypotonia—poor Moro reflex, parachute sign
- Flat occiput/brachycephaly
- Excess skin, back of the neck
- Upslanting palpebral fissures (see Fig. 4.5)
- Small and anomalous auricles

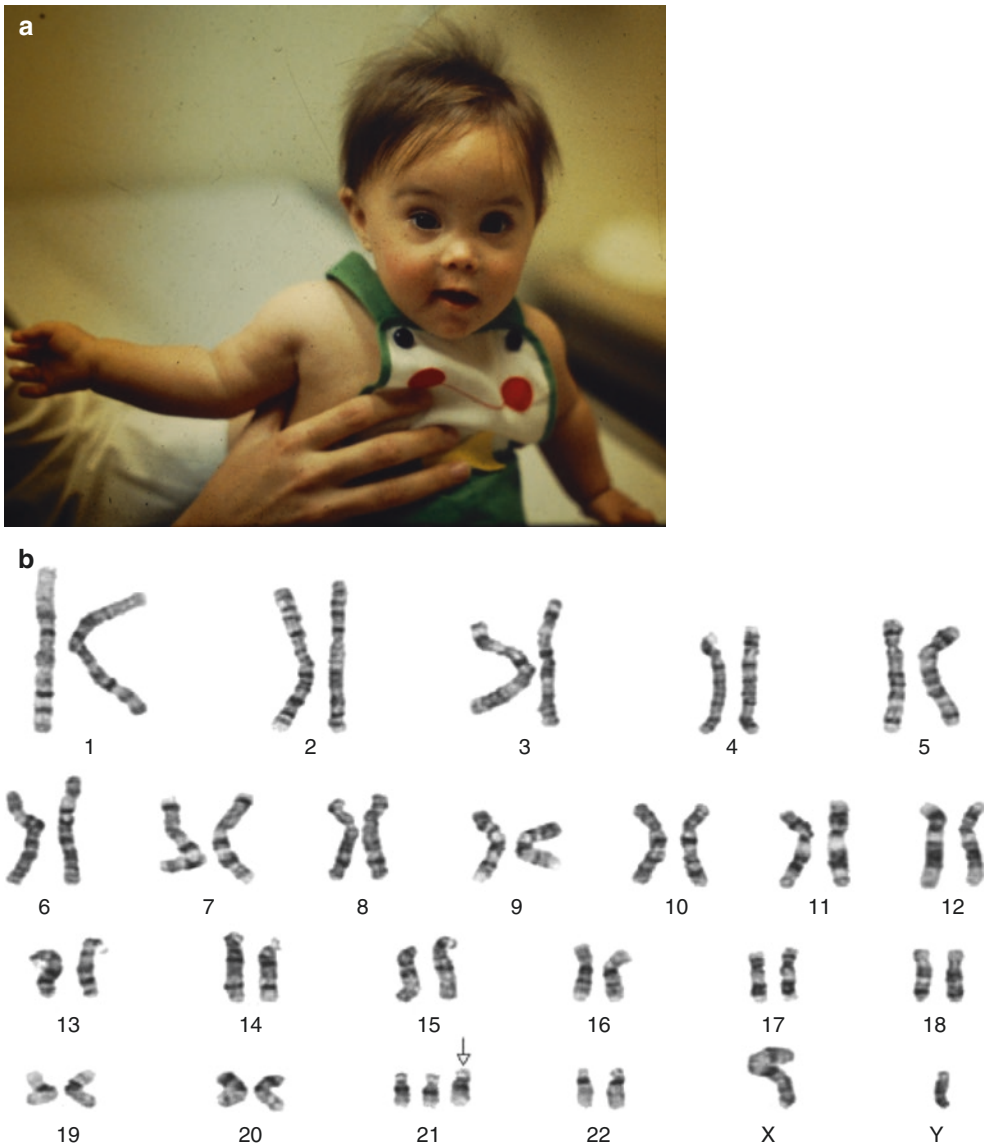


Fig. 4.5 (**a**) Upslanting palpebral fissures, epicanthal folds consistent with trisomy 21 Down syndrome in a 1-year-old girl; (**b**) 47,XY,+21: Abnormal male karyotype with trisomy 21, consistent with Down syndrome

Major abnormalities

- Development: ID—IQ range 25–50 with occasional individuals above 50; social performance averages 3–4 years over mental age; most children friendly, musical, treasured by families
- Growth: Short stature with frequent failure to thrive
- Neural: Microcephaly, atlanto-axial instability
- Eye: Hyperopia/astigmatism, strabismus, blepharitis
- Ear: Small canals, chronic otitis, cholesteatoma
- Vision and hearing deficits: Hearing loss, middle ear fluid
- Dental: Tooth anomalies, periodontal disease
- Cardiac (40–50%): Endocardial cushion (atrioventricular septal) defects are most common
- Respiratory: Obstructive sleep apnea, frequent infections
- Skin: Keratosis/dry skin, pustules, and cellulitis
- Gastrointestinal (GI) defects: duodenal atresia, Hirschsprung anomaly, celiac disease (look for classic double bubble sign indicating duodenal atresia on abdominal radiograph)

- Thyroid: Hypothyroidism, usually acquired with high thyroid-stimulating hormone (TSH)
- Genital: Cryptorchidism
- Hematology: Leukemoid reactions, transient myeloproliferative disorder (TMD), polycythemia; TMD regresses but confers a 10–30% risk for later leukemia (1% risk overall for Down syndrome)

Minor anomalies—nonspecific but useful for diagnosis

- Brachycephaly/flat occiput
- Central placement of the posterior hair whorl
- Upslanting palpebral fissures
- Flat midface
- Full cheeks
- Epicanthal folds
- Speckled iris (Brushfield spots)
- High arched palate
- Absent to very small nipple buds
- Single palmar creases (40%)
- Hypoplasia of fifth finger middle phalanx causing clinodactyly (50%)
- Wide (sandal) gap between great and second toes (50%)

Health supervision and preventive care [6]

Counseling

- Initial supportive counseling outlining suspicion of diagnosis and associated medical problems, ideally to alert mother with spouse or support person present
- Informative counseling when chromosome studies are returned, emphasizing modern improved prognosis with better healthcare, positive adjustment by most families (visit by experienced parent if possible)

Examination

- Complete physical examination from head to toe
- Rectal and abdominal examination at birth; monitor for reflux, constipation, other GI defects

Investigations

- Cord blood karyotype for confirmation if diagnosed prenatally, microarray analysis if routine in locale, routine blood karyotype to distinguish trisomy from translocation if microarray shows excess 21 material
- Brainstem auditory evoked response or otoacoustic emission hearing screen at birth
- Echocardiography after birth even if no murmur
- Thyroid function testing in the newborn period with state newborn screens, repeated at 6 months, 12 months, and yearly thereafter; endocrine referral if abnormal (watch for high TSH with normal T4)
- Monitor neonatal jaundice, obtain complete blood count and differential at birth to evaluate for myeloproliferative disorders and polycythemia; continue monitoring for signs of leukemia; check hemoglobin level annually starting at 1 year of age to screen for iron deficiency anemia
- Obtain a radiographic swallowing assessment for infants with slow feeding, choking with feeds, recurrent pneumonia, or other recurrent or persistent respiratory symptoms and unexplained failure to thrive
- Sleep study at age 1 year to exclude obstructive apnea due to narrow airway and hypotonia
- Celiac screening at age 2 years or with symptoms
- Sport pre-participation screening for atlantoaxial instability (AAI) symptoms e.g., neck pain, torticollis, gait disturbance, or weakness. Routine neck x-ray for asymptomatic patients with DS is no longer recommended.

Referrals

- Early childhood intervention (ECI) and local Down syndrome group
- Speech and occupational therapy to support breastfeeding because of oromotor hypotonia, reflux, and constipation

- Eye evaluation at birth for red reflex and cataract; ophthalmology referral before age 6 months and then annually to screen for strabismus and other eye disorders
- Ear-nose-throat/otolaryngology (ENT), referral at 6 months
- Audiology if speech abnormally delayed
- Pulmonologist to assess for airway anomalies if stridor, wheezing, noisy breathing
- Hematology oncology if TMD and polycythemia
- Endocrine referral if abnormal

General

- If constipation is present, evaluate for restricted diet or limited fluid intake, hypotonia, hypothyroidism, or GI tract malformation/stenosis
- Parents of infants with TMD should be counseled regarding the risk of leukemia and made aware of the signs, including easy bruising, petechiae, onset of lethargy, or change in feeding patterns
- Atlantoaxial subluxation or instability at each visit by history and physical exam
- Physical therapy and exercise are extremely important and postpone dementia in adults
- Car safety seat evaluation for infants before hospital discharge due to risks for postural apnea, bradycardia, or oxygen desaturation from hypotonia, neck flexibility—increased risk after cardiac surgery
- Immunizations—all routine immunizations should be given

Trisomy 18 (Edwards Syndrome) (Fig. 4.6)

Background

- Second most common trisomy among live born children
- Recurrence risks for trisomy 18 are less than 1% provided a translocation is not involved
- 50% die in the 1st week, 90–95% in the 1st year, median survival 14.5 days, death often from central apnea
- Associated anomalies can mimic those of VACTERL syndrome

Major abnormalities

- Altered gestational timing, 1 in 3 premature and 1 in 3 postmature
- Development: Severe ID with most unable to walk or communicate verbally beyond single words; many will smile, laugh, and interact with their families
- Growth: Intrauterine growth retardation, severe postnatal deficiency
- Neural: Microcephaly, hypertonia, absent corpus callosum, spina bifida
- Apneic episodes, poor feeding, marked failure to thrive with cleft lip/cleft palate in 6%
- Eye, skeletal, vertebral, limb, cardiac, renal, and genital defects are common

Minor anomalies—nonspecific but useful for diagnosis

- High forehead, prominent occiput
- Redundant neck skin
- Short sternum
- Clenched fist, overlapping fingers with hypoplastic nails and dermal pads
- Ulnar deviation of hands (club hands)
- Rocker bottom feet
- Hypoplastic muscle and adipose tissue

Trisomy 13 (Patau Syndrome) (Figs. 4.7 and 4.8)

Background

- Prevalence 1 in 5000 newborns, similar by sex and ethnicity
- The least common and most severe of the viable autosomal trisomies
- Risk of recurrence in future pregnancies for trisomy 13 is less than 1%
- Death by 1 month (82%), median survival 7 days, death often from central apnea due to brain anomalies

Major abnormalities

- Development: Severe ID—no walking or speech; react to touch, tickling, voices

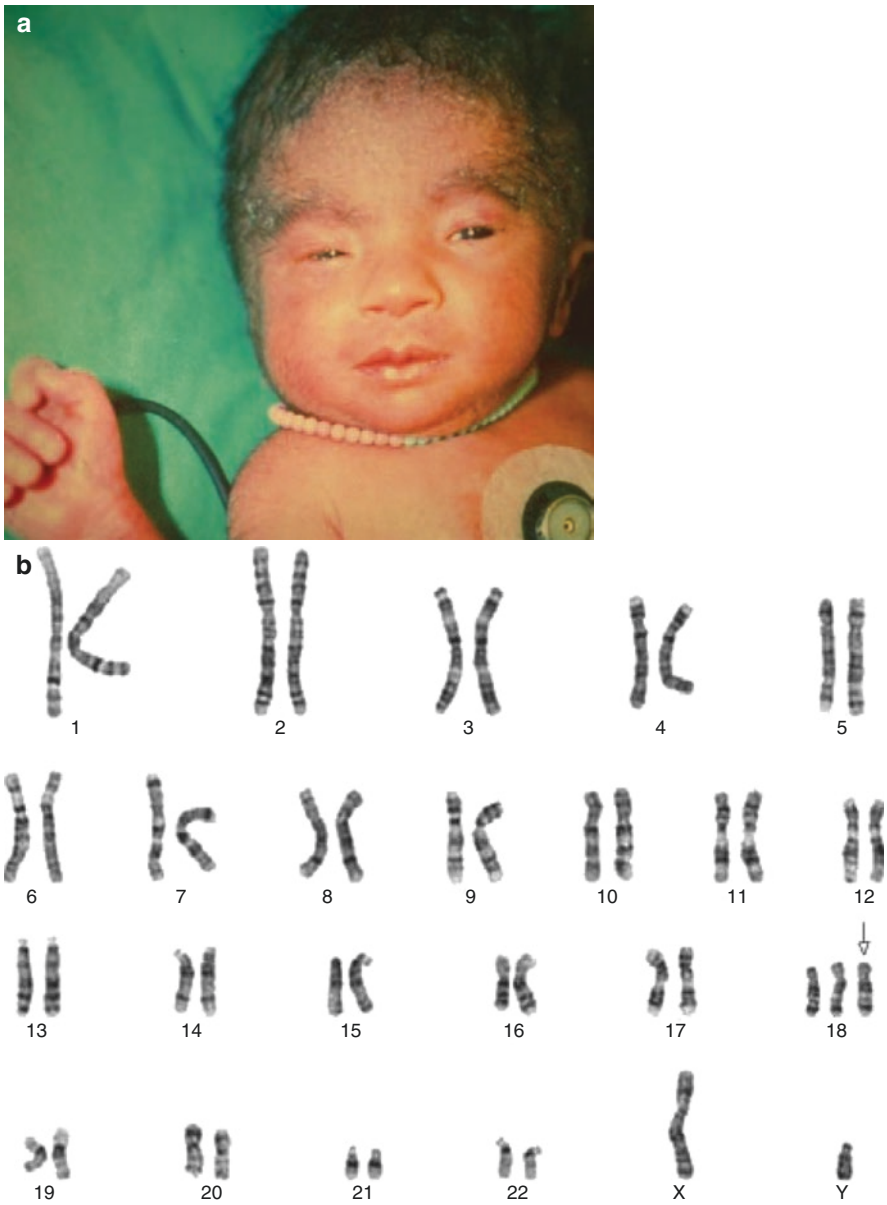


Fig. 4.6 (**a**) Small face relative to head size, arched eyebrows, narrow palpebral fissures consistent with trisomy 18 Edwards syndrome; (**b**) 47,XY,+18: Abnormal male karyotype with trisomy 18, consistent with Edwards syndrome

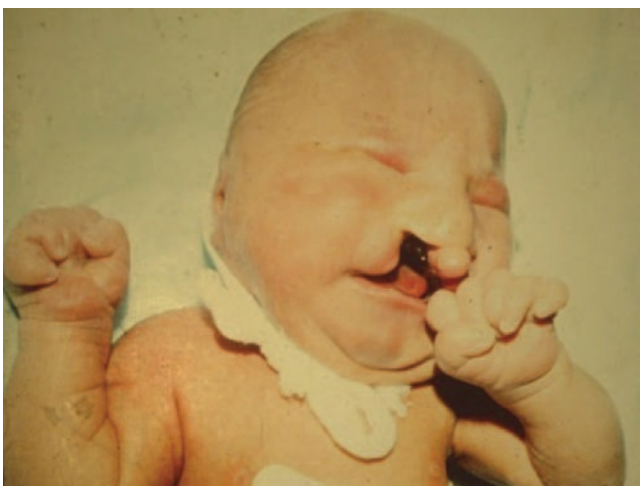


Fig. 4.7 Cleft lip and palate, postaxial polydactyly consistent with trisomy 13 Patau syndrome

- Growth: Intrauterine growth retardation, severe postnatal deficiency
- Neural: Microcephaly, hypertonia, holoprosencephaly, spina bifida, sensorineural deafness, blindness
- Apneic episodes, poor feeding, failure to thrive, cleft lip/palate in 50–60%
- Eye, ear, skeletal, cardiac, GI, renal, genital defects are common

Minor anomalies—nonspecific but useful for diagnosis

- Scalp defect, wide sutures, sloping forehead
- Redundant neck skin
- Small eyes, hypotelorism

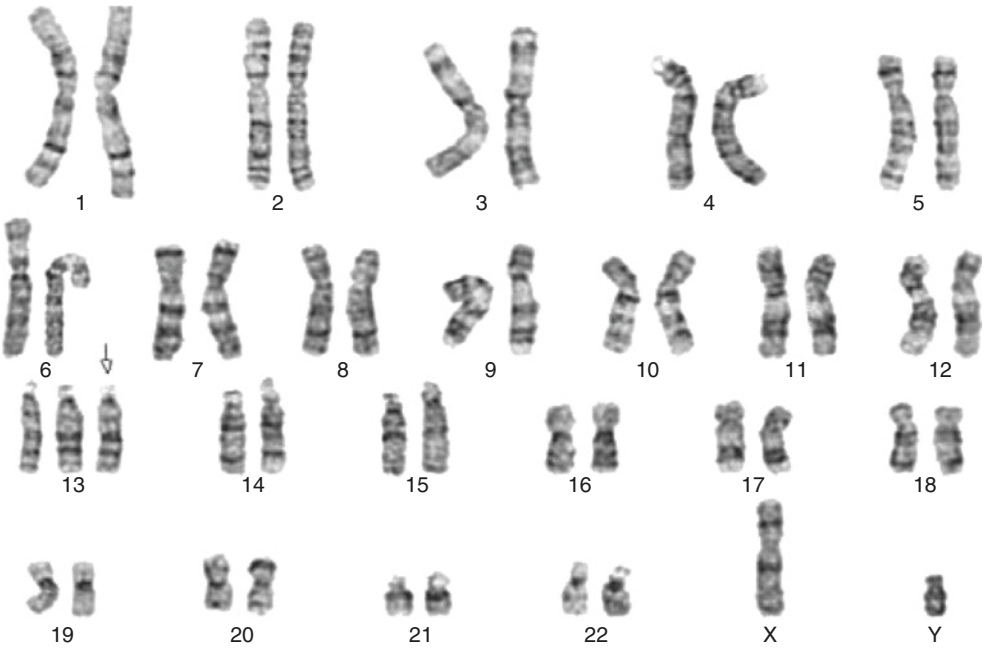


Fig. 4.8 47,XY,+13: Abnormal male karyotype with trisomy 13, consistent with Patau syndrome

- Clenched fist, sometimes overlapping fingers as in trisomy 18
- Hyperconvex fingernails, hypoplastic toenails
- Rocker bottom feet as with trisomy 18

Health supervision and preventive care for trisomy 18 and Patau

- Cord blood karyotype for confirmation if diagnosed prenatally, microarray analysis if routine in locale, routine blood karyotype (see Fig. 4.8) to distinguish trisomy from translocation if microarray shows excess 13 or 18 material
- Initial and informative counseling, ideally involving a multidisciplinary care team experienced in discussing poor prognosis and palliative care

EXAMPLES OF CHROMOSOME DISORDERS: SEX CHROMOSOME ANEUPLOIDIES

Klinefelter Syndrome (Fig. 4.9)

Background

- Klinefelter syndrome is the most common chromosomal disorder associated with male hypogonadism and infertility
- Routine karyotype or microarray analysis will show a 47,XXY karyotype with more severe variants that have additional X and Y chromosomes (48,XXXY, 48,XXYY, 49,XXXXY)
- Individuals with 47,XXY/46,XY mosaicism have better prognosis for fertility

Neurobehavioral abnormalities

- Learning differences: IQ ranges between 85 and 90 with better verbal performance
- Academic difficulties with problems in expressive language, auditory processing, and memory
- Behavior problems include immaturity, shyness, poor self-esteem, and social and peer-interaction difficulties
- Fatigue and weakness with less goal-directed thinking and self-motivation
- Intention tremor

Physical and medical abnormalities

- Growth: Tall stature with asthenic build and long limbs (low upper to lower segment ratio)
- Gynecomastia with increased risk for male breast cancer (20 times that of healthy men)
- Hypogonadism with hypogenitalism, small penis and testes, extragonadal germ cell cancers
- Infertility with azoospermia, small, firm testes

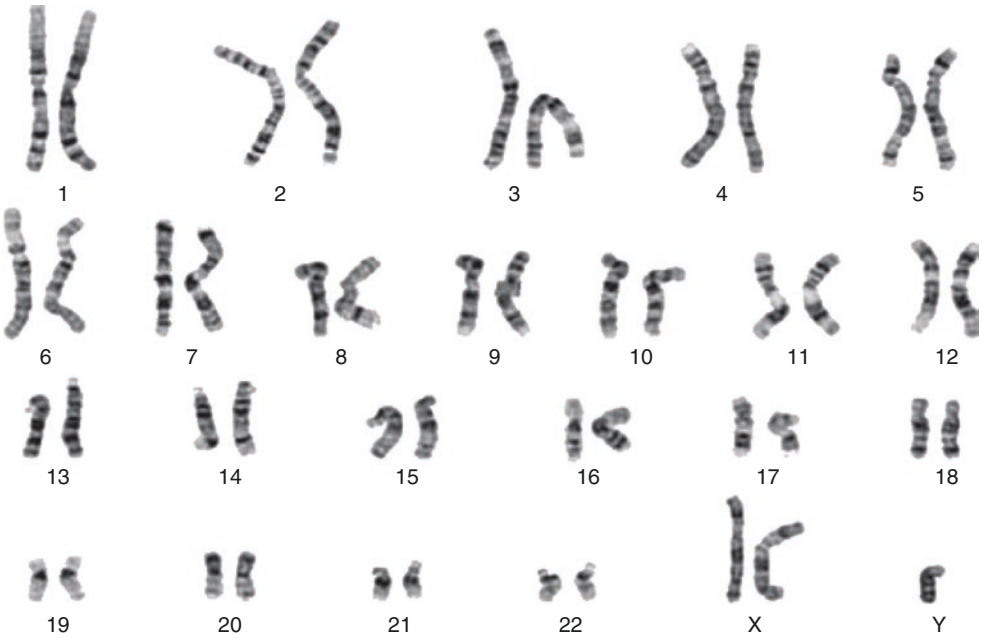


Fig. 4.9 47,XXY: Abnormal karyotype with an extra X sex-chromosome, consistent with Klinefelter syndrome

- Low serum testosterone levels
- High luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol levels
- Delayed secondary sexual characteristics, subnormal libido, erectile dysfunction,
- Eye: Coloboma, strabismus, corneal opacity
- Cardiac: Aortic stenosis, mitral valve prolapse
- Connective tissue: Scoliosis when young, pectus excavatum, inguinal hernias
- Skeleton: Radioulnar synostosis, genu recurvatum, osteoporosis
- Autoimmune problems such as diabetes have increased incidence

Health supervision and preventive care

- Early suspicion of the diagnosis allows testosterone therapy for those with insufficiency
- Ophthalmology, cardiology, and endocrinology referrals
- Discussion of reproductive options
- Monitoring for breast cancer in adulthood

XYY Syndrome

Background

- XYY syndrome is often recognized during evaluation for behavior differences
- Microarray analysis or routine karyotype will show the extra Y chromosome material
- Despite theoretical XY and Y gametes, risk for XYY offspring is very low
- Tall stature is not evident until they are 5–6 years old

Physical and medical abnormalities

- Development: IQ is often normal, ranging between 80 and 140 with early speech delay
- Behavior problems include distractibility, hyperactivity, and temper tantrums, but the publicized aggression is often controlled by adolescence
- Tall stature with acceleration in mid-childhood, increased length versus breadth, and large hands and feet
- Other skeletal and genital defects may occur

Turner Syndrome

Background

- Prevalence: 1 in 2000 live-born female infants compared to about 1 in 40 conceptuses
- 15% of pregnancies end in spontaneous abortions and 15% of those have Turner syndrome

- Distinctive phenotype mostly due to missing genes on the X short arm
- Most patients have a 45,X karyotype (two-thirds are missing the X from their father)
- Other karyotypes e.g., 45,X/46,XY mosaicism leading to gonadoblastoma
- Girls with amenorrhea and absent breast development by age 13 and those with unexplained short stature should have microarray analysis followed by karyotyping (Fig. 4.11)
- Deletion of the *SHOX* gene produces the similar Leri-Weill dyschondrosteosis short stature syndrome with Madelung deformity of the wrist

Neonatal findings

- Decreased birth length and weight (average 2900 g)
- Congenital lymphedema with puffiness over dorsa of fingers and toes
- Low posterior hairline with webbing of neck (Fig. 4.10) (pterygium colli), reflecting pronounced fetal lymphedema
- Often heralded prenatally by lymphedema
- Broad chest with widely spaced nipples
- Narrow, hyperconvex, or deeply set nails
- Pedal edema

Abnormalities

- Development: Mild learning difficulties with average IQ 90
- Growth: Short stature beginning at birth and continuing to adulthood
- Neural: Visual-spatial and fine motor deficits, clumsiness, perceptive hearing impairment
- Genital: Ovarian dysgenesis and failure (suspect in girls with no breast development/amenorrhea at ages 12–14
- Other: Anomalous ears, chronic otitis, strabismus, cardiac defects (bicuspid aortic valve, coarctation of the aorta with hypertension, later aortic root dilation), horseshoe kidney
- Elevated levels of LH and FSH confirm ovarian failure and prognosis for infertility
- Pubic hair development is normal
- Increased risk for autoimmune disorders—Hashimoto thyroiditis (up to 30% develop hypothyroidism), diabetes with carbohydrate intolerance, tendency for obesity

Health supervision and preventive care [7]

- Cord blood karyotype for confirmation if diagnosed prenatally, microarray analysis if routine in locale, routine blood karyotype (see Fig. 4.11) to distinguish 45,X from variants and detect 45,X/46,XX mosaicism with better prognosis for reproduction and 45,X/46,XY mosaicism with risks for gonadoblastoma
- Abdominal ultrasound
- Newborn hearing screen and audiology monitoring
- Thyroid functions, including TSH at age 1 year and every 1–2 years
- Endocrine referral at age 2 if thyroid function normal—for monitoring and discussion of growth and other hormonal supplementation that has been shown to increase adult stature (see also Chap. 12 Endocrinology)

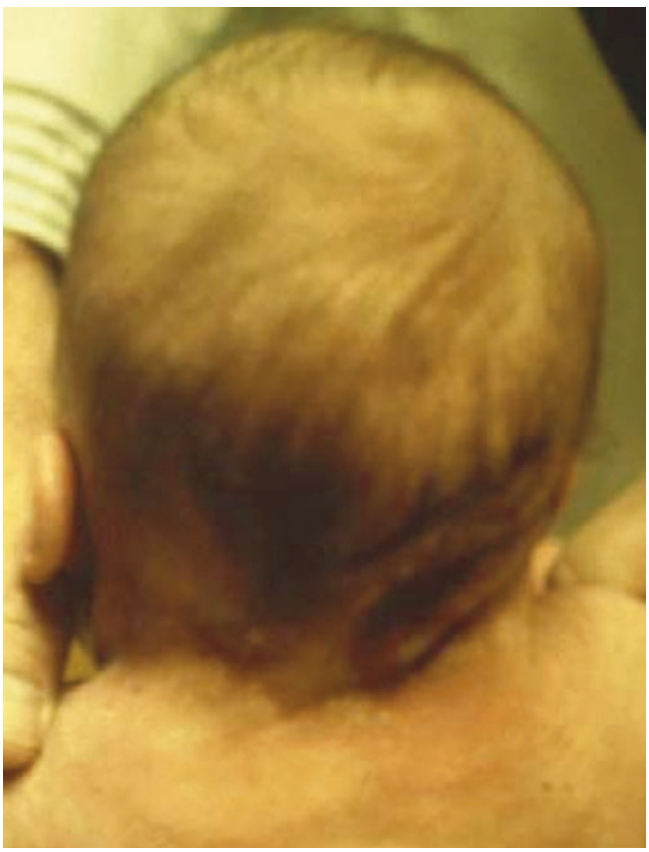


Fig. 4.10 Female infant with webbed neck and low posterior hairline due to lymphedema consistent with Turner syndrome

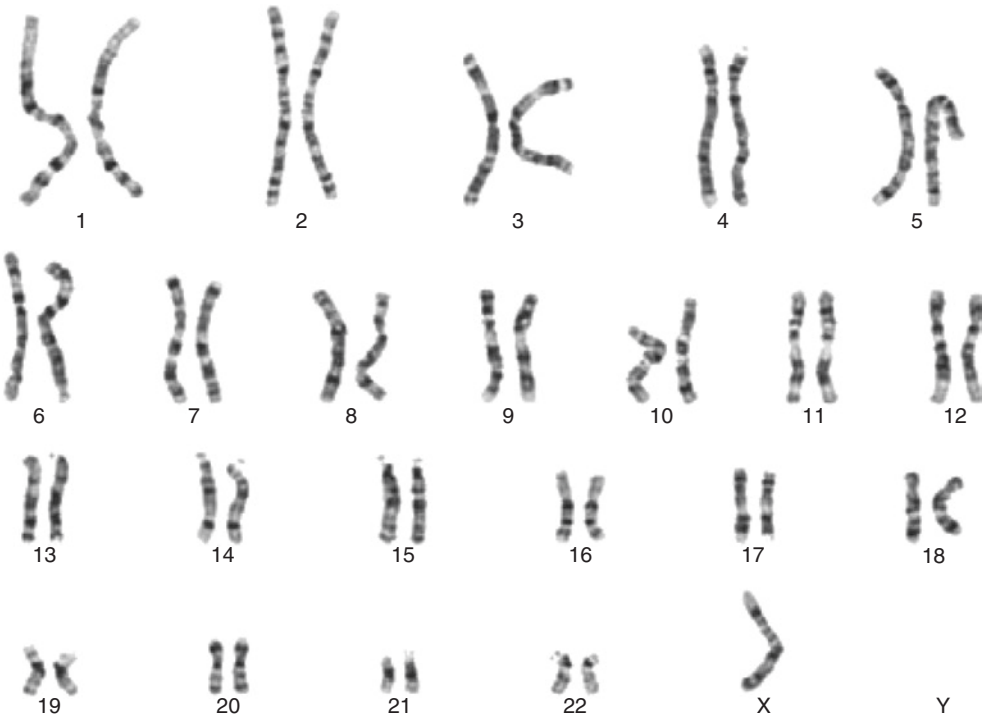


Fig. 4.11 45,X: Abnormal karyotype with one X sex chromosome, consistent with Turner syndrome

- Cardiac monitoring for aortic dilatation during teen and adult years
- Reproductive genetic referral to evaluate uterine thickness and prognosis for fertility and pregnancy
- Long-term hormonal treatment: See Chap. 12 Endocrinology

Triple X (XXX) Syndrome

Background

- Routine karyotype needed to quantify frequent mosaicism (46,XX/47,XXX)
- Risk for 47,XXX or 47,XXY offspring is 1–5%
- Rare cases with additional X chromosomes occur (e.g., 48, XXX, 49, XXXX), women with 49,XXXX resembling Down syndrome

Abnormalities

- Development: Delays particularly in speech with IQ range 30–80, average of 55; 60% require special education in high school
- Growth: Tall stature with smaller head size (20th percentile average) and narrow shoulder girdle
- Facies: Not dramatically unusual with midface hypoplasia, epicanthal folds, taurodontism
- Skeletal: Fifth finger clinodactyly, radioulnar synostosis
- Genital: Normal puberty, variable or absent menses, normal or reduced fertility

EXAMPLES OF CHROMOSOME DISORDERS: PARTIAL ANEUPLOIDIES

Wolf-Hirschhorn Syndrome (Fig. 4.12)

Chromosome 4 short/p arm deletion (4p-)

Background

- Prevalence: 1 in 20,000–50,000 births
- Deletion of the chromosome 4 short arm (4p-) demonstrated by routine karyotype or microarray analysis

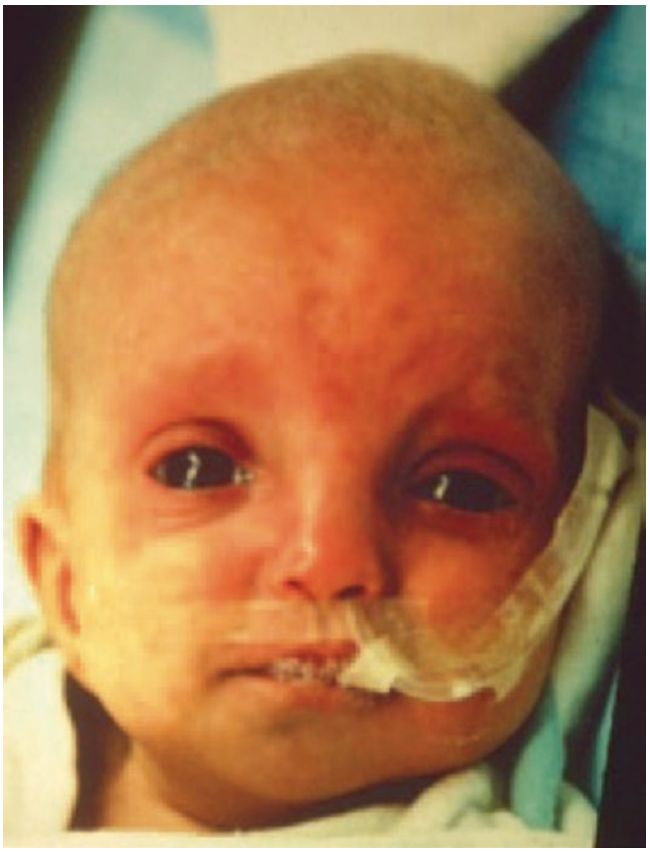


Fig. 4.12 Hypertelorism with prominent brow and broad nasal root typical of Wolf-Hirschhorn syndrome

Abnormalities

- Development: Severe ID in patients with larger deletions—40% become ambulatory, 10% toilet-trained, and 90% have seizures
- Growth: Severe deficiency, failure to thrive, feeding problems often needing gastrostomy
- Neural: Feeble fetal activity, postnatal hypotonia, microcephaly, absent septum pellucidum
- Face: Unusual appearance that in extremes resembles a Greek warrior helmet with its midline metal prong—the prominent forehead and nasal root/glabella highlight this appearance
- Face: Ocular hypertelorism, beaked nose, "carp"-like mouth with down-turned corners, cleft lip
- Eye, ear, cardiac, and skeletal anomalies

Health supervision and preventive care

- Newborn: Hearing screen with subsequent audiology, cardiology evaluation
- Infancy: Early childhood intervention, ophthalmology, renal ultrasound, neurology/electroencephalogram (EEG), feeding and swallowing monitoring

Cri-du-Chat Syndrome

Chromosome 5 short/p arm deletion (5p-)

Background

- Prevalence: 1 in 20,000–50,000 births
- Deletion of the chromosome 5 short arm (5p-) can be demonstrated by routine karyotype or microarray analysis

Abnormalities

- Mewing cry in infants (may be due to laxity or abnormalities in the larynx)
- Development: Severe ID—some affected children attain developmental ages of 5–6 years and half have adequate communication for basic needs
- Growth: Low birth weight (72% less than 2.5 kg), failure to thrive, short stature
- Neural: Microcephaly, hypotonia
- Face: Unusual appearance with round face, hypertelorism, epicanthal folds, flat nasal bridge, down-slanting palpebral fissures, low-set and/or malformed ears
- Eye, cardiac, skeletal, and genitourinary defects

Health supervision and preventive care

- Newborn: Hearing screen with subsequent audiology, cardiology evaluation
- Later monitoring of feeding, growth, hearing, vision; check for skeletal changes

De Grouchy Syndrome

Chromosome 18 long (q) arm deletion (18q-)

Background

- Deletion of the chromosome 18 long arm (18q-) demonstrated by routine karyotype or microarray analysis

Abnormalities

- Development: Moderate ID with IQ ranging from 40 to 85; visual and hearing problems may worsen cognitive prognosis
- Growth: Normal birth weight with short stature (lower segment hypoplasia), growth hormone deficiency
- Neural: Microcephaly, hypotonia, hydrocephalus, porencephaly, cerebellar hypoplasia
- Face: Unusual appearance with midface hypoplasia, deep-set and small eyes, downturned corners of the mouth, elevated lower lip, high palate, cleft palate (30%), malformed ears with small canals
- Eye, cardiac, genitourinary defects with low IgA and thyroid dysfunction

EXAMPLES OF CHROMOSOME DISORDERS: MICRODELETIONS

Williams Syndrome

Microdeletion or microduplication of band 7q11.23

Background

- Prevalence: 1 in 10,000 births, the majority with 7q11.23 microdeletion
- Submicroscopic deletion or duplication of chromosome band 7q11.23 can be demonstrated by targeted FISH or, more generally, by microarray analysis
- Parental FISH studies should be considered if symptoms present

Major abnormalities

- Development: Moderate ID, IQ range 41–80 with mean of 56, higher language than cognitive ability; those with microduplication more severe with higher incidence of autism
- Behavior: Strikingly friendly and loquacious personality, anxiety, hyperactivity
- Growth: Mild prenatal growth deficiency, postnatal deficiency around 75% of normal, early feeding problems with colic and constipation often cause early failure to thrive
- Neural: Microcephaly, early hypertonia and mild spasticity, poor coordination, and motor function
- Eye and ear defects, typical supravalvular aortic or pulmonic stenosis, early hypercalcemia in 67% can lead to renal failure
- Connective tissue changes include enamel hypoplasia, kyphosis, pectus excavatum, inguinal hernias, joint laxity and contractures, and lax skin

Minor anomalies—nonspecific but useful for diagnosis

- Distinctive and recognizable facial appearance (Fig. 4.13)
- Coarse or elfin facies due to early periorbital fullness that can mimic a storage disease
- Stellate pattern of the iris
- Anteverted nares with long philtrum
- Prominent lips

Health supervision and preventive care [8]

- Neonatal hearing screen, cardiology and ophthalmology consults, renal functions and ultrasound, calcium and electrolyte levels, early childhood intervention, and optimistic counsel
- Monitor growth, feeding, bowel function, calcium levels, renal functions, hearing, and vision in childhood
- Screening for autistic behaviors, particularly in microduplication cases; developmental pediatrician for behavior and school difficulties

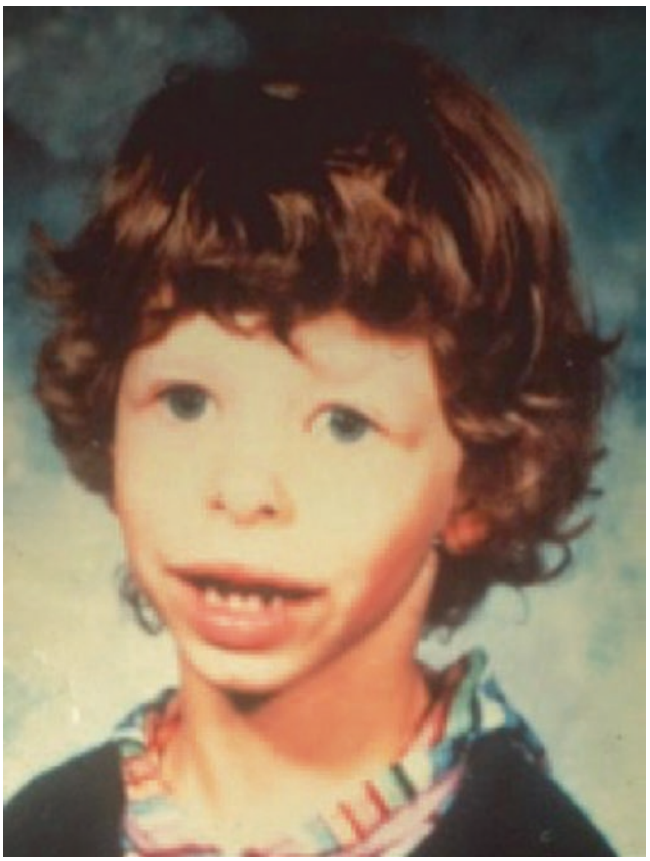


Fig. 4.13 Coarse "elfin" facies of Williams syndrome with stellate irides and prominent lips

Wilms Tumor-Aniridia-Growth Delay-Retardation (WAGR) Syndrome

Background

- Prevalence: Rare—around 70 cases reported
- Microarray analysis or targeted FISH shows a microdeletion on the short (p) arm of chromosome 11 (11p13-)
- Correlates with the two-hit model of carcinogenesis, the WAGR microdeletion being the first hit present in all tissues with a second "hit" (*WT1* gene mutation) within developing urogenital tissue producing Wilms tumor

Abnormalities

- Growth/development: Moderate to severe ID with short stature
- Face: Prominent lips, small jaw, ear anomalies
- Eye: Aniridia in most, congenital cataracts, nystagmus, vision loss
- Urogenital: Cryptorchidism, hypospadias
- Tumors: Wilms tumor, gonadoblastoma

Health supervision and preventive care

- Patients with aniridia should have FISH for the WAGR deletion to ascertain risks for Wilms tumor
- Monitoring for Wilms tumor is controversial; one recommendation is to screen when the risk is over 5% [9]
- Wilms tumor monitoring is clearly indicated for WAGR patients; renal sonography every 4 months up to age 7 years suggested for disorders with strong genetic predisposition [9]

Alagille Syndrome

Background

- Prevalence: Rare—around 200 cases reported
- Microarray analysis will show microdeletion of the 20p12 region containing the *JAG1* gene in 7%
- Mutations in the *JAG1* gene account for 70% of cases
- Both microdeletion and mutation cases follow autosomal dominant inheritance with a 50% recurrence risk for affected patients
- Prognosis depends on severity of cholestasis and cardiac disease, survival to age 20 in 75% for all patients, 60% in those requiring liver transplantation

Abnormalities

- Development: Mild ID in 16%
- Growth: Short stature, occasional hypothyroidism or growth hormone deficiency
- Face: Typical and recognizable—triangular face, broad forehead, long nose with flat tip, prominent and pointed chin, hypodontia, low-set and/or malformed pinnae, inner ear anomalies with hearing loss

- Eye: Posterior embryotoxon affecting cornea and anterior chamber angle, Axenfeld anomaly
- Cardiac defects (peripheral pulmonary stenosis or tetralogy of Fallot), renal and skeletal defects
- GI problems: Cholestasis with elevated serum bile acids within first 3 months, in 100% by age 3 years

DiGeorge or Velocardiofacial Syndrome: Microdeletion 22q11.2 (Fig. 4.14)

Background

- Prevalence: 1 in 10,000 births
- Targeted FISH or more generally microarray analysis will show microdeletion of 22q11.2
- Targeted FISH for 22q11.2 microdeletion often performed routinely on patients with tetralogy of Fallot
- Variable clinical expression ranging from neonatal problems (DiGeorge presentation) to palatal/speech defects (Shprintzen/velocardiofacial presentation) to behavioral differences similar to schizophrenia
- Patients with the microdeletion have a 50% risk of transmission
- Palatal cleft/dysfunction, mandibular hypoplasia, parathyroid, thymic, and cardiac defects represent abnormal branchial arch development

Major abnormalities

- Development: ID (40%), IQ range 55–78 with higher verbal performance
- Behavior: Impulsive behavior, bland affect, phobias, psychosis in some
- Growth: Failure to thrive with dysphagia and reflux, short stature
- Neural: Microcephaly, seizures, obstructive sleep apnea (50% of neonates), hearing loss
- Face: Narrow choanae, cleft palate, submucous cleft, velar paresis, hypotonic pharynx, Robin sequence

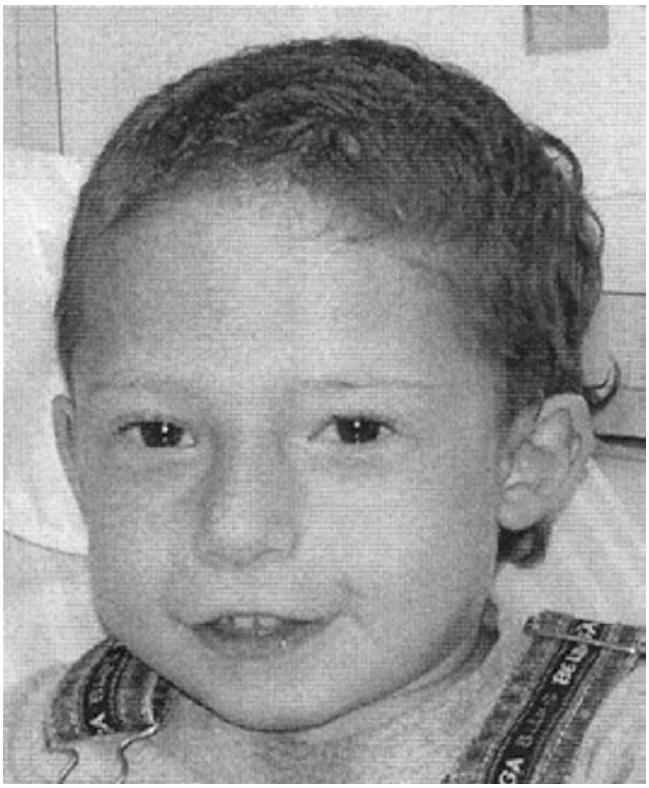


Fig. 4.14 Narrow palpebral fissures and smaller jaw typical of velocardiofacial syndrome (DiGeorge)

- Eye (cataracts) and cardiac defects (ventricular septal defect [VSD], tetralogy of Fallot), parathyroid agenesis with hypocalcemia, thymic aplasia with hypothyroidism and immune deficiency, urogenital defects (ureteral reflux, hypospadias)

Minor anomalies

- Some but not all have a characteristic facial appearance
- Narrow palpebral fissures, prominent nose, malar hypoplasia
- Micrognathia sometimes severe enough to cause Robin sequence

Health supervision and preventive care

- Cord or neonatal blood for microarray analysis if pre- or postnatal diagnosis by FISH—deletions can vary in size, and clinical prognosis correlates with particular deleted regions

- Neonatal hearing screen, renal sonogram, chest radiograph to view thymus
- ENT, cardiology, and appropriate cleft palate team involvement
- Monitoring of feeding, growth, immune, thyroid, and renal function

EXAMPLES OF CHROMOSOME DISORDERS-MICRODELETIONS WITH IMPRINTING

Prader-Willi Syndrome (PWS)

Background

- Prevalence: 1 in 10,000–15,000 births
- The loss of paternally imprinted genomic material at the 15q11.2q13 locus results in Prader-Labhart-Willi syndrome (PWS)
- Absence of the 15q11q13 band by high-resolution chromosome analysis, the 70% of cases that have microdeletions can be diagnosed by targeted FISH or microarray analysis
- Reduced life expectancy if morbid obesity occurs

Major abnormalities

- Diminished fetal activity leading to severe neonatal hypotonia
- Development: ID is mild in 63%, moderate in 31% and severe in the rest; 75% require special education at some point with decreased reading (12-year level) and math (9-year level) skills
- Behavior: Obsessive eating and hyperphagia due to lack of satiety sensation in hypothalamus, cheerful with periods of rage and stubbornness, interest in puzzles, bizarre foraging and eating, skin picking
- Growth: Early failure to thrive due to oromotor dysfunction, short stature with small hands and feet, morbid obesity if hyperphagia not strictly controlled
- Neural: Microcephaly, poor fine and gross motor coordination, high pain threshold, hypernasal speech, temperature instability
- Sleep disorders: Daytime somnolence, snoring, restless sleep, cataplexy, sleep apnea
- Face: Thick and scanty saliva, dental malocclusion, increased dental caries, poor enamel
- Eye (strabismus), and skeletal (kyphoscoliosis, club foot) defects
- Genital: Hypogonadotropic hypogonadism—small labia-clitoris or penis-scrotum, cryptorchidism (80%), precocious puberty, early adrenarche, amenorrhea (60%), or delayed menses (as late as 28 years)
- Endocrine: Hypothalamic dysfunction, growth hormone deficiency, diabetes, insulin requirement

Minor anomalies

- Bitemporal hollowing due to hypotonia with narrow bifrontal diameter
- Light hair and eye color with frontal upsweep of scalp hair
- Almond shape of palpebral fissures, downturned corners of the mouth (Fig. 4.15)
- Narrow, small hands with straight ulnar border
- Hypogonadism may be subtle

Health supervision and preventive care

- Cord or neonatal blood for karyotype and microarray analysis if pre- or postnatal diagnosis by FISH or DNA methylation analysis
- Neonatal hearing screen, feeding evaluation by specialists, apnea and sleep assessment
- Early childhood intervention, ophthalmology, and endocrine referral—growth hormone therapy is beneficial but has a small risk of death in the few months after initiation of treatment

Angelman Syndrome

Background

- The loss of maternally imprinted genomic material at the 15q11.2q13 locus results in Angelman syndrome (AS)
- Absence of the 15q11q13 band by high-resolution chromosome analysis, the 70% of cases

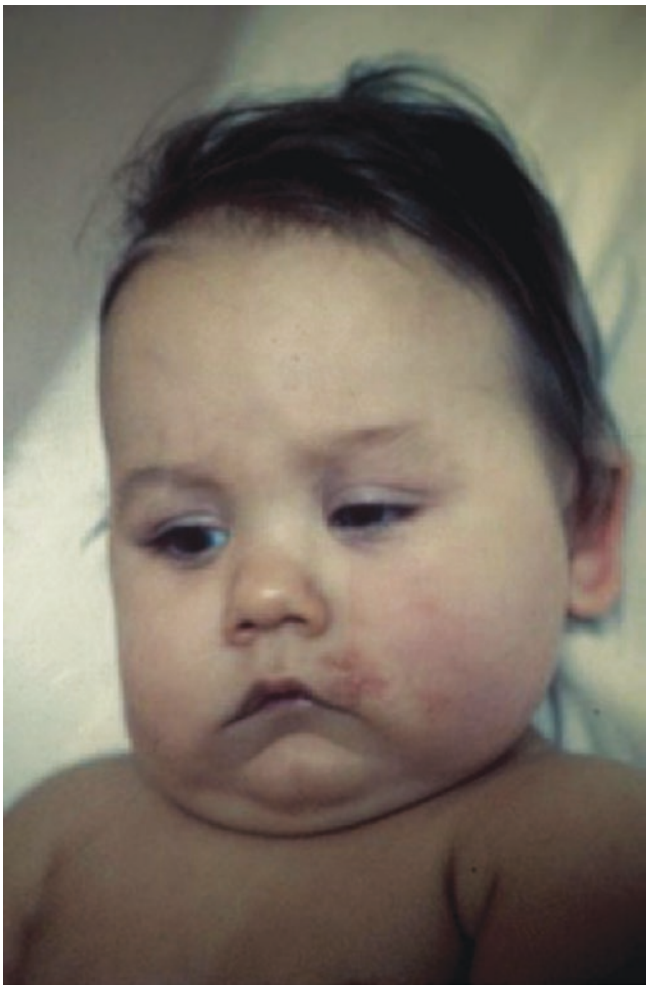


Fig. 4.15 Broad nasal root and down-turned corners of mouth indicating prenatal hypotonia in Prader-Willi syndrome

that have microdeletions can be diagnosed by targeted FISH or microarray analysis

- In contrast to PWS, only 2% of AS cases result from inheriting two copies of the paternal chromosome 15 (uniparental disomy) and require DNA methylation analysis to show absence of the maternal methyl-group (imprinting) pattern

Abnormalities

- Development: Severe ID, absent speech or fewer than 6 words, most toilet-trained by day and some at night; all incapable of independent living
- Behavior: Paroxysmal laughter, sometimes associated with gelastic seizures (epilepsy with bursts of energy like laughing or crying), related to brainstem defects rather than happiness or humor
- Neural: Microbrachycephaly, hypotonia, seizures, self-mutilation, sleep issues, puppet-like gait (ataxia with jerky arm movements) that with the laughter led to the pejorative term "happy puppet syndrome"
- Face: Large mouth and prominent jaw due to posturing, tongue protrusion, drooling, and eye defects

EXAMPLES OF MENDELIAN SYNDROMES: ID AND SUBTLE DYSMORPHOLOGY

Fragile X Syndrome [10]

Background

- X-linked inheritance
- Isolation of DNA from the Xq28 fragile site showed unusual structure with a series of trinucleotide repeats near the transcription initiation site of what became known as the fragile X mental retardation-1 or *FMR1* gene
- Affected males had dramatic expansion in the range of 400–1000 triplet repeats, accounting for the microscopically visible fragile site, while fathers who transmitted an unstable X to their daughters had 60–100 repeats (repeat expansions of 60–200 repeats in males and females are called premutations)
- Mild expansion of the triplet repeats as seen in premutation males leads to additional instability with some slight further expansion in their carrier daughters
- Premutations in carrier females undergo dramatic expansion during female meiosis, explaining the generational worsening of symptoms (genetic anticipation) seen in fragile X syndrome

Major abnormalities

- Development: Usually severe ID in males with IQ ranging from 30 to 55; some milder exceptions especially in females with higher repeat values (IQ less than 70 in 30–50%)
- Behavior: Hyperkinetic/autistic/aggressive behaviors; anxiety in females
- Neural: Early hypotonia, seizures with abnormal EEG, cluttered speech, stuttering
- Connective tissue dysplasia leading to eye (strabismus), cardiac (mitral valve prolapse, aortic dilation), and skeletal (scoliosis, flat feet) defects with joint and skin laxity
- Genital: Macro-orchidism, premature ovarian failure in symptomatic females

Minor anomalies

- Proportionate macrocephaly
- Long and narrow face (60%)
- High palate with prominent jaw (usually after puberty)
- Large, flexible ears with decreased cartilage
- Testicular enlargement may be subtle

Health supervision and preventive care [10]

- Neurologic, developmental, and genetic referrals when diagnosis made
- Cardiac and behavioral monitoring

EXAMPLES OF MENDELIAN SYNDROMES: MILD ID AND PROPORTIONATE GROWTH DELAY

Noonan Syndrome

Background

- Prevalence 1 in 1000–2500
- DNA testing for several mutations in the RAS-MAPK signaling pathway will show mutations responsible for Noonan syndrome
- Gene panels are available, 50% have mutations in the tyrosine phosphatase (*PTPN11*) gene on chromosome 12
- The presence of a Turner-like appearance gave rise to the term "male Turner syndrome," erroneous because the condition has equal sex distribution

Major abnormalities

- Findings are based on patients with the clinical diagnosis and may vary when genetic testing defines specific subtypes—see those disorders for refined complication risks [3]
- Development: Mild ID (IQ range 64–127, median 102), speech differences
- Behavior: Stubbornness, mood disorders, rare autistic manifestations
- Growth: Frequent failure to thrive, feeding difficulties, later proportionate and mild short stature (50%)
- Neural: Motor delays, vision deficits, hearing loss (usually conductive)
- Connective tissue dysplasia: Scoliosis, pectus (upper carinatum, lower excavatum), joint laxity, lax skin, bleeding diathesis
- Eye (strabismus), cardiac (pulmonic stenosis, septal defects, hypertrophic cardiomyopathy), urogenital (obstructive uropathy, cryptorchidism) defects
- Lymphatic: Pulmonary lymphangiectasia, chylothorax, non-immune hydrops
- Tumors: Pheochromocytoma, ganglioneuroma, juvenile myelomonocytic leukemia (often with *PTPN11* gene rearrangements/amplification

Minor anomalies

- Short, webbed neck (Fig. 4.16)
- Low posterior hairline
- Ptosis, down-slanting palpebral fissures
- Low-set or abnormal pinna ("jug-handle" ears)
- Cubitus valgus, single palmar creases
- Edema of the hands and feet

Health supervision and preventive care

- Neonatal hearing screen, renal sonogram, ophthalmology, cardiology referrals

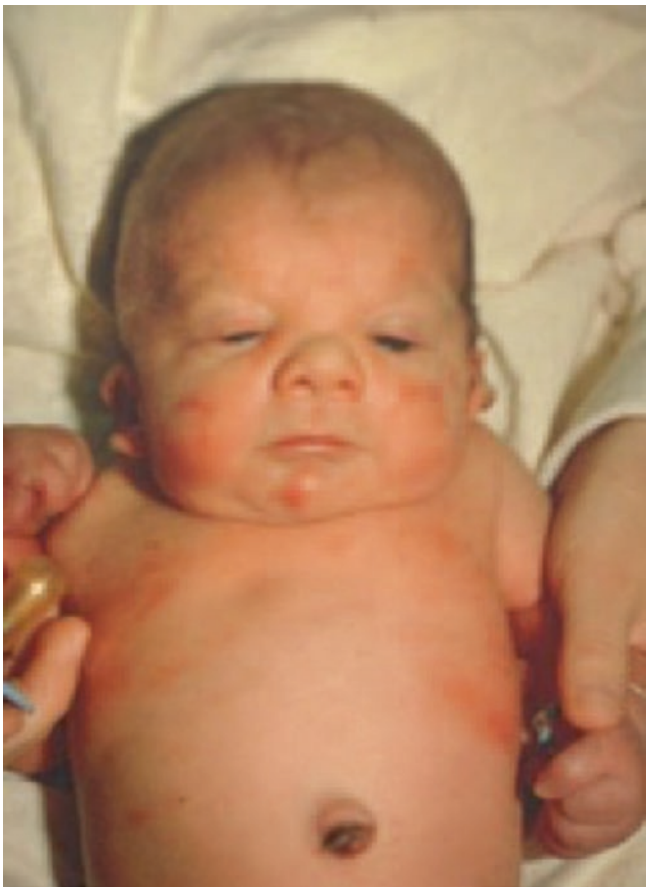


Fig. 4.16 Short webbed neck of an infant with Noonan syndrome

- Monitor thyroid, renal functions; regular cardiac monitoring for aortic and valve changes
- Cervical spine radiographs before sports, anesthesia

EXAMPLES OF MENDELIAN SYNDROMES: CRANIOFACIAL DEFECTS AS MAJOR FINDING

Waardenburg Syndrome

Background

- Prevalence: About 1 in 40–50,000 births, having a 1.4% incidence in congenitally deaf children
- Like Noonan syndrome, an array of different gene mutations (*PAX3, MITF, EDN3*, etc.) and subtypes have been described, all except some cases of type IV exhibiting autosomal dominant inheritance
- The condition involves abnormal neural crest development, accounting for pigmentary changes and, in some cases, Hirschsprung disease

Abnormalities

- Development: Mild cognitive delays that can be related to the hearing loss
- Neural: Sensorineural hearing loss, nonprogressive, unilateral or bilateral, due to hypoplasia of structures in the organ of Corti and semicircular canals (evident on head computed tomography)
- Eye: Iris pigmentary abnormality—heterochromia (eyes of different colors), bicolored iris, pale blue eyes with hypoplastic iridic stroma, hypopigmented fundus, peripheral retinal pigmentation
- Hair: Hypopigmentation with poliosis (white forelock), white hairs on other body regions, premature graying
- Face: Medial flare of bushy eyebrows, dystopia canthorum (lateral displacement of inner canthi), high and broad nasal bridge with hypoplastic alae nasae
- Cardiac, skeletal, and urogenital defects occur in some

Health supervision and preventive care

- ENT and audiology team after diagnosis, deaf community and physician team discussion of cochlear implant and hearing aid options
- Alertness for symptoms of cardiac, skeletal, and GI defects

Treacher Collins Syndrome

Background

- Prevalence: 1 in 50,000 births
- Targeted DNA testing or whole exome sequencing will show a mutation in the treacle (*TCOF1*) gene in the chromosome 5q31.3q32 region

- Autosomal dominant inheritance pattern with 50% transmission risk in affected individuals
- Most severe cases are new mutations
- Confusion with the low genetic risk Goldenhar syndrome/association may also occur if eye and malar changes are not dramatic

Abnormalities

- Development: ID (5%), usually normal unless compromised by unrecognized hearing loss
- Growth: Early failure to thrive because of feeding difficulties, airway abnormalities
- Neural: Conductive deafness due to ear anomalies
- Craniofacial: Mandibulofacial dysostosis with underdeveloped mandibular and zygomatic bones causing small jaw and malar hypoplasia, projection of scalp hair onto lateral cheek
- ENT: Choanal atresia, pharyngeal hypoplasia with macro- or microstomia, cleft palate, external and middle ear anomalies with canal stenosis and ear tags

Craniosynostosis Syndromes

Background

- Prevalence: 4–6 per 10,000 births if primary and secondary synostosis are included; craniosynostosis syndromes range from 1 in 25,000 (Saethre-Chotzen) to 1 in 100,000 births (Apert) or rarer
- Craniosynostosis refers to premature fusion of cranial sutures, often causing abnormal head shape
- Can have primary (ossification defect) or secondary causes (failure of brain growth, rickets)
- Occurs as an isolated defect or as part of over 90 syndromes
- Types of craniosynostosis
  - Scaphocephaly: Early fusion of sagittal sutures, long and narrow head shape
  - Anterior plagiocephaly: Early fusion of one coronal suture, unilateral flattening of the forehead
  - Posterior plagiocephaly: Early closure of one lambdoid suture
  - Brachycephaly: Early bilateral coronal suture fusion
  - Trigonocephaly: Early fusion of metopic sutures, keel-shaped forehead and hypotelorism
  - Turricephaly: Early fusion of coronal, sphenofrontal, and frontoethmoidal sutures, cone-shaped head
  - Clover-leaf skull or Kleeblattschädel anomaly
- Syndromes involving craniosynostosis (coronal synostosis most common, but any suture can be involved)
  - Apert syndrome: Craniosynostosis, hand syndactyly
  - Crouzon syndrome: Craniosynostosis, no limb defects
  - Pfeiffer syndrome: Craniosynostosis, broad thumb and toes
  - Saethre-Chotzen syndrome: Craniosynostosis, often asymmetrical, brachydactyly and syndactyly
  - Carpenter syndrome: Tower or clover-leaf skull due to multiple fused sutures, preaxial polydactyly, obesity
- All syndromes but Carpenter (autosomal recessive) exhibit autosomal dominant inheritance.
- Isolated craniosynostosis, like other single birth defects, exhibits multifactorial determination with 3–5% recurrence risk
- Mutations in specific genes have been defined for the major syndromes, often in fibroblast growth factor receptor (FGFR) genes
- Specific gene testing or gene panels can provide a molecular diagnosis with options for prenatal diagnosis in subsequent pregnancies

Abnormalities

- Development: Surgical release of craniosynostosis can prevent ID, but IQ often in 70–74 range
- Neural: Restriction of brain growth, increased intracranial pressure causes ID, visual, and hearing defects
- Cranial: Abnormal shape as discussed for various suture fusions above
- Plagiocephaly occurs with asymmetric synostosis; mild cases due to uterine constraint must be distinguished
- Face: Midface hypoplasia, palatal clefts, jaw changes
- Early airway obstruction may require tracheostomy
- Eye: Shallow orbits, exophthalmos/ocular proptosis, exposure keratitis due to sphenoidal synostosis
- Cervical vertebral, cardiac, and limb defects often occur
- Types of limb defects rather than the involved suture(s) guide craniosynostosis syndrome diagnosis

Health supervision and preventive care

- Most craniosynostosis conditions are evident at birth and require immediate involvement of a craniofacial team to prevent cognitive and sensory deficits
- Craniofacial surgery team evaluation, including neurosurgery, ophthalmology, ENT, and cleft palate expertise
- Monitoring of hearing, vision, and development is critical in the more severe syndromes

EXAMPLES OF MENDELIAN DISORDERS WITH DISPROPORTIONATE GROWTH DELAY (DWARFISM)

Achondroplasia (Fig. 4.17)

Background

- Prevalence: 1 in 16,000–25,000 births
- Achondroplasia is the most common type of short limb dwarfism, involving rhizomelic hypoplasia
- Skeletal radiologic survey to define affected bone regions can tailor the differential of skeletal dysplasia, often suggesting the diagnosis of achondroplasia by its typical spine and hip changes

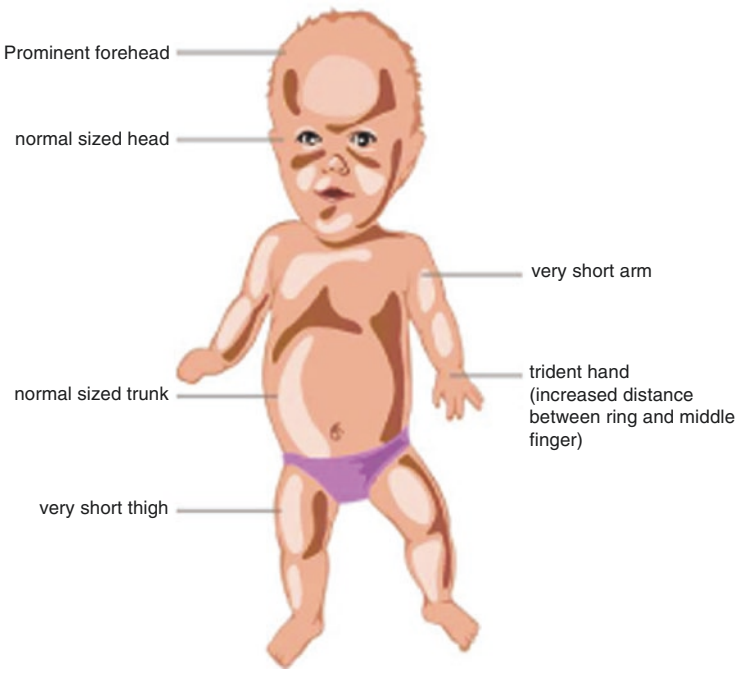


Fig. 4.17 General manifestations of achondroplasia

- Specific mutation in fibroblast growth factor receptor 3 (*FGFR3*) gene on chromosome
- Other mutations in this gene cause severe thanatophoric dwarfism or milder hypochondroplasia
- Autosomal dominant inheritance with a 50% recurrence risk for affected individuals
- More than 80% of patients are due to new mutations

Abnormalities

- Lifespan: Sudden infant death in 5% and depression common
- Development: Normal if complications like hearing loss or cervical cord compression are prevented, motor milestones often lag by 3–6 months because of macrocephaly and early hypotonia
- Growth: Short stature with males averaging 130 cm (~4 ft-2) and females 123 cm (4 ft)
- Neural: Altered cerebrospinal fluid (CSF) circulation, cord compression, conductive and sensorineural hearing loss
- Cranial: Macrocephaly, platybasia, narrow foramen magnum, maxillary hypoplasia
- Face: Frontal bossing, myopia, shallow nasal bridge, myopia, chronic otitis media
- Respiratory issues: Due to small chest, upper airway obstruction, and sleep-disordered breathing
- Skeleton: Rhizomelic limbs causing extra skin folds, cervical spine fusion, kyphoscoliosis, joint laxity leading to arthritis and injuries, splayed fingers (trident hands)
- Genital: Uterine fibroids, menorrhagia, narrow pelvis requiring cesarean delivery

Health supervision and preventive care

- Monitor for feeding difficulties and apnea
- Infantile respiratory and sleep evaluations, anesthesia precautions
- Childhood ophthalmology, ENT, and orthopedic follow-up
- Somatosensory potentials to measure transmission through foramen magnum, and check for cord compression
- Flexion-extension radiography to assess cervical instability/respiratory obstruction
- Management controversies include use of decompressive surgery for cervical cord compression, limb-lengthening procedures, and growth hormone therapy as many have poor response

EXAMPLES OF MENDELIAN DISORDERS WITH LAX CONNECTIVE TISSUE (CONNECTIVE TISSUE DYSPLASIAS)

Marfan Syndrome (Figs. 4.18, 4.19, and 4.20)

Background

- Prevalence is 1 in 1000–2500
- Marfan syndrome is one of many disorders grouped by McKusick as heritable disorders of connective tissue
- Criteria developed for clinical diagnosis are less important now that targeted DNA testing will demonstrate mutations in the fibrillin-1 (*FBN1*) gene on chromosome 15
- Practical clinical criteria involve one major finding (eye or heart) along with several minor findings listed below (e.g., Marfanoid habitus, arachnodactyly maneuvers, skin changes)
- Marfan syndrome exhibits autosomal dominant inheritance with an equal sex ratio and variable expression

Abnormalities

- Lifespan: The major cause of death is aortic dissection, preventable by beta-blocker or losartan therapy

Fig. 4.18 A child with Marfan syndrome, showing the fragile and aged face with pectus excavatum

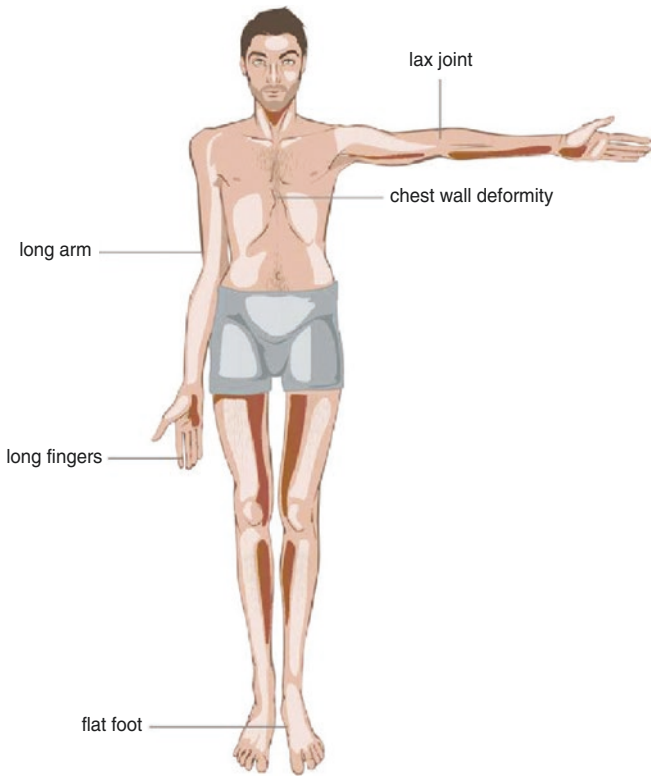
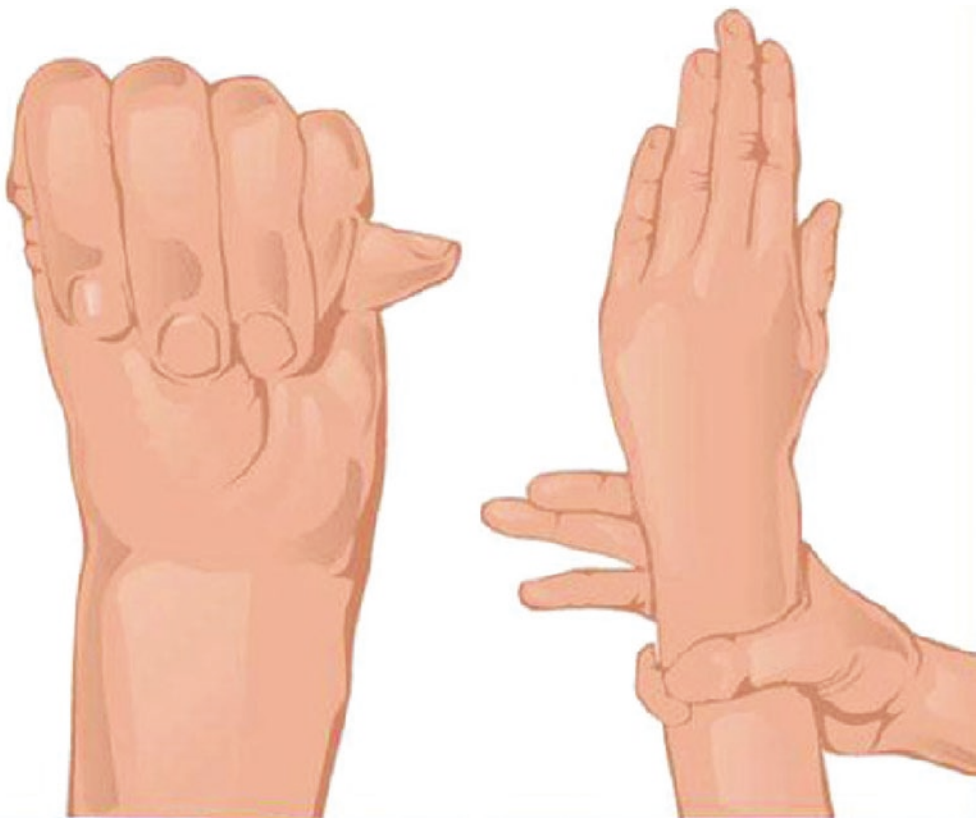


Fig. 4.19 General manifestations of Marfan syndrome

Fig. 4.20 Thumb and wrist signs in Marfan syndrome



- Development: Normal with occasional verbal performance discrepancy and visual attention problems
- Growth: Tall stature, low upper to lower segment ratio, thin and fragile habitus
- Neural: Dural ectasia, sacral meningocele, anterior or posterior disc herniation
- Cranial: Dolichocephaly, prominent supraorbital ridges, temporomandibular joint disease
- Eye defects: Ectopia lentis, myopia, retinal detachment
- Cardiac: Aortic enlargement, mitral valve dysfunction and prolapse, arrhythmias, aneurysms of the aorta or pulmonary artery
- Pulmonary: Reduced vital capacity, spontaneous pneumothorax emphysema
- Skeletal: Scoliosis, spondylolisthesis, flat feet, joint laxity
- Arachnodactyly: Evidenced by ability to perform the Walker-Murdoch (overlap of thumb—5th finger when encircling the wrist; see Fig. 4.20) and Steinberg (protruding thumb beyond ulnar hand border with clenched fist) signs
- Epidermal: Atrophic striae (stretch marks), recurrent incisional hernias
- Hematologic: Clotting tendencies, renal vein thrombosis

Health supervision and preventive care [11]

- Cardiology and ophthalmology evaluations when diagnosis suspected
- Monitoring of aortic root size at intervals dictated by symptom severity (6 months to 3–4 years), often accompanied by beta-blockers or losartan therapy
- Activity and physical therapy to strengthen muscles with frequent prohibition of collision sports

Ehlers-Danlos Syndrome (EDS)

Background

- Prevalence: Listed as 1 in 5000 births for all types but much more common if patients with more subtle joint laxity/hypermobility and skin elasticity are included
- 20% of women, 10% of men are hypermobile defined by scores > 4–5 on the 9-point Beighton scale [12]
- Early recognition of hypermobility can guide activities that prevent adolescent injury and early arthritis
- Diagnosis allows treatment of associated autonomic imbalance (tachycardia, chronic fatigue, bowel issues)
- Associated autonomic imbalance (dysautonomia) leads to treatable postural orthostatic tachycardia (POTS), low bowel motility/irritable bowel syndrome (IBS), and mast cell activation disorder (MCAD)
- Nonspecific diagnoses like fibromyalgia, chronic fatigue syndrome, and serum-negative rheumatoid arthritis are often due to EDS with dysautonomia
- Diagnostic criteria less important in era of genomic testing, but a practical approach could include:
  - For classical or hypermobile EDS:
    - Major criteria: Joint hypermobility and skin elasticity/scarring
    - Minor criteria: Smooth/velvety skin and joint subluxation/injury
  - For vascular EDS:
    - Major criteria of typical "tight, chiseled face," arterial aneurysm/dissection and/or bowel rupture
    - Minor criteria of translucent skin, muscle/joint rupture

Abnormalities

- Lifespan: Generally normal with the exception of vascular EDS
- Development: Early motor delays, normal cognitive function, anxiety, depression from chronic pain
- Growth: Early colic and failure to thrive due to low bowel motility/IBS; eosinophilic esophagitis (MCAD)
- Central nervous system: Migraines, chronic daily headaches, Chiari deformation, fragile dura contributing to CSF leaks
- Peripheral nerves: Carpal-tunnel syndrome, chronic regional pain syndromes

Fig. 4.21 Marked skin extensibility in a patient with Ehlers-Danlos syndrome

- Joints: Hypermobile with subluxations, ligament/tendon tears, osteoarthritis, plica bands, areas of dead bone
- Skin: Elastic, thin and translucent, easy bruising, striae, white-surfaced and keloid scars, slow healing (Fig. 4.21)
- Face: Distinctive only in some with vascular EDS—bulging eyes, thin nose and lips due to tight skin
- Eye (myopia, retinal detachment); mouth (dental, temporomandibular joint [TMJ] issues); GI (IBS, low motility); cardiovascular (tachycardia, valvular prolapse, aneurysm); skeletal (kyphoscoliosis, flat feet, herniated disc) defects
- Allergy/pulmonary: Frequent asthma/shortness of breath, food and medication intolerances, transient rashes/hives, anaphylaxis, spontaneous pneumothorax
- Urogenital: Pelvic congestion with menorrhagia, endometriosis, ovarian cysts; hyperactive bladder with increased urinary tract infections, bladder and uterine prolapse

Health supervision and preventive care

- Usual diagnosis as teen or young adult—cardiology, orthopedic, GI, allergy/mast cell referrals with monitoring for joint pain/injury, tachycardia, fatigue, anxiety, constipation/diarrhea, reflux, allergy, skin reactivity
- Evaluate for head and neck pain, especially posterior, and consider upright head magnetic resonance imaging (MRI) study for Chiari
- Encourage swimming and light weight lifting rather than running
- POTS treated with hydration, salt, high protein diet, medications (beta-blockers, midodrine, fludrocortisone)
- Mast cell activation treated by allergists with antihistamine protocols (triple-drug therapy: cetirizine/ranitidine/montelukast)

Osteogenesis Imperfecta

Background

- Prevalence: 1 in 20,000 births if all types are included
- Four major types are recognized with craniofacial changes, deafness, bowed limbs, and fractures—type II is an outlier with lethal dwarfing limb and chest changes
- Heterozygous mutations in the genes for the alpha-1 and alpha-2 chains of collagen I (*COL1A1, COL1A2*)
- Autosomal dominant inheritance patterns
- Targeted *COL1* gene testing will provide the diagnosis in over 80% of cases

The four types of osteogenesis imperfecta (Sillence classification):

- Type I: Near normal growth with blue-gray sclerae, multiple fractures, and later hearing loss
- Type II: Extremely severe with usual death in the perinatal period and rare survival for months; poorly mineralized cranium and long bones with large fontanel, hydrocephalus, hypotonia, short and bowed limbs distorted by multiple fractures in utero and callus formation

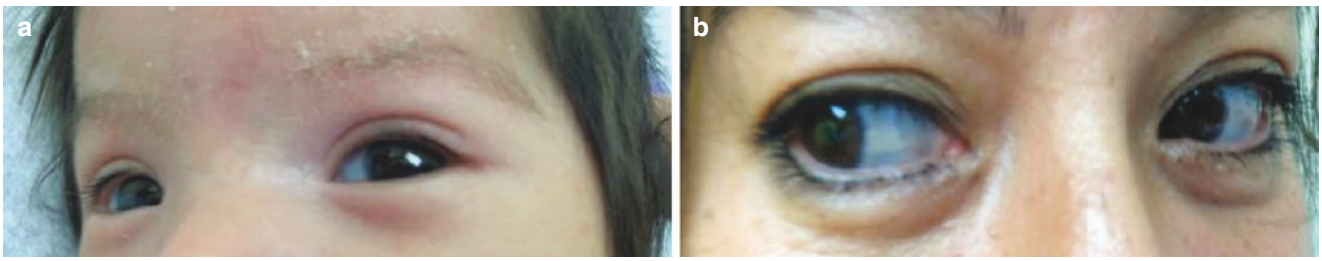


Fig. 4.22 Blue sclera in a 23-day old female infant and her mother who have type I osteogenesis imperfecta

- Type III: Prenatal growth deficiency, multiple fractures at birth, limb bowing, severe kyphoscoliosis leading to respiratory compromise; dentinogenesis imperfecta is severe, bluish sclerae less after infancy
- Type IV: Short stature with limb deformities; femoral bowing in infancy that improves; dental changes
- Other types have been added, including a type VI with vertebral fractures and lack of *COL1* mutations

Abnormalities are listed for the most common type I as a prototype

- Development: Usually normal since hearing loss occurs late (third decade)
- Growth: Prenatal deficiency and short stature with significant limb fractures
- Neural: Hearing impairment due to otosclerosis
- Cranial: Macrocephaly, Wormian bones, malocclusion of jaw
- Face: Blue-gray sclera, dentin/pulp hypoplasia, translucent blue-gray teeth, caries (Fig. 4.22)
- Fractures (92% overall): 8% at birth, 23% infancy, 45% preschool, 17% school, less after puberty
- Connective tissue: Lower limb bowing, kyphoscoliosis, easy bruising, inguinal and umbilical hernias

Health supervision and preventive care

- Neonatal skeletal radiologic survey to ascertain fractures and extent of deformities
- Orthopedic care with later hearing screening
- Endocrine consultation may help with bisphosphonate therapy
- Vitamin D and calcium supplementation if hypophosphatasia with large fontanel, fractures, and similar dental problems is excluded

EXAMPLES OF MENDELIAN DISORDERS WITH OVERGROWTH (GIGANTISM)

Beckwith-Wiedemann Syndrome (BWS)

Background

- Prevalence: 1 in 12,000 births and probably higher, with some cases having only macroglossia
- Caused by deletion, gene mutations, or altered imprinting of the 11p15 region
- Usually sporadic with low recurrence risk but some cases are autosomal dominant
- Insulin-like growth factor-2 is up-regulated in the paternal chromosome 11 and suppressed by genes on the maternal chromosome 11, so maternal translocation/deletion or paternal duplication/uniparental disomy (20%) are more common causes of BWS

Abnormalities

- Lifespan: Infant mortality is significant (20%) due to hypoglycemia, polycythemia, respiratory problems
- Development: Occasional mild/moderate ID, perhaps from early hypoglycemia
- Growth: Large birth weight (average 4 kg), tall stature at 95th percentile through adoles-

cence, weight 75th–95th percentile, macrosomia with large muscles and thick subcutaneous tissue, organomegaly, hemihypertrophy
- Craniofacial: Large fontanels, metopic ridge, nevus flammeus on forehead and eyelids, posterior ear pits/creases, macroglossia interfering with respiration and feeding
- Endocrine: Hypoglycemia responsive to steroid therapy resolving by 1–4 months
- Cardiac (septal defects, tetralogy of Fallot); GI (omphalocele, umbilical hernia); genitourinary defects
- Skeletal: Advanced bone age, hemihyperplasia of limbs, polydactyly (4%)
- Tumors: Abdominal (4–7.5%), including Wilms, hepatoblastoma, gonadoblastoma, adrenocortical carcinoma

Health supervision and preventive care
- Neonatal attention to hypoglycemia, respiratory obstruction, feeding
- Prone positioning as with Robin sequence may aid respiration
- Macroglossia can persist through early childhood
- Tumor monitoring using renal sonography and serum alpha-fetoprotein levels every 4 months up to age 7 years [9]

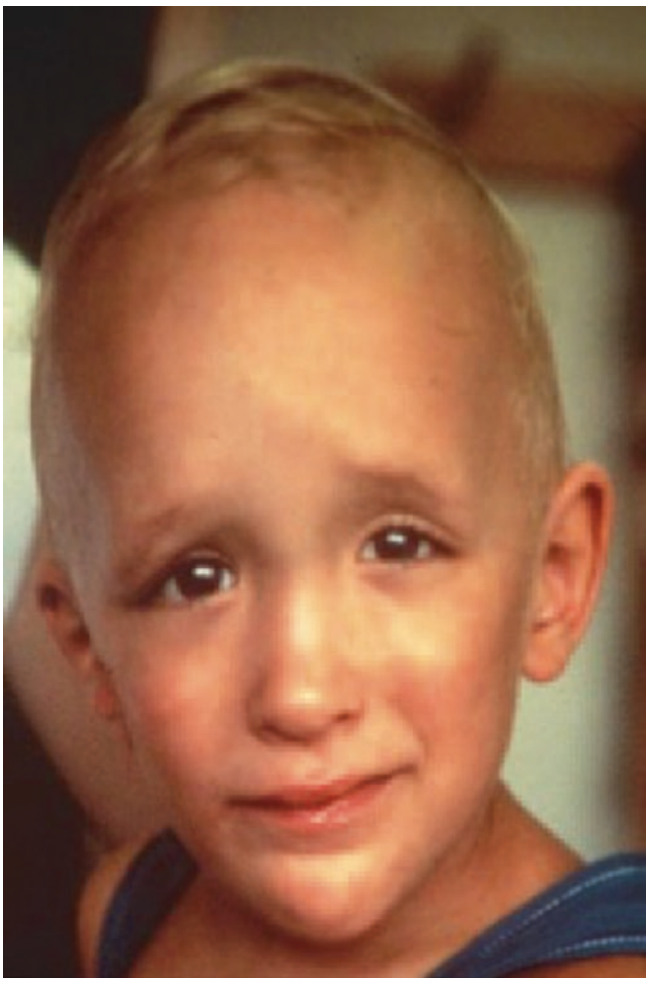


Fig. 4.23 Macrocephaly in a child with Sotos syndrome

SOTOS SYNDROME (CEREBRAL GIGANTISM)

Background
- Prevalence: 1 in 20,000–30,000 births
- Targeted testing for mutation or deletion (rare except in Japanese) of the *NSD1* gene at 5q35 is diagnostic
- Autosomal dominant inheritance with most cases representing new mutations

Abnormalities
- Development: Mild ID with IQ range of 40–129, mean of 78
- Behavior: Excessive size/poor coordination complicates social adjustment, autism, aggressiveness
- Growth: Large birth size (mean weight 3.9 kg, length 55.2 cm), increased growth velocity with increased bone age and stature persisting over 97th percentile with ultimate height in upper-normal range
- Neural: Macrocephaly (Fig. 4.23), seizures, dilation of cerebral ventricles, early hypotonia/poor feeding (40% tube-fed)
- Face: Characteristics with prominent forehead, triangular shape, down-slanting palpebral fissures, pointed chin
- Eye (strabismus), ear (otitis with conductive hearing loss), mouth (high palate, worn teeth) defects
- Cardiac (atrial septal defect, patent ductus arteriosus) defects, and skeletal/connective tissue (large hands/feet, joint laxity, flat feet) defects

- Tumors: Slight increased risk for malignancy (2.2%), including Wilms tumor, several others

BIRTH DEFECT COMBINATIONS AND ASSOCIATIONS

Goldenhar Syndrome/Hemifacial Microsomia

Background

- Prevalence: 1 in 5000 live births
- Variable defect pattern from hemifacial microsomia to multiple facial, cardiac, and vertebral defects
- Goldenhar syndrome and VACTERL association occur in infants of diabetic mothers
- Presence of minor anomalies mandates genetic testing for chromosomal or Mendelian syndromes

Abnormalities

- Development: ID (5–15%) that correlates with craniofacial severity
- Growth: Low birth weight, failure to thrive due to dysphagia, decreased salivation, palatal defects
- Neural: Seizures, facial palsies, encephaloceles, lipomas, Arnold-Chiari malformation
- Face: Hemifacial microsomia, external and middle ear anomalies (Fig. 4.24), preauricular tags
- Eye: Epibulbar dermoids (outer quadrant), lipoepidermoid cysts (inferior quadrant), microphthalmia
- Cardiopulmonary (VSD, tetralogy of Fallot, lung hypoplasia) and renal (agenesis, hydronephrosis) defects
- Skeletal: Cervical vertebral fusion/Klippel-Feil defects, vertebral anomalies, radial defect

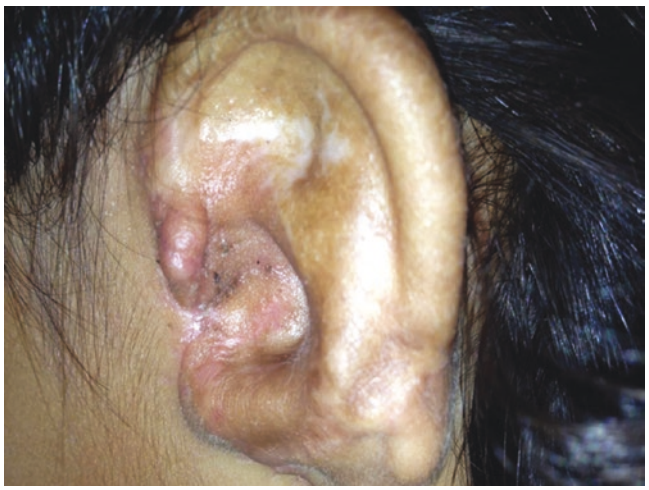


Fig. 4.24 A child with Goldenhar syndrome has incomplete development of the ear

Health supervision and preventive care

- Microarray analysis should be performed to exclude chromosome imbalance and whole exome sequencing considered to exclude other Mendelian syndromes with branchial arch defects
- Those with severe craniofacial deformity should have head MRI to exclude brain anomalies
- Craniofacial surgery team evaluation, including neurosurgery, ophthalmology, ENT, and feeding expertise

Poland Sequence

Background

- Prevalence: 1 in 20,000, three times more common in males, 75% right-sided
- Poland sequence is hypothesized to derive from abnormal subclavian and/or vertebral artery blood flow in the 6-week embryo [13], linking it to Moebius and Klippel-Feil sequence with vertebral anomalies
- Usually sporadic, but parent-child and cousin concurrence has been reported

Abnormalities (all unilateral)

- Chest: Absent to hypoplastic pectoralis major muscle, absent nipple and areola, rib defects, dextrocardia without other heart defects
- Limbs: Ipsilateral upper limb hypoplasia with syndactyly, oligodactyly, and sometimes more severe reduction defects (10% of patients with hand syndactyly are thought to have Poland sequence)
- Other: Rare Sprengel anomaly, hemivertebrae, renal defects

Pierre Robin Sequence

- Prevalence: Range from 1 in 2000 to 1 in 30,000 births because of variable definition
- Named after surgeon Pierre Robin and not hyphenated
- Fetal jaw growth deficiency or constraint before 17 weeks is posited to be the primary anomaly, leading to defective fusion of the posterior (soft) palate and protrusion of the tongue
- True isolated Robin sequence is an embryologic error with sporadic occurrence
- Many chromosomal and Mendelian syndromes (e.g., trisomy 18, velocardiofacial, Shprintzen syndromes) have Robin sequence as part of their anomaly pattern and must be excluded

Abnormalities

- Lifespan: Mortality rates can be as high as 30%, often in early infancy due to obstruction/apnea
- Face: Mandibular hypoplasia (microretrognathia) with displacement of the tongue (glossoptosis)
- Palate: Interrupted closure of the lateral palatine ridges with posterior U-shaped cleft of the soft palate (the cleft in cleft lip/palate is V-shaped and more anterior due to defects in the primary palate)
- Respiratory: Obstruction and distress with poor feeding

Health supervision and preventive care

- Prone positioning to bring jaw forward is mandatory

AMNIOTIC BAND DISRUPTION SEQUENCE

Background

- Prevalence: 1 in 2000 births, much higher in abortuses
- Amniotic or Streeter's bands, like prenatal vascular breakdown, interfere with development of intrinsically normal tissue and thus are termed disruptions rather than malformations
- Sporadic occurrence with cocaine as a common cause

Abnormalities

- Band-produced clefts most commonly occur on the face and limbs but may disrupt any surface region
- Constricting limb bands can cause amputations (Fig. 4.25)
- Orofacial clefts caused by bands follow a geographic rather than embryonic distribution and can be surmised even without persisting band remnants

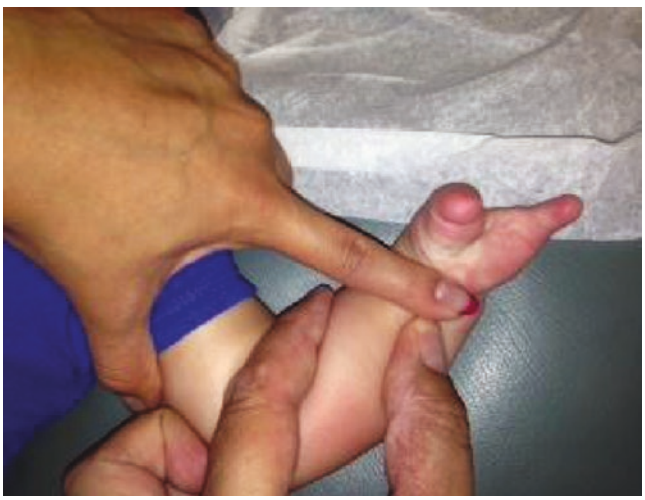


Fig. 4.25 Six-month-old female with amniotic bands resulting in congenital amputation (oligodactyly)

- Management depends on location and ranges from extensive craniofacial surgery with parental support to hand and orthopedic surgery referrals

VACTERL Association (VATER Association)

Background

- Prevalence: 1.6 per 1000 births
- Defined as an acronym for *V*ertebral, *A*norectal, *C*ardiac, *T*racheo-*E*sophageal, *R*adial, *R*enal, and *L*imb defects, three defects required for secure diagnosis ("trill the R" for radial and renal)
- The anomalies arise from embryonic mesodermal at 3–4 weeks post-conception
- Sporadic with low recurrence risk, provided minor anomalies are not present to suggest a syndrome
- Higher prevalence in infants of diabetic mothers

Major abnormalities

- Development: Normal brain function, but delays and disability may ensue from a turbulent infancy with multiple surgeries and feeding issues
- Growth: Prenatal deficiency can occur with frequent failure to thrive, particularly with tracheo-esophageal and anal defects
- Head/neck: Large fontanels, plagiocephaly, torticollis, Klippel-Feil sequence
- Neural: Spina bifida, hydrocephalus, tethered cord
- Cardiac (VSD, others) and pulmonary (tracheoesophageal fistula, laryngeal stenosis, horseshoe lung) defects
- GI (esophageal atresia), skeletal (radial aplasia/club hand), renal (horseshoe kidney) defects
- Genital defects: Cryptorchidism, hypospadias, micropenis, vaginal atresia

Minor anomalies

- Single umbilical artery (35%) is frequent, but others may suggest syndromes like trisomy 18

Health supervision and preventive care

- Thorough neonatal physical examination and appropriate imaging studies to document anomalies
- Finding of one cognate anomaly should prompt evaluation for the others
- Generous use of genetic evaluation and testing, since multiple defects often indicate syndromes

PEARLS AND PITFALLS

Pearls

- Rare or extreme diseases are more likely to have a significant genetic predisposition.
- For conditions with several modes of inheritance (e.g., deafness, epilepsy, myopathy), autosomal recessive inheritance will produce more severe symptoms than X-linked or autosomal dominant inheritance.
- Children with significant dysmorphology and ID are more likely to have chromosome changes, while those with normal appearance and acute deterioration are more likely to have metabolic disorders.
- A good physical examination, including ascertainment of minor anomalies like the single palmar crease is paramount for distinguishing morphologic from metabolic disorders.
- It is more important to recognize the likelihood of a syndrome with its risks for ID and birth defects than to recognize a specific syndrome diagnosis; chromosome and gene testing appropriate to a morphologic disorder will provide the diagnosis.

Pitfalls

- One cannot provide accurate recurrence risks without a diagnosis.
- Diagnosis of an isolated birth defect with its low recurrence risk will be misleading if the minor anomalies and facial changes of a chromosomal or Mendelian syndrome are not appreciated.
- Assuming low risks for chromosome disorders like Down or Patau can be inaccurate if cytogenetics to exclude translocations has not been performed.
- Overly negative and inaccurate counseling for parents adjusting to new genetic diagnoses can disrupt infant-parent bonding and parent-physician relationships.

References

1. Wyandt HE, Wilson GN, Tonk VS. Chromosome structure and variation: heteromorphism, polymorphism, and pathogenesis. Singapore: Springer; 2017.
2. Tonk VS, Wilson GN. Inaccuracy of noninvasive prenatal screening demands cautious counsel and follow-up. Am J Med Genet A. 2016;170A(4):1086–7.
3. Jones KL, Jones MC, Del Campo M. Smith's recognizable patterns of human malformation. 7th ed. Philadelphia: Elsevier-Saunders; 2013.
4. Wilson GN, Cooley WC. Preventive health care for children with genetic conditions: providing a primary care medical home. 2nd ed. Cambridge, UK: Cambridge University Press; 2006.
5. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine. Online Mendelian Inheritance in Man. https://www.omim.org/. Accessed 17 Dec 2018.
6. Bull MJ, Committee on Genetics. Health supervision for children with Down syndrome. Pediatrics. 2011;128(2):393–406. *Erratum* in: Pediatrics. 2011;128(6):1212.
7. Frías JL, Davenport ML, Committee on Genetics and Section on Endocrinology. Health supervision for children with Turner syndrome. Pediatrics. 2003;111(3):692–702.
8. Committee on Genetics. American Academy of Pediatrics: health supervision for children with Williams syndrome. Pediatrics. 2001;107:1192–204.
9. Scott RH, Walker L, Olsen ØE, Levitt G, Kenney I, Maher E, et al. Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. Arch Dis Child. 2006;91(12):995–9.
10. Hersh JH, Saul RA, Committee on Genetics. Health supervision for children with fragile X syndrome. Pediatrics. 2011;127(5):994–1006.
11. Tinkle BT, Saal HM. Committee on genetics. Health supervision for children with Marfan syndrome. Pediatrics. 2013;132(4):e1059–72.
12. The Ehlers-Danlos Society. Assessing joint hypermobility: the Beighton scoring system. https://www.ehlers-danlos.com/assessing-joint-hypermobility/. Accessed 17 Dec 2018.
13. Bavinck JN, Weaver DD. Subclavian artery supply disruption sequence: hypothesis of a vascular etiology for Poland, Klippel-Feil, and Möbius anomalies. J Med Genet. 1986;23(4):903–18.

Suggested Reading

American Board of Pediatrics. Content Outlines, https://www.abp.org/content/content-outlines-0. Accessed 17 Dec 2018.

American Academy of Pediatrics. Genetics in Primary Care Institute. A toolkit to improve care for pediatric patients with genetic conditions in

primary care. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/genetics-in-primary-care/Documents/GPCI_Toolkit.pdf. Accessed 17 Dec 2018.

Committee on Bioethics; Committee on Genetics, and; American College of Medical Genetics and; Genomics Social; Ethical; Legal Issues committee. Ethical and policy issues in genetic testing and screening of children. Pediatrics. 2013;131(3):620–2.

American Academy of Pediatrics. Genetics in Primary Care Institute. Genetics in primary care. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/genetics-in-primary-care/Pages/default.aspx. Accessed 17 Dec 2018.

Metabolic Disorders

5

Osama I. Naga

MAJOR CLASSIFICATIONS OF INHERITED METABOLIC DISORDERS (TABLE 5.1)

Clinical Approach to a Newborn with Suspected Inborn Errors of Metabolism (Fig. 5.1)

Clues to Metabolic Disorders

- Most infants are healthy at birth then become progressively sick
- May present hours to years after birth, depending on the underlying type of metabolic disorders and possible triggers, e.g., fasting or illness

Initial laboratory evaluation

- Complete blood count (CBC)
  - To screen for sepsis, neutropenia, anemia, and thrombocytopenia
- Serum electrolytes, bicarbonate, and blood gases levels
  - To detect electrolyte imbalances and to evaluate the anion gap (usually elevated) and acid/base status
- Blood urea nitrogen (BUN) and creatinine levels
  - To evaluate renal function

Table 5.1 Major classifications of inherited metabolic disorders

Major classifications	Inherited metabolic disorders
Protein	
Organic acidemias	Isovaleric acidemia, propionic acidemia, 3-methylcrotonyl-CoA carboxylase deficiency, multiple carboxylase deficiency (biotinidase deficiency), methylmalonic acidemia, maple syrup urine disease (MSUD), glutaric acidemia type 1
Disorders of amino acid metabolism	Phenylketonuria, tyrosinemia, alkaptonuria homocystinuria, nonketotic hyperglycinemia
Urea cycle defects	Ornithine transcarbamylase deficiency (OTC), carbamoyl phosphate synthetase I deficiency
Fat	
Fatty acid oxidation defects	Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD)
Carbohydrate	
Disorders of carbohydrate metabolism	Galactosemia, glycogen storage diseases, McArdle disease, Pompe disease, fructose metabolic diseases
Others	
Lysosomal storage disorders–MPS	Hurler/Hunter/San Filippo/ Morquio syndromes
Lysosomal storage disorders–Lipids	Gaucher disease, Niemann-Pick disease, Tay-Sachs disease, Fabry disease
Disorders of peroxisomal function	Zellweger syndrome, X-linked adrenoleukodystrophy (X-ALD)
Disorders of porphyrin metabolism	Acute intermittent porphyria
Disorders of purine or pyrimidine metabolism	Lesch-Nyhan syndrome

O. I. Naga (✉)
Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, USA
e-mail: osama.naga@ttuhsc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_5

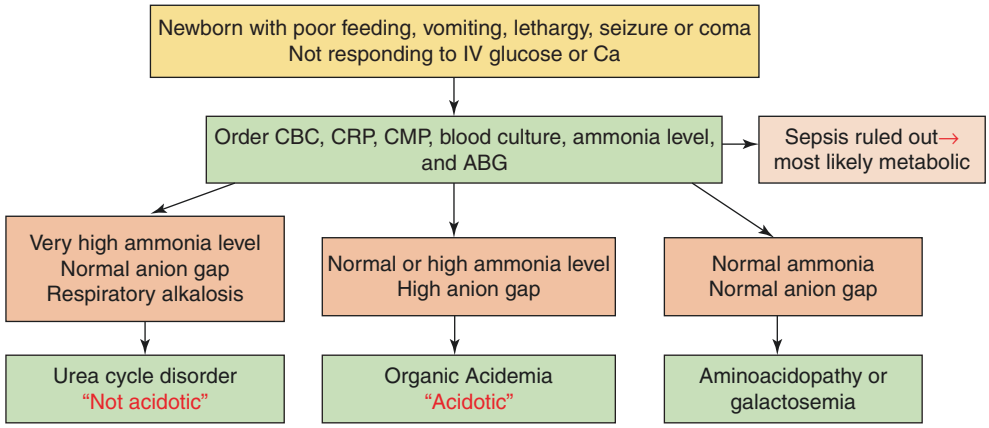


Fig. 5.1 Clinical approach to a newborn with suspected inborn errors of metabolism. *IV* intravenous, *CBC* complete blood count, *CRP* C-reactive protein, *CMP* complete metabolic panel, *ABG* arterial blood gas

- Bilirubin level, transaminases levels, prothrombin time, and activated partial thromboplastin time
  - To evaluate hepatic function
- Ammonia level
  - If an altered level of consciousness, persistent or recurrent vomiting, primary metabolic acidosis with increased anion gap, or primary respiratory alkalosis in the absence of toxic ingestion
- Blood glucose and urine pH, ketones, and reducing substances levels
  - To evaluate for hypoglycemia
- Lactate dehydrogenase, aldolase, creatinine kinase, and urine myoglobin levels
  - If any evidence of neuromyopathy

Secondary tests

- Plasma quantitative amino acids and acylcarnitines
- Urine organic acids, acylglycine, and/or orotic acid
- Serum lactate and pyruvate levels
- Cerebrospinal fluid (CSF) lactate, pyruvate, organic acids, neurotransmitters, and/or disease-specific metabolites
- Other tests depending on individual case

General management

- ABCs: airway, breathing, circulation
- Intravenous (IV) access
- Nothing by mouth (NPO), especially no protein, galactose, or fructose
- IV dextrose (D10–D15 with electrolytes to maintain serum glucose level at 120–170 mg/dL)
- If necessary, treat hyperglycemia with insulin
- Dextrose is a lifesaver in most cases of metabolic disorders

Hyperammonemia

- Hyperammonemia therapy is indicated when urea cycle defects cause encephalopathy
- Ammonul (benzoate/phenylacetate) must be given by central line. Arginine HCl can be mixed with Ammonul
- Hemodialysis
- If ammonia is ≥ 500–600 mg/dL before administering Ammonul, or is ≥ 300 mg/dL after giving Ammonul, consider hemodialysis

Pyridoxine (B6)

- Give B6 for possible pyridoxine-responsive inborn-errors-of-metabolism (IEM) seizures unresponsive to conventional anticonvulsants

General Rules

- Metabolic acidosis
  - Metabolic acidosis usually with elevated anion gap occurs with many IEMs and is a hallmark of organic acidemias; manifestations include tachypnea, vomiting, and lethargy
- Hypoglycemia
  - Hypoglycemia (plasma glucose level < 50 mg/dL) is rare in children and may be associated with undiagnosed fatty acid oxidation defect or endocrine disorder
- Ammonia level

  - Ammonia level greater than 100 mcg/dL in the neonate and greater than 80 mcg/dL beyond the neonatal period is considered elevated
  - Ammonia is highest in the urea cycle defects often exceeding 1000 mcg/dL and causing primary respiratory alkalosis sometimes with compensatory metabolic acidosis
  - Ammonia in organic acidemias, if elevated, rarely exceeds 500 mcg/dL, and in fatty acid oxidation defects is usually less than 250 mcg/dL
- **Most are autosomal recessive enzyme deficiencies;** carriers with one rather than two abnormal alleles have sufficient enzyme (50%) for metabolism (enzyme reserve); exceptions include:
  - Ornithine transcarbamylase deficiency (OTC), Hunter, Fabry, Lesch-Nyhan, and X-linked adrenoleukodystrophy (X-ALD) exhibit X-linked recessive inheritance
  - Mitochondrial diseases exhibit maternal inheritance if caused by mitochondrial rather than nuclear DNA mutations
  - Some porphyrias exhibit autosomal dominant inheritance
- Testing of organic acids is most sensitive in urine, and testing of amino acids is most sensitive in blood
- DNA testing to demonstrate mutations in the genes encoding an enzyme is now easier than documenting deficient enzyme activity, allowing diagnosis using cheek swab/blood samples and subsequent preimplantation genetic/prenatal diagnosis

ORGANIC ACIDEMIA

- Isovaleric acidemia
- Maple syrup urine disease (MSUD)
- Methylmalonic acidemia
- Propionic acidemia
- 3-Methylcrotonyl-CoA carboxylase deficiency
- Biotinidase deficiency
- Glutaric acidemia type 1

Keywords to all cases of organic acidemia
- *Normal or high ammonia level*
- *High anion gap*
- *Metabolic acidosis*
- *Neutropenia*

Isovaleric Acidemia (Sweaty Feet Odor)

Background
- Also called isovaleric aciduria (IVA)
- Caused by isovaleric acid CoA dehydrogenase deficiency
- A rare autosomal recessive that disrupts or prevents normal metabolism of the branched-chain amino acid leucine
- Characteristic type of organic acidemia

Clinical presentation
- Newborn period
  - Episodes of severe metabolic acidosis with ketosis
  - Vomiting
  - Encephalopathy progressing to coma and death if untreated
  - Sweaty feet odor
- During childhood
  - Usually precipitated by an infection or increased protein intake
  - Pancytopenia and acidosis in infants who survive the acute attack

Diagnosis
- Sweaty feet odor is a keyword
- Urine organic acids show elevated C5 acylcarnitine
- DNA testing

Treatment
- IV glucose and bicarbonate in an acute attack
- Restriction in leucine intake
- Carnitor to preserve free carnitine for mitochondrial transport and glycine to increase conversion of isovaleryl-CoA to isovaleryl-glycine

Maple Syrup Urine Disease (MSUD)

Background

- MSUD is an aminoacidopathy secondary to an enzyme defect in the catabolic pathway of the branched-chain amino acids leucine, isoleucine, and valine
- Accumulation of these three amino acids and their corresponding keto acids leads to encephalopathy and progressive neurodegeneration in untreated infants
- Early diagnosis and dietary intervention prevent complications and may allow for normal intellectual development

Clinical presentation

- Urine smells like maple syrup with a sweet, caramel-like odor
- Feeding difficulty
- Irregular respiration
- Loss of Moro reflex
- Severe seizures
- Opisthotonos rigidity
- Death from cerebral edema

Diagnosis

- Metabolic acidosis due to ketoacidosis
- Increased anion gap
- Increased leucine, isoleucine, and valine in plasma (urine levels less reliable)
- Detection of L-alloisoleucine is diagnostic for MSUD (most sensitive marker)
- DNA testing

Treatment

- Dietary control of leucine, isoleucine, and valine
- Frequent monitoring of branched-chain amino acids (even every 1–2 days in early life) is essential because of the changing protein requirements of the newborn

Prognosis

- Normal growth and development can progress if diagnosis and treatment occur before 10 days of age

Methylmalonic Acidemia

Background

- Autosomal recessive
- Deficiency of methylmalonyl-CoA mutase or its vitamin B12 cofactor

Clinical presentation

- Vomiting
- Ketoacidosis
- Hyperammonemia
- Thrombocytopenia
- Failure to thrive in chronic cases
- Renal failure may occur

Diagnosis

- Elevation of methylmalonic acid in urine and, in the case of B12 deficiency, homocysteine in blood
- DNA testing

Treatment

- Restriction of dietary protein
- Carnitine is useful to prevent depletion and to maintain mitochondrial transport
- Liver and kidney transplantation may be curative
- Give betaine and intramuscular (IM) vitamin B12 if the patient has methylmalonic aciduria and homocystinuria

Propionic Acidemia

Background

- Autosomal recessive
- Deficiency in propionyl-CoA carboxylase

Clinical presentation

- Severe ketoacidosis with or without hyperammonemia in neonates
- Infants may present with encephalopathy, vomiting, and bone marrow suppression
- Some infants may present with ketoacidosis due to infection or vomiting
- Cardiomyopathy is a late onset complication

Diagnosis
- Urine organic acids
- Large amount of 3-hydroxypropionic and methylcitric acids in urine is the most specific
- Abnormal ketone bodies
- DNA testing

Treatment
- Dietary restriction of protein < 1 g/kg/day
- Carnitine is helpful in preventing deficiency and in increasing excretion of propionyl-CoA

Prognosis
- Most children die young

Isolated Beta-Methylcrotonyl-CoA Carboxylase Deficiency

Background
- Autosomal recessive
- Due to enzyme inadequate to break down leucine
- Age: 1–3 years

Clinical presentation
- Vomiting
- Diarrhea
- Metabolic acidosis
- Hypotonia
- Hypoglycemia

Treatment
- Long-term leucine restriction

Biotinidase Deficiency

Background
- Deficiency in holocarboxylase synthetase or biotinidase
- Many states in the USA do newborn testing for biotinidase

Clinical presentation
- Alopecia
- Skin rash (periorificial dermatitis)
- Failure to thrive
- Hypotonia
- Encephalopathy
- Without treatment, the patient may develop intractable seizures, hearing loss, and blindness
- Sudden infant death syndrome (SIDS)

Diagnosis
- Urine organic acid
- Increased 3-methylcrotonylglycine and 3-hydroxyisovaleric acid with lactic acid in urine
- DNA testing

Treatment
- Oral biotin

Glutaric Aciduria Type I or Glutaric Acidemia

Background
- Deficiency of glutaryl-CoA dehydrogenase
- A defect in catabolism of lysine, hydroxylysine, and tryptophan

Clinical presentation
- May present with macrocephaly at birth but generally normal development until they have a stressor, e.g., febrile illness, then they may develop hypotonia, spasms, jerking, rigidity or dystonia
- Retinal hemorrhage and subdural hematoma are usually mistaken for child abuse

Treatment
- Carnitine

Summary (Table 5.2)

Table 5.2 Organic acidemia disorders

Disorders	Keywords (metabolic acidosis, high anion gap, normal or high ammonia level)
Isovaleric acidemia	Sweaty feet odor
Maple syrup urine disease (MSUD)	Urine smells like maple or with an odor, loss of Moro reflex, severe seizures, opisthotonos rigidity, positive plasma l-alloisoleucine
Methylmalonic acidemia	Thrombocytopenia, massive urinary methylmalonic acid in urine
Propionic acidemia	Encephalopathy, bone marrow suppression, a large amount of 3-hydroxypropionic and *methylcitric acid* in urine
Biotinidase deficiency	Intractable seizures, hypotonia, ataxia, developmental delays, vision problems, hearing loss, alopecia, skin rash
Glutaric aciduria type 1	Macrocephaly, retinal hemorrhage and subdural hematoma (can be mistaken for child abuse)

DISORDERS OF AMINO ACID METABOLISM

- Phenylketonuria
- Tyrosinemia
- Homocystinuria
- Alkaptonuria
- Nonketotic hyperglycinemia

Phenylketonuria (PKU)

Background

- The most common inborn error of amino acid metabolism
- The deficiency of phenylalanine hydroxylase (PAH) enzyme impairs the body's ability to metabolize the essential amino acid phenylalanine
- Elevated phenylalanine levels negatively impact cognitive function

Clinical presentation

- Fair skin and hair
- Hair loss
- Eczema (including atopic dermatitis)
- Light sensitivity
- Increased incidence of pyogenic infections

Other manifestations of untreated PKU

- Intellectual disability (ID) (the most common finding overall)
- Musty or mousy odor
- Epilepsy (50%)
- Extrapyramidal manifestations (e.g., parkinsonism)
- Eye abnormalities (e.g., hypopigmentation)

Diagnosis

- Elevated phenylalanine levels
- DNA testing to demonstrate mutations in phenylalanine hydroxylase (PAH) genes or, rarely, in the genes promoting synthesis of its tetrahydrobiopterin (BH4) cofactor

Imaging studies

- Brain magnetic resonance imaging (MRI) studies may be indicated in older individuals with deficits in motor or cognitive function
- Brain MRI may show areas of demyelination and volume loss in severe cases

Dietary treatment

- Newborn screening can detect PKU in nearly 100% of cases; thus, cognitive deficits can be prevented by treatment with a low-protein diet and a phenylalanine-free medical formula as soon as possible after birth
- Genetic testing to confirm the diagnosis
- Essential amino acid, vitamin, and mineral supplementations

Pharmacologic management

- Sapropterin, a form of the BH4 cofactor, may lower phenylalanine levels in some patients

Non-classic phenylketonuria

- Deficiency of tetrahydrobiopterin, a cofactor for the enzyme phenylalanine hydroxylase
- Usually presents with marked hypotonia, spasticity, posturing, and psychomotor developmental delay

Homocystinuria

Background

- Classic homocystinuria follows an autosomal recessive inheritance and has a prevalence of 1:200,000 live births
- Caused by deficiency of cystathionine beta-synthase

Clinical presentation (Table 5.3)

- Marfanoid habitus
- Pectus excavatum, pectus carinatum, and genu valgum
- Limited joint mobility
- Lens dislocated downward and medially
- Developmental delay
- ID
- Increased risk of thromboembolism

Diagnosis

- Homocystinuria
- Serum methylmalonic acid is the most specific
- High serum methionine
- Megaloblastic anemia
- DNA testing

Treatment

- 50% respond to large doses of pyridoxine, folic acid, cobalamin, and betaine with concurrent methionine restriction

Prognosis

- Near-normal life expectancies with some having progressive ID
- Half of the patients with homocystinuria will have a psychiatric disease, and one-fifth will have seizures
- Acute stroke symptoms may occur in these patients

Alkaptonuria

Background

- Autosomal recessive
- Due to deficiency of homogentisic acid dioxygenase

Clinical presentation

- Black urine when left standing
- Dark brown or black pigments in the diaper
- Slate blue or gray discoloration may be found in the sclerae or ear cartilage
- Calcifications may be palpable in the discolored areas, e.g., ear cartilage
- Arthritis
- Mitral or aortic valvulitis

Diagnosis

- Homogentisic acid in urine can be identified
- DNA testing

Management

- Reduction of phenylalanine and tyrosine is a reasonable approach
- Vitamin C
- Older individuals may require removal of lumbar discs with fusion, also may need replacement of the affected joints

Table 5.3 Difference between homocystinuria and Marfan syndrome

Homocystinuria	Marfan syndrome
Autosomal recessive	Autosomal dominant
Intellectual disability	Normal intelligence
Ocular lens usually dislocated downward (ectopia lentis)	Ocular lens usually dislocated upward (ectopia lentis)
Limited joint mobility	Lax joint (hyperflexibility)
Normal aorta	Aortic dilatation
Associated with thromboembolism	Associated with easy bruising and fragile skin

Glycine Encephalopathy (Nonketotic Hyperglycinemia)

Background
- Autosomal recessive
- Due to a defect in the glycine cleavage system, an enzyme complex responsible for glycine catabolism

Clinical presentation
- Glycine encephalopathy
- Unremitting seizures
- Apnea
- Hiccups
- Hypotonia
- Burst suppression pattern on electroencephalogram (EEG)
- Coma
- Death in infancy

Diagnosis
- Increase glycine in CSF
- DNA testing for glycine cleavage system gene mutations (over 6 genes in all)

Treatment
- Sodium benzoate may help for seizures; treatment is usually unsuccessful

Tyrosinemia Type I (Hepatorenal Tyrosinemia)

Background
- Due to deficiency of fumarylacetoacetate hydrolase enzyme
- Infants affected early, and most have a rapid course to death

Clinical presentation
- Failure to thrive
- Hepatomegaly
- Hepatoblastoma
- Associated with renal tubular acidosis (RTA), resembling Fanconi syndrome, as well as radiographic fraying of rickets

Diagnosis
- High level of tyrosine in plasma and succinylacetone in blood and urine
- DNA testing

Treatment
- Nitisinone to block tyrosine metabolism, diet low in tyrosine and phenylalanine

Tyrosinemia Type II (Oculocutaneous Tyrosinemia)

Cause
- Due to deficiency of tyrosine aminotransferase

Clinical presentation
- ID in 50%
- Corneal ulcer, eye pain, and excessive tearing
- Painful red papular keratotic lesions on palms and soles

Management
- Diet low in tyrosine, but even this may not be curative

Summary (Table 5.4)

Table 5.4 Disorders of amino acid metabolism

Disorders	Keywords (normal anion gap, normal ammonia level)
Phenylketonuria	Fair hair and skin, eczema, musty odor, intellectual disability, eye hypopigmentation
Homocystinuria	Marfanoid features, intellectual disability, eye lens located downward and medially, thromboembolism
Alkaptonuria	Dark urine, calcification of ear cartilage, arthritis
Nonketotic hyperglycinemia	Seizure, apnea, hiccups, coma, death, increased glycine in CSF
Hepatorenal tyrosinemia (type I)	Failure to thrive, hepatomegaly, RTA
Oculocutaneous tyrosinemia (type I)	ID, corneal ulcers, painful skin lesions in palms and soles

CSF cerebrospinal fluid, *RTA* renal tubular acidosis, *ID* intellectual disability

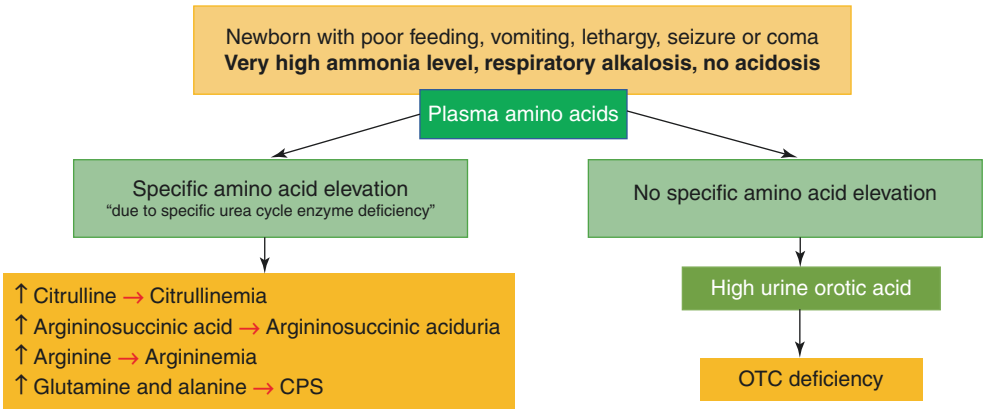


Fig. 5.2 Clinical approach to a child with suspected urea cycle disorders. *CPS* carbamoyl phosphate synthetase, *OTC* ornithine transcarbamylase deficiency

UREA CYCLE DISORDERS (UCD)

- OTC
- Citrullinemia
- Argininemia
- Argininosuccinic aciduria
- Carbamoyl phosphate synthetase (CPS) deficiency

Keywords: *Serum ammonia levels may exceed 2000 mg/dL and very low BUN level, normal anion gap, and respiratory alkalosis* (Fig. 5.2)

Ornithine Transcarbamylase (OTC) Deficiency

Background

- OTC deficiency is an X-linked genetic disorder of the urea cycle
- Associated with very high level of ammonia in the blood
- Mysteriously presents in childhood in otherwise healthy individuals
- More severe in males than females and tends to present earlier

Clinical presentation

- Heavy or rapid breathing
- Lethargy
- Vomiting
- Hypothermia
- Somnolence
- Seizures
- Cerebral edema
- Decorticate or decerebrate posturing
- Coma
- Death (if treatment is not forthcoming or effective)
- Female may present with a severe migraine-like headache after excessive protein intake

Diagnosis

- Plasma ammonia levels may exceed 2000 mg/dL
- Very low BUN level
- Normal anion gap and respiratory alkalosis
- Normal liver and kidney function in most cases, unless hypoxia or shock supervenes
- Elevated ornithine, glutamine, and alanine levels and relatively low citrulline levels
- Elevated urinary orotic acid level
- DNA testing

Management

- Immediate temporary discontinuation of protein intake
- Compensatory increases in dietary carbohydrates and lipids
- Hemodialysis for comatose patients with extremely high blood ammonia levels; rapid reduction can be achieved with hemodialysis
- IV administration of sodium benzoate, arginine, and sodium phenylacetate

FATTY ACID OXIDATION DEFECTS (FAOD)

- Medium-chain acyl-CoA dehydrogenase deficiency
- Glutaric acidemia type II

Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)

Keywords: *Fasting, anorexia from illness, hypoglycemia and hyperammonemia without ketosis*

Background

- Hypoketotic hypoglycemia due to MCAD
- Beta-oxidation of fatty acids for the production of energy is only required during periods of fasting
- Clinical manifestations do not become apparent unless substantial fasting has occurred
- Most common in the first 2 years of life

Clinical presentation

- Vomiting and diarrhea
- Fasting-induced lethargy and hypoglycemia
- Seizure and coma are very common
- Associated with Reye syndrome and SIDS
- Between episodes of illness, affected patients are normal

Diagnosis

- Laboratory findings during periods of decompensation include hypoketotic hypoglycemia and hyperammonemia provoked by fasting
- Elevated C6, C8, and C10 on plasma acylcarnitine (PAC) profile (Fig. 5.3)

Treatment

- Treatment of these disorders usually includes the avoidance of fasting, supplementation with carnitine, and administration of dextrose during acute episodes

Prevention

- Avoid fasting more than 4–5 h (fasting is contraindicated)
- Carbohydrate snacks at bedtime
- Carnitine is important to prevent depletion of free carnitine by fatty acylcarnitines and inhibition of mitochondrial transport
- 25% of infants die before the result of the newborn screen

Glutaric Acidemia Type II

Cause

- Deficiency of any of three genes producing the electron transfer flavoprotein cofactor for glutaryl-CoA dehydrogenase (glutaric acidemia type I results from deficiency of this enzyme)
- Inability of the body to use the protein and fat for energy

Clinical presentation

- Neonates may present with severe hypoglycemia, metabolic acidosis, and hyperammonemia
- Sweaty feet odor
- Cardiomyopathy
- Severe renal cystic dysplasia

Treatment

- Avoid fasting
- Carnitine to avoid depletion

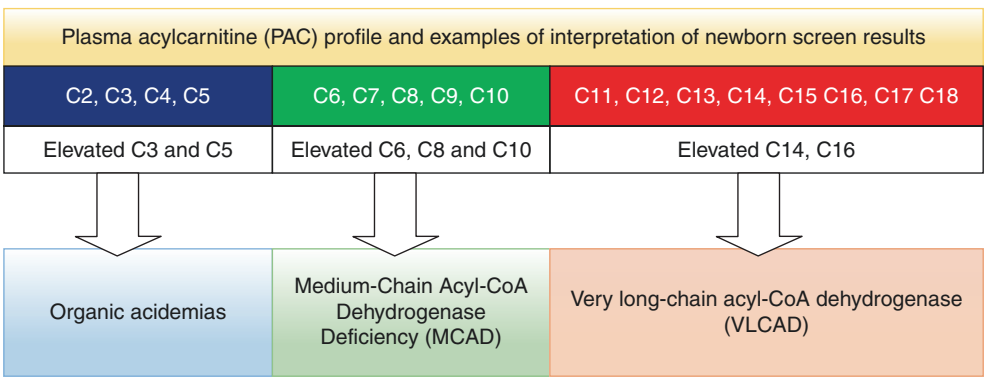


Fig. 5.3 Newborn screening: Using tandem spectrometry detection of single plasma samples or blood spots—Three plasma acylcarnitine (PAC) profiles and examples of interpretation. *Left panel:* organic acidemias. *Center panel*: MCAD. *Right panel*: VLCAD

DISORDERS OF CARBOHYDRATE METABOLISM

- Galactosemia
- Galactokinase deficiency
- Glycogen storage diseases
- Von Gierke disease
- Pompe disease
- McArdle disease
- Adenylate deaminase deficiency
- Deficiency of fructose 1, 6-bisphosphate aldolase
- Fructokinase deficiency

Keywords: *Hypoglycemia, hepatosplenomegaly, jaundice, weakness*

Galactosemia

Background
- Hereditary galactosemia is among the most common carbohydrate metabolism disorders
- Can be a life-threatening illness during the newborn period
- Galactose-1-phosphate uridyl transferase (GALT) deficiency is most common

Clinical presentation
- Jaundice
- Vomiting
- Lethargy
- Irritability
- Hypoglycemia
- Seizure
- Cataract
- Vitreous hemorrhage
- Hepatosplenomegaly
- Cirrhosis
- Ascites
- Poor weight gain
- ID

Diagnosis
- Clinically
- Reducing substance in urine
- Important not to exclude the diagnosis of galactosemia because the urine does not contain reducing substances
- GALT assay in erythrocytes followed by DNA analysis for GALT mutations
- Prenatal diagnosis is possible using DNA analysis of chorionic villi or cultured amniotic cells
- Heterozygous and homozygous mothers are instructed to follow a galactose-free diet throughout their pregnancies

Treatment
- Elimination of galactose from the diet

Complications
- *E. coli* sepsis could be the initial presentation
- Ovarian failure, amenorrhea
- Developmental delay and learning disability even with proper treatment

Galactokinase Deficiency

- Cataract alone
- Chromosome 17
- Treatment is a restriction of galactose

Glycogen Storage Diseases

- 0—Glycogen synthase deficiency
- Ia—Glucose-6-phosphatase deficiency (von Gierke disease)
- II—Acid maltase deficiency (Pompe disease)
- III—Debranching enzyme deficiency (Forbes-Cori disease)
- IV—Transglucosidase deficiency (Andersen disease, amylopectinosis)
- V—Myophosphorylase deficiency (McArdle disease)
- VI—Phosphorylase deficiency (Hers disease)
- VII—Phosphofructokinase deficiency (Tarui disease)

Von Gierke Disease (Glucose-6-Phosphate Deficiency)

Background
- Autosomal recessive
- Age: Early infancy

Clinical presentation
- Hypoglycemia
- Lactic acidosis
- Hyperuricemia
- Hyperlipidemia
- Neutropenia
- Hepatomegaly without elevated liver enzymes
- Doll-like face (fatty cheeks), thin extremities
- Failure to thrive
- Seizures

Associated problems
- Gout
- Hepatic adenoma
- Pulmonary hypertension
- Pancreatitis

Diagnosis
- No response to glucagon or epinephrine
- DNA testing

Management
- For older children, uncooked cornstarch will sustain blood glucose for 4–6 h
- For young children, continuous nasogastric tube feeding of glucose is necessary to sustain normal blood glucose level, especially at night
- If surgery is required, a continuous infusion of glucose 24–48 h prior to surgery

Pompe Disease

Background
- Autosomal recessive
- Located on chromosome 17
- Type II glycogen storage disease
- Due to acid alpha-1, 4-glucosidase deficiency

Clinical presentation
- Infantile form
  - Most severe form
  - Infant is usually normal at birth but soon develops generalized muscle weakness, macroglossia, hepatomegaly, and cardiomegaly
  - Death < 1 year
- Juvenile/late childhood
  - Muscle weakness
  - Respiratory and digestive symptoms without cardiac involvement
  - Death may occur before the 20s

Diagnosis
- Electrocardiogram (ECG) shows high voltage QRS and shortened PR interval
- Elevated CPK, AST, and LDH
- The muscle biopsy will show vacuoles that full of glycogen on staining
- DNA testing

Treatment
- Unfortunately, no cure exists
- Enzyme replacement therapy (ERT) may benefit the patients, especially if combined with immune modulation

McArdle Disease, Muscle Phosphorylase Deficiency

Background
- Autosomal recessive
- Chromosome 11q13

Clinical presentation
- Usually in the 20s to 30s
- Exercise-induced cramps and exercise intolerance

- Burgundy-colored urine due to myoglobinuria and rhabdomyolysis

Diagnosis
- Elevated CPK at rest
- DNA testing

Treatment
- Avoid strenuous exercise to prevent rhabdomyolysis
- Oral fructose/glucose intake can improve exercise tolerance

Adenylate Deaminase Deficiency

Background
- Autosomal recessive trait

Clinical presentation
- Muscle weakness
- Cramping after strenuous exercise

Diagnosis
- CPK level may be increased
- No myoglobinuria
- Muscle biopsy is normal
- DNA testing

Treatment
- Oral D-ribose may prevent the symptoms if given at the beginning of the exercise

Fructose 1,6-Diphosphatase Deficiency

Keywords: *Healthy infant begins to have symptoms after the introduction of juice or any source of fructose or sucrose*

Background
- Autosomal recessive
- Age 4–6 months

Clinical presentation
- Infant is healthy until fructose or sucrose is ingested, e.g., juice or sweetened cereals
- Jaundice, vomiting, lethargy, seizures, and irritability
- Hepatomegaly
- Elevated liver enzyme
- Prolonged clotting factors
- If sugar intake continued, will lead to hypoglycemia, organ failure, and death

Diagnosis
- Reducing substances in urine during the episode
- IV fructose will cause hypoglycemia and hypophosphatemia

Treatment
- Avoid all sources of fructose, sucrose, and sorbitol

Prognosis
- Very good; however, reversal of damage and ID is uncommon

Fructokinase Deficiency

Background
- Deficiency of the enzyme hepatic fructokinase is a clinically benign condition characterized by the incomplete metabolism of fructose in the liver, leading to its excretion in urine

Clinical presentation
- Asymptomatic

Diagnosis
- Fructosuria
- Reducing substance in urine
- DNA testing

Treatment
- No treatment required

Summary (Table 5.5)

Table 5.5 Disorders of carbohydrate metabolism

Disorders	Keywords
Galactosemia	Hypoglycemia, cataracts, jaundice, hepatosplenomegaly, seizures
Von Gierke disease (glucose-6-phosphate deficiency)	Hypoglycemia, hyperlipidemia, hyperuricemia, lactic acidosis, hepatosplenomegaly, distended abdomen, doll-like faces with chubby cheeks, thin extremities, short stature
Pompe disease	Muscle weakness, cardiomegaly, elevated CPK
McArdle disease	Muscle cramps with exercise, myoglobinuria, elevated CPK
Fructose 1,6-diphosphatase deficiency	Healthy infant until juices (sucrose or fructose) are introduced, hypoglycemia, seizures, vomiting, hepatomegaly, coma if fructose or sucrose intake continued
Fructokinase deficiency	Asymptomatic fructosuria

LYSOSOMAL STORAGE DISORDERS: MUCOPOLYSACCHARIDOSES

Mucopolysaccharidosis (MPS)

Background

- Group of disorders due to a defect in the catabolism of glycosaminoglycans and accumulation of macromolecules in target organs
- All MPS autosomal recessive except Hunter syndrome, which is X-linked
- Patients with MPS have normal development initially
- Abnormalities are seen in infancy or sometimes later in childhood

MPS Type I (Hurler Syndrome)

- Defect in L-iduronidase

Clinical presentation

- Coarsened facial features
- Midface hypoplasia
- Large tongue
- Umbilical or an inguinal hernia, large head > 95%
- Recurrent upper respiratory infections
- Hepatosplenomegaly
- Cardiac disease (valvular or coronary involvement)
- Atlantoaxial subluxation
- Corneal clouding
- Deafness

Prognosis

- Related to cardiac involvement: Can involve early cardiomyopathy and death
- Some mildly affected due to different iduronidase alleles, formerly grouped as MPS V or Scheie syndrome

MPS Type II (Hunter Syndrome)

- Defect in iduronate-2 sulfatase on chromosome Xq27-28
- Only males are affected (only in females with non-random lyonization)

Clinical presentation

- Present in the first 2 years of life
- No corneal clouding
- Coarse facial features
- Learning difficulties
- Middle ear disease
- Joint stiffness
- Hepatosplenomegaly
- Skin rash: pebbly ivory skin lesions on the back, arms, and thighs (pathognomonic but rare in children)

MPS Type III (Sanfilippo Syndrome)

- Inability to catabolize heparan sulfate

Clinical presentation

- Coarse hair
- Clear cornea

- Developmental delay
- Severe challenging behavior and hyperactivity
- Aggression and unaware of self-harming
- Sleep disturbance
- Progressive dementia
- Swallowing dysfunction
- May deteriorate to vegetative state

MPS Type IV (Morquio Syndrome)

- Defect in galactosamine-6-sulfatase
- Leads to defective degeneration of keratan

Clinical presentation

- Short trunk dwarfism (final height < 125 cm)
- Fine corneal deposits
- Skeletal dysplasia
- Normal intelligence
- Odontoid dysplasia

General treatment of MPS

- Bone marrow transplantation may prevent intellectual deterioration and increase survival rate
- Enzyme replacement therapy is the treatment of choice
- Orthopedic surgery for spinal deformity

Summary (Table 5.6)

Table 5.6 Lysosomal storage disorders—mucopolysaccharidoses (MPS)

Disorders	Keywords
MPS general features	Coarse facial features, organomegaly, bony deformities, developmental regression, sensory loss (hearing and vision)
Hurler syndrome (MPS type I)	MPS general manifestations, mental deficiency, cloudy cornea
Hunter syndrome (MPS type II)	Mild MPS general manifestations, a boy (x-linked R) with no cloudy cornea
Sanfilippo syndrome	Behavioral problems, aggression, self-harming, progressive dementia, clear cornea
Morquio syndrome	Short stature, short trunk dwarfism, bone dysplasia, fine corneal opacities

LYSOSOMAL STORAGE DISORDERS: LIPIDOSES

- Gaucher disease
- Niemann-Pick disease
- Krabbe disease
- Tay-Sachs disease
- Fabry disease
- Wolman disease
- Metachromatic leukodystrophy

Keywords: *Splenomegaly, seizures, cherry-red spot*

Gaucher Disease

Background

- Gaucher disease is a lipid storage disease characterized by the deposition of glucocerebroside in cells of the macrophage-monocyte system
- The disorder results from the deficiency of the enzyme glucocerebrosidase
- Autosomal recessive
- Age 2–18 years
- Mutations in Ashkenazi Jews > 95%
- All forms of Gaucher usually develop hepatosplenomegaly, bone lytic lesions, and some lung diseases

Types of Gaucher disease

- Type 1—non-neuronopathic form (most common and does not affect the CNS)
- Type 2—acute neuronopathic form
- Type 3—chronic neuronopathic form

Clinical presentation

- Growing pain in lower extremities, especially at night due to bone infiltration
- Skin pigmentation
- Splenomegaly
- Abdominal protuberance due to the very large spleen
- Hypersplenism; significant thrombocytopenia, can result in severe bleeding, pallor, and anemia

Diagnosis
- Bone marrow aspiration: Gaucher storage cells wrinkled paperlike tissue
- Deficiency of glucocerebrosidase in leukocytes and cultured skin
- Loss of bone tabulation on radiograph
- DNA testing

Treatment
- Splenectomy is contraindicated
- Enzyme replacement therapy (ERT) for type 1 Gaucher disease, e.g., imiglucerase (Cerezyme)

Niemann-Pick Disease (NPD)

Background
- NPD is a lipid storage disorder
- Due to deficiency of acid sphingomyelinase
- NPD type A
  - Very rare neurovisceral disease
  - Occurs mainly in Ashkenazi Jews
  - Hepatosplenomegaly
  - Progressive loss of motor skills
  - Cherry-red spot
- NPD type B
  - Common in Ashkenazi Jews
  - Inherited as autosomal recessive traits
  - Isolated splenomegaly
- NPD type C
  - Results from defects in cholesterol metabolism
  - Located on chromosome 18
  - Age: 3–4 years of age
  - Due to cholesterol ester accumulation in the lysosome

Clinical presentation of NPD type C
- Dysphagia is common and may lead to a feeding tube
- Hepatosplenomegaly
- Poor school performance in older children
- Cataplexy and narcolepsy are very common
- Ataxia
- Supranuclear and vertical-gaze palsy
- Voluntary, vertical eye movement is usually lost, but reflex and doll-eye movement are preserved
- Death in the teens is common

Diagnosis
- Intra-lysosomal accumulation of unesterified cholesterol in cultured fibroblast
- DNA testing

Krabbe Disease

Background
- Autosomal recessive
- Mutation in the *GALC* gene located on chromosome 14 (14q31)
- β-Galactocerebrosidase deficiency and white matter accumulation of galactosylceramide in peripheral and central myelin, resulting in spasticity and cognitive impairment

Clinical presentation
- Convulsions
- Quadriplegia
- Blindness, deafness
- ID
- Progressive neurologic symptoms that lead to death by age 2

Treatment
- No cure
- Bone marrow transplantation may benefit early in the course of the disease

Tay-Sachs Disease

Background
- Autosomal recessive
- Due to deficiency of beta-hexosaminidase alpha subunit
- Neurons have lamellar inclusions
- No visceral involvement

Clinical presentation

- Noise or light startles the infant with a quick extension of the arms and legs with clonic movement (unlike Moro reflex, this does not diminish with repeated stimuli)
- Axial hypotonia
- Extremities hypertonia and hyperreflexia
- Seizure to auditory stimuli
- By 2–3 years of age, the child is usually in decerebrate posture, has become blind, and is unable to respond to stimuli
- Cherry-red spot > 90% of cases

Juvenile and adult form

- Occurs in Ashkenazi Jews
- Affected children usually labeled clumsy and awkward
- Proximal muscle weakness occurs with fasciculations
- Anxiety, depression, suicide
- May ambulate until the age of 60s

Fabry Disease

Background

- Deficient activity of lysosomal enzyme α-galactosidase (α-Gal A)
- Only sphingolipidoses transmitted as X-linked

Clinical presentation

- Severe episodic pain in hands and feet
- Hypohidrosis or anhidrosis
- Angiokeratoma (dark red, blue-black, flat or slightly raised punctate skin lesions)
- Corneal opacities
- Congestive heart failure
- Chronic abdominal pain and diarrhea
- Renal failure
- Autonomic nervous system dysfunction
- Seizures, hemiparesis, and ataxia

Diagnosis

- (α-Gal A) activity may be measured in plasma, serum, and leukocytes
- DNA testing

Treatment

- Painful peripheral neuropathy may respond to carbamazepine or gabapentin
- IV alpha-galactosidase may relieve pain
- Renal transplant for end-stage renal disease

Wolman Syndrome

Keywords: *Relentless vomiting in the 1st week after birth, failure to thrive, and calcification of adrenal glands*

Background

- A milder form of lipoprotein lysosomal acid lipase deficiency
- Termed cholesteryl ester storage disease
- May not manifest until adult life

Clinical presentation

- Feeding difficulties with frequent vomiting shortly after birth
- Diarrhea, steatorrhea
- Failure to gain weight or sometimes weight loss
- Abdominal distention
- Hepatosplenomegaly
- Liver dysfunction or failure
- Severe anemia
- Calcifications of adrenal glands (pathognomonic)
- Increased risk of premature atherosclerosis
- Very few infants with Wolman disease survive beyond the 1st year of life

Diagnosis

- Variable hypertriglyceridemia usually present
- Hypercholesterolemia
- Bilateral adrenal calcifications on CT scan
- DNA testing

Metachromatic Leukodystrophy

Background

- Lysosomal storage diseases
- Progressive, inherited, and neurodegenerative disorders

Table 5.7 Lysosomal storage diseases—lipidoses

Disorders	Keywords
Gaucher disease	Protruded abdomen, splenomegaly, bone pain, bone lytic lesions, pathologic fractures, thrombocytopenia, anemia
Niemann-Pick disease	Hepatosplenomegaly, psychomotor retardation, cherry-red spot, death by 3 years of age
Krabbe disease	Convulsions, mental deterioration, spasticity, blindness, most die by 3 years of age
Tay-Sachs disease	Seizure to auditory stimuli, ataxia, hypertonia, cherry-red spot, mental deterioration
Fabry disease	Burning pain in hands and feet, angiokeratoma, hypohidrosis, corneal opacities
Wolman disease	Relentless vomiting after birth, failure to thrive, calcification of adrenal glands
Metachromatic leukodystrophy	Inability to walk, motor delay, diminished reflexes, hypotonia, optic atrophy, seizures

Clinical presentation
- Gait disturbances
- Loss of motor developmental milestones
- Loss of previously achieved skills
- Truncal ataxia
- Memory deficits
- Seizures (may be present)
- Tremors
- Optic atrophy

Diagnosis
- Arylsulfatase A enzyme activity may be decreased in leukocytes
- DNA testing

Treatment
- No effective treatment to reverse neurological deterioration
- **Summary** (Table 5.7)

PEROXISOMAL DISORDERS

- Peroxisomes are essential for beta-oxidation of very long-chain fatty acids (VLCFA) and detoxification of hydrogen peroxide
- Peroxisomes are also involved in the production of cholesterol, bile acids, and plasmalogens, which contribute in great part to the phospholipid content of the brain white matter

Examples of peroxisomal disorders
- Zellweger syndrome
- X-ALD

Keywords: *Hypotonia, seizures, elevated VLCFA*

Zellweger Syndrome

Clinical presentation
- Typical craniofacial dysmorphism; high forehead, a large anterior fontanelle, hypoplastic supraorbital ridges, broad nasal bridge, micrognathia, deformed earlobes, and redundant nuchal skinfolds
- Neurologic features; severe psychomotor retardation, profound hypotonia with depressed deep tendon reflexes (DTRs), neonatal seizures, and impaired hearing
- Brain, cortical dysplasia
- Ocular features; congenital cataract, glaucoma, and retinal degeneration
- Calcific stippling of the epiphysis or patella
- Small renal cysts
- Liver cirrhosis

Diagnosis
- Suspect diagnosis by increased VLCFA or decreased plasmalogens
- DNA testing to demonstrate mutations in genes mediating peroxisomal biogenesis and/or transport

Prognosis
- Most die by 1 year of age

X-Linked Adrenoleukodystrophy (X-ALD)

Background
- Affects males
- Accumulation of VLCFA in the white matter, peripheral nerves, adrenal cortex, and testis

- DNA testing allows diagnosis of carrier females and preimplantation genetic/prenatal diagnosis

Clinical presentation

- Early development is entirely normal
- Development may regress after 3–5 years of age
- Early manifestations are often mistaken for attention deficit hyperactivity disorder (ADHD)
- Progressive neurological disorders include impaired auditory discrimination, visual disturbances, spatial disorientation, and poor coordination; seizures ensue later in the disease
- Adrenal insufficiency
- Progression leads to a vegetative state in 2 years and then death

Diagnosis

- Elevated level of VLCFA
- Brain MRI pattern is quite characteristic:
  - Lesions are symmetrical, and demyelination is progressive
  - Late in the disease, the brain stem and ultimately the cerebellum may be involved
- DNA testing allows diagnosis of carrier females and preimplantation genetic/prenatal diagnosis

Summary (Table 5.8)

Table 5.8 Peroxisomal disorders

Disorders	Keywords
Zellweger syndrome	Abnormal facial features, severe weakness, hypotonia, failure to thrive, eye abnormalities, elevated VLCFA
X-linked adrenoleukodystrophy (X-ALD)	ADHD-like symptoms, vision problems, poor coordination, adrenal insufficiency, elevated VLCFA, brain MRI shows demyelination

VLCFA very long-chain fatty acids

DISORDERS OF PORPHYRIN METABOLISM (PORPHYRIAS)

- Enzyme defect in heme synthesis
- Overproduction and accumulation of porphyrin

Keywords: *Skin hypersensitive to sunlight, skin hyperpigmentation, liver dysfunction*

Acute Intermittent Porphyria (AIP)

Background

- AIP is an autosomal dominant disease that results from defects in the enzyme porphobilinogen-deaminase
- This enzyme speeds the conversion of porphobilinogen to hydroxymethylbilane

The most common drugs induce AIP

- Barbiturate, sulfa, carbamazepine, valproic acid, griseofulvin, birth control pills

Clinical presentation

- Abdominal pain is the most common symptom
- Ileus, abdominal distension, and decreased bowel sounds
  - Nausea and vomiting
  - No abdominal tenderness and no fever because it is neurological and not inflammatory
- Dysuria and urinary retention may occur
- Limb, neck, and chest pain
- Mental changes: anxiety, depression, insomnia, and paranoia during the acute attacks
- Peripheral neuropathy: Proximal muscle weakness, some sensory changes
- Most patients are symptom-free between attacks

Diagnosis

- Elevated level of porphobilinogen (> 6 mg/L) on a spot urine test during an acute attack will confirm diagnosis
- DNA diagnosis

Treatment

- High doses of glucose can inhibit heme synthesis and are useful for the treatment of mild attacks
- Hematin in severe attacks with severe neurological symptoms
- Narcotics, laxatives, and stool softeners

Porphyria Cutanea Tarda

Background

- Occur after exposure to halogenated aromatic hydrocarbons, e.g., excess alcohol
- Excess iron and estrogen are also a common cause
- The most common of porphyrias
- Due to the deficiency in hepatic URO-decarboxylase

Clinical presentation

- Cutaneous photosensitivity
- Fluid-filled vesicles and bullae on sun-exposed areas
- Hypertrichosis
- Hyperpigmentation

Diagnosis

- Presence of high level of porphyrin in the liver, plasma, urine, and stool helps with diagnosis
- Low level of hepatic URO-decarboxylase in red blood cells (RBCs)
- DNA diagnosis

Treatment

- Avoid exposure to offending agents, e.g., sunlight, estrogen, alcohol, or tobacco smoking
- Therapeutic phlebotomy reduces iron stores

Erythropoietic Protoporphyria

Background

- Autosomal dominant
- Due to partial deficiency of ferrochelatase

Clinical presentation

- Hypersensitivity to sunlight exposure (painful skin)
- Skin hyperpigmentation
- Skin edema, erythema, and petechiae after more prolonged exposure to sunlight
- Blisters, crusted erosions, and scarring may occur
- Gallstones with or without abdominal pain
- Hepatotoxicity and jaundice may exacerbate photosensitivity

Diagnosis

- Elevated levels of protoporphyrin in bone marrow, RBCs, plasma, bile, and feces is diagnostic
- DNA diagnosis

Treatment

- Avoidance of sunlight (protective clothing and lifestyle changes)
- Vitamin D3
- Activated charcoal may increase excretion of protoporphyrin
- Transfusion and IV heme may be helpful in reducing protoporphyrin production

Summary (Table 5.9)

Table 5.9 Disorders of porphyrin metabolism (porphyrias)

Disorders	Keywords
Acute intermittent porphyria	Abdominal pain, psychiatric symptoms, peripheral neuropathies, completely free symptoms between attacks
Porphyria cutanea tarda	Skin photosensitivity, hyperpigmentation, hypertrichosis
Erythropoietic protoporphyria	Painful skin after sun exposure, skin edema with or without redness, gallstones, abdominal pain, jaundice, photosensitivity

DISORDERS OF PURINE OR PYRIMIDINE METABOLISM

Lesch-Nyhan Disease (Hypoxanthine-Guanine Phosphoribosyltransferase Deficiency)

Keywords: *Kidney stones, high uric acids, and self-mutilation*

Background
- Lesch-Nyhan disease is X-linked
- Affects mainly boys
- Due to deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency

Clinical presentation
- Usually, males are healthy at birth
- Failure to thrive
- Vomiting
- Self-mutilation
- Lips and finger biting
- Kidney stones
- Gout

Diagnosis
- High level of uric acid
- HPRT deficiency on RBCs
- DNA diagnosis

Treatment
- Supportive
- Hydration and allopurinol (inhibiting the metabolism of hypoxanthine and xanthine to uric acid)

VARIOUS METABOLIC DISORDERS

Familial Hypercholesterolemia

Background
- Very common 1/200–1/500
- Autosomal dominant

Clinical presentation
- Xanthomas: planar xanthomas with yellow-to-orange discolorations on hands, elbows, buttocks, or knees. Tendon xanthomas (especially on extensor tendons of hands or Achilles tendon)
- An untreated male will develop coronary heart disease 100%, untreated female, 75%

Diagnosis
- Cholesterol level 600–1000 mg/dl
- DNA diagnosis showing LDL receptor mutations

Management
- Statins are the recommended initial therapy for dyslipidemia in children and adolescents (see also Chap. 19 Cardiology)

Differential diagnosis
- Sitosterolemia: Tendon xanthoma in the first decade but only moderate hypercholesterolemia

Smith-Lemli-Opitz Syndrome

Keywords: *Low cholesterol, abnormal facial features, and developmental delay*

Background
- Autosomal recessive
- A defect in cholesterol biosynthesis
- Deficient activity of 7-dehydrocholesterol reductase
- Cholesterol is important for embryogenesis
- Survival is unlikely if cholesterol is < 20 mg/dL

Clinical presentation
- Microcephaly
- Narrow bifrontal diameter
- ID
- Ptosis
- Hypertelorism
- Cataracts
- Low-set ears
- Anteverted nostrils
- Broad maxillary alveolar ridge
- Cleft palate
- Micrognathia
- Postaxial polydactyly
- Hypospadias
- Ambiguous genitalia

Diagnosis
- Elevated dehydrocholesterol
- Low cholesterol or normal
- DNA diagnosis

Treatment
- Dietary cholesterol (egg yolk)
- Statins to prevent the synthesis of toxic precursors proximal to the enzymatic block

Menkes Disease (Kinky Hair Disease)

Keywords: *Presents at birth, kinky and sparse hair, hypoglycemia, seizures, progressive neurological and developmental deterioration*

Background
- X-linked disease
- Impaired uptake of copper

Clinical presentation
- Premature delivery
- Abnormal feature: Facies, pudgy cheeks; sagging jowls and lips
- Hair and eyebrows are sparse
- Kinky hair (pili torti under the microscope)
- Hypothermia or temperature instability
- Hypotonia
- Hypoglycemia
- Seizures
- Loss of milestones
- Progressive neurological deterioration

Diagnosis
- Low-serum copper and ceruloplasmin
- Copper and ceruloplasmin levels may be normal in the milder variants and in the neonatal period
- DNA testing for mutations in the *ATP7A* gene

BODY ODORS

Trimethylaminuria, also called fish odor syndrome
- Decaying fish odor

MSUD
- Caramel, maple syrup, or malty odor

Phenylketonuria
- Musty like odor

Multiple acyl-CoA dehydrogenase deficiency
- Variable sweaty feet body odor

Isovaleric acidemia
- Cheesy, acrid, sweaty feet odor

Tyrosinemia
- Cabbage or rancid butter odor

Diabetes mellitus and diabetic ketoacidosis
- Fruity breath

3-methylcrotonylglycinuria

- Male cat urine like odor

Cystinuria

- "Rotten egg" odor because cystine is one of the sulfur-containing amino acids

Hypermethioninemia

- Fishy, sweet and fruity, rancid butter or boiled cabbage odor

NEWBORN METABOLIC SCREENING

- Is intended to detect congenital genetic and metabolic disorders that can result in early mortality or lifelong disability
- Such screening was a pediatric innovation where the principle of beneficence was first applied: **Screen only if diagnosis improves outcome**
- Uses heel stick blood spots, engineered to have frequent false positives so that diagnoses are rarely missed
- Began using phenylalanine (phe)-dependent bacteria with turbid growth showing elevated phe levels (Guthrie test for phenylketonuria, hence often called the "PKU' test)
- In the USA such screening is state coordinated, dictating that pediatricians collect initial (1–3 days) and follow-up samples as needed (poor feeding may cause negative screens)
- States provide reports of abnormal screens to pediatricians with instructions for family communication, follow-up, and ACTion (ACT) sheets outlining initial therapy
- Now tandem mass spectrometry (MS/MS) is used to detect any elevated metabolite in heel-stick blood spots:
  - MS/MS is sensitive, reliable, and more comprehensive than Guthrie methods
  - Elevations in the first spectrogram are routed to the second (tandem) spectrometer to define metabolite structure
  - MS/MS displays all amino or organic acid metabolites, diagnosing ~56 disorders (expanded newborn screen) when combined with testing for hemoglobinopathies, congenital adrenal hyperplasia (CAH), and cystic fibrosis (CF); trypsin

PEARLS AND PITFALLS

- Nothing by mouth (NPO) and IV dextrose is the best initial treatment for any newborn or a child with suspected metabolic disorders, regardless of the type of metabolic disorder, and is a life saver.
- Organic acidemia should be suspected in a patient who presents with hypoglycemia and hyperammonemia in the presence of metabolic acidosis.
- Some organic acidemias also result in granulocytopenia and thrombocytopenia and are mistaken for sepsis.
- Urea cycle defects are associated with very high ammonia level, normal anion gap (not acidotic), and respiratory alkalosis.
- MSUD in a newborn who appears well in the first 1 or 2 days after birth and then becomes irritable, feeds less, drowsy, lethargic, apneic; opisthotonus, hypertonia, ketonuria, and a maple syrup odor.

Acknowledgment I gratefully acknowledge the review and suggestions of Golder N. Wilson, MD, PhD, Clinical Professor of Pediatrics, Texas Tech University Health Science Center, Lubbock, Texas.

Suggested Reading

Berry GT, Segal S, Gitzelmann R. Disorders of galactose metabolism. In: Fernandes J, Saudubray M, van den Berghe G, Walter JH, editors. Inborn metabolic diseases—diagnosis and treatment. 4th ed. New York: Springer; 2006.

Grabowski GA. Phenotype, diagnosis, and treatment of Gaucher's disease. Lancet. 2008;372:1263–71.

Kim HJ, Park SJ, Park KI, Lee JS, Eun HS, Kim JH, et al. Acute treatment of hyperammonemia by continuous renal replacement therapy in a newborn patient with ornithine transcarbamylase deficiency. Korean J Pediatr. 2011;54:425–8.

Rezvani I, Rezvani G. Approach to inborn errors of metabolism. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011. p. 416–48.

Rezvani I, Yukoff M. Urea cycle and hyperammonemia. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011. p. 447–53.

Wanders RJ. Peroxisomes, lipid metabolism, and human disease. Cell Biochem Biophys. 2000;32(Spring):89–106.

Mental and Behavioral Health

6

Mohamed Hamdy Ataalla

NEURODEVELOPMENTAL DISORDERS

Intellectual Disability (ID)

- Previously called mental retardation
- Subnormal intellectual ***and*** adaptive functioning with onset in the developmental period
- Classification according to IQ level (Table 6.1)
  1. Mild IQ 50–70 (majority of cases)
  2. Moderate 35–49
  3. Severe 20–34
  4. Profound < 20
- Prevalence: 1–2%, higher in ethnic minorities and with lower socioeconomic status

Table 6.1 Classification of intellectual disability (ID)

ID level	Educational level	Independence/skills achievement
Mild IQ (50–69)	Up to sixth grade	Independent in personal care and activities of daily living with minimal support; independent employment with a possible need for minimal supervision or support
Moderate IQ (36–49)	Up to third grade	Can care for personal needs and activities of daily living; limited support needed in daily situations; supportive living, e.g., group home; supported or supervised work; unskilled or semiskilled job
Severe IQ (20–35)	Limited academic skills	Needs support for personal care and activities of daily living at all times; safety supervision; possible recognition of critical words (e.g., "no"); needs a nursing home; sheltered work with extensive support needed in all daily activities
Profound IQ (< 20)	Not applicable	Dependent on others for every aspect of daily activities, needs nursing care, not employable

Causes

- Congenital infections (e.g., cytomegalovirus, rubella, toxoplasmosis)
- Central nervous system infections (e.g., meningitis, encephalitis)
- Trauma
- Malignancy
- Genetic abnormalities (e.g., trisomy 21, fragile X syndrome)
  - Down syndrome: Most common genetic cause of ID
- Inborn errors of metabolism
- Teratogens (e.g., alcohol, illicit and prescription drugs, lead, radiation)

Clinical presentation

- May suffer significant psychiatric problems: Same range of psychiatric disorders but higher rate and more difficult to diagnose
- Those with severe or profound ID may present with dysmorphic features and other signs of congenital anomalies

The original version of this chapter was revised. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-21267-4_34

M. H. Ataalla (✉)
Department of Child and Adolescent Psychiatry, Texas Tech University Health Sciences Center, El Paso, TX, USA

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_6

- Prader–Willi syndrome: Hyperphagia and compulsive behaviors
- Fragile X syndrome: Attention and social problems
- Angelman syndrome: Inappropriate laughter
- Sanfilippo syndrome: Coarse facial features and mild hepatosplenomegaly
- Fetal alcohol syndrome: Differences in growth (i.e., weight and/or height ≤ 10th percentile), smooth philtrum, thin upper lip, small palpebral fissures; central nervous system abnormalities (e.g., microcephaly, seizures, intellectual disability, learning disabilities, attention-deficit/hyperactivity disorder [ADHD])

Differential diagnosis/associated conditions

- Language disorder: For children with language difficulties, use nonverbal IQ test
- Autistic spectrum disorder (sometimes associated with ID)
- Specific learning disability (academic underperformance despite normal IQ level)

Management

- Psychosocial interventions
- Cognitive and adaptive interventions
- Treat associated psychiatric and medical conditions
- General quality of life measures

Autism Spectrum Disorders

- All previously called pervasive developmental disorders now fall under the diagnosis of autism spectrum disorder (ASD), according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5)*

Diagnostic criteria

- ASD is diagnosed clinically
- Three cardinal features:

  1. Impairment in social interaction
  2. Impaired verbal and nonverbal communication
  3. Restricted range of interests and stereotypical body movements
- Early problems with joint attention behaviors, e.g., lack of eye contact, no pointing to share attention
- ASD presentation can be very heterogeneous with various levels of cognitive functioning and language skills
- Asperger syndrome: Formerly (before DSM-5) classified as a separate pervasive developmental disorder diagnosis, as these patients had higher verbal ability compared to the other autistic patients

Differential diagnosis/associated conditions

- Intellectual disability (frequently occurs with ASD)
- Epilepsy
- Specific developmental language disorders
- Early-onset psychosis (e.g., schizophrenia)
- Selective mutism and social anxiety
- Simple stereotypic movements: Normal in children less than 3 years old
- Stereotypic movement disorders: Complex, persisting after the age of 3 years; absence of impairment in communication and social interactions
- Emotional neglect, and reactive attachment disorder (inhibited type)

Screening and testing

- Early detection: *Checklist for Autism in Toddlers* (CHAT), the *Modified Checklist for Autism in Toddlers* (M-CHAT) (https://m-chat.org/), and the *Pervasive Developmental Disorders Test II (PDDST-II)* screening test
- School district referral for comprehensive evaluation in children 3 years and older
- The gold standard diagnostic tools: The *Autism Diagnostic Interview-Revised* (ADI-R) and the *Autism Diagnostic Observation Schedule* (ADOS)

- Neuropsychological and achievement assessment, e.g., IQ testing
- Medical workup to rule out associated genetic condition if clinically indicated or neuropsychiatric syndromes

Management

- Educational interventions: Social, communicative, and cognitive skills
- Behavioral modifications, e.g., applied behavioral analysis
- Rehabilitative (occupational and physical therapy)
- Referral to early childhood intervention (ECI) in children less than 3 years of age
- Referral to local school district in children 3 years and older for evaluation
- Pharmacotherapy:
  - Risperidone and aripiprazole are approved by the US Food and Drug Administration (FDA) for treating associated aggression
  - Other drugs, e.g., selective serotonin reuptake inhibitors (SSRIs) for anxiety, and medications used to treat ADHD symptoms

Prognosis

- The better the language skills and IQ, the better the prognosis
- Early detection and providing intensive services improve the outcome
- Delayed diagnosis may lead to a poorer outcome

Sensory Over-Responsivity

- Exaggerated behavioral responses to sensory stimuli
- Usually associated with various developmental and behavioral impairments
- Possibly comorbid with autism, anxiety disorders, and ADHD
- Parent management training/family coaching and referral to occupational therapy might be helpful

COMMUNICATION DISORDERS

Speech Disorders

- Phonological speech disorders (speech sound disorder): Difficulties related to motor production of speech
- Stuttering: Disturbance in the flow of speech

Language Disorders

- Persistent difficulties in acquisition and use of language across different modalities (spoken, written, or other)
- Receptive language disorder
- Expressive language disorder
- Mixed receptive–expressive language disorder

Social Communication Disorder

- Persistent difficulties in the social use of verbal and nonverbal communication

Screening

- Formal audiology evaluation should be done to determine if hearing loss is a cause or contributor.
- Psychoeducational testing: To test specific learning difficulties
- Neuropsychological testing: To test cognitive functions
- IQ testing
- Addressing the language difficulties

Management

- Individual or small group therapy administered by a certified language pathologist
- Psychiatric and psychoeducational interventions as indicated
- For hearing impaired children, three educational/communication methods are commonly used:

  - Oral communication method: uses the child's residual hearing, speech, and lip-reading to develop spoken language
  - Manual communication method: uses signing and fingerspelling
  - Sign language: uses hand and body movements and facial expressions to fully express ideas

LEARNING DISORDERS

Specific Learning Disabilities (LD)

Diagnosed based on one of two criteria:

1. Aptitude–achievement discrepancy: Discrepancy between IQ level and unexpected school failure in one or more of school subjects
2. Failure to respond to treatment intervention targeting areas of academic weakness
   - Reading disorders: Difficulties with reading accuracy and decoding (dyslexia), spelling difficulties, and/or difficulties with reading comprehension
   - Mathematics (dyscalculia): Difficulties with computation or mathematics that requires problem-solving
   - Written expression (dysgraphia), nonverbal learning disorders, and learning disorders not otherwise specified

Learning Disorder = Learning Disability

- Etiology: Intrinsic and extrinsic factors affecting brain maturation and function
- More in boys than in girls
- Underrepresented in minorities
- Majority of cases identified in middle and high school

Earlier signs of LD may assist in earlier identification

- Children with preschool speech and language disorder may later experience educational difficulty; for example difficulty in recognizing and drawing of shapes in the preschool period may portend problems in letter recognition or writing
- Performance of formal developmental screening at the 30-month visit may identify these related preschool problems
- Performance at the 48-month visit may identify specific problems in early decoding, writing, and sound/symbol association

Associated conditions

- ADHD
- Disruptive behavior disorder
- Anxiety and depression
- Educational underachievement
- Employment difficulties

Screening

- Psychoeducational testing: To test specific learning difficulties, usually done at school
- Neuropsychological testing: To test cognitive functions
- IQ testing

Management

- Special education service (individualized education program by school system)
- Primary prevention: High-level education for all children
- Secondary prevention: Interventions directed to children with academic difficulties not responding to primary prevention
- Tertiary prevention: Advanced and intensive services to those who continue to have difficulties despite initial interventions provided
- The US *Individuals with Disabilities Education Act* requires that special educa-

tion services be provided in the least restrictive environment (students are not to be removed from regular classes as much as possible)
- Treat associated comorbidities if any

Practical issues in the management of learning disorder
- The pediatric clinician can play a critical role not only in identifying the child with LD, but also in the ongoing management.
- The pediatrician or pediatric nurse practitioner should inquire about every child's academic performance and school behavior
- Implementation of the medical home model for chronic condition management
- Psychoeducational evaluation with the family to ensure that he or she is receiving appropriate educational remediation, accommodations, modifications, and therapies
- Investigation for related disorders, such as ADHD, adjustment disorder, or anxiety disorder, should be considered
- Education of families is also critically important to help them access appropriate treatment
- Example on family education: At a minimum, families should leave the physician's office understanding that reading disorder is not due to a primary visual deficit and that letter reversals, a common finding in a typically developing 7-year-old, is not diagnostic of reading disorder

Poor School Performance [1]

Background
- Education is critical for human resource development
- Poor academic achievement should be considered a symptom reflecting an underlying problem in children
- Poor school performance can cause low self-esteem or even depression

Causes
- Medical problems, e.g.,
  - Malnutrition
  - Chronic iron deficiency anemia
  - Worm infestations
  - Preterm or low birth weight
  - Hearing impairment
    - Otitis media with effusion and associated conductive loss is associated with lower scores in math and expressive language between kindergarten and second grade
    - Mild sensorineural hearing loss is associated with difficulty in multiple educational and functional test measures in school-aged children
  - Visual impairment
    - Amblyopia or other refractive disorders if left uncorrected may harm school performance
  - Asthma and allergic rhinitis
    - Children with poorly controlled asthma have increased school absenteeism
  - Obstructive sleep apnea
    - May present with ADHD-like symptoms and poor school performance
- Below-average intelligence
- Specific learning disability
- ADHD
- Emotional problems
- Poor sociocultural home environment
- Psychiatric disorders

Management
- Identify and treat the underlying causes
- Referral of children with hearing impairment to otolaryngologist or audiologist for treating the underlying cause of hearing loss
- Referral of children with visual impairment to a pediatric ophthalmologist for treating refractive disorders

Attention-Deficit/Hyperactivity Disorders (ADHD)

Background

- ADHD is often underdiagnosed; however, it could also be overestimated
- More prevalent in males
- Distractibility in preschoolers is difficult to differentiate from inattentive symptoms of ADHD
- Expect to find more hyperactive symptoms in preschoolers, combined ADHD symptoms in elementary students, and more inattentive symptoms in middle and high graders
- Not a single cause but multiple risk factors: Genetics, pregnancy, birth complications, and brain injury
- Multiple neurotransmitters involved, particularly dopamine and norepinephrine
- Multiple brain regions are affected, particularly the prefrontal lobe and the basal ganglia

Diagnostic criteria

- Two groups of symptoms: Inattentive and hyperactive/impulsive
- Three subtypes of the disorder: Predominantly inattentive, predominantly hyperactive/impulsive, and combined presentation
- For each subtype, must have at least six symptoms from the corresponding group, lasting at least 6 months
- Symptoms should be out of normal developmental level, associated with impairment, and present in two or more settings
- Symptoms were present before the age of 12 years according to *DSM-5* (changed from 7 years old in *DSM-IV*)
- Symptoms are not manifestations of another psychiatric disorder, e.g., depression or anxiety
- Impairment is not only academic but also behavioral (more in preschoolers), interpersonal, and psychological, e.g., low self-esteem

Associated conditions

- Comorbid psychiatric diagnosis: Oppositional defiant disorder (ODD), conduct disorder (CD), learning disabilities, and anxiety disorders

Screening and rating scales

- Diagnosis is made through careful history (e.g., family history) and clinical interview
- Child with ADHD may not manifest symptoms in the office setting
- Rating scales are useful to assess the symptoms, e.g., the *Vanderbilt ADHD Rating Scales* and the *Conners Comprehensive Behavior Rating Scales (CBRS)*
- As needed, physical examination and laboratory tests to work up differential diagnosis
- Psychoeducational testing if specific learning disorder is suspected
- IQ and other neuropsychological testing (e.g., continuous performance test) are not routinely ordered unless indicated

Differential diagnoses (Tables 6.2 and 6.3)

- Medical illness that may affect a child's attention: Headaches, seizures, allergies, hematologic and endocrine disorders, childhood cancer
- Medications, e.g., for asthma, steroids, anticonvulsants, and antihistamines
- Other psychiatric disorders might present with inattention, restlessness, and poor organization, e.g., depression and anxiety disorders
- Sleep disorders, e.g., obstructive sleep apnea
- Substance abuse

Table 6.2 Diagnostic symptoms of attention-deficit/hyperactivity disorder (ADHD)

Inattention symptoms	Hyperactivity and impulsive symptoms
Often fails to give close attention to details or makes careless mistakes in schoolwork or during other activities	Often fidgets with or taps hands or feet; squirms in seat
Often has difficulty sustaining attention in tasks or play activities	Often leaves seat in situations when remaining seated is expected
Often does not seem to listen when spoken to directly	Often runs about or climbs in situations where it is inappropriate
Often does not follow through on instructions and fails to finish schoolwork or chores	Often unable to play or engage in leisure activities quietly
Often has difficulty organizing tasks and activities	Often "on the go," acting as if "driven by a motor"
Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort	Often talks excessively
Often loses things necessary for tasks or activities	Often blurts out an answer before a question has been completed
Often easily distracted by extraneous stimuli	Often has difficulty waiting his or her turn
Often forgetful in daily activities	Often interrupts or intrudes on others

Table 6.3 Conditions to be ruled out that may give the picture of attention-deficit/hyperactivity disorder (ADHD) symptoms

Environmental conditions	Other neuropsychiatric conditions	Medical conditions
Cases of physical or sexual abuse	Fragile X syndrome	Obstructive sleep apnea
		Thyroid disorders
Cases of inappropriate parenting practice	Fetal alcohol syndrome	Heavy metal poisoning
Cases of parental psychopathology	Pervasive developmental disorders	Medication side effects
Inappropriate classroom setting	Anxiety disorders	Effects of abused substances
	Tourette's syndrome	Sensory deficits
	Attachment disorder	Auditory and visual processing disorders
	Post-traumatic stress syndrome	Neurodegenerative disorder
		Post-traumatic head injury

Management

- Treatment should be comprehensively planned: Medications and educational and/or behavior therapy
- Psychosocial treatments: Psychoeducation and parent training in behavioral management
- Educational: Provide school services through Section 504 (a part of the US Rehabilitation Act of 1973 that prohibits discrimination based upon disability) or under individualized educational plan. Address comorbid learning disorders if any
- Stimulants are more effective than providing behavioral treatments alone
- Start medication treatment with a stimulant (highly efficacious), either from the methylphenidate or amphetamine group (Table 6.4)
- Increase gradually over weeks with frequent monitoring until symptoms are controlled or side effects develop
- Side effects: Decreased appetite (weight monitoring), insomnia, anxiety, tics, and headaches (Table 6.5 [2])
- Cardiac: If significant cardiac history in the family, consider electrocardiogram (EKG)
- Cardiovascular risks and risk of abuse and dependence are black box warnings for stimulant medications. (However, treating ADHD reduces risk of drug abuse)

Table 6.4 Medications for treatment of attention-deficit/hyperactivity disorder (ADHD)

Brand name	Duration of action (in hours)	Time to peak in blood (hours after the dose)	Dosage range	Side effects
Methylphenidate immediate release (generic name)				
Ritalin	4	1–3	5, 10, 20 mg tabs	Appetite suppression
Methylin SOL	4	1–2	5 mg/5 ML, 10 mg/5 ML	Insomnia Transient weight loss Irritability Emergence of tics
Methylphenidate extended release (generic name)				
Metadate ER	4–6		10, 20 mg extended-release tabs	Same as above
Methylin ER	4–6			
Concerta	10–12	Initial peak at 1 h and max peak at 7	18, 27, 36, 54 mg caps	
Ritalin LA	8–10	1st peak 1–3 2nd peak 6.5	10, 20, 30, 40 mg caps	
Metadate CD	8–10	1st peak 1.5 2nd peak 4.5	10, 20, 30 mg extended-release caps	
Quillivant XR SUSP 25 mg/5 ml	12	1 h	From 4 to 12 ml (20–60 mg)	
Methylphenidate sustained-release (generic name)				
Ritalin SR	4–6	4.7	20 mg sustained-release tabs	Same as above
Methylphenidate SR	≥ 12	8–10	10 mg/9 h, 15 mg/9 h, 20 mg/9 h, 30 mg/9 h	Same as above
Transdermal methylphenidate (generic name)				
Daytrana patch	Long-acting	Apply 2 h before desired effect; remove after 9 h (may remove earlier)	10, 15, 20, 30 mg transdermal patch	Erythema especially when patch not removed after 9 h
Dexmethylphenidate (generic name)				
Focalin	4	1–1.5	2.5, 5, and 10 mg tabs	Same as above
Focalin XR	Up to 12	1st peak 1.5 2nd peak 4.5	5, 10, 15, 20, 25, 30, 35, 40 mg	
Mixed amphetamine salts (generic name)				
Adderall	4–6	3	5, 10, 20 mg tabs	Same as above
Adderall XR	8–12	7	5, 10, 15, 20, 25, 30 mg caps	
Dextroamphetamine (generic name)				
Dexedrine	4–6	3	5, 10, and 15 mg tabs	Same as above
Dexedrine spansule	6–8		5, 10, and 20 mg tabs	
Lisdexamfetamine (generic name)				
Vyvanse	≤ 12	1	30, 50, and 70 mg tablets	Same as above
Amphetamine suspension (generic name)				
Dyanavel XR 2.5 mg/ml	13	1 h	From 1 to 8 ml	Same as above
Atomoxetine (generic name)				
Strattera	Long-acting	Weeks	10, 18, 25, 40, 60 mg caps	Dry mouth Nervousness Fatigue Dizziness Severe liver injury (rare) Suicidal ideation (rare)

Table 6.4 (continued)

Brand name	Duration of action (in hours)	Time to peak in blood (hours after the dose)	Dosage range	Side effects
α2-adrenergic agonists				
Catapres (clonidine)	8–12	3–5	0.1, 0.2, 0.3 mg tabs	Sedation
				Depression
				Dry mouth
				Rebound hypertension on discontinuing the medicine
				Confusion
Kapvay (clonidine, extended release)	Long-acting		0.1 mg	Same as above
Intuniv ER (guanfacine)	13–14	1–4	1, 2, 3, 4 mg tabs	Hypotension
				Light-headedness

Table 6.5 Management of common side effects of attention-deficit/hyperactivity disorder (ADHD) medications [2]

Methylphenidate/amphetamine derivatives common side effects	Management
Loss of appetite, abdominal pain, headaches, irritability, and sleep problems	May be lessened if the medication is taken with food
Rebound (irritability, increased activity, or mood swings) when medicine wears off	Administering a low dose of an immediate-release (short-acting) stimulant at this time may be helpful
Social withdrawal and lethargy	May be lessened by lowering the dose
Weight loss	Cyproheptadine may be helpful if weight and appetite loss are significant
Tics. (Stimulants are not believed to cause tics, but they may lower the threshold for the development of tics)	The presence of tics is not a contraindication to stimulant use
Sudden cardiac death	Before using stimulants, refer to a pediatric cardiologist if preexisting cardiovascular disease or symptoms suggesting cardiovascular disease

- Contraindications: Glaucoma, uncontrolled seizures, or cardiac disease or active drug abuse
- Atomoxetine (non-stimulant) can be used if the first and second trial of stimulants fail. Has less effect on sleep and appetite. Can help with anxiety symptoms if any. Little risk of suicidal thinking reported (Table 6.6)
- Guanfacine extended release (Intuniv) is approved to treat ADHD (age 6 years and older). May cause hypotension or sedation
- Refer to specialist if treatment fails or in case of other psychiatric comorbidities
- ADHD medications do not cause tics but may make it more obvious
- Behavioral techniques for ADHD [2]
  - Positive reinforcement, e.g., rewards or privileges for desired behaviors
  - Time-out, e.g., removal of access to enjoyable activities or loss of privilege for certain time
  - Response cost, e.g., withdrawing rewards or privileges because of undesired behavior or action
  - Token economy, e.g., child earns points (stars, chips, or tickets), for completing certain work or activities or loses stars for undesired action or behavior; then child cashes the sum of points at the end of the week for a prize

Table 6.6 Adverse effects of non-stimulant ADHD medications

Non-stimulant ADHD medications	Adverse effects	Comment
Atomoxetine	Decreased appetite, abdominal pain, nausea, and somnolence	(Long half-life) steady-state not reached for up to 6 weeks
	Less common: headaches, fatigue, dyspepsia, vomiting, and diarrhea	
	Hepatitis (rare and reversible)	
Clonidine ($\alpha 2$-adrenergic agonists)	Dry mouth, somnolence, dizziness, hypotension, and constipation	Can be helpful in treating hyperactivity, tics, or delayed sleep onset
Guanfacine	Dry mouth, somnolence, dizziness, and constipation	

ADHD Attention-deficit/hyperactivity disorder

Administration of medications to children who may have difficulty with swallowing capsules and tablets

- Long-acting tablets (e.g., Concerta, methylphenidate tablets) should be swallowed whole; it cannot be crushed or chewed
- Capsules: May sprinkle the contents on applesauce; swallow without chewing the beads
- Vyvanse (lisdexamfetamine): May sprinkle contents in a glass of water; needs to be consumed immediately
- Liquid forms of stimulant medications: Short (Methylin) and long acting (Quillivant XR, Dyanavel XR)

Prevention

- Earlier detection, diagnosis, and treatment
- Parent training

Prognosis

- ADHD symptoms may continue into adulthood in 60% of cases
- Untreated ADHD: Risk of criminal behavior, accidents, employment and marital difficulties; more likely to have teen pregnancies

DISRUPTIVE, IMPULSE-CONTROL, AND CONDUCT DISORDERS

Background

- All children are defiant at times; such behavior is a normal part of adolescence
- Normal stubbornness (3 years), defiance and temper tantrums (4–5 years), and argumentative (6 years)
- Most disruptive symptoms peak between 8 and 11 years
- Disorder may be present if the behaviors interfere with family life, school, or peer relationships or put the child or others in danger
- 5% of children between 6 and 18 years meet the diagnosis of ODD or CD

Oppositional Defiant Disorder (ODD)

- Persistent pattern of angry outbursts, arguing, and disobedience to authority figures (such as parents and teachers)
  - Often loses temper
  - Often argues with adults
  - Often actively defies or refuses to comply with adults' requests or rules
  - Often deliberately annoys people
  - Often blames others for his or her mistakes or misbehavior
  - Often moody or easily annoyed by others
  - Often angry and resentful
  - Often spiteful or vindictive

Conduct Disorder (CD)

- Persistent pattern of serious rule-breaking behavior and violating others' rights with lack of guilt:
  - Often bullies, threatens, or intimidates others
  - Often initiates physical fights
  - Has used a weapon that could cause serious physical harm to others
  - Physical cruelty to people or animals
  - Stealing while confronting a victim
  - Forcing someone into sexual activity

Associated conditions

- CD versus ODD: In ODD, there is absence of severe physical aggression and antisocial behavior
- ADHD
- Bipolar disorder
- Developmental disorders
- Communication disorders

Screening and rating scales

- Routinely, remember to screen for behavioral problems
- Use rating scales if answer to screening question is positive, e.g., the *Pediatric Symptom Checklist (PSC)*
- Significant scoring on rating scale requires referral to mental health specialist

Management

- ODD: Parent management training directed to the child's caregivers. Social–emotional skills training directed to the child
- CD: Multisystem therapy
- Pharmacotherapy used to address comorbidities, e.g., SSRIs, stimulants, mood stabilizers, and antipsychotics
- Intractable conduct disorder may need residential or specialized foster care treatment

Prevention

- Educate the community and target high-risk populations
- Teach parents and teachers effective behavior management skills
- Child-focused social–emotional skills training

Prognosis

- The earlier the onset, the worse the prognosis
- Comorbidity with ADHD worsens the diagnosis
- 65% of children with ODD will not have the diagnosis in 3-year follow-up. 30% will progress to CD
- CD may continue as antisocial personality disorder into adulthood
- Other psychiatric comorbidities in adulthood
- Multiple adverse outcomes: Social, educational, drugs, and legal problems

Antisocial Behaviors and Delinquency

- Etiology is genetic and environmental
- Risk factors: Poverty, association with delinquent peers, absence of a role model, history of violence, and poor family functioning

Clinical presentation

- Illegal offenses and acts
- Examples: Stealing, destruction of property, threatening or assault behaviors to people or animals, driving without a license, prostitution, rape
- Associated signs: Poor school performance, truancy, poor self-esteem, and low frustration tolerance
- Signs and symptoms of disruptive behavior disorder or other psychiatric comorbidities

Associated conditions

- ADHD
- Mood disturbances, e.g., depression
- Anxiety disorder
- Psychotic disorder

Screening and rating scales

- Rating scales to screen for associated conditions, e.g., *Conners* for ADHD
- **FISTS** mnemonic:
  - **F**: Fighting (How many fights were you in last year? What was the last?)
  - **I**: Injuries (Have you ever been injured? Have you ever injured someone else?)
  - **S**: Sex (Has your partner hit you? Have you hit your partner? Have you ever been forced to have sex?)
  - **T**: Threats (Has someone with a weapon threatened you? What happened? Has anything changed to make you feel safer?)
  - **S:** Self-defense (What do you do if someone tries to pick a fight? Have you carried a weapon in self-defense?)

Management

- Evaluation: Comprehensive biopsychosocial approach
- Multisystemic treatment
- Family involvement is important: Family therapy and parent management training
- Cognitive behavioral therapy (CBT)
- Pharmacotherapy and appropriate referrals for associated conditions

Prevention

- Individual approaches, e.g., teaching coping strategies
- Relationship approaches: Focus more on family and peer relationships
- Community-based approaches: Community education
- Societal approaches: Through advocacy and legislative actions

AGGRESSION

- Not every oppositional behavior is an aggressive disorder, unless aggression is pervasive and out of control
- Etiology: Genetic tendencies; prenatal exposure to substances including cocaine, alcohol, and tobacco; and environmental factors
- A difficult temperament and later aggressiveness are related. More in boys
- History of abuse, neglect, or abandonment and inconsistent discipline
- Corporal punishment in children: Stimulates anger and teaches that violence is an acceptable way of solving problems
- Later in adulthood: Childhood aggression is positively associated with aggression, criminal and antisocial behavior, and adult abuse of one's own child or spouse
- Violence in the media: Desensitizes children to violence; may lead to aggressive and antisocial behaviors

Clinical presentation

- Aggression: Reactive/affective aggression vs. proactive unemotional aggression. Direct versus indirect aggression
- Temper tantrums: Common during the first few years of life
- Biting:
  - Toddlers may bite to communicate frustration or when they experience a stressful event
  - Preschoolers: Occasional or rare biting to exert control over a situation, for attention, as a self-defense, or out of extreme frustration and anger
  - After age of 3 years, frequent biting may indicate a behavioral problem or sensory integration dysfunction
- Breath-holding spells: Sign of frustration and emotional distress

- Bullying
- Lying: In young children can be a way to express fantasy, to explore with language, or to avoid consequences. In school-aged children and adolescents, chronic lying is a problem
- Stealing: Preschoolers and school-aged children may steal more than once or twice. Requires evaluation when it becomes a pattern
- Truancy and running away
- Fire setting: Unsupervised fire setting is always inappropriate

Associated conditions

- ADHD
- ODD and/or CD
- Depression and bipolar disorder
- Developmental disorders

Screening and rating scales

- *Child Behavior Checklist* and *Overt Aggression Scale*
- Other rating scales to rule out associated conditions, e.g., *Conners* for ADHD, IQ testing

Management

- Early interventions for severe cases
- Need to address any biological, psychiatric, or somatic disorders while controlling for environmental triggers
- Pharmacotherapy for associated conditions, e.g., stimulants to treat ADHD
- Need to involve school and family members to provide collateral information and to participate in the treatment plan
- Refer to mental health intervention: Those who show no empathy or remorse and those with severe comorbidities
- Temper tantrums: Time-out and discuss the reason of frustration when the child calms down
- Breath-holding spells: Advise the parents to intervene before emotional escalation. Help the child to calm down by offering 2–3 min time-out
- Truancy and running away: Always assess and address the underlying problem
- Stealing: Behavioral modification and teach the child better coping skills
- Lying: Educate the child that lying is unacceptable. Provide support and set limits
- Fire setting always requires intervention by mental health specialist

Bullying [3]

Background

- Bullying is a form of aggression in which one or more children repeatedly and intentionally intimidate, harass, or physically harm a victim who is perceived as unable to defend himself or herself
- School can be unfriendly and dangerous place for bullied children

Consequences of bullying

- Fear
- Permanent anxiety
- Insecurity
- Depression
- Low self-esteem
- Chronic absenteeism
- Drop in grades

Role of the pediatrician

- Identifying the problem
- Counseling parents, children, and perhaps school personnel regarding intervention and prevention
- Screening for, treating, or referring to psychiatrists or psychologists when mental comorbidities are present

- Advocating for violence prevention and for the right of children to attend school and live free of threat of violence by other children

ANXIETY DISORDERS

Background

- Common psychiatric disorder in children
- Females may report anxiety disorder more than males
- Multiple risk factors
- Genetics: Parents with anxiety disorder
- Temperamental style: Inhibited
- Parenting styles: Overprotective, overcontrolling, and overly critical
- Insecure attachment relationships with caregivers: Anxious/resistant attachment

Common developmental fears (Table 6.7)

- Separation anxiety (decreases with age)
- Fear of loud noises and strangers (common in infants)
- Fear of imaginative creature and darkness (common in toddler)
- Fear of injuries or natural events (e.g., storms)
- Worries about school performance, social competence, and health issues (children and adolescents)
- Fears and worries become disorder when they are impairing and if they do not resolve with time
- Anxious child may present with somatic complaints (headache and stomachache) or disruptive behaviors (defiance, anger, crying, and irritability) while trying to avoid anxiety-provoking stimuli

Table 6.7 Difference between fears and phobia

Fears	Phobia
Fears may be appropriate to age	Excess fears
Child can overcome the fear	Associated with impairment in some cases

Separation anxiety disorder

- Separation anxiety is developmentally normal in infants and toddlers until approximately age 3–4 years
- Separation anxiety disorder: Symptoms usually present after the age of 6 years
- Symptoms should present for at least 4 weeks to make the diagnosis
- Excess distress due to fear of separation from attachment figure
- Excess worrying about own or parent's safety
- Nightmares with themes of separation, somatic complaints, and school refusal

Specific phobia

- Marked and persistent fear of a particular object or situation that is avoided or endured with great distress, e.g., fear of animals or injections
- Five categories: Animal, natural environment, blood injection, situational (e.g., flying), and others

Generalized anxiety disorders

- Chronic, excessive worry in a number of areas such as schoolwork, social interactions, family, health/safety, world events, and natural disasters with at least one associated somatic symptoms for at least 6 months

Social phobia

- Feeling scared or uncomfortable in one or more social settings (discomfort with unfamiliar peers and not just unfamiliar adults) or performance situations

Selective mutism

- Persistent failure to speak, read aloud, or sing in specific situations (e.g., school) despite speaking in other situations (e.g., with family)

Panic disorder

- Recurrent episodes of intense fear that occur unexpectedly

- Associated with at least 4 of 13 autonomic anxiety symptoms such as pounding heart, sweating, shaking, difficulty breathing, and chest pain

Associated conditions
- Depression
- Externalizing behaviors disorders, e.g., ODD
- ADHD
- Selective mutism
- School refusal

Screening and rating scales
- *Multidimensional Anxiety Scale for Children* (MASC)
- *Screen for Child Anxiety-Related Emotional Disorders* (SCARED)

Management
- Provide education, e.g., educate parents that phobias are not unusual and are not associated with impairment in most cases
- Combined psychotherapy and pharmacotherapy are most effective
- Psychotherapy (could be offered alone in mild anxiety cases)
  - Cognitive behavioral therapy (CBT)
  - Specific phobias: Graded exposure and systematic desensitization
  - Selective mutism: Behavioral therapy
  - Parent–child and family intervention
  - Psychodynamic psychotherapy for selected adolescent cases
- Pharmacotherapy: SSRIs, e.g., fluoxetine and sertraline
- School refusal: Do not advise school leave. Treat underlying anxiety as above

Prognosis
- Pediatric generalized anxiety disorder is associated with adulthood anxiety and major depression disorder
- Pediatric separation anxiety disorder may be associated with panic disorder in adulthood

Obsessive Compulsive Disorders (OCD)

- Prevalence is between 0.2% and 1.2% with equal sex distributions
- Etiology is strongly genetic

Clinical presentation
- Common obsessions in adolescents: Dirt and germs, relationship problems, exactness, symmetry, religious themes
- Common compulsions: Cleaning rituals, repeating rituals (doing and undoing), checking rituals
- Remember to ask about the family's reaction to the child's OCD behavior

Associated conditions
- Tic disorder, major depression, and specific developmental disabilities
  - Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Condition reported in some cases of sudden-onset OCD and tics. The validity of this diagnosis is controversial

Screening and rating scale
- *Yale–Brown Obsessive Compulsive Scale* (CY-BOCS)

Therapy or management or treatment
- Treat with cognitive behavioral therapy (CBT). Add medications for moderate to severe cases (Y-BOCS > 21)
- Four FDA-approved medications for OCD:
  - Tricyclic antidepressants: clomipramine (Anafranil)
  - SSRIs: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox)
- Family education: Refer to the OCD Foundation website resource section at *http://www.ocfoundation.org*

TRAUMA- AND STRESSOR-RELATED DISORDERS

- Acute stress disorder
- Adjustment disorders
- Post-traumatic stress disorder (PTSD)
- Reactive attachment disorder
- Disinhibited social engagement disorder

Acute Stress Disorder

Background

- Acute stress due to exposure to actual or threatened death, serious injury, or sexual violation
- Witnessing violent/traumatic loss of loved one, death of one parent, grandparent, or a sibling

Clinical presentation

- Recurrent, involuntary, and intrusive distressing memories of the traumatic event
- Recurrent distressing dreams
- Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were recurring
- Sleep disturbance (e.g., difficulty falling or staying asleep or restlessness during sleep)
- Difficulty with concentration
- Exaggerated startle response

Diagnosis

- Duration of the disturbance is 3 days to 1 month after trauma exposure
- Fulfill the diagnostic criteria (*DSM-5*) for acute stress disorder (ASD)

Management

- Reduce stress
- Provide support
- Promote coping mechanisms
- Avoid increasing stress
- Psychological and behavioral intervention
- Pharmacotherapy, e.g.,
  - Beta-blockers may limit hyperarousal symptoms, both initially and over the longer term
  - Diphenhydramine and other medications may be helpful for improving sleep
  - SSRIs can be helpful in dealing with the core symptoms (including anxiety, depression, withdrawal, and avoidance)

Post-Traumatic Stress Disorder (PTSD)

- Persistent pattern of avoidance behavior, flashbacks, and emotional distress that lasts 6 months after exposure to severe distress or trauma
- In *DSM-5*, PTSD is listed under "Trauma- and Stressor-Related Disorders." It is no longer listed under "Anxiety Disorders"

Management

- Trauma-focused cognitive behavioral therapy (TFCBT)
- SSRIs are considered the medications of choice for managing anxiety, depression, avoidance behavior, and intrusive recollections
- Consultation with therapists and child psychiatrists with expertise in the treatment of PTSD in children is generally warranted

Reactive Attachment Disorder

- A consistent pattern of inhibited, emotionally withdrawn behavior toward adult caregivers in a child more than 9 months and less than 5 years, e.g., a child who rarely or minimally seeks comfort when distressed

Disinhibited Social Disengagement Disorder

- A pattern of behavior in which a child actively approaches and interacts with unfamiliar adults in an impulsive, incautious, and overfamiliar way, e.g., a child willing to approach a stranger for food, to be picked up, or to receive a toy

- The child has a developmental age of at least 9 months

Adjustment Disorders

Background

- Adjustment disorder is a stress-related, short-term, nonpsychotic disturbance

Clinical presentation

- Depressed/irritable mood
- Sadness
- Anxiety
- Sleep disturbances
- Poor concentration
- Poor performance in school
- Anger, disruptive behavior
- Loss of self-esteem
- Hopelessness
- Feeling isolated or cut off from others

Diagnosis

- Emotional or behavioral symptoms occur after an identifiable stressor or stressors within 3 months of the onset of the stressor
- Marked distress that is out of proportion to the severity or intensity of the stressor
- Significant impairment in social, occupational, or other areas of functioning
- Not related to other mental disorders
- Symptoms do not represent normal bereavement
- Symptoms persist for no longer than an additional 6 months

Management

- Brief psychotherapy

HABIT DISORDERS

Trichotillomania (hair-pulling disorder) (Fig. 6.1)

- Repeated behavior of hair pulling to the extent of hair loss, associated with increased tension prior to hair pulling and relief during and after it

Fig. 6.1 Child with loss of upper eyelid lashes due to trichotillomania

Teeth grinding (bruxism)

- Common behavior
- When persists, it may be a manifestation of anxiety
- May cause dental problems that need to be addressed by appropriate dental referral
- Dental occlusal splints are occasionally used in the treatment of oral destructive habits
- Nocturnal biofeedback

Thumb-sucking

- Few studies advocating thumb-sucking as a preventive measure against sudden infant death syndrome (SIDS)
- The incidence of thumb-sucking among children decreases with age: Onset during the first few months and peak at 18–21 months
- Self-soothing behavior that is normal in infants and toddlers
- **Management**
  - Most children spontaneously stop thumb-sucking between 2 and 4 years of age
  - School-aged children with persistent thumb-sucking should be referred to a pediatric dentist
  - Prolonged thumb-sucking can affect a child's teeth alignment and mouth shape
  - If persistent, behavioral evaluation is necessary
  - Usually, treatment is required in severe cases, e.g., if continued beyond age 4–5 years, dental problems, increased risk of accidental ingestions and pica, thumb calluses and skin breakdown, deformities of the fingers and thumbs, and paronychia

  - Gloves or adhesive plasters can remove the antecedent stimulus for thumb-sucking
  - Have the child fold his or her arms when the stereotypy occurs

Head banging
- Not always a manifestation of autistic disorder
- Helmets may be required for children with severe and persistent head banging, especially in children with intellectual disability

Nail biting
- In excess can manifest anxiety

General management of habit disorders
- Educate parents that the habit may resolve if ignored
- Treatment is indicated if impairment is associated
- Behavioral therapy is the main line of treatment, e.g., habit reversal and relaxation training (e.g., breathing exercises)
- Trichotillomania: CBT psychotherapy is superior to medication treatment, e.g., SSRIs and clomipramine
- Need to explore and treat comorbidities, e.g., developmental disorders, anxiety, and depressive disorders
- Remember not to confuse habit-forming disorder with tic disorder/Tourette syndrome
- Tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization

MOOD AND AFFECT DISORDERS

- Spectrum disorder with symptoms ranging from subsyndromal to syndromal
- Depressive disorders: Major depression, persistent depressive disorder, disruptive mood dysregulation disorder, premenstrual dysphoric disorder
- Bipolar-related disorders: Bipolar I disorder, bipolar II disorder, cyclothymic disorder

Major Depression

Background
- More common in adolescents than in children
- Male–female ratio of 1:1 during childhood and 1:2 during adolescence
- Highly familial disorder with both genetic and environmental influences

Risk factors
- Parental psychopathology, impaired parenting, loss of a parent
- Lack of social support
- Exposure to domestic and community violence
- Low socioeconomic status
- Physical and sexual abuse and neglect usually increase the risk of depression
- Chronic medical conditions

Diagnostic criteria
- At least 2 weeks in which mood is depressed or irritable and/or loss of interest or pleasure in nearly all activities (anhedonic mood)
- The symptoms should be present for most of the day, nearly every day
- Associated vegetative and cognitive symptoms, including disturbances in appetite, sleep, and energy; impaired concentration; and thoughts of worthlessness, guilt, and suicide
- To meet the syndromal diagnosis: Need to have abnormal mood plus four or more of associated symptoms
- These symptoms are clear change from baseline and are associated with impairment

Differential diagnosis of depressive (and bipolar) symptoms
- General medical conditions and medications causing mood symptoms
- Substance abuse-induced depressive symptoms
- Other psychiatric disorders anxiety, ADHD, disruptive behavior, developmental disorders

- "Normal ups and downs" of children and adolescents: Not associated with functional impairment. Not severe and do not last long enough to be considered an episode
- "Adolescent anhedonia": Depressive symptoms and variability of mood in normal adolescents

Associated conditions

- The most common comorbid diagnosis is anxiety disorder
- Other comorbidities include disruptive behavior, ADHD, and substance use disorder
- Could occur concurrently with dysthymic disorders (double depression)

Screening and rating scales

- Screen all children and adolescents for the key depressive symptoms: Sadness, irritability, and anhedonia
- *Beck Depression Inventory for Primary Care* (BDI-PC)
- *Children's Depression Inventory* (CDI)
- *Patient Health Questionnaire for Adolescents* (PHQ-A)
- Positive response of depression indicates asking if any suicidal ideation

Management

- Family education about the causes, symptoms, course, and treatments and the associated risks
- Mild depression: 4–6 weeks of supportive psychotherapy. May not need medication
- Moderate depression: 8–12 weeks of CBT or interpersonal therapy. May respond without need for medication
- Severe depression: Combined medication and therapy
- Recurrent, chronic, or severe major depression may require longer than 12 months
- Refer suicidal, psychotic, and bipolar depressed patients to specialized treatment
- Family involvement: Work on dysfunction and stressors and maximize support
- Contact school to provide accommodation needed. Parent should consent to this

Medications

- SSRIs: 50% will respond, and 30% experience symptom remission
- Start medication low and monitor for side effects
- FDA approved: Fluoxetine (> 8 years) and escitalopram (> 12 years)
- Fluoxetine can be started at 5–10 mg daily, increasing the dose gradually at 2-week intervals up to a target range of 20–80 mg daily
- Initiating therapy with higher-than-recommended doses is associated with increased self-harm episodes
- The most common side effects include irritability, gastrointestinal symptoms, sleep disturbance, restlessness, headaches, and sexual dysfunction
- Rare but serious side effects: Predisposition to bleeding and increased suicidal thoughts
- Successful treatment should continue for 6–12 months
- Follow up every 3 months after remission to monitor symptoms and to assess for adverse effects of medication

Therapy and prevention

- CBT strategies, e.g., correcting automatic negative attributions
- Interpersonal therapy for adolescent depression
- Lifestyle modifications (e.g., regular and adequate sleep, exercise, and relaxation)

Prognosis

- 60% will suffer suicidal ideation, and 30% will attempt suicide
- Rate of recurrence of depression reaches 70% after 5 years
- 20% of adolescents with major depression develop bipolar disorder within 5 years of the onset of depression
- High risk of substance abuse and other psychiatric disorders

- Difficulties with school, peers, and family
- Difficulties adjusting to life stressors; physical illness

Persistent Depressive Disorder (Dysthymic Disorders)

- One year of suffering depressed/irritable mood plus two or more of the associated vegetative and cognitive symptoms of depression
- Diagnosis requires association with significant distress or impairment
- If a dysthymic patient develops an episode of major depression, then both diagnoses may be given (it is also called double depression)

Depressive Disorders Not Otherwise Specified

- (Subsyndromal depression) presence of depressive symptoms that are not enough to meet full diagnostic criteria for major depressive disorder or dysthymic disorder

Bipolar Disorders

Background

- Bipolar disorder type I: One episode of mania is enough to make the diagnosis. Often alternates with episodes of major depression
- Bipolar disorder type II: Requires one episode of major depression that alternates with at least one episode of hypomania but ***no*** manic episodes
- Bipolar not otherwise specified (subsyndromal bipolar disorder): Mixture of depressive and manic symptoms that are not enough to diagnose type I or II disorders
- Early-onset bipolar disorder may not present with classic symptoms and distinct mood episodes. Irritability and increased energy episodes are commonly present
- Cyclothymic disorders: Multiple episodes of hypomania and subsyndromal depression for at least 1 year
- The lifetime prevalence of each of the bipolar disorders and cyclothymic disorders is about 0.6%
- Equal sex distribution

Diagnostic criteria

- In mania: There is one week of persistently elevated, expansive, or irritable mood
- In hypomania: Abnormal mood lasts at least 4 days but less than a week, and the impairment is not as severe
- Associated cognitive and behavioral symptoms: Increased energy, grandiosity, reduced need for sleep, pressured speech, distractibility, racing thoughts, engaging in multiple activities and tasks, and impulsively doing things that have the potential for harm in excess

Associated conditions

- Other psychiatric disorders, including ADHD, anxiety, eating, and substance use disorders

Screening and rating scales

- Screen for the cardinal manic symptoms: Elation and grandiosity, increased energy with decreased need for sleep
- If screening is positive: Refer to a specialist for comprehensive evaluation
- Always remember to assess for risk of harm to self or others
- Specific instruments:
  - *Young Mania Rating Scale* (YMRS)
  - *Schedule for Affective Disorders and Schizophrenia*

Management of bipolar disorders

- Start with psychoeducation. Family and school involvement (as in treatment of major depression)
- Be aware of different side effects of the medication used. Need to monitor baseline and follow-up parameters
- Medications to treat manic episode: Lithium FDA-approved (for youth > 13 year) or atypi-

cal antipsychotics (aripiprazole, olanzapine, risperidone, quetiapine)
- Medications to treat bipolar depressive episodes: Lurasidone and olanzapine (> 10 years)
- Lithium common side effects: Cardiac, renal, thyroid, and hematologic effects; toxicity; teratogenicity
- Valproate (Depakote, AbbVie): Hematologic, hepatic, and ovarian (polycystic ovarian syndrome); teratogenicity
- Atypical antipsychotics: Weight gain; metabolic (diabetes, hyperlipidemia); cardiac effects
- For comorbid ADHD: May use stimulants when the mood is stable
- Psychotherapy needs to be offered to address impairment in different domains and provide support to the patient and family
- Refer suicidal and psychotic bipolar depressed patients to psychiatric hospitalization

Prevention
- For those with cyclothymic mood disorder: Adequate mood stabilization may decrease risk for subsequent bipolar disorder development
- Identify and address social and psychological stressors that may precipitate mood decompensation

Prognosis
- 80% will have recurrences after recovery from the first mood episode
- Completed suicide (10–15% of those with bipolar I disorder)
- Poor outcome with no treatment: Unemployment and legal problems

Suicidal Behaviors

Background
- Third leading cause of death among young people aged 15–24 years
- Fourth leading cause of death among young people aged 10–14 years
- Completing suicide: More in males (by firearms) than in females (by poisoning)
- Attempting suicide: More in females. Ingestion of medication the most common method
- Ethnic groups with the highest risk: American Indians and Alaska Natives
- Ethnic groups with the lowest risk: African Americans, Hispanics, and Asians

Risk factors for attempting suicide
- Suffering psychiatric illness (in most suicides): Major depression (most common)
- History of self-harming behavior even with no explicit intention to die (e.g., self-cutting)
- Cognitive functioning: Poor self-esteem and lack of coping strategies
- Stressful life events: Academic or relationship problems, being bullied, family instability
- Newly diagnosed medical condition or a recent or anticipated loss
- Difficulties with sexual orientation and homosexuality
- Physical and sexual abuse
- Suicide of a close person
- Suicide by imitation: Exposure to suicide in the media or a book's hero who commits suicide
- Stress of acculturations for the immigrants

Risk factors for completed suicide
- Male gender
- History of suicide attempt
- Having suicidal intent, a written note, or a plan
- Showing acute signs of depression, mania, and psychosis or substance intoxication
- Lack of family support and supervision to maintain safety at home

Screening and assessment
- Ask about suicidal ideation during routine visits
- Ask specifically about suicidal ideation: "It will not implant the idea in his/her head"

- Obtain collateral information from parents and other resources
- Psychiatric evaluation of the severity of suicidality and the risk factors

Management
- Psychiatric hospitalization for severe suicidal cases and after attempts
- Close outpatient follow up: When risk factors for committing suicide are not present and the patient is able to contract for safety

Prevention
- Remember to screen for suicidal risk
- Address suicidal risk factors
- Schools and public-based suicide prevention program

Prognosis
- Remember: Even when suicidal intent is ambiguous, an impulsive suicidal act may lead to death

CHILDHOOD SCHIZOPHRENIA

Background
- Schizophrenia is a heterogeneous clinical syndrome
- Childhood-onset schizophrenia is rare. More in males
- Risk factors, e.g., advanced parental age and genetic (e.g., 22q11 deletion)

Clinical presentation
- Course of illness
- Prodrome: Functional deterioration before the onset of psychotic symptoms
- Acute phase: Marked by prominent positive symptoms (i.e., hallucinations, delusions, disorganized speech and behavior) and a significant deterioration in functioning
- Recuperative/recovery phase: Generally, a several months period. Negative symptoms (flat affect, anergia, social withdrawal) predominate
- Residual phase: Several months or more, when there are no significant positive symptoms
- Auditory hallucinations suggestive of schizophrenia: Commentary voice or multiple voices

Differential diagnosis
- Hallucinations that are not psychotic: In response to anxiety or stress
- Affective psychosis
- Post-traumatic stress disorder
- Autism spectrum disorders
- Medical conditions and drug abuse

Screening
- Screen for hallucination during regular visits
- *Abnormal Involuntary Movement Scale* (AIMS): Screen and monitor for antipsychotics' extrapyramidal side effects

Management
- Psychoeducation
- Risk management and case management services
- Educational placement: Specialized educational programs should be considered within the school system
- 1st generation antipsychotics are not commonly used due to high risk of extrapyramidal side effects e.g., haloperidol
- 2nd generation antipsychotics are the mainstay of treatment e.g., risperidone, aripiprazole (abilify), or clozapine (for resistant cases)
- Side effects: Metabolic syndrome (obesity, hypertension, dyslipidemia, and insulin resistance) and extrapyramidal symptoms (e.g., dystonia and akathisia)
- Clozapine: Increase the risk for agranulocytosis and seizures

Prognosis
- Early-onset schizophrenia is a risk factor for more impairment from the illness
- High risk of suicide

PSYCHOSOMATIC DISORDERS

- Somatic symptoms disorder: Excess worries about somatic symptoms, longer > 6 months. Prevalence is very common, 10–15%
- Headaches are the most common overall. Functional abdominal pain is the most common in preschoolers
- The symptoms could be a symbolic attempt to resolve unresolved and unconscious conflicts (primary gain)
- Conversion disorder (functional neurological symptom disorder), e.g., weakness, paralysis, seizures, abnormal movement, or seizures. Not as common in Western countries

Clinical presentation

- Serious physical illness was ruled out
- Somatic symptoms and psychosocial stressors occurred around the same time
- Presence of comorbid psychiatric disorder
- Associated conditions: Anxieties, depressive symptoms, substance abuse disorder, inhibited temperament
- The symptoms often result in increased attention for the patient (secondary gain)
- Any form of stress could contribute to psychosomatic disorders; these include bullying and physical or sexual abuse

Differential diagnosis of conversion symptoms include

- Psychophysiology hypochondriasis
- Malingering
- Somatic delusions

Screening and rating scales

- *Children's Somatization Inventory* (CSI)
- *Functional Disability Inventory* (FDI)

Management

- Educate parents and provide reassurance in considerate nonjudgmental way
- Convey encouragement and support
- Advise to continue with school attendance
- Positive reinforcement
- Teach self-monitoring techniques (e.g., hypnosis, relaxation, and biofeedback), family and group therapies
- Aggressively treat comorbid psychiatric conditions
- Avoid unnecessary workup
- CBT and family therapy
- Psychiatric consultation
- Psychopharmacologic interventions as appropriate

SLEEP DISORDERS

Background

- Child with chronic insufficient sleep may manifest with difficult learning and irritability or picture of ADHD
- Electrophysiologically, sleep can be divided into:
  - Rapid eye movement (REM) sleep
  - Non-rapid eye movement (NREM) sleep

Sleep needs according to age

- Newborn: 10–19 h per 24 h
  - REM sleep occupies 50% of total sleep. Decreases with age
  - Frequent awakening may require attention only if > 2–3 awakenings per night > 30 min
- Infant: 12–13 h
- Toddler: 11–13 h
- Preschool (3–5 year): nighttime 10–13 h
- Middle childhood (6–12 year) 9–11 h
- Adolescence (> 12 year) 9 h

Parental education

- Sleep hygiene and behavioral approach to address behavioral insomnia of childhood, e.g., bed routines, avoid overstimulation, address separation anxiety at bedtime

Classifications of Sleep Disorders

- Insomnia secondary to another condition, e.g., medical or psychiatric illness

- Sleep disorders: subdivided into parasomnias and dyssomnias

Parasomnias

- Abnormal events upon a normally organized sleep-wake process
- Includes nightmares, night terrors, sleepwalking, and sleep talking

Nightmares

- Occur during REM sleep, commonly after 2 a.m.

Clinical presentation

- Nightmares usually occur during the second half of REM sleep
- Recurrent episodes of awakening from sleep
- Recall of an intensely disturbing bad dream
- Full alertness on awakening, with little confusion or disorientation
- Delayed return to sleep after the episode

Management

- Reassure the child that he or she had a bad dream
- Leave the bedroom door open, use a nightlight, and demonstrate that there are no monsters under the bed.
- Discuss dream the following day.
- If frequent, need to explore and address the source of anxiety.
- Avoid scary movies or TV shows.

Night Terrors

- Occur during stage 4 NREM sleep, first third of the night

Clinical presentation (Table 6.8)

- The child is screaming unresponsive for few minutes and then falls back asleep again.
- Will not recollect the episode in the morning
- Manifestations of intense fear
- Difficulty in arousing the child, and the child wants to fall asleep soon after the episode

Table 6.8 Difference between night terrors and nightmares

Night terrors	Nightmares
Occurs during Non-REM sleep	Occurs during REM
Sudden episode of crying or loud scream with intense fear	Recurrent episodes of awakening from sleep with recall of an intensely disturbing dream
Does not recall the dream	Recall of dream is immediate and clear
Difficulty in arousing the child	Delayed return to sleep after the episode
Help child to return to sleep	Reassure the child it was a bad dream
Protect the child from injury	

REM rapid eye movement

- Mental confusion when awakened from an episode; child is inconsolable

Management

- Parental and child education and reassurance.
- Advise regarding sleep hygiene
- Awaken child 15 min before terrors occur. Avoid overtiredness
- Be calm; speak in soft, soothing, repetitive tones; help the child return to sleep
- Protect the child from injury

Sleepwalking and sleep talking

- Stage 4 NREM sleep events, with no recall in the morning
- Parental education and reassurance
- Secure bedroom surroundings to avoid accidental injuries to the sleepwalker

Bedtime Refusal/Frequent Awakening

- Appropriate management
  - Quiet routine before bedtime, e.g., story time, bathing, making the room dark
  - Bedtime should be the same every night
  - Allow the child to take a favorite belonging to bed each night, e.g., teddy bear
  - Ensure that the child is comfortable, e.g., door left slightly open
  - Children should not be allowed to sleep in the same bed with parents

  - Parents not to return to the child's room every time he or she complains or calls out, e.g., give more time before response, because the child may fall asleep
  - Keeping the room dark and quiet upon return to the child's room
  - The process may take time; negative response can sometimes make a sleep problem worse
  - Medications, e.g., melatonin can be used in addition to good sleep hygiene in children with neurodevelopmental conditions and sleep disorders

Dyssomnias

- Difficulties initiating and/or maintaining sleep

Primary insomnia
- After psychiatric disorder is ruled out, sleep hygiene is the main line of treatment Address emotional concerns and worries in the child in general
- No TV in the bedroom
- Melatonin can be helpful
- Appropriate referral to sleep study for resistant chronic cases

Primary hypersomnia
- Increased need for daytime sleep despite adequate nighttime sleep
- Rule out organic causes, e.g., medication side effects or hypothyroidism
- If diagnosis is established, may be treated with stimulants

Circadian rhythm disorder
- Managed through gradual advance of bedtime (15 min per night)
- For severe cases: Phase delay therapy
- Naps are discouraged during trials to restore normal circadian rhythms

Narcolepsy
- Characterized by sleep attacks upon wakefulness and cataplectic attacks

Restless leg syndrome
- May be associated with low iron storage that could benefit from iron therapy

Benign Sleep Myoclonus of Infancy

Background
- This is a benign disorder that typically starts in early infancy and resolves over 2–3 months

Clinical presentation
- Jerking movements of the limb(s)
- Occurs when the infant is asleep
- Arousing the infant stops the movements
- The limb jerking occurs for variable intervals, from a few seconds or minutes up to 30 min
- It may move from 1 limb to another and then back to the first limb
- There is no alteration in breathing

Management
- Reassurance

SEXUAL BEHAVIORS

Examples of Inappropriate Sexual Behaviors That May Indicate Sexual Abuse

- Sexual knowledge inappropriate to age
- Heightened sexual interest, e.g., drawing genitals or asking to engage in sexual act
- Masturbating with objects and compulsive masturbation
- Inserting objects in vagina or rectum
- Close physical boundaries
- Sexual promiscuity and prostitution in adolescence

Masturbation

- During the preschool years: Genital interest and play are fairly common

- About 80% of adolescents report masturbating by age of 13 years, more in boys
- Adolescents may experience inappropriate anxiety and/or guilt related to this behavior
- Provide information on normal sexual development and reassurance
- Masturbation in public suggests poor awareness of social reality
- Masturbation seldom produces self-induced injury in childhood
- Hazards of excessive masturbation: Genital itching, sexual overstimulation, environmental deprivation

Sexual Identity Development

- Core gender identity: Basic sense of being male or female
- Gender role: Expected behaviors from the person related to his/her gender
- Social sex role: How the person behaves in congruence/incongruence with the gender role (as in gender nonconformity)
- Sexual orientation: How the person is attracted to the same or the opposite sex. Starts around mid-adolescence

Homosexuality

- 30% of early adolescents may engage in homosexual play once or twice, but it is usually not persistent
- Comorbidities associated with homosexuality
  1. Social stigma may inflict guilt and anxiety on the homosexual teen
  2. Disclosure to friends and family may lead to significant distress and turmoil
  3. Academic complications and dropping out due to bullying and lack of support at school
  4. Psychiatric complications, e.g., higher risk of suicidal behavior, substance abuse, and eating disorders
- **Sexually transmitted diseases (STDs)**
  - Risk in homosexuals is the same as in heterosexuals if protection is not used. However, homosexuals who engage in rectal intercourse may be at higher risk
- **Recommendations**
  - Explore sexual orientation without heterosexual assumptions
  - Provide nonjudgmental care or refer patients to better resources
  - Education and counseling regarding STDs
  - Referral to social support groups

Gender Dysphoria GD (Gender identity disorder)

- GD in children: Six or more of cross-gender behaviors for at least 6 months duration during toddler or preschool age, e.g., cross-dressing and preference for playmate of opposite sex
- GD in adolescents: Two or more of cross-gender behaviors for at least 6 months duration
- Comorbidities: Pervasive developmental disorders and externalizing behavioral problems
- Treatment: Early onset GD may respond to therapeutic interventions (controversial)

TOILET TRAINING

Readiness for Toilet Training Is Associated with

- Awareness of bladder filling
- Ability to contract the external sphincter
- Able to indicate wants and needs verbally
- Able to sit on, and rise from, the potty chair
- Motivation of the child to stay dry
- At 2–4 years, the child is developmentally ready to begin toilet training
- Girls usually attain bladder control before boys
- Bowel control typically is achieved before bladder control

Delayed Toilet Training

- Delayed toilet training can cause parental frustration and abuse
- Some toddlers are ready as early as 18 months, and some are not ready until beyond third birthday
- Initiating toilet training too early can create stress for the child and ultimately prolong the toilet training process

Effective approaches in toilet training

- Training is started when the child is interested, ready physically, and willing to cooperate
- Nonpunitive, reward-based techniques are more effective
- Recognition and affection are the best rewards
- Training takes time, and occasional relapses are normal
- Use of correctly sized potty for the child
- Watching and learning from parents, motivation with cartoon underwear, allow for naked time so the child can readily access the potty

SUBSTANCE ABUSE DISORDERS (SEE CHAP. 3 "ADOLESCENT MEDICINE")

Cannabis use

- The most common presentation among adolescents
- 15% for cannabis use disorder[1]
- Up to 45% for experimenting with cannabis

Stimulant abuse

- Stimulants include use of cocaine and methamphetamine and misuse of prescription stimulants, e.g., ADHD medications
- Cocaine: 0.8%, more in males
- Methamphetamine: 1.2%
- Prescription stimulants: 2%

Depressant abuse

- **Prescription sedatives**: Benzodiazepines: alprazolam (Xanax), diazepam (Valium), lorazepam (Ativan), 2%
- **Prescription tranquilizers**: Barbiturates (pentobarbital) and sleep medications: eszopiclone (Lunesta), zolpidem (Ambien), 2.3%

Hallucinogens

- D-lysergic acid diethylamide (LSD): 0.9%
- 3,4-methylenedioxy-methamphetamine (MDMA) or ecstasy: 0.4%

Prescription medications

- Misuse of prescription pain relievers (e.g., oxycodone, hydrocodone); estimated prevalence rate of 4.7%; ages 18–25 years prevalence rate 8.5%

Steroids (anabolic)

- Estimated prevalence rate of 0.6%

Treatment of substance abuse disorder

- Referral to adolescent medicine or mental health specialists may be appropriate for subsequent evaluation, counseling, and possible pharmacotherapy
- Referral to a detoxification center:
  - Treatment initially consists of managing the varied symptoms of withdrawal, which can range from a longing to reuse to hallucinations and seizures
- Multimodal treatment to modify social factors in the family and at school that contribute to substance misuse behaviors
- Specific therapeutic intervention: Motivational interviewing

PEARLS AND PITFALLS

- Maintain empathetic, relaxed and nonjudgmental attitude when inquiring about mental health is critical during patient encounter.
- Avoid undertreating mental health conditions, risking an "act of omission."

[1]Numbers reflect prevalence rates for the past year in the US in 2015 among those aged 12 years or older, unless other age group is specified.

- Interview the adolescent individually, which helps to establish confidentiality and trust.
- Asking adolescent about depression and suicidal thoughts does not trigger the problem; depressed children may not express sadness or a depressed mood to their parents.
- Screen all adolescents from the age of 12 years and yearly after that about mood changes, irritability, dropping grades, social withdrawal, sadness, poor self-esteem, and difficulty concentrating.
- Cognitive behavioral therapy (CBT) is an effective treatment for depression by altering bad and negative thoughts into positive thoughts and a better outcome.
- Combination of CBT and medication is the best treatment for adolescent moderate to severe depression and more effective than using either therapy alone.
- Do not forget to always educate on possible side effects of medications.
- The course of symptoms may change/evolve across different developmental stages.
- Provide close follow-up visits when indicated and refer promptly as needed.
- Promote resilience/hope and appreciate the strength of the child and family, not only their weaknesses.
- Masturbation is frequent in young children but is usually stopped when children are older and aware of social norms. Behavioral modification, distraction, and redirection are the best strategies to limit masturbation behavior.
- Most children will outgrow thumb-sucking and finger sucking without intervention.
- Positive reinforcement, aversive techniques, competitive responses, and orthodontic devices may be helpful in altering the habit of thumb-sucking if it persists beyond 4 years of age and complications are present.
- Bullying usually when teachers are not around; school and families must collaborate to prevent this problem by having students supervised during breaks, by implementing school anti-bullying policies, and by parental training.
- Cognitive behavioral therapy/behavior management training is the first-line treatment for crimes committed by minors (juvenile delinquency). Wilderness camps, boot camps, and juvenile awareness programs are ineffective.
- Exposure of children to 2 or multiple languages at home is not a reason for language delay.
- Language delay, struggle in school, and learning problems can be the earliest signs of intellectual disabilities.
- Psychoeducational tests (IQ and achievement tests) are used for evaluation of intellectual disability; IQ test scores greater than 2 SD below the mean (< 70) in both cognitive and adaptive measures are suggestive of intellectual disability.
- Down syndrome (trisomy 21) is the most common genetic cause of intellectual disability in general.
- Fragile X is the second most common genetic cause of intellectual disability after Down syndrome.
- Screen for autism at the age of 18 months and 24 months or at any time if there is concern about autism spectrum disorder (ASD).
- Refer to early childhood intervention children less than 3 years with suspected ASD.
- Refer to local school district children 3 years and older with suspected ASD.
- Speech therapy, occupational therapy, and applied behavioral analysis are the best treatment for children with autism.
- No genetic studies or specific laboratories are indicated for children with ASD except if there are dysmorphic features, family history of intellectual disabilities, or possible underlying condition.
- Recommended workup for ASD with intellectual disability or global developmental delay includes a DNA analysis for fragile X syndrome and a chromosome microarray analysis.

- Behavioral intervention alone is not effective in the treatment of attention-deficit/hyperactivity disorder (ADHD).
- Stimulants are the first-line and most effective treatment in classic cases of ADHD.

References

1. Karande S, Kulkarni M. Poor school performance. Indian J Pediatr. 2005;72(11):961–7. Review.
2. Floet AM, Scheiner C, Grossman L. Attention-deficit/hyperactivity disorder. Pediatr Rev. 2010;31(2):56–69.
3. Glew G, Rivara F, Feudtner C. Bullying: children hurting children. Pediatr Rev. 2000;21(6):183–9; quiz 190. Review.

Suggested Reading

American Psychiatric Association. DSM-5 task force. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: The American Psychiatric Association; 2013.

Chang WW. Pediatric sedation. Updated 8 May 2018. Medscape. n.d.. https://emedicine.medscape.com/article/804045-overview#a8. Accessed 15 Oct 2018.

Kliegman RM, Stanton B, St Geme J, Schor N, Behrman RE. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011.

Martin A, Volkmar FR, Lewis M. Lewis's child and adolescent psychiatry: a comprehensive textbook. 4th ed. Philadelphia: Lippincott; 2007.

Rutter M, Bishop D, Pine D, Scott S, Stevenson JS, Taylor EA, Thapar A. Rutter's child and adolescent psychiatry. 5th ed. Hoboken: Wiley-Blackwell; 2010.

Emergency Medicine

7

Jo-Ann O. Nesiama, Jennifer McConnell, and Kenneth Yen

RESPIRATORY DISTRESS

Definitions

- Respiratory distress
  - Interruption of the respiratory tract or the systems that control respiration
  - One of the most common pediatric complaints in the emergency room
- Respiratory failure
  - Inability of the respiratory system to meet metabolic demand for oxygenation or ventilation
  - Prominent cause of pediatric deaths, particularly in infants
  - Respiratory failure is a primary cause of pediatric cardiac arrest

Special Considerations in the Anatomy of the Pediatric Airway

- Large occiput
  - Causes flexion of airway when supine
- Large tongue
  - May obstruct posterior pharynx when supine
- Obligate nose breathers (particularly < 4 months)
  - Nasal suctioning can significantly relieve respiratory distress due to nasal congestion
- Omega-shaped and floppy epiglottis
  - Structures easily collapse, and are not as rigid as adult airway structures
- Anterior airway with higher glottic opening at C2–C3 (versus C4–C5 in adults)
  - More difficult to visualize larynx during intubation
- Significant anatomic variation with age
  - Shorter trachea
    - Technically difficult intubation
    - Easy to insert endotracheal tube too far (right mainstem intubation)
    - Easy to lose artificial airway (dislodged tube, esophageal intubation)
- Smaller tracheal diameter:
  - Small increase in tracheal thickness causes disproportionately larger obstruction
    - Poiseuille's law: Resistance varies inversely with fourth power of the radius
      - Example: 1 mm thickening of trachea decreases tracheal diameter by 20% in an adult and 80% in a small child
- Narrowest portion of airway at cricoid ring (versus at vocal cords in adults)
  - Uncuffed endotracheal tubes may provide adequate seal at "natural" cuff

J.-A. O. Nesiama · J. McConnell · K. Yen (✉)
Division of Pediatric Emergency Medicine, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Ken.yen@utsouthwestern.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_7

- Small cricothyroid membrane
  - Needle cricothyrotomy difficult
  - Surgical cricothyrotomy impossible in small children

Localizing physical findings

- A careful physical can help rapidly localize the etiology of distress (Table 7.1)

Common causes of respiratory distress by anatomical location

- Many causes of respiratory distress in pediatric patients are commonly encountered and have well-defined clinical syndromes

Upper airway

- Upper airway obstruction

Table 7.1 Physical exam findings seen in pediatric patients in respiratory distress

Physical finding	Description	Physiology	Important notes
Retractions	Accessory muscle usage (supraclavicular, intercostal, abdominal)	Counteract high negative intrathoracic pressure via increased respiratory effort	Generalized finding of respiratory distress
Head bobbing	Flexion–extension movement of head and neck during inspiration and expiration	Emerges due to severe accessory muscle use, seen particularly in small children and infants	Indicative of severe respiratory distress, potential impending respiratory failure
Flaring	Widening of the lateral nares	Increases the upper airway diameter as an attempt to help relieve obstruction	Often a late finding of respiratory distress seen in small children and infants
Stertor	Low pitched, loud, rumbling, snoring sound	Upper airway obstruction: may be due to large tongue, tonsils, or adenoids; poor muscle tone; or altered mental status	Can improve with repositioning ("sniffing position") or jaw thrust
"Hot potato" voice	Muffled, soft voice	Obstruction of upper airway, typically oropharynx or pharynx	May be seen in retropharyngeal abscess or peritonsillar abscess
Hoarseness	Rough or harsh characteristic to voice	Obstruction or abnormality of vocal cords or larynx	Can indicate benign/minor pathology such as viral URI or concerning pathology such as injury to vagus or recurrent laryngeal nerve
Barky cough	Loud, "seal-" or "dog-like" hacking cough	Pathology or obstruction of subglottic area	Commonly seen in acute viral croup
Stridor	Harsh multiphonic, high-pitched upper airway noise, "noisy breathing"	Obstruction of upper airway results in turbulence and subsequent noise; inspiratory stridor most commonly glottic/subglottic in origin, expiratory stridor more likely lower airway, e.g., carina	Can indicate acute viral croup, or other concerning pathology such as aspirated foreign body or epiglottitis
Grunting	Soft, quick "puffing" expiratory noise	Expiration against partly closed glottis, attempt to maintain lung volume and prevent atelectasis via "auto-PEEP"	Often late finding of respiratory distress, seen in small children and infants
Wheezing	Musical, continuous noise	Expiratory wheezing indicates bronchi and bronchiolar obstruction	Expiratory wheezing commonly heard in asthma and bronchiolitis
Rales (fine crackles)	Inspiratory, high-pitched, "Velcro-like" sounds	Opening of collapsed alveoli filled with secretions, indicate pathology at lung tissue level	Typically will not clear with repositioning and coughing
Rhonchi (coarse crackles)	Inspiratory, mid- to low-pitched "popping" sounds	Turbulence and secretions from secretions or inflammation within bronchi and bronchioles	More likely to clear with repositioning and coughing

URI upper respiratory infection

  - Anaphylaxis (hives, angioedema, atopy, history of exposure to antigen, stridor, hoarseness)
  - Nasal congestion/obstruction (congestion, rhinorrhea, concurrent upper respiratory infection [URI])
  - Foreign body (history of coughing or choking event, stridor, drooling)
  - Congenital/developmental airway anomalies (choanal atresia, adenotonsillar hypertrophy, laryngotracheomalacia, subglottic stenosis/web/hemangioma, branchial cleft abnormalities)
- Upper airway infection
  - Croup (URI symptoms, barky cough, fever, inspiratory stridor)
  - Epiglottitis (toxic appearance, fever, dysphagia, drooling, inspiratory stridor)
  - Peritonsillar abscess (fever, sore throat, trismus, dysphagia, drooling, vocal changes, uvular displacement)
  - Retropharyngeal abscess (fever, dysphagia, drooling, vocal changes, neck stiffness/pain with extension, torticollis)
  - Tracheitis (toxic appearance, fever, stridor—similar appearance to epiglottitis, usually will have risk factors)

Lower airway

- Lower airway obstruction
  - Anaphylaxis (hives, angioedema, atopy, history of exposure to antigen, wheezing)
  - Asthma/reactive airway disease (atopy, history of bronchodilator use, expiratory wheezing, prolonged inspiratory to expiratory ratio)
  - Bronchiolitis (previously healthy, no prior wheezing, concurrent URI symptoms)
  - Foreign body
  - Tracheobronchomalacia (recurrent stridor or noisy breathing, acute or chronic exacerbations with concurrent URI)
- Lower airway infection
  - Pneumonia (cough, tachypnea, fever)

Extrapulmonary

- Mediastinal masses (orthopnea, B symptoms, hoarseness, hemoptysis, lymphadenopathy)
- Pericardial tamponade (history of trauma, orthopnea, hypotension, jugular vein distention, pulsus paradoxus, muffled heart sounds)
- Pleural effusion (risk factors such as pneumonia/chemotherapy/autoimmune disorders, orthopnea, pleuritic pain)
- Pneumothorax/tension pneumothorax (possible history of trauma or spontaneous sudden onset, unilateral absent breath sounds, possible hypotension, deviated trachea with mediastinal shift if tension is present)

An approach to the differential diagnosis by clinical syndrome

Respiratory distress with signs of upper airway obstruction (stridor, stertor, vocal change, dysphagia, drooling):

- If acute onset with fever, consider infection
  - Croup, peritonsillar abscess, retropharyngeal abscess, tracheitis, epiglottitis
- If acute onset without fever, consider
  - Anaphylaxis, foreign body
- If chronic, consider
  - Masses, congenital/developmental abnormalities such as tonsillar hypertrophy, vocal cord dysfunction, laryngotracheomalacia, psychogenic causes

Respiratory distress with signs of lower airway pathology (wheezes, rales):

- If acute onset with presence of fever, consider infection/inflammation
  - Bronchiolitis, pneumonia, subacute foreign body, myocarditis
- If acute onset without fever, consider
  - Asthma, bronchiolitis, viral/atypical pneumonia, foreign body aspiration, anaphylaxis

Respiratory distress with no signs of airway obstruction, with the presence of tachypnea:

- If acute onset tachypnea with fever, broaden the differential to include a more systemic illness

  - Pneumonia, subacute foreign body, pulmonary embolism, myocarditis, pericarditis, sepsis
- If acute-onset tachypnea without fever and with concern for cardiac abnormality (arrhythmia, rubs, gallops, new murmurs, hepatomegaly, poor perfusion), consider
  - Congenital heart disease, myocarditis, pericarditis, pericardial effusion/tamponade, congestive heart failure, pleural effusion
- If acute-onset tachypnea without fever and no concern for cardiac abnormality:
  - Very large differential diagnosis, obtain thorough history and physical
    - Respiratory disorder (pneumonia, atelectasis, pulmonary embolism, pulmonary deformity or mass)
    - Metabolic (acidosis, hyperammonemia, hyperglycemia, hepatic/renal disease)
    - Toxic (ingestions, methemoglobinemia)
    - CNS disorder (seizure, mass, encephalopathy, neuromuscular disease, anxiety, pain)
    - Intra-abdominal pathology (abdominal pain, distention, mass)
    - Hematologic (anemia, methemoglobinemia)

Initial Emergency Care for Patient in Acute Respiratory Distress

Airway management

- Leading cause of pediatric cardiac arrest is from respiratory failure
- Timely management of the pediatric airway is key to resuscitation of pediatric patients with acute respiratory distress

Categorize the airway

- Airway is clear: Airway is open and non-obstructed for normal breathing
  - Patient is able to vocalize clearly (speaking or loud crying)
- Airway is maintainable: Airway is obstructed but maintained with simple measures (Table 7.2)
  - Patient able to vocalize, but abnormally (stertor, stridor, choking, coughing, dysphonia, etc.)
- Airway is not maintainable: Airway is obstructed and requires advanced intervention such as intubation
  - Unable to speak or absence of cry (gurgling, gasping, cyanosis, loss of consciousness, extreme agitation, etc.)

Table 7.2 Initial simple airway maneuvers for patients in acute respiratory distress

Airway maneuvers	Description
Airway clearing	Suctioning oro-/nasopharynx to remove secretions or debris
	Nasopharyngeal airway
	Oral airway in patient with altered mental status
Airway positioning	Allow an awake child to assume position of comfort (e.g., tripoding)
	Head tilt and chin lift ("sniffing" position) to compensate for large occiput
	Jaw thrust/chin lift to open airway and bring tongue forward
	Shoulder roll to prevent forward flexion of cranium due to large occiput

Breathing management

- Pediatric patients are less tolerant of hypoxemia and hypercarbia
  - Higher metabolic rate means more metabolic demand

Support oxygenation and ventilation

- Provide supplemental oxygen for hypoxemia
- Provide ventilatory support for hypercarbia or inadequate/absent respiratory effort
- Make timely interventions for patient in acute respiratory distress (Table 7.3) (see Chap. 8 "Critical Care" for additional details)

Table 7.3 Initial interventions in resuscitation of patients in acute respiratory distress

Intervention	Common uses
Nasal cannula	Hypoxemia alone, will dry nasal mucosa over time
Simple face mask	Hypoxemia alone, significant room air entrainment and mixing
Non-rebreather face mask	Hypoxemia alone, allows for greater FIO2 via a reservoir
Heated high flow nasal cannula	Hypoxemia and increased respiratory effort, allows humidification and heating, higher oxygen flow rates
Noninvasive positive pressure ventilation	Hypoxemia and hypercarbia in select patients with respiratory failure but adequate airway protection and mentation; allows for positive pressure delivery via sealed mask
Bag–valve–mask ventilation	Hypoxemia and hypercarbia, insufficient/absent respiratory effort, a temporizing but life-saving measure while definitive airway/ventilatory support is being planned
Inhaled bronchodilators: albuterol and ipratropium	States of reversible bronchospasm (i.e., asthma exacerbation)
Nebulized racemic epinephrine	Suspected upper airway obstruction and edema with stridor (i.e., acute infectious croup)
Intramuscular epinephrine	Suspected anaphylaxis

Summary

- Correction of respiratory distress ultimately needs identification of the underlying cause
- Any disorder that causes respiratory distress has the potential to be life-threatening
- Remember the unique characteristics of the pediatric airway
- Initial resuscitation of the patient in acute respiratory distress requires attention to airway, breathing, and circulation

THE ACUTE ABDOMEN

The following section will focus on the presentation of the pediatric acute abdomen in the setting of emergency care, with a particular emphasis on the identification of surgical abdominal emergencies. Abdominal emergencies in the setting of pediatric abdominal trauma will be covered in the Trauma and Burns section.

The Pediatric Acute Abdomen

- Abdominal complaints in pediatric patients are common and often benign
- Surgical abdominal emergencies must not be missed, due to high morbidity and mortality, and require prompt recognition and timely surgical evaluation

Findings that may indicate a surgical abdomen

- Bilious emesis
  - Bilious emesis in infants is a surgical emergency
- Guarding
  - Active guarding
  - Passive guarding/rigidity
- Distention
- Bowel sounds
  - Absent bowel sounds may indicate ileus
- Tenderness
  - Rebound tenderness is indicative of peritonitis
- Associated symptoms
  - Fever can signify a systemic inflammatory response
  - Bloody diarrhea can signify bowel wall necrosis and malperfusion

Age-dependent presentation

The age of the presentation can significantly shape the differential diagnosis

- Infant: Maintain higher suspicion for congenital anomalies
  - Intussusception, malrotation with midgut volvulus, incarcerated hernias, Meckel diverticulum, pyloric stenosis
- School-aged child: Infectious causes become increasingly common
  - Acute appendicitis
- Adolescent:
  - Acute appendicitis, ectopic pregnancy, ovarian torsion, testicular torsion

General Principles of Management

- Definitive treatment must be targeted at the etiology of the acute abdomen
- There are general treatment principles that can be applicable in most cases

Initial resuscitation

- Attend to the ABCs (airway, breathing, circulation)
  - Be alert for signs of shock and poor perfusion
  - Restore intravascular volume as clinically appropriate
- Pain control
  - Use an appropriate regimen to treat escalating degrees of pain
  - If warranted, opioids can be safely used in pediatric patients
- *Nil* per os (NPO) status
  - Do not allow the patient to eat or drink
- For active bilious emesis and abdominal distention, consider decompression
  - Nasogastric tube
- Early surgical consultation
  - In the presence of suspicion for an acute surgical abdomen, prompt and early surgical consultation is important and should not be delayed
- Imaging options
  - Abdominal plain radiographs can be helpful in the evaluation of an acute abdominal obstruction, foreign body, bowel perforation, or constipation
    - Identification of free air
    - Air-fluid levels indicating ileus
    - Dilated loops of bowel in obstruction
    - Radiopaque ingested foreign body
    - Evaluation of stool burden
  - Ultrasonography is the preferred first line in many cases
    - Acute appendicitis, intussusception, ovarian torsion, pyloric stenosis, cholecystitis, pancreatitis, nephrolithiasis, pregnancy
  - Computed tomography (CT) imaging
    - CT of the abdomen/pelvis is the radiation exposure equivalent of more than 100 plain radiographs of the chest
    - CT of the abdomen/pelvis increases risk of radiation-induced solid cancers in children
    - Due to radiation exposure risks:
      - CT is not recommended in the routine evaluation of abdominal pain
      - Ultrasound should be considered first in the evaluation of acute appendicitis in children
  - Magnetic resonance imaging (MRI) will typically not be obtained in the emergency setting for the evaluation of abdominal pain

Select surgical abdominal emergencies (Table 7.4)

Nonsurgical Causes for an Acute Abdomen

- Due to the small size of pediatric patients and possibility for referred pain, many extraintestinal or nonsurgical diseases can present with an acute abdomen and acute abdominal pain
- Abdominal
  - Gastroenteritis, viral or bacterial
  - Constipation
  - Mesenteric adenitis
  - Gastritis/peptic ulcer disease
  - Pancreatitis
  - Gallbladder disease
  - Hepatitis
- Head, eyes, ears, nose, and throat (HEENT)
  - Streptococcal pharyngitis
  - Infectious mononucleosis
- Pulmonary
  - Pneumonia
- Cardiac
  - Pericarditis, myocarditis
- Renal
  - Spontaneous bacterial peritonitis (with peritoneal dialysis)

Table 7.4 Selected surgical abdominal emergencies, clinical features, and management

Features	Disease process	Clinical pearls	Clinical pitfalls	Initial management
Periumbilical pain migrating to the right lower quadrant at McBurney's point	Acute appendicitis	Most common abdominal emergency in children, with peak incidence between 9 and 12 years; many will have pain with walking or jumping; may also have anorexia, vomiting, diarrhea, and fever	The anatomic location of the appendix can vary, causing nonclassical sites of pain	Fluid resuscitation, pain control, appendix ultrasound, surgical consultation
Suspected acute appendicitis followed by sudden relief of pain, then development of generalized peritonitis	Perforated appendicitis	More likely to occur if appendicitis present for > 72 h, will often present with increasing signs of peritonitis and toxicity	Although appendicitis in infants is rare, the young child is more likely to present with perforation due to difficulty in the abdominal exam early on	Fluid resuscitation, pain control, appendix ultrasound, surgical consultation
Extreme colicky pain with periods of normalcy, currant jelly stools	Intussusception	Typically, 3 months to 6 years old, invagination of bowel at lead point, most common is ileocolic	Intussusception can present with emesis and altered mental status alone	Fluid resuscitation, ileocolic ultrasound, barium or air contrast enema, surgical consultation if unsuccessful, anticipatory guidance as intussusception can recur
Tense inguinal bulge, vomiting	Incarcerated inguinal hernia	Common cause of intestinal obstruction in infants and children, 60% occurring within the 1st year of life	May not have known prior history of hernia; incarceration can progress to strangulation and bowel necrosis within 24 h	May need inguinal ultrasound or abdominal radiograph if unclear diagnosis; otherwise, attempt immediate manual reduction if no sign of bowel necrosis, and early surgical consultation
Infant, projectile nonbilious emesis, hungry after emesis	Pyloric stenosis	Hypertrophied pylorus in infant 2–5 weeks old, occurs in 1 in 250 births, more common in first-born males, can cause hypokalemic, hypochloremic metabolic alkalosis	Does not present with acute abdomen, but due to potential for profound electrolyte disturbance, prompt diagnosis is important; alkalosis can be severe enough to cause apnea	Fluid resuscitation, careful electrolyte management, pyloric ultrasound, surgical consultation
Acute-onset bilious emesis, abdominal pain	Malrotation with midgut volvulus	Most serious cause of intestinal obstruction; congenital malrotation with abnormal fixation of bowel predisposes it to volvulize and obstruct; usually presents neonatally; however, 25% present > 1 year	Variable presentation, from asymptomatic to failure to thrive; complete volvulus for > 1 h causes gut necrosis; a midgut volvulus can cause death of entire small bowel and ascending colon	Resuscitation in case of signs of shock, flat and upright radiographs of abdomen, upper GI series, immediate surgical consultation

(continued)

Table 7.4 (continued)

Features	Disease process	Clinical pearls	Clinical pitfalls	Initial management
Bilious emesis, abdominal distention, significant abdominal surgical history	Surgical adhesions with obstruction	Any child with prior abdominal surgery or peritonitis can develop adhesions; requires low threshold of suspicion	Presentation can occur within days, or months to years after surgery	Fluid resuscitation, abdominal radiographs with more than one view (e.g., flat, upright, and decubitus), gastric decompression, early surgical consultation
Abdominal distention with systemic signs of illness (lethargy, apnea, temperature instability) in neonate	Necrotizing enterocolitis	Typically presents in premature infants or neonates within 10 days of birth, may have history of birth asphyxia or stress	Although most common in premature infants, can occur in term infants	Resuscitation if signs of shock, radiographs of abdomen, prompt surgical and neonatal subspecialty consultation

- Genitourinary
  - Testicular torsion
  - Ovarian torsion
  - Ectopic pregnancy
  - Pelvic inflammatory disease
  - Dysmenorrhea
- Urinary
  - Cystitis, pyelonephritis
  - Nephro-/urolithiasis
- Endocrine/metabolic
  - Diabetic ketoacidosis
- Autoimmune/inflammatory
  - Inflammatory bowel disease
  - Henoch–Schönlein purpura

Summary

- The differential diagnosis of the acute abdomen in pediatric patients is broad, ranging in nature from benign to life-threatening
- A careful history and physical are important to identify surgical emergencies
- Infants present a particularly diagnostic challenge due to difficulty of exam and nonspecific nature of presentation
- Maintain a low threshold for early surgical consultation

ANAPHYLAXIS

Definition

- Serious, systemic, rapid-onset allergic/hypersensitivity reaction
- Variable clinical presentation and severity
- Immunoglobulin E (IgE)-mediated, type I hypersensitivity reaction to antigen

Pathophysiology

- Antigen exposure leads to systemic mast cell and basophil degranulation with large histamine and cytokine release
  - Vasodilation
  - Smooth muscle spasm (can also cause coronary artery vasospasm)
  - Increased vascular permeability
  - End stage: Loss of intravascular volume and hypotension
- Common likely antigens
  - Food allergies (most common in pediatrics)
    - Peanut
    - Tree nuts (cashews, pecans, walnuts, etc.)
    - Milk
    - Wheat
    - Soy
    - Seafood (crustaceans)
    - Fruit

- Other miscellaneous allergens
  - Antibiotics (penicillins, cephalosporins, sulfonamides)
  - Insect stings (*Hymenoptera*, fire ants)

Diagnosis

- Primarily a clinical diagnosis
- If the presentation is unclear, a serum tryptase can help assist future subspecialty management

Clinical criteria

- Anaphylaxis is highly likely with any of the three clinical syndromes, in the context of an exposure to a likely antigen:
  1. Acute onset of illness with skin and/or mucosal symptom, and with one of the following symptoms:
     - Respiratory compromise (such as wheezing or stridor)
     - Hypotension or altered mental status (AMS)/syncope ***or***
  2. Two or more symptoms of the following occurring acutely after exposure to likely antigen:
     - Skin/mucosa (90%) (urticaria, angioedema, flushing)
     - Respiratory (50–70%) (rhinorrhea, oropharyngeal/laryngeal edema, hoarseness, stridor, wheezing, shortness of breath)
     - Gastrointestinal (40%) (nausea, abdominal pain, diarrhea, vomiting)
     - Circulatory (30%) (hypotension, tachycardia)
     - Neurologic (syncope, sense of impending doom, seizures, AMS) ***or***
  3. Age-specific decrease in systolic blood pressure (BP) > 30% from normal or hypotension

Biphasic presentation

- Immediate phase: Occurs within minutes to hours after exposure
- Delayed phase/recurrence: Occurs from hours to days after exposure (up to 72 h)

Differential diagnosis

- Anaphylactoid reaction
  - Non-IgE-mediated anaphylaxis
  - Most commonly caused by aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), or radiographic contrast
  - Clinically indistinguishable from anaphylaxis
  - Treatment is identical to anaphylaxis

Treatment

- Always attend to the ABCs
- Intramuscular epinephrine is the first-line treatment of choice in anaphylaxis and must be administered immediately
  - Dosage: 0.01 mg/kg intramuscular
    - Maximum of 0.3 mg in prepubertal child
    - Maximum of 0.5 mg in adolescent
  - Timing: Immediate
    - Repeat at 5- to 15-min intervals
    - Up to 19% of patients will need a second intramuscular dose
  - Location: Mid-lateral thigh (vastus lateralis)
  - Autoinjector dosing options
    - Autoinjectors can come in 0.1 mg, 0.15 mg, and 0.3 mg forms:
      - 0.1 mg (7.5–14 kg)
      - 0.15 mg (15–30 kg)
      - 0.3 mg (>30 kg)
  - Pharmacokinetics
    - Alpha- and beta-adrenergic agonist induces bronchodilation, vasoconstriction, and decreased vascular permeability
    - Effectively treating upper airway edema, hypotension, and shock in addition to bronchodilator and positive cardiac inotropic and chronotropic effects

- Intramuscular epinephrine achieves peak concentration faster than subcutaneous injection
  - Intramuscular epinephrine is far safer than intravenous (IV) epinephrine
  - Serious adverse effects of appropriately dosed intramuscular epinephrine are rare
  - Side effects mimic signs of endogenous catecholamine release: Pallor, anxiety, tachycardia, tremor

- Adjuncts therapies: Do not prioritize administration of adjuncts over epinephrine
  - Diphenhydramine (H1 blockers)
  - Ranitidine (H-2 blockers)
  - Albuterol or racemic epinephrine
  - Glucocorticoids

Patient disposition

- Due to potential for rebound anaphylaxis and rapid deterioration, careful consideration of patient risk factors must be made at time of disposition from emergency care
- Risk factors that may necessitate admission to the hospital for observation:
  - First presentation
  - Infants
  - Concomitant asthma
  - Unknown antigen

Home care after anaphylaxis

- Counseling and follow-up are key for safe disposition home after anaphylaxis
  - Avoidance of identified allergen
  - Discussion of signs and symptoms of anaphylaxis
  - Epinephrine auto-injector instruction
    - Because anaphylaxis has highly variable clinical presentation between patients and between episodes, it is not possible to predict disease severity
    - All patients with anaphylaxis should be prescribed an epinephrine auto-injector
    - High-risk patients:
      - Coexisting asthma
      - Reaction to trace amounts of food
      - Idiopathic anaphylaxis
      - Generalized urticaria from insect sting (higher risk of more severe reaction)
      - Patient lives in a remote or rural area
  - Referral to an allergy/immunology specialist

TRAUMA AND BURNS

General principles of pediatric trauma

- Primary survey (identify and treat any life-threatening problems)
  - **A** Airway maintenance
  - **B** Breathing and ventilation
  - **C** Circulation with hemorrhage control
  - **D** Disability; neurologic status (Glasgow Coma Scale [GCS], pupils)
  - **E** Exposure/environment (remove clothing and keep normal body temperature)
- Secondary survey
  - Vital signs
  - Detailed head-to-toe examination
  - History of traumatic event
    - AMPLE history: Allergies, medications, past illnesses, last meal, events or environment related to injury

Pediatric Head Trauma

- Most pediatric head trauma is not serious and requires only observation
- Identification of serious head trauma in pediatric patients requires careful physical examination and understanding of warning signs

Red flags in pediatric head trauma

- Severe mechanisms of injury
  - Motor vehicle collision (MVC) with
    - Patient ejection
    - Fatalities
    - Rollover

  - Motor vehicle vs. pedestrian crash (MPC) or cyclist injury in those without helmets
  - Height of fall
    - Infants under 2 years with falls greater than 3 ft
    - Children 2 years and over with falls greater than 5 ft
  - High-impact or high-speed object striking head
- Patients at higher risk
  - Infants in general, but particularly if < 3 months
  - Known bleeding disorder or anticoagulated
  - Multisystem injuries
  - Suspected nonaccidental trauma
- Patient with findings that are higher risk
  - AMS or acute change in mental status
    - Lethargy
    - Irritability
    - Loss of consciousness
  - Persistent vomiting
  - Severe headache
  - Bulging fontanelle
  - Focal neurologic findings
  - Seizures

Presentation and Localizing Findings of Serious Injury

Basilar Skull Fracture

Clinical presentation

- Raccoon eyes (periorbital ecchymosis, bruising around eyes)
- Battle sign (mastoid ecchymosis, bruising behind the ears)
- Hemotympanum
- Cerebrospinal fluid (CSF) otorrhea or rhinorrhea
- At increased risk for meningitis
- 75% will have a temporal skull fracture

Evaluation and management

- CT scan to evaluate for other fractures and bleeding
- If nondisplaced, then usually heals without intervention
- At higher risk for meningitis, but the utility of prophylactic antibiotics is unclear

Temporal Skull Fracture

Clinical presentation

- Bleeding from ear or hemotympanum
- Facial paralysis
- CSF otorrhea and rhinorrhea
- Vestibular symptoms, vertigo
- Leads to conductive, sensorineural, or both types of hearing loss

Evaluation and management

- CT scan (evaluate for longitudinal or transverse type)
- MR angiography/venography (MRA/MRV), CT angiography/venography (CTA/CTV)
- Usually bedrest and raise head of bed initially
- Surgery if CSF still leaking after 1 week
- Facial paralysis, hearing loss, and vertigo are longer-term issues

Subdural Hematoma

- Bleeding between the inner layer of the dura mater and the arachnoid mater
  - Tearing of the bridging veins across the subdural space
  - Result of acceleration/deceleration mechanism (MVC, shaken babies)
  - Associated with cerebral contusion
  - If acute, the most lethal injury, but can be chronic, developing over days to weeks

Clinical presentation

- Gradually increasing headache and confusion

- Ataxia, slurred speech
- Loss of consciousness or fluctuating level of consciousness

Diagnosis and management

- CT scan (concave, crescent-shaped hematoma)
- Treatment ranges from monitoring to a small burr hole to drain the hematoma to an open craniotomy. Treatment depends on size and speed of growth

Epidural Hematoma

- Bleeding between the dura mater and the skull
  - Often occurs from a break in temporal bone with bleeding from the middle meningeal artery

Clinical presentation

- Classically causes loss of consciousness (LOC) after head injury, followed by brief regaining of consciousness (lucid period), and then LOC again
- Headache, confusion, vomiting
- With progression of bleed, pupils ipsilateral to injury become fixed and dilated (compression of CN III) and gaze is "down and out" (unopposed action of CN IV and VI)
- Seizures and weakness on contralateral side due to compression of crossed pyramidal pathways
- Final stage is tonsillar herniation and death

Diagnosis and management

- CT scan (biconvex, lens-shaped hematoma)
- Emergency burr hole and/or craniotomy

Subarachnoid Bleed

- Bleeding between the arachnoid membrane and pia mater
  - Result of head trauma or can occur spontaneously (e.g., ruptured cerebral aneurysm)

Clinical presentation

- Severe headache of rapid onset
- Vomiting
- Loss of consciousness
- Fever
- Seizures

Diagnosis and management

- CT scan
- Support until neurosurgery

Retinal Hemorrhage

- In an infant, this can indicate possible nonaccidental trauma

Considerations in the Use of Head Computed Tomography (CT)

- Children are at greater risk of developing malignancy as a result of radiation exposure
- Because pediatric head trauma is common and often benign, the use of CT imaging should be applied judiciously and after careful consideration
- The age of the patient, presence of other injuries, suspicion for nonaccidental trauma, and presence or absence of warning signs should all help guide the application of screening head CT (Table 7.5) [1]

Management of Clinically Significant Head Trauma

- Attention to the ABCs, with particularly focus on
  - Protection and establishment of a secure airway
    - Particularly if unresponsive or GCS less than 8
  - Close hemodynamic monitoring and repeat neurologic assessments
  - Avoidance of hypothermia or hyperthermia

Table 7.5 Prediction rules for identification of children at low risk for clinically important traumatic brain injury found on computed tomography (CT) imaging of the head

Age is less than 2 years old	**CT is not recommended if the following criteria are met (risk of clinically important TBI is low)**	**Observation vs. CT recommended if any of the following are present (risk of clinically important TBI is slightly elevated)**	**CT recommended if any of the following are present (risk of clinically important TBI is high)**
	GCS 15 and no altered mental status	Occipital, parietal, or temporal hematoma	GCS less than 15 or altered mental status
	No palpable skull fracture	History of loss of consciousness	Palpable skull fracture
	Frontal hematoma only	Severe mechanism of injury	
	No loss of consciousness	Not acting normally per caretaker	
	Nonsevere mechanism of injury		
	Acting normally per caretaker		
Age is equal to or greater than 2 years old	**CT is not recommended if the following criteria are met (risk of clinically important TBI is low)**	**Observation versus CT recommended if any of the following are present (risk of clinically important TBI is slightly elevated)**	**CT recommended if any of the following are present (risk of clinically important TBI is high)**
	GCS 15 and no altered mental status	History of loss of consciousness	GCS less than 15 or altered mental status
	No signs of basilar skull fracture	History of vomiting	Signs of basilar skull fracture
	No loss of consciousness	Severe mechanism of injury	
	No vomiting	Severe headache	
	Nonsevere mechanism of injury		
	No severe headache		

Pediatric Emergency Care Applied Research Network validated clinical prediction rules; adapted from Kuppermann et al. [1], with permission
TBI traumatic brain injury, *GCS* Glasgow coma scale

  - Monitoring for signs of hypovolemic or neurogenic shock
  - Support to maintain cerebral perfusion pressure (CPP)
    - CPP = mean arterial pressure (MAP) – intracranial pressure (ICP) (or central venous pressure [CVP])
- Watch for clinical signs of increasing ICP
  - Unequal pupil dilation (pressure on cranial nerves)
  - Abnormal posturing
  - Cushing's triad: Irregular, decreased respirations (caused by impaired brainstem function), bradycardia, and systolic hypertension (widening pulse pressure)
- Management of increasing ICP
  - Mild hyperventilation
  - Intravenous mannitol or hypertonic saline (3%) may be needed
  - Immediate consultation to neurosurgery can be life-saving for serious intracranial injuries

Neck/Cervical Spine Trauma

- Penetrating neck injuries generally all need surgical evaluation
- Blunt neck injury may warrant further evaluation for vessel injury and cervical spine injury

Cervical Spine Injury

- Relatively uncommon
- MVC, sports, and falls are most common etiologies
- Children have different injury patterns because of increased physiologic motion due to:

  - Larger size of head compared to trunk, which creates a larger fulcrum
  - Horizontally oriented facet joints
  - Elevated ligamentous laxity
  - Weaker muscles
- Children < 8 years old 87% of spinal injuries are above C3
- Children > 8 years old more commonly have lower cervical injury (adult injury pattern)

Clinical presentation

- Always suspect if head injury or facial fractures
- Full neurologic exam, but note that > 20% with injuries will have normal exam

Diagnosis and management

- Cervical spine neck radiograph
- CT
- MRI
- Proper cervical spine immobilization initially for all
- Some may need longer-term immobilization (halo) or surgery

Abdominal Trauma

- Children are smaller in size; organs are proportionally larger; less fatty tissue around major organs; weaker musculature; more compliant rib cage, all which increase risk of solid organ injury
- Most are MVC, others are MPC, sports, falls, and nonaccidental trauma
- Most common unrecognized fatal injury

Clinical manifestation

- Exams may be difficult due to age, verbal ability, and fear
- Tachycardia can be the only sign (even with 45% circulating blood volume)
- Have high index of suspicion for abdominal injuries
  - Seatbelt sign (ecchymosis of abdominal wall) after MVC has increased risk of intra-abdominal injuries, primarily due to increased risk of gastrointestinal (GI) injuries
  - Handlebar mark (handlebar-shaped ecchymosis over abdominal wall) at increased risk of small bowel hematoma and others

Diagnosis and management

- Complete blood count (CBC), lipase, aspartate transaminase (AST)/alanine transaminase (ALT) coagulation studies, uric acid (elevated AST/ALT combined with positive physical exam has good sensitivity)
- Abdominal radiograph to evaluate for free air
- CT scan (without contrast, with IV contrast, with IV and oral contrast)
- Focused assessment with sonography in trauma (FAST) exam is of unproven utility in pediatrics but combined either with physical exam or serial exams can have good sensitivity and specificity
- Conservative management for most, laparoscopy for some
- Laparotomy for significant injuries

PEDIATRIC WOUNDS AND LACERATIONS

Laceration

- A laceration is a traumatic disruption to the dermis layer of the skin.
- Common locations are the face (~60%) and upper extremities (~25%)
- Most lacerations in pediatric patients are non-life-threatening but require appropriate management
- Severe and life-threatening lacerations must be evaluated and treated promptly
  - Hemostasis: Apply pressure or tourniquet as necessary
  - Injury to deeper structures: Especially at high-risk areas like the neck (carotid) arter-

ies, jugular veins, trachea, and esophagus must be considered

Management and treatment

- Repair may be more difficult in pediatrics due to fear, anxiety, and lack of cooperativity
  - Anesthetic and anxiolytic options
    - Topical anesthetic LET (4% lidocaine, 1:2000 epinephrine, 0.5% tetracaine)
      - Effective 20–30 min after application
      - Blanching of the site after application most often indicates achievement of effective anesthesia
    - Local anesthetic may be used to prepare for placement of sutures
      - Injectable lidocaine alone or with epinephrine
    - Distraction and soothing techniques
      - Child life experts, toys, movies, music, etc.
    - Oral/intranasal pharmacologic options
    - Inhaled and IV pharmacologic options for procedural sedation
- Wound preparation
  - Wound irrigation is the standard of care
  - Evaluation for possible foreign bodies or complications
  - Suspicion for foreign body or associated bony fracture should prompt radiographs of the affected site
  - Tissue adhesive
    - With selection of appropriate type of laceration, tissue adhesive has good cosmetic outcome with benefit of no need for suture or suture removal
- Suture and staples
  - Selection of suture material (absorbable versus nonabsorbable) will depend upon the location and depth of the injury
  - As a general rule, sutures should be evenly spaced
- Wound aftercare
  - All patients should be given follow-up instructions for local wound care, cleansing, timing (if necessary) of removal of suture, monitoring for infection, and use of sunscreen to decrease scar formation
- Consider the need for tetanus prophylaxis
  - Prophylactic antibiotics not recommended with simple, uncontaminated lacerations
    - Lacerations due to bites will typically require antibiotics
    - Lacerations to hands and fingers with associated distal fingertip fracture

Specialized Scenarios

- Lip lacerations
  - An injury crossing the vermilion border will likely require subspecialist repair
  - Failure to align the vermilion border can result in a poor cosmetic outcome and permanent lip deformity
  - Young and uncooperative patients may additionally require varying degrees of anxiolysis and possibly sedation to repair well
- Nail bed lacerations
  - Repair of nail bed lacerations can be particularly painful and anxiety-provoking and may require a higher level of care
  - Approximately half of all nail bed injuries are associated with a fracture of the distal phalanx and will likely require subspecialist repair
    - Low threshold for obtaining plain radiographs of the digit to evaluate for associated fracture
    - Nail bed laceration with associated distal phalanx fracture may be an open fracture
      - Open fractures require antibiotic therapy
- Ear lacerations
  - Significant ear lacerations will likely require subspecialty repair
  - Lacerations of the ear have the potential to involve the avascular cartilaginous support

  - Timely repair of ear laceration and close follow-up are important to avoid complications
    - Auricular hematoma: Disruption to cartilage and underlying perichondrium can lead to a hematoma, which, if untreated, can cause cosmetic deformity of the ear ("cauliflower ear")
- Timing of suture removal
  - Timely removal of sutures reduces likelihood of suture tracks; better cosmetic outcome
  - Face: 3–5 days
  - Scalp: 5–7 days
  - Trunk: 5–7 days
  - Extremities: 7–10 days

Animal and Human Bites

- Dog bites
  - Typically causes a crushing-type wound
  - The extreme pressure of a dog bite may damage deeper structures such as bones, vessels, tendons, muscles, and nerves
  - Dog bites are contaminated and require antibiotic therapy
    - *Staphylococcus* species, *Eikenella* species, *Pasteurella* species
- Cat bites
  - The sharp pointed teeth of cats usually cause puncture wounds and lacerations that may inoculate bacteria deep into the tissues
  - Infections caused by cat bites generally develop faster than those of dogs
  - Cat bites are contaminated and require antibiotic therapy
    - *Pasteurella* species, *Bacteroides* species
- Other animals
  - Foxes, raccoons, skunks, and bats carry a high risk for rabies
  - Bat bites may be asymptomatic
    - If a bat is discovered within a patient's sleeping quarters, rabies treatment should be given regardless of history of a known bite
- Human bites
  - Three general types of injuries can lead to complications:
    - *Closed-fist injury*
    - *Chomping injury to the finger*
    - *Puncture*-type wounds about the head caused by clashing with a tooth
  - Human bites are contaminated and require antibiotic therapy
    - *Eikenella corrodens, Staphylococcus* species, *Streptococcus* species
    - Human bites can also transmit the following organisms: Hepatitis B, hepatitis C, herpes simplex virus (HSV), and syphilis

General evaluation

- Time and location of event
- Type of animal and its status (i.e., health, rabies vaccination history, behavior)
- Circumstances surrounding the bite (i.e., provoked or defensive bite versus unprovoked bite)
- Location of bites

General management

- Local public health authorities should be notified of all animal bites and may help with recommendations for rabies prophylaxis
- Consider tetanus and rabies prophylaxis for all wounds (Tables 7.6 and 7.7) [2, 3]

Table 7.6 Indications for tetanus vaccine and tetanus immune globulin in the United States

Vaccine status	Clean and minor wounds	Contaminated wounds (soil, dirt, feces, saliva)
Unknown or not up to date (< 3 doses)	Tetanus vaccine only	Tetanus vaccine and tetanus immune globulin
Series completed (> 3 doses) less than 5 years ago	No tetanus vaccine or immune globulin	No tetanus vaccine or immune globulin
Series completed but > 5 years since final dose	If > 10 years since final dose, tetanus vaccine only	If > 5 years since final dose, tetanus vaccine only

Centers for Disease Control and Prevention [CDC] Advisory Committee on Immunization Practices on Tetanus 2018. Adapted from Liang et al. [2]

Table 7.7 Indications for rabies prophylaxis and treatment in the United States

Vaccination status	Intervention	Description
No prior vaccine	Human rabies vaccine	Human rabies vaccine (human diploid cell vaccine) should be administered IM on days 0, 3, 7, and 14
	Human rabies immune globulin (HRIG)	Immune globulin (20 IU/kg) should be administered via direct infiltration around the wound, with any remaining volume administered IM at an anatomical site distant from the vaccine site (e.g., the opposite deltoid or lateral thigh)
Previously vaccinated	Human rabies vaccine	Human rabies vaccine (human diploid cell vaccine) should be administered IM on days 0 and 3
	Human rabies immune globulin (HRIG)	Not indicated

Centers for Disease Control and Prevention [CDC] Advisory Committee on Immunization Practices, 2010. Adapted from Rupprecht et al. [3]
IM intramuscular

Laboratory

- Fresh bite wounds without signs of infection do not need to be cultured
- Infected bite wounds should be cultured to guide antibiotic therapy

Imaging studies

- Radiography is indicated if any concerns exist that deep structures are at risk (e.g., hand wounds, deep punctures, crushing bites, especially over joints)

Antibiotic therapy

- All human and animal bites should be treated with antibiotics
- The choice between oral and parenteral antimicrobial agents should be based on the severity of the wound and on the clinical status of the victim
- Oral amoxicillin–clavulanate is the initial drug of choice for empiric oral therapy
- Amoxicillin alone does not provide adequate coverage
- Parenteral ampicillin–sulbactam is the drug of choice in severe cases
- Clindamycin in combination with trimethoprim/sulfamethoxazole can be given if penicillin allergic

Wound care

- Debridement and removal of devitalized tissue
- Irrigation is key to prevention of infection
- 100 ml of irrigation solution per centimeter of wound
- Primary closure may be considered in limited bite wounds that can be cleansed effectively (this excludes puncture wounds, i.e., cat bites)
- Other wounds are best treated by delayed primary closure

Snake Bites

- Most are nonpoisonous and are delivered by nonpoisonous species
- North America is home to 25 species of poisonous snakes
- Characteristics of most poisonous snakes:
  - Triangular head
  - Elliptical eyes
  - Pit between the eyes and nose
  - Examples: Rattlesnakes, cottonmouth and copperheads
  - Few snakes with round head are venomous
    - Example: Coral snakes ("red on yellow—kill a fellow")

Clinical presentation

- Local manifestations
  - Local swelling, pain, and paresthesias may be present
  - Soft pitting edema that generally develops over 6–12 h but may start within 5 min
  - Bullae
  - Streaking

  - Erythema or discoloration
  - Contusions
- Signs of systemic toxicity
  - Hypotension
  - Petechiae, epistaxis, hemoptysis
  - Paresthesias and dysesthesias—Indicate neuromuscular blockade and should be aware of possible respiratory distress (more common with coral snakes)
- The time elapsed since the bite is a necessary component of the history
  - Determine history of prior exposure to antivenin or snakebite (this increases risk and severity of anaphylaxis)
  - Assessment of vital signs, airway, breathing, and circulation

Evaluation and management

- Laboratory
  - CBC with differential and peripheral blood smear
  - Coagulation profile, fibrinogen and split products
  - Blood chemistry, including electrolytes, blood urea nitrogen (BUN), creatinine
  - Urinalysis for myoglobinuria
- Management
  - Support and transfer to definitive care
  - Bitten extremities should be marked proximal and distal to the bite, and the circumference at this location should be monitored every 15 min for progressive edema and compartment syndrome
  - Antivenom
    - Hemodynamic or respiratory instability
    - Abnormal coagulation studies
    - Neurotoxicity, e.g., paralysis of the diaphragm
    - Evidence of local toxicity with progressive soft tissue swelling
    - Antivenom is relatively specific for the snake species against which they are designed to protect
    - There is no benefit to administer antivenom to unrelated species due to risk of anaphylaxis and expense
  - Surgical assessment focuses on the injury site and concern for the development of compartment syndrome
  - Fasciotomy is indicated only for those patients with objective evidence of elevated compartment pressure

Black Widow Spider Bite

- Black spider with bright-red or orange abdomen
- Neurotoxin acts at the presynaptic membrane of the neuromuscular junction; decreased reuptake of acetylcholine and severe muscle cramping

Clinical presentation

- Pricking sensation that fades almost immediately
- Uncomfortable sensation in the bitten extremity and regional lymph node tenderness
- A “target” or “halo” lesion may appear at the bite site
- Proximal muscle cramping, including pain in the back, chest, or abdomen, depending on the site of the bite
- Dysautonomia that can include nausea, vomiting, malaise, sweating, hypertension, tachycardia, and a vague feeling of dysphoria

Management

- Analgesics should be administered in doses sufficient to relieve all pain
  - Oral or IV opioid analgesics
  - Benzodiazepines are adjunctive for cramping
- Hydration
- Management of severe hypertension

Brown Recluse Spider Bite

- Dark, violin-shaped mark on the thorax
- Venom causes significant local skin necrosis

Clinical presentation

- Typically, initially painless bite

- Rarely is the spider found or recovered
- Erythema, itching, and swelling begin one to several hours after the bite
- Central ischemic pallor to a blue/gray irregular macule to the development of a vesicle
- The central area may necrose, forming an eschar
- Induration of the surrounding tissue peaks at 48–96 h
- Lymphadenopathy may be present
- The entire lesion resolves slowly, often over weeks to months

Management

- Tetanus status should be assessed and updated
- Signs of cellulitis treated with an antibiotic that is active against skin flora
- Treatment is directed at the symptoms

Scorpion Stings

- The only scorpion species of medical importance in the United States is the Arizona bark scorpion (*Centruroides sculpturatus*)
- Toxins in its venom interfere with activation of sodium channels and enhance firing of axons

Clinical presentation

- Local pain is the most frequent symptom
- Small children may have more severe symptoms
- Peripheral muscle fasciculation, tongue fasciculation, facial twitching, and rapid disconjugate eye movements, which may be misdiagnosed as experiencing seizures
- Agitation
- Extreme tachycardia
- Salivation
- Respiratory distress

Management

- Supportive care
  - Airway support and ventilation in severe cases
  - Analgesia and sedation
- Antivenom therapy also may obviate or reduce the need for airway and ventilatory support

BURNS

Pediatric Burn Classification

- Superficial burn (formerly first degree)
  - Epidermal injury, intact dermis
  - Erythematous, dry, and painful
  - Minor injuries that heal within 1 week without scarring
- Partial thickness burn (formerly second degree)
  - Partial injury of the dermis, often with edema and blistering
  - Commonly are caused by scald injuries and result from brief exposure to the heat source
  - Blanchable pink or mottled red, often with blisters and moist appearance
  - Typically, painful
  - Healed within 1–3 weeks with minimal scarring
- Deep partial thickness burn (formerly second degree)
  - Injury to epidermis and dermis
  - Dry, pale appearance, non-blanchable, may have speckled appearance
  - Less painful than partial thickness, although some sensation preserved
  - Heals after many weeks, often with significant scarring requiring surgical subspecialty care for optimal cosmetic outcomes
- Full thickness burn (formerly third degree)
  - Most serious and deepest type of burn
  - Destruction of epidermis and entire dermis with necrosis
  - Pearly white, charred, hard, or parchment-like appearance
  - Destruction of cutaneous nerves makes the burn typically nonpainful

  - Loss of tissue elasticity makes the skin scar-like and unable to expand
    - Circumferential or near-circumferential burns can cause compartment syndrome, vascular compromise of distal extremity, respiratory distress if present on the chest
  - Burn cannot re-epithelialize and requires surgical subspecialty care and often skin grafting

Inhalation Injury

- A large percentage of burn-related deaths are due to associated smoke and inhalation injuries
- Evaluate all burn victims for potential for inhalational injury:
  - Signs of respiratory compromise: Coughing, stridor, wheezing, hoarseness
  - Signs of neurologic compromise: Irritability or lethargy
  - Facial burns
  - Black (carbonaceous) sputum
  - Burned nasal hair and eyebrows
- Early and aggressive airway management prior to onset of airway obstruction
  - Suspected inhalation injury with signs of airway compromise will need intubation and bronchoscopy

Electrical Burns

- Electrical current can cause significant internal damage via the arc of current through the body
- External visible injury may be minimal
- Depending upon the arc of the electrical current, multiple complications can arise
  - Cardiac arrhythmia (ventricular fibrillation) and myocardial damage
  - Rhabdomyolysis and renal failure
- Neurologic damage can develop in the years following an electrical burn
- Oral electrical burns affecting the commissure of the lips can be very scarring and at risk of bleeding from the labial artery

Description of Burn

- The percent body surface area is an important calculation in the classification of burns
- "Rule of Nines" can aid in calculation of percent body surface area
  - Imagine the body as a flattened shape, with front and back surface areas added separately (Fig. 7.1) [4]
- Palmar method
  - Surface of palm of hand can be used to approximate 1% body surface area in older children
  - Not useful in small children and infants

Management of Burns

Supportive home therapy for minor burns

- Superficial burns (< 10% total body surface area) can typically be treated on an outpatient basis with supportive care, unless abuse is suspected
  - Cotton gauze occlusive dressing to protect the damaged skin from bacterial contamination:
    - Eliminate air movement over the wound (thus reducing pain)
    - Decrease water loss
    - Change dressings daily
  - Topical antimicrobial agent should be applied to the wound prior to the dressing for prophylaxis
    - Silver sulfadiazine or bacitracin
  - Application of various wound membrane dressings can promote healing and lessen pain of dressing changes
  - Pain control

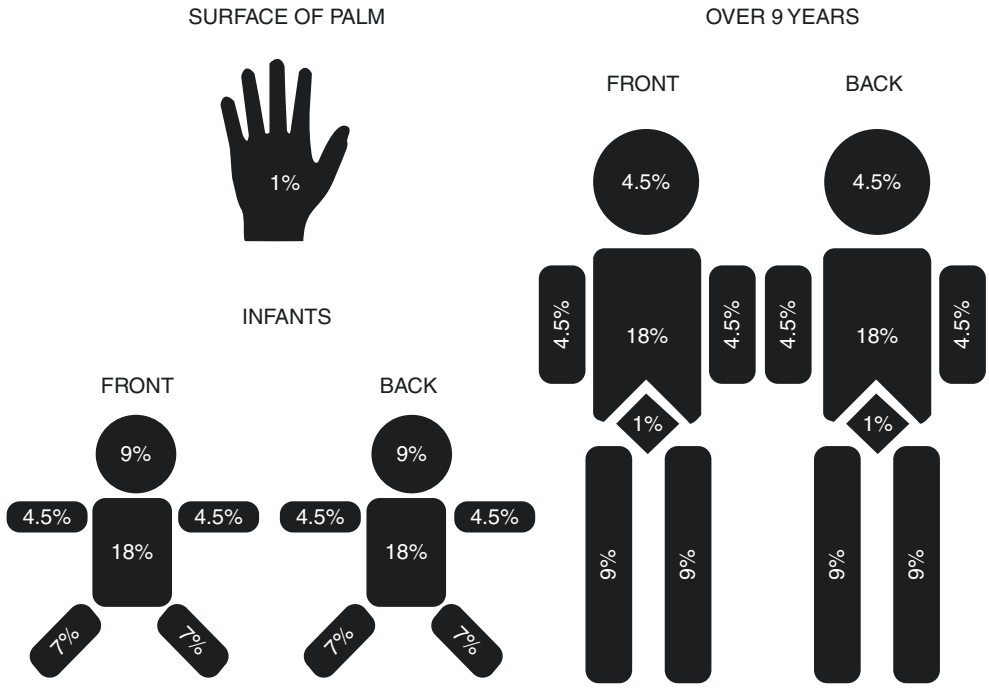


Fig. 7.1 Rule of nines: Infants versus children over 9 years old. (From Suguitan [4]), with permission)

- Alternating over-the-counter medications
- Opioid-containing medications for breakthrough pain
  - Caution in overreliance on opioids due to risk for dependence, withdrawal, and opioid-induced hyperalgesia

Initial treatment of extensive burns

- Extensive burns (> 10% total body surface area) and burns to high-risk areas (face, hands, neck, genitalia) will often require subspecialty care
- Identification of airway involvement due to risk for concomitant inhalation injury
  - Early and aggressive airway management recommended
- Fluid resuscitation to prevent shock
- Early excision and grafting of the burn wound coupled with early nutrition support
- Measures to treat sepsis
- Fluid administration
  - Once the nature and extent of injury are assessed, fluid resuscitation is begun
  - Two large-bore IV catheters
  - Parkland formula for fluid requirements:
    - 4 ml/kg/day for each percent of body surface area (BSA) burned
    - The first half of the fluid load is infused over the first 8 h post-burn
    - The remainder is infused over the ensuing 16 h
    - The infusion rates should be adjusted to maintain a urine flow of 1 ml/kg per hour
    - During the second 24 h, fluid administration is reduced 25–50%

STATUS EPILEPTICUS

Definitions

- A seizure that lasts more than 30 min ***or***
- Multiple seizures that occur without return of the individual to baseline, for a duration of not less than 30 min

Causes and risk factors

- Many conditions can cause status epilepticus
  - Infection (viral, bacterial, fungal, parasitic)
  - Trauma (intracranial hemorrhage, diffuse axonal injury, cerebral contusion)
  - Subtherapeutic anticonvulsant levels (patients with known epilepsy)

- Congenital abnormality
- Metabolic (hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia, hypercarbia, inborn errors of metabolism, pyridoxine deficiency in neonates)
- Vascular (hypoxic ischemic injury, cerebrovascular accident, hypertensive encephalopathy)
- Toxicologic (tricyclic antidepressants, isoniazid, pesticides (organophosphates), heavy metals (lead), topical anesthetic overdose)
- Endocrine (hyper-/hypothyroidism, Addison's disease)

Management

- Treatment should be based on an institutional protocol

General principles of management

- Attend to the **ABC**s before starting any pharmacologic intervention
  - **Airway**
    - Place patient in the lateral decubitus position to avoid aspiration of emesis and to prevent epiglottis closure over the glottis
    - Make further adjustments of the head and neck if necessary to improve airway patency
    - Suction secretions
    - Immobilize the cervical spine if trauma is suspected
  - **Breathing**
    - Administer 100% oxygen by face mask
    - Assist ventilation
    - Use artificial airways (e.g., endotracheal intubation) as needed
    - Decompress the stomach as needed with a nasogastric tube
  - **Circulation**
    - Carefully monitor vital signs, including BP
    - Carefully monitor the temperature, as hyperthermia may worsen brain damage
    - In the first 5 min of seizure activity, before starting any medications, try to establish IV access and obtain samples for laboratory tests
    - Infuse isotonic IV fluids plus glucose. In children younger than 6 years, use intraosseous (IO) infusion if IV access cannot be established within 5–10 min

Laboratory studies

- Finger-stick blood glucose
  - If serum glucose is low or cannot be measured, give children 2 ml/kg of D25% glucose
- Obtain basic metabolic panel, antiepileptic drug levels, and other labs, depending on the history and physical examination
- If the seizure fails to stop within 4–5 min, prompt administration of anticonvulsants may be indicated

Potential anticonvulsant medication options

- Anticonvulsant medication—selection can be based on seizure duration as follows:
  - Initial seizure activity (5–15 min):
    - Benzodiazepines are first-line GABA receptor blocker
      - Preferred options: Lorazepam IV or diazepam IV/rectal gel
      - Others: Midazolam IM or intranasal
  - Prolonged seizures (> 15 min), if refractory to benzodiazepines:
    - Many options exist with no clear literature to support a particular therapy
    - Selection should be made in consultation with a pediatric neurologist
    - Some options:
      - Phenytoin or fosphenytoin IV
      - Levetiracetam IV
      - Valproic acid IV
  - Continued seizure activity despite second- and third-line agents
    - General anesthesia may be required
    - Options include inhalational agents, pentobarbital anesthesia, continuous benzodiazepines

        - Anesthesia is titrated to achieve electroencephalogram (EE with burst suppression or flat line
    - By this point, advanced airway must be established, if not already
  - Other specific treatments may be indicated if the clinical evaluation identifies precipitants of seizures
    - Pyridoxine—IV/IM for possible dependence/deficiency or isoniazid toxicity
      - Pyridoxine-dependent seizures are a rare but reversible cause of refractory seizures in neonates: Consider administration of pyridoxine for neonatal status epilepticus
    - Naloxone: IV preferably (if needed may administer IM or subcutaneous) for narcotic overdose
    - Antibiotics: If meningitis is strongly suspected, initiate treatment with antibiotics prior to CSF analysis or CNS imaging

Anticipatory guidance

- Patients with history of status epilepticus will need:
  - Rescue abortive benzodiazepine (e.g., rectal diazepam) for prolonged seizures for home administration prior to arrival of emergency medical services
  - Seizure first aid teaching
- Consideration of additional benzodiazepine to raise seizure threshold during times of illness

ALTERED MENTAL STATUS (AMS)

Definitions

- AMS is a state of abnormally activated or abnormally suppressed awareness/consciousness
- It is a symptom and not a diagnosis—caused by an underlying disease or by trauma
- Altered level of consciousness or cognition—varying degrees of alteration of awareness
- Coma—the most severe form of altered level of consciousness in which an individual is not aware of his or her surroundings and cannot be easily aroused. A state lacking consciousness (both wakefulness and awareness) that cannot be overcome by stimulation
- Lethargy—state of altered level of consciousness that resembles deep sleep, from which a person can be aroused but immediately returns to that state. Depressed consciousness that, with adequate stimulation, can be overcome
- Obtunded—state of altered level of consciousness in which a person has greatly decreased responses and/ or is slow to respond
- Delirium (agitation)—abnormally activated consciousness with decreased awareness of environment from fluctuating global cerebral dysfunction, with inability or decreased ability to focus, shift, or sustain attention
- Consciousness
  - State of being awake and aware
  - Result of complex interplay of system controls
    - Ascending reticular activating system (ARAS) in brainstem and pons regulate wakefulness
    - Connections from the ARAS project out to the cortex and regulate awareness
    - Function is dependent on many factors
      - Requires adequate perfusion; adequate perfusion pressure; energy substrate (oxygen, glucose, hydration); electrolyte and acid-base balance (glucose, carbon dioxide, blood pH); removal of toxins (waste products); body temperature; absence of neuronal excitation/irritation (seizures)

Etiology of AMS

- The differential diagnosis of AMS is extremely broad and spans all possible organ systems
- Many possible causes of AMS have the potential to be life-threatening

- Trauma
  - Head trauma (subdural hematoma, epidural hematoma, cerebral edema, severe concussions)
- Infection
  - Meningitis, encephalitis, sepsis, brain abscess, subdural empyema
  - Sepsis with hypotension
- Neoplasm
  - Primary brain neoplasms or secondary brain involvement, blockage of CSF
- Vascular disease
  - Cerebral hemorrhage vs. infarct (arteriovenous malformation, aneurysm, hemangioma, thrombotic stroke), hypertensive emergency
- Obstruction to CSF
  - Malfunctioning ventriculoperitoneal (CSF) shunt
  - Hydrocephalus
- Metabolic anomalies
  - Hypoglycemia, hyponatremia, hypocalcemia, hypo-/hypermagnesemia, hypophosphatemia, metabolic acidosis and metabolic alkalosis, Reye syndrome
- Toxic ingestions
  - Many kinds of ingestions can cause AMS (e.g., severe aspirin ingestion, carbon monoxide poisoning, salicylates, barbiturates, alcohol, antihistamines, narcotics, phenothiazines, GHB [gamma hydroxybutyrate])
- Advanced stages of medical illnesses
  - Liver failure, kidney failure, heart failure, respiratory failure
- Specific disease states
  - Dehydration
  - Hypoxemia or hypercarbia
  - Hypothermia or hyperthermia
  - Hemolytic uremic syndrome: CNS infarction in basal ganglia
  - Intussusception: Infants can present initially with lethargy
  - Seizures: Postictal state, subclinical status epilepticus
  - Psychiatric disorders (pseudoseizure, conversion disorder)

Table 7.8 Glasgow coma scale [5, 6]

Score	Infant	Child	Adult
Eye opening			
4	Spontaneous	Spontaneous	Spontaneous
3	Opens to speech	Opens to speech	Opens to sound
2	Opens to pain	Opens to pressure	Opens to pressure
1	None	None	None
Best verbal response			
5	Coos and babbles	Oriented, appropriate	Oriented, appropriate
4	Irritable or cries	Confused	Confused
3	Cries in response to pain	Words	Words
2	Moans in response to pain	Sounds	Sounds
1	None	None	None
Best motor response			
6	Moves spontaneously and purposefully	Obeys commands	Obeys commands
5	Withdraws to touch	Localizing	Localizing
4	Withdraws to pain	Normal flexion	Normal flexion
3	Abnormal flexion to pain	Abnormal flexion	Abnormal flexion
2	Abnormal extension to pain	Extension	Extension
1	None	None	None

Glasgow Coma Scale

- The Glasgow Coma Scale (GCS) score can be used to help convey the level of AMS (Table 7.8) [5, 6]
  - GCS is 15 for individuals with normal level of mentation
  - GCS < 15 indicates an altered mental state
    - The subcategory including the lowest number should be indicated, e.g., a GCS of 13 (−2 M) indicates −2 from the motor subcategory

Management

- Treatment of AMS requires identification and treatment of the underlying cause
- In all patients, attend to ABCs promptly
  - Vital signs
    - Blood pressure
      - Attend to hypotension or severe hypertension
      - Fluid resuscitation
    - Heart rate
      - Attend to severe bradycardia or tachycardia
    - Hypothermia or hyperthermia
      - Thermoregulate patient
    - Pulse oximetry
      - Administer supplemental oxygen
      - Assess risk for methemoglobinemia or carboxyhemoglobinemia
    - Inadequate respiratory effort
      - Assist ventilation
  - Point-of-care glucose
    - Correction of hypoglycemia
  - Point-of-care blood gas
  - Consider empiric naloxone if clinical concern for opioid exposure

Specific disease categories:

- Trauma
  - This may be related to single system trauma (e.g., involving injury to the head/brain alone) or multisystem trauma
  - Decreased GCS with head trauma is presumed to be increased ICP until proven to be otherwise
  - May not have a history of a traumatic event if nonaccidental trauma is involved or injury was unwitnessed
  - Initial steps
    - Attend to airway, breathing, and circulation
    - Maintain cervical-spine immobilization
    - Obtain emergent noncontrast head CT and prompt neurosurgical consultation
    - Neuroprotective measures: May need 3% saline or mannitol, elevation of head to 30°, midline positioning of head
    - Other ongoing resuscitation measures may also be indicated
- Infection
  - In the presence of fever with meningismus, presume CNS infection
  - Attend to airway, breathing, and circulation promptly
  - Attempt diagnostic lumbar puncture if patient is stable enough to tolerate it
  - Order broad-spectrum IV antibiotics or antifungal medications if suspected fungal process, and do not delay administration
    - Order additional broad-spectrum IV antivirals for febrile neonate with risk factors for HSV encephalitis
  - If focal neurologic deficit or seizures are present, obtain noncontrast head CT prior to lumbar puncture
- Neoplasm
  - Space-occupying mass lesions in the brain can predispose to rapid decompensation
  - Attention to airway, breathing, circulation, and neuroprotective maneuvers and interventions
  - Requires prompt consultation with appropriate subspecialties (neurosurgery, oncology)
- Metabolic abnormalities
  - May be determined from results of testing or if adequate history is obtained, can help aid diagnosis
  - Therapy is directed at the specific abnormal electrolyte abnormality
    - Examples: Administration of glucose in the form of dextrose for hypoglycemia, or calcium for hypocalcemia
- Toxic ingestions
  - Attention to airway, breathing, circulation, and neuroprotective maneuvers and interventions
  - For specific antidotes, see Table 7.10
- Suspected CSF shunt malfunction
  - Attention to airway, breathing, circulation, and neuroprotective maneuvers

- Emergent head CT and radiographs to confirm shunt continuity ("shunt series")
- Timely neurosurgical consultation

POISONING AND TOXIC EXPOSURE

Background

- Children less than 6 years have the greatest risk
- Adolescent exposure either intentional or occupational

Prevention of poisoning

- Child-resistant packaging
- Anticipatory guidance in well childcare
  - Best provided at 6 months well child visit prior to the onset of mobility
  - Poison-proofing child's environment
    - Labeling all hazardous material
    - Locking medicine cabinets and securing cleaning products
    - Securing all medications in purses and handbags

Evaluation of a potentially toxic exposure

- Call the poison control center, describe the toxin, read the label, and follow the instructions
- Determine amount of exposure, number of pills, number of the remaining pills, and/or amount of liquid remaining
- Determine time of exposure
- Evaluate for progression of symptoms (any pattern of toxidromes)
- Consider associated ingestions and underlying medical conditions

General measures for toxic exposures

- For external exposures, remove clothes and wash the skin with soap and water
- For ingestions, can use activated charcoal if within 60 min of ingestion
  - Absorbs substances and decreases bioavailability
  - It is ineffective in the following (mnemonic CHEMICaL)
    - Caustics
    - Hydrocarbons
    - Ethanol (alcohols)
    - Metals
    - Iron
    - Cyanide
    - Lithium
- Ipecac
  - No longer recommended
  - Induction of emesis is particularly contraindicated with ingestions of hydrocarbons and caustics
- Gastric lavage
  - Contraindicated in hydrocarbons, alcohols, and caustics
  - Not recommended in most ingestions
  - May be considered with careful consideration if life-threatening ingestion occurred within 30–60 min of seeking medical attention
- Whole bowel irrigation
  - Reduces drug absorption by decontaminating the entire GI tract via large amounts of an osmotically balanced polyethylene glycol-electrolyte solution (PEG-ES) to induce a liquid stool and empty the bowel
  - Conclusive evidence that it improves outcomes is lacking
  - May cause vomiting and abdominal distention and lead to risk of aspiration
  - Should not be performed routinely, but may be considered for
    - Potentially toxic ingestions of sustained-release or enteric-coated drugs
    - Drugs not adsorbed by activated charcoal (e.g., lithium, potassium, and iron)
    - Removal of illicit drugs in the body (e.g., "packers" or "stuffers")

SPECIFIC INGESTIONS (TABLES 7.9, 7.10, AND 7.11) [7, 8]

Acetaminophen

- Responsible for one-third of all pediatric emergency department visits for ingestions
- The single toxic acute dose is generally considered to be > 200 mg/kg in children, and more than 7.5–10 g in adults and can cause hepatic injury or liver failure
- Any child with history of acute ingestion of > 150 mg/kg of acetaminophen should be referred for assessment and measurement of acetaminophen level

Clinical presentation (4 phases)

- First 24 h
  - Asymptomatic or nonspecific signs
  - Nausea, vomiting, dehydration, diaphoresis, pallor
  - Elevation of liver enzymes

Table 7.9 Toxidromes

Group	Vital signs	Mental status	Pupils	Other
Anticholinergics	Increased P, T	Delirium	Mydriasis	"Dry as a bone, red as a beet" … [a]
Cholinergics	Varies	Normal to depressed	Varies	"Drowning in secretions" DUMBBELLS[a]
Opioids	Decrease BP, P, R, T	Depressed	Miosis	Hyporeflexia
Withdrawal from opioids	Increase BP, P	Normal to anxious	Mydriasis	Vomiting, diarrhea, rhinorrhea
Sympathomimetics	Increase BP, P, R, T	Agitated	Mydriasis	Tremor and seizures
Ethanol or sedatives/hypnotics	Decrease BP, P, R, T	Depressed, agitated	Varies	Hyporeflexia and ataxia
Withdrawal from ethanol or sedatives/hypnotics	Increase BP, P, R, T	Agitated, disoriented	Mydriasis	Tremor and seizures

Adapted from Hoffman et al. [5] with permission McGraw Hill Education
BP blood pressure, *P* Heart rate, *R* Respiratory rate, *T* temperature
[a]See appropriate section

Table 7.10 Common antidotes for poisoning

Poison	Antidote
Acetaminophen	N-acetylcysteine (Mucomyst)
Anticholinergics	Physostigmine
Benzodiazepines	Flumazenil
β-blockers	Glucagon; insulin/glucose
Calcium channel blockers	Insulin and calcium salts
Carbon monoxide	Oxygen
Cyanide	Hydroxocobalamin (B12), Nitrites
Digitalis	Digoxin-specific fragments antigen-binding (Fab) antibodies
Ethylene glycol and methanol	Fomepizole
Iron	Deferoxamine
Isoniazid (INH)	Pyridoxine
Lead and other heavy metals, e.g., mercury and arsenic	British anti-Lewisite (BAL) (dimercaprol)
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Organophosphates	Atropine and pralidoxime
Salicylates	Sodium bicarbonate
Sulfonylureas	Octreotide
Tricyclic antidepressants	Sodium bicarbonate

Table 7.11 Differential of toxic related findings (with mnemonic devices)

Finding	Differential diagnosis	
Anion gap metabolic acidosis	**C**	Carbon monoxide, cyanide
(Anion gap = Na – (HCO3 + Cl)	**A**	Aminoglycosides
	T	Theophylline, toluene (glue sniffing)
	M	Methanol, metformin
	U	Uremia
	D	Diabetic ketoacidosis, starvation
	P	Paraldehyde, paracetamol/acetaminophen, propylene glycol
	I	Iron, isoniazid, ibuprofen, inborn errors of metabolism
	L	Lactic acidosis
	E	Ethylene glycol
	S	Salicylates/aspirin
Widened QRS	Bupivacaine, bupropion, carbamazepine, class I (quinidine, amiodarone, procainamide) antiarrhythmics, class Ic (flecainide, propafenone, moricizine) antiarrhythmics, cocaine, diphenhydramine, lamotrigine, tricyclic antidepressants	
Prolonged QTc	**T**	Thiazides
	O	Ondansetron (antiemetics), opioids (methadone)
	Q	Quinidine (class Ia), quinolones (antibiotics)
	R	Risperidone (antipsychotics)
	S	Sotalol (class III)
	A	Antihistamines
	D	antiDepressants (TCA)
	E	Erythromycin and other macrolides
	S	SSRI (fluoxetine, sertraline)
Hypoglycemia	**H**	Hypoglycemic (sulfonylureas not metformin)
	O	Others (quinine, quinolones, pentamidine)
	BB	β Blockers, Bactrim
	I	Insulin
	E	Ethanol
	S	Salicylates
Bradycardia and hypotension	**C**	Calcium channel blockers (diltiazem, verapamil, amlodipine)
	O	Opiates
	P	Propranolol and other beta-blockers (metoprolol, esmolol)
	A	Anticholinergics (organophosphates, carbamates, neostigmine, sarin, VX)
	C	Clonidine and other central α-2 receptor agonist (guanfacine, dexmedetomidine, oxymetazoline)
	E	Ethanol
	D	Digoxin and cardiac glycosides (oleander, foxglove, lily of the valley)

- 24 to 72 h post-ingestion
  - Tachycardia and hypotension
  - Right upper quadrant pain with or without hepatomegaly
  - Liver enzyme is more elevated
  - Elevated prothrombin time (PT) and bilirubin in severe cases
- 3 to 4 days post-ingestion
  - Liver failure
  - Encephalopathy, with or without renal failure
  - Possible death from multiorgan failure or cerebral edema
- 4 to 14 days post-ingestion
  - Complete recovery or death

Management

- Measure serum acetaminophen level 4 h after the reported time of ingestion
- Acetaminophen level obtained < 4 h after ingestion cannot be used to estimate potential toxicity
- Check acetaminophen level 6–8 h if it is co-ingested with other substance that slows GI motility, e.g., diphenhydramine
- Check liver function AST/ALT/coagulation parameters, renal function
- Start N-acetylcysteine (NAC)
  - If acetaminophen level is above the treatment line on Rumack-Matthew nomogram (4 h and after) (Fig.7.2) [6]
  - If acetaminophen level is low or undetectable with abnormal liver function
  - Patients with a history of potentially toxic ingestion more than 8 h after ingestion (single dose > 200 mg/kg in children and more than 7.5–10 g in adults)
- Liver transplant for liver failure

Ibuprofen

- Inhibit prostaglandin synthesis

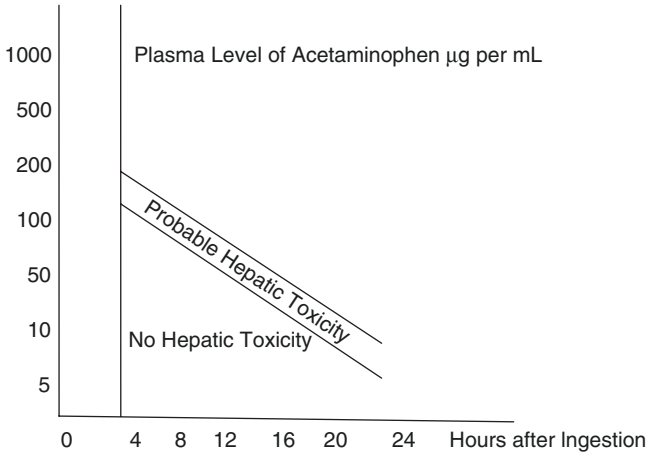


Fig. 7.2 Rumack-Matthew nomogram for acetaminophen poisoning [6]

Clinical presentation

- Nausea, vomiting, and epigastric pain
- Drowsiness, lethargy, and ataxia may occur
- Anion gap metabolic acidosis, renal failure, seizure, and coma may occur in severe cases (usually > 400 mg/kg)
- May cause GI irritation, ulcers, decrease renal blood flow, and platelet dysfunction

Management

- Activated charcoal
- Supportive care

Salicylic Acid

- Aspirin, certain antidiarrheal medications, topical agents, e.g., keratolytics and sports creams
- Refer to an emergency department for ingestions > 150 mg/kg
- Ingestion of > 200 mg/kg is generally considered toxic; > 300 mg/kg is more significant toxicity; > 500 mg/kg is potentially fatal

Clinical presentation

- Acute salicylism
  - Nausea, vomiting, diaphoresis, and tinnitus

- Moderate toxicity
  - Tachypnea, hyperpnea, tachycardia, and AMS
- Severe toxicity
  - Hyperthermia and coma

Management

- Consider activated charcoal
- Check blood gas (respiratory alkalosis, metabolic acidosis, and high anion gap)
- Check serum level every 2 h until it is consistently down trending
- IV fluids
- Sodium bicarbonate therapy in the symptomatic patients
- Goal of therapy includes a urine pH of 7.5–8.0, a serum pH of 7.5–7.55, and decreasing salicylate levels

Anticholinergics

- Diphenhydramine, atropine, scopolamine, hyoscyamine, jimsonweed (*Datura stramonium),* and deadly nightshade (*Atropa belladonna*)

Clinical presentation (anticholinergic symptoms)

- Dry as a bone: Dry mouth, decreased sweating, and urination
- Red as a beet: Flushing
- Blind as a bat: Mydriasis, blurred vision
- Mad as a hatter: Agitation, seizures, hallucinations
- Hot as a hare: Hyperthermia
- Bloated as a toad: Ileus, urinary retention
- Heart runs alone: Tachycardia

Management

- Consider activated charcoal
- Supportive care
- Physostigmine can be considered for severe or persistent symptoms

Beta-Blockers

- Acebutolol, atenolol, bisoprolol, metoprolol, nadolol, sotalol, and propranolol

Clinical presentation

- Hypotension, bradycardia, atrioventricular (AV) block, heart failure
- Bronchospasm
- Hypoglycemia, hyperkalemia
- Stupor, coma, seizures

Management tailored to the symptoms

- Consider dose of activated charcoal
- Hypotension/bradycardia/AV block: Fluid boluses, beta-agonists, vasopressors, atropine, possibly pacing
- Hypoglycemia: Glucose
- Hyperkalemia: Calcium gluconate, dextrose and insulin, sodium bicarbonate, possibly dialysis
- Two special cases
  - Propranolol → causes sodium channel blockade → QRS widening → treat with sodium bicarbonate
  - Sotalol → causes potassium efflux blockade → prolonged QT → monitor for *torsades*

Carbamazepine

Clinical presentation

- Mild ingestion:
  - CNS depression
  - Drowsiness
  - Vomiting
  - Ataxia
  - Slurred speech
  - Nystagmus
- Severe intoxication:
  - Seizures

  - Coma
  - Respiratory depression

Management
- Activated charcoal
- Supportive measures
- Charcoal hemoperfusion for severe intoxication

Cardiac Glycosides (Digitalis)

- Digoxin, foxglove plants, oleander, lily of the valley (*Convallaria*)

Clinical presentation
- Nausea and vomiting
- CNS depression (confusion)
- Blurry vision
- Cardiac conduction abnormalities (irregular pulse, bradycardia or tachycardia)

Management
- Electrocardiogram (ECG) and digoxin levels
- Activated charcoal
- Atropine, cardiac pacing (for severe bradycardia)
- Magnesium sulfate (for premature ventricular contractions [PVCs])
- Management of hyperkalemia, hypokalemia, hypomagnesemia
- If severe, digoxin-specific antibody fragments

Clonidine

- Antihypertensive medication with α-2 adrenergic receptor blocking ability
- Commonly used in children with attention-deficit hyperactivity disorder (ADHD)
- Dose as small as 0.1 mg can cause toxicity in children

Clinical presentation
- Lethargy
- Miosis
- Bradycardia
- Hypotension
  - Can cause transient initial hypertension
- Apnea

Management
- Supportive care, e.g., intubation, atropine, dopamine as needed
- Charcoal usually not recommended due to CNS depression

Opiates

- Morphine, heroin, methadone, propoxyphene, codeine, meperidine
- Most cases are drug abuse

Clinical presentation
- Common triad of opiate poisoning:
  - Pinpoint pupil
  - Mental depression (lethargy to coma)
  - Respiratory depression
- Hypotension with no change in heart rate
- Decreased GI motility, nausea, vomiting, abdominal pain

Management
- Supportive care, e.g., airway, breathing, and circulation; intubation; fluids as necessary
- Naloxone as needed
  - Half-life of naloxone is short
  - Repeat doses and continuous infusions may be necessary
  - Cautious use in known opioid-dependent patients
    - Can induce withdrawal

Phenothiazines

- Promethazine, prochlorperazine, and chlorpromazine

Clinical presentation
- Hypertension

- Cogwheel rigidity
- Dystonic reaction (spasm of the neck, tongue thrusting, oculogyric crisis)
- CNS depression

Management
- Activated charcoal
- Manage high BP
- Diphenhydramine for dystonic reaction

Tricyclic Antidepressants (TCAs)

- TCAs can cause significant toxicity in children even with ingestion of 1–2 pills (10–20 mg/kg)

Clinical presentation
- Anticholinergic toxidrome: Delirium, mydriasis, dry mucous membrane, tachycardia, hyperthermia, hypotension, and urinary retention
- Cardiovascular and CNS symptoms dominate the clinical presentation
- Most common cardiac manifestations: Widening of QRS complex, PVCs, ventricular arrhythmia
- Refractory hypotension is poor prognostic indicator and is the most common cause of death in TCA toxicity

Management
- Supportive measures, ABCs
- ECG:
  - A QRS duration > 100 ms identifies patients at risk for seizures and cardiac arrhythmia
  - An R wave in lead aVR of > 3 mm is an independent predictor of toxicity
- Start sodium bicarbonate therapy: QRS duration > 100 ms, ventricular dysrhythmias, hypotension, and seizures

Carbon Monoxide (CO)

- Wood-burning stove, old furnaces, and automobiles

Prevention of CO poisoning
- CO detectors
- Maintenance of fuel-burning appliances
- Yearly inspection of furnaces, gas pipes, and chimneys
- Car inspection for exhaust system
- No running engine in a closed garage
- Avoid indoor use of charcoal and fire sources

Clinical presentation
- Headache, malaise, nausea, and vomiting are the most common flu- or food poisoning-like early symptoms
- Confusion, ataxia, syncope, tachycardia, and tachypnea at higher exposure
- Coma, seizure, myocardial ischemia, acidosis, cardiovascular collapse, and potentially death in severe cases

Management
- Evaluate for COHb level in symptomatic patients
- Arterial blood gas with CO level
- Check creatine kinase in severe cases
- ECG in any patient with cardiac symptoms
- 100% oxygen to enhance elimination of CO, use until CO < 10% and symptoms resolve
- Severely poisoned patient may benefit from hyperbaric oxygen especially if COHb > 25%, significant CNS symptoms, or cardiac dysfunction

Cyanide

- Seeds (cherries, apricots, peaches, apples, plums); cassava; burning plastics (nitrile-containing products); nitroprusside; some pesticides
- Amygdalin is contained in seeds and produces hydrogen cyanide, which is a potent toxin
- Inhibition of cellular respiration (cytochrome c oxidase) stops ATP production

Clinical presentation
- Decreased level of consciousness

- Low exposures—weakness, headache, dizziness, confusion
- Severe exposures—seizure, apnea, cardiac arrest
- Cherry red skin

Management
- Supportive measures
- Hydroxocobalamin (vitamin B12), nitrites

Ethylene Glycol Ingestion (Antifreeze)

Clinical presentation
- Nausea, vomiting, CNS depression, anion gap metabolic acidosis
- Hypocalcemia, renal failure due to deposition of calcium oxalate crystals in the renal tubules

Management
- Osmolar gap can be used to estimate ethylene glycol level
- IV fluids, glucose, and bicarbonate as needed for electrolyte imbalances and dehydration
- Fomepizole
- Ethanol can be used if fomepizole is unavailable

Methanol

- Toxicity primarily caused by formic acid

Clinical presentation
- Drowsiness, nausea, and vomiting
- Metabolic acidosis
- Visual disturbances: blurred and cloudy vision, feeling of being in a snowstorm, and untreated cases can lead to blindness

Management
- Osmolar gap (may be used as surrogate marker until methanol blood level is available)
- IV fluids, glucose and bicarbonate as needed for electrolyte imbalances and dehydration
- Fomepizole
- Ethanol can be used if fomepizole is unavailable
- Hemodialysis (consider if > 30 ml methanol ingested)

Iron

- Ingestion of > 60 mg/kg/dose is toxic

Clinical presentation
- Gastrointestinal stage (30 min–6 h)
  - Nausea, vomiting, and abdominal pain
  - Hematemesis and bloody diarrhea in severe cases
- Stability stage (6–24 h)
  - No symptoms: Patient must be observed during this stage
- Systemic toxicity within (48 h)
  - Cardiovascular collapse
  - Severe metabolic acidosis
- Hepatotoxicity and liver failure (2–3 days)
- Gastrointestinal and pyloric scarring (2–6 weeks)

Management
- Abdominal radiograph (may show pills and need for GI decontamination)
- Serum iron < 300 mcg/dl is nontoxic
- Chelation with IV deferoxamine if serum iron > 500 mcg/dl

Mushrooms

- Ingestion of mushrooms can have fatal consequences in species that harbor amatoxins (e.g., *Amanita*) and related compounds

Clinical presentation
- Nausea, vomiting, and diarrhea; delayed onset (6 h)
- A second latent period is followed by acute and possibly fulminant hepatitis beginning 48–72 h after ingestion

Management

- Activated charcoal
- Whole bowel irrigation
- Supportive care, including liver transplant, if necessary, is the mainstay of therapy

Caustic Ingestion

- Strong acid and alkalis < 2 or > 12 pH can produce severe injury even in small-volume ingestion
- Patient can have significant esophageal injury without visible oral burns

Clinical presentation

- Pain, drooling, vomiting, and abdominal pain
- Difficulty in swallowing, or refusal to swallow
- Stridor and respiratory distress are common presenting symptoms
- Esophageal stricture caused by circumferential burn; requires repeated dilation or surgical correction

Management

- Supportive measures, ABCs
  - Inducing emesis and lavage are contraindicated
  - Endoscopy should be performed within 12–24 h in symptomatic patients, or on basis of history and characteristics of ingested products

Hydrocarbons

- Products contain hydrocarbon substances, mineral spirits, kerosene, gasoline, turpentine, and others
- Aspiration of even small amount can be serious and potentially life-threatening
- Pneumonitis is the most important manifestation of hydrocarbon toxicity
- Benzene is known to cause cancer
- Inhalants, including toluene, propellants, and volatile nitrite, can cause dysrhythmias and sudden death

Clinical presentation

- Cough, tachypnea, respiratory distress

Management

- Emesis and lavage are contraindicated
- Activated charcoal should be avoided due to risk of inducing vomiting
- Observation and supportive care

Organophosphate and Carbamate Insecticides (Nerve Gas Agents)

- Inhibit anticholinesterase

Clinical presentation

- (DUMBBELLS) "Drowning in your own secretions"
  - Diarrhea
  - Urination
  - Miosis
  - Bradycardia
  - Bronchospasm
  - Emesis
  - Lacrimation
  - Lethargy
  - Salivation and Seizures

Management

- Wash all exposed skin with soap and water and immediately remove all exposed clothing
- Fluid and electrolyte replacement, intubation, and ventilation if necessary
- Atropine and pralidoxime

FOREIGN BODY ASPIRATION AND INGESTION

Foreign Body Aspiration

- Occurs in the context of child's play/exploration of environment
- Foreign bodies may lodge in the upper or lower respiratory tract

Upper airway

- The most commonly implicated foods are
  - Candy, meat, hot dogs, grapes
- Associated symptoms include
  - Choking, coughing, stridor, respiratory distress
  - May result in complete airway obstruction
- In patients with complete airway obstruction, emergency procedures may be life-saving
  - Back blows in infants
  - Heimlich maneuvers in older children
  - If patient becomes unconscious, may need to initiate cardiopulmonary resuscitation (CPR)
    - Convert to rescue breaths and chest compressions
  - If all of the above are unsuccessful, then advanced airway techniques may be necessary

Lower airway

- More common in younger children
- Foreign body may lodge in the right or left lung
- Symptoms may involve coughing, choking, wheezing, or may be asymptomatic
- Diagnosis may be delayed due to lack of symptoms

Management

- If the patient is stable and not in respiratory distress, neck and/or chest radiographs may help with diagnosis
  - Not all inhaled foreign bodies are radiopaque and may not be visualized on radiographs even if present
- Bilateral decubitus views may aid in diagnosis: Bilateral to compare which lung exhibits air trapping, which may be where the foreign body is lodged
- The presence of normal chest radiographs does not exclude this diagnosis in the presence of a compelling history
- For patients in severe respiratory distress, immediate bronchoscopy to remove the foreign body emergently is key to treatment

Foreign Body Ingestion

- Most children will have a history of ingested foreign body, often reported by a caregiver or playmate/sibling
- Most commonly ingested foreign bodies are
  - Food (meat)
  - Followed by coins, pins, toy parts, button batteries, magnets
- Most will pass harmlessly through the GI tract
- Foreign bodies may lodge in areas where there is physiological/anatomic narrowing of the lumen of the GI tract
  - Lodging may occur secondary to pathological narrowing of the lumen of the GI tract (e.g., from previous surgeries such as in tracheoesophageal fistula, esophageal/duodenal webs)
- Symptoms, if present, may include coughing, choking, foreign body sensation, throat pain, drooling, vomiting, refusal or inability to tolerate fluids/food
- Children may also be completely asymptomatic

Esophagus

- The esophagus is the most common site for ingested foreign bodies to become lodged
- Ingested foreign bodies typically become lodged in one of three sites:
  - At the thoracic inlet

  - Mid-esophagus, at the level of the carina and aortic arch
  - Esophago-gastric junction

Management

- If the patient is asymptomatic and there is no airway compromise, may do neck and/or chest radiographs
- If foreign body is not visualized and patient is asymptomatic, then can do an esophagram
- If foreign body is lodged in the esophagus, may need removal by esophagoscopy
- Some authorities report the use of glucagon with varying degrees of success
- Emergent removal is indicated for two or more magnets, button batteries, lodged sharp objects

Stomach and Lower Gastrointestinal Tract

- Most foreign bodies in the stomach will pass harmlessly through the remaining portion of the GI tract
- Single, not sharp foreign bodies may be managed conservatively and observed
- Parents may be advised to watch patient stools, or have repeat abdominal radiographs within 1 week to assess if foreign body has been eliminated
- If two or more button batteries or magnets are located in any portion/part of the GI tract, consultation with a gastroenterologist to facilitate removal is necessary
  - If not removed, the magnets may "adhere" together across tissues/tissue planes and cause necrosis with ensuing perforation
- Sharp objects (particularly if longer than 5 cm) in the stomach and lower GI tract require consultation with a gastroenterologist

DIABETIC KETOACIDOSIS (DKA)

DKA in Pediatric Patients

- DKA is a severe complication of type 1 diabetes
- Occurs in 25–40% of new-onset type 1 diabetes
- Inadequate relative or absolute deficit of insulin leads to starvation of insulin-dependent tissue (muscle, liver, fat) with resultant hyperglycemia
- Starvation state triggers a cascade of hormonal release such as glucagon, catecholamines, cortisol, cytokines
- Results in a catabolic state with lipolysis, proteolysis, adipose tissue metabolism into free fatty acids, hepatic conversion of fatty acid to keto-acids, and anion gap metabolic acidosis
- Hyperglycemia causes osmotic diuresis with hypovolemia and dehydration

Diagnostic laboratory findings

- Acidosis (venous pH < 7.3, serum bicarbonate < 15 mEq/L)
- Serum glucose > 200 mg/dL
- Glucosuria, ketonemia, and ketonuria

Degrees of severity of DKA

- Mild: pH > 7.2 and < 7.3, bicarbonate < 15 mEq/L
- Moderate: pH > 7.1 and < 7.2, bicarbonate < 10 mEq/L
- Severe: pH < 7.1, bicarbonate < 5 mEq/L

Review of pathophysiology

- Inadequate insulin secretion
  - Decrease in cell uptake of glucose, leading to hyperglycemia
  - Hyperglycemia causes osmotic diuresis, leading to dehydration

  - Compounded by stress response with activation of gluconeogenesis, glycogenolysis, and increased insulin resistance
- Protein catabolism
  - Adipose tissue broken down into fatty acids
  - Fatty acids converted to keto-acids in the liver
- Dehydration
  - Osmotic diuresis from hyperglycemia
  - Compounded by acidosis with nausea, vomiting, and oral intolerance
  - Typically occurs in setting of several weeks of polyuria, polydipsia, and weight loss
  - Dehydration can be profound and lead to shock state
- Acidosis
  - Keto-acids from protein catabolism cause anion gap acidosis
  - Poor tissue perfusion in setting of severe dehydration causes lactic acidosis
- Electrolyte abnormalities
  - Potassium
    - Acidosis causes extracellular shift of potassium with hyperkalemia
    - Excess serum potassium is cleared by kidney
    - Hypovolemia stimulates secondary hyperaldosteronism and further urinary potassium excretion
    - Factors leads to total body potassium depletion in all patients with DKA
    - Measured serum potassium levels are highly variable at presentation (hypokalemia, normal, or hyperkalemia) and do not correlate with degree of total body potassium losses
  - Phosphate
    - Acidosis stimulates phosphate depletion due to renal phosphate excretion
  - Sodium
    - Hyperglycemia and osmotic diuresis lead to renal sodium losses and typically hyponatremia

Cerebral Edema

- Most serious immediate risk to child in DKA with mortality rate of 40–90%
- Occurs in 1/100 pediatric cases during the first 24 h of DKA
- Causes 50–60% of diabetes-related pediatric deaths
- Pathophysiology of cerebral edema is controversial
- Risk factors for cerebral edema continue to be studied
  - New-onset diabetes
  - Age < 3 years
  - High BUN at presentation
  - Low PCO2
  - Treatment with bicarbonate
  - Failure of serum sodium to correct with therapy

Signs

- AMS, from agitation to frank coma
- Severe headache
- Heart rate deceleration
- Focal neurologic deficit

Treatment

- Immediate recognition
- Immediate mannitol 1 g/kg over 10–20 min
- Cerebral edema is a reversible condition with prompt treatment

Principles of initial resuscitation of DKA in the emergency department

- Treatment of DKA is often based on institutional protocol
- General concepts are
  - Initial rehydration with isotonic fluid
    - 10–20 ml/kg of 0.9% normal saline over 1–2 h
    - Goals: adequate tissue perfusion, not normovolemia
  - Administration of insulin as continuous IV infusion
    - Regular insulin 0.1 unit/kg/h via IV line

  - Addition of dextrose in fluid after serum glucose begins to fall
    - Varying concentrations of dextrose from 5% up to 12.5% via IV line
    - Plasma glucose target range 200–300 mg/dL
  - Careful correction of electrolyte disturbances
    - Addition of potassium once serum K < 5.0 mEq/L
    - Addition of phosphate as potassium phosphate as serum phosphate allows
  - Prompt subspecialty consultation
  - Frequent laboratory monitoring
  - Frequent neurologic assessments to monitor for cerebral edema

Life-Threatening Complications to Consider in the Emergency Department

- Cerebral edema
- Shock/cardiovascular collapse
  - Dehydration can be profound
  - Requires prompt restoration of intravascular volume
  - Consider infection/sepsis as trigger for stress response and hyperglycemia if clinically warranted
- Hyperkalemia or hypokalemia
  - Obtain ECG in critically ill child
  - May cause life-threatening arrhythmias or cardiovascular collapse
- Profound metabolic acidosis
  - Insulin infusion is necessary to stop primary ketoacidosis
  - Insulin infusion should never be stopped in DKA: If hypoglycemia occurs, adjust dextrose in fluids or rate of fluids to maintain plasma glucose levels
- Hypophosphatemia
  - Caution with replacement of phosphate is advised due to risk of precipitating hypocalcemia, renal failure, and arrhythmias

Ongoing management

- Children with DKA typically require subspecialty monitoring
- Admission frequently required to specialized unit or to the intensive care unit
- Continued monitoring
  - Hourly plasma glucose
  - Hourly neurologic assessments
  - Hourly intake and output
  - Serial measurements of serum potassium, calcium, phosphate, magnesium
  - Serial venous blood gas

Goals of treatment

- These goals are typically achieved in the inpatient setting
  - Resolution of hyperglycemia
  - Correction of dehydration
  - Closure of anion gap acidosis (anion gap normalized between 10 and 12)
  - Oral tolerance to feeds
  - Resolution of other symptoms

CONCUSSION/HEAD INJURY

Definition

- Concussion can be defined as
  - An acute injury to the brain from an external physical force
  - Resultant confusion, disorientation, brief loss of consciousness, self-limited post-traumatic amnesia and/or other transient neurologic abnormalities
  - GCS score of 13–15 after 30 min following the injury
- Also known as a mild traumatic brain injury

Epidemiology and mechanism of pediatric concussions

- Major cause across all age groups for pediatric visits to emergency care
- Arises from either a direct or transmitted blow to the head, face, or neck
- Subsequent injury to the brain is the result of an interplay of pathophysiologic processes, induced by biomechanical forces, without evidence of structural brain injury on standard neuroimaging

Risk factors for a concussion

- An individual's risk for a concussion is multifactorial with no single element being absolutely predictive
  - Boys reportedly affected more than girls due to predilection for more injuries/inclusion in more sports-related activities
  - Girls more likely to report symptoms of concussion
  - History of ADHD or learning problems raises lifetime risk
  - History of prior concussion raises risk for future concussion

Risk factors for prolonged concussion symptoms

- An individual's risk for prolonged symptoms is multifactorial with no single element being absolutely predictive
  - Prior history of concussion-like symptoms
  - Known history of intracranial abnormalities
  - Psychiatric disorders, headache disorders
  - Family and social stressors
  - Female sex predictive of symptoms lasting more than 4 weeks
  - Older age

Signs and symptoms

- The signs and symptoms of pediatric concussions are variable
  - Cognitive
    - Amnesia—may be retrograde or anterograde
    - Confusion
    - Difficulty concentrating
    - Disorientation
    - Persistent crying
  - Neurologic
    - Headache
    - Dizziness
    - Gait abnormalities
    - Sensitivity to light/noise
    - Slurred speech
    - Fatigue
  - Behavioral
    - Increased sleep
    - Emotional lability
  - Gastrointestinal
    - Nausea
    - Vomiting
    - Refusal to feed

Management

- Diagnosis is typically clinical
  - Neuroimaging is not routinely indicated for a diagnosis of a concussion
    - For further considerations of head imaging in association with pediatric head trauma, see Trauma and Burns and Table 7.5 [1]
- Conservative management is the mainstay of treatment for pediatric concussions
  - Antiemetics may be used for nausea and/or vomiting
  - Pain control with nonopioid medications (e.g., ibuprofen and acetaminophen)
  - Stepwise approach to cognitive and physical rest (see Chap. 14 "Sports Medicine")
    - Complete bed rest may be required for a variable length of time (typically no more than 2–3 days)
    - Additional avoidance of activities that have high cognitive load is based upon the patient's individual risk factors and developmental stage
    - Gradual return to daily activities and increasing cognitive and noncontact physical activity in a manner that does not exacerbate symptoms

- Return to full activities only if patient is asymptomatic and has passed prior stages of recovery
- Anticipatory guidance is important to manage expectations and promote recovery
  - Inadequately treated concussions can prolong symptomatology and place patient at risk for reinjury
  - Warnings signs and symptoms to watch for that could indicate more severe injury
  - Recovery time is unique to each patient and for each incidence of head trauma
  - Concussions can cause physical, cognitive, and psychological impairments

DROWNING

Definition

- Drowning is defined as
  - The process of experiencing respiratory impairment from submersion in a liquid
  - Avoid using confusing older terms: Near drowning, secondary drowning, and wet drowning
- Classification of drowning
  - Fatal
  - Nonfatal with no morbidity
  - Nonfatal with morbidity (moderate, severe, vegetative state, brain death)

Epidemiology

- Drowning is a major cause of injuries and death
  - Seasonal variation, with increasing incidence in summer months
- Incidence follows a bimodal distribution
  - First peak occurs in children < 5 years of age
    - Children < 1 year
      - Often drown in bathtubs, buckets, and toilets
      - Over half of infants in bathtubs
    - Children 1–4 years of age
      - Over half of young children drown in swimming pools where they have been unsupervised temporarily (usually for < 5 min)
      - Typical incidents involve a toddler left unattended temporarily or under the supervision of an older sibling
  - Second peak: Occurs at ages 15–24 years
    - Primarily male adolescents and young adults
    - Most incidents occur in natural water

Mechanism of injury

- Initial progression of injury
  - Swallowing of water
    - Laryngospasm
    - Loss of consciousness due to hypoxemia
    - Hypoxia
    - Loss of circulation
    - Tissue ischemia
    - CNS injury (the most common cause of death)
- Secondary progression of injury
  - After nonfatal drowning, further complications can develop:
  - Pulmonary
    - Aspiration pneumonia
    - Acute respiratory distress syndrome (ARDS)
  - Cardiac
    - Myocardial depression, arrhythmias
  - Neurologic
    - Cerebral edema, increased ICP
  - Metabolic
    - Metabolic and respiratory acidosis
  - Hematologic
    - Hemolysis, coagulopathy
  - Renal
    - Acute tubular necrosis

Management

- At the scene
  - Immediate cardiopulmonary resuscitation (CPR) once a submersion has occurred is the most important initial step
- Prompt attention to airway, breathing, and circulation

- Early intubation if
  - Signs of neurologic deterioration
  - Inability to protect airway
  - Inability to maintain adequate oxygenation or ventilation despite supplemental oxygen
    - Remember orogastric tube for gastric decompression if intubated
- Administer 100% oxygen immediately to maintain SpO2 > 94%
  - Prevent further hypoxemia and acidosis
- Support work of breathing
  - If patient does not require intubation but has signs of impaired gas exchange, can elect to use noninvasive positive pressure ventilation such as continuous positive airway pressure (CPAP).
  - If advanced airway is established, mechanical ventilation with positive end-expiratory pressure (PEEP)
- Judicious fluid and shock resuscitation
  - Especially important with high levels of positive airway pressure required for adequate ventilation with poor lung compliance, with resultant increased intrathoracic pressure and decreased venous return to the heart
  - Vasopressors as indicated
  - After hemodynamic stability achieved, severe drowning may require fluid restriction and diuretic therapy due to pulmonary edema
- Cervical spine immobilization if suspected head/neck trauma is present
  - Classic example: Dive into shallow water
- Serial measurements
  - Cardiopulmonary monitoring, temperature, and neurologic assessments
    - Pediatric drowning victims typically are hypothermic even if the water is warm
    - Abrupt change in mental status can reflect worsening lung function and hypoxemia
- Initial laboratory studies
  - Point-of-care glucose, complete blood cell count, electrolytes, urinalysis
- Initial imaging
  - Chest radiograph: indicated for all patients
  - Head CT: may be indicated for patients presenting with AMS

Disposition

- If CPR is required at the scene, recommend admission regardless of clinical status upon presentation
- If patients with mild symptoms on arrival, recommend admission for monitoring
- If patient is asymptomatic with the following criteria, the patient may be monitored for 6–8 h prior to discharge home with close follow-up instructions
  - GCS 15
  - Normal chest radiograph
  - Normal lung exam
  - Normal oxygen saturations
  - Safe home

Prevention and guidance

- Prevention is the key intervention in pediatric drowning
  - Installation of 4-sided fencing
    - Completely prevents direct access to the pool from the house and yard
    - At least 4 ft high (or higher if required by local ordinance) and climb-resistant
    - Distance from bottom to ground less than 4 in.
    - Gate should be self-latching and self-closing, with the latch placed at least 54 in. above the bottom of the gate, open away from the pool, and should be checked often
    - Effective in preventing more than 50% of swimming-pool drownings of young children
- Supervision needs to be close, constant, and capable
  - Never—even for a moment—leave small children alone or in the care of another young child while in bathtubs, pools, spas, or wading pools or near irrigation ditches or other open standing water

  - A supervising adult with swimming skills should be in the water, within an arm's length, providing "touch supervision"
  - With older children and better swimmers, the eyes and attention of the supervising adult should be constantly focused on the child
  - The adult should not be engaged in other distracting activities that can compromise this attention, such as talking on the telephone, socializing, tending chores, or drinking alcohol
  - Children should never swim alone without an adult

Swim lessons

- Swim lessons for children > 4 years: Recommended
- Swim lessons for children 1–4 years: Insufficient data to recommend at this time

Equipment

- Personal flotation devices (PFDs or life jackets) are recommended
- Air-filled swimming aids (inflatable arm bands, floaties) are not recommended
- Do not use air-filled swimming aids in place of PFDs

HYPERTENSIVE CRISIS

With climbing rates of obesity among children, hypertension is now increasingly common among children. This section will discuss an approach to children presenting with hypertension and make distinctions between hypertensive urgencies and hypertensive emergencies (see Chap. 23 "Nephrology" for further details on hypertension in pediatric patients).

Definitions

- Hypertensive urgency
  - Significantly elevated BP with potential for harm but without findings of end-organ damage
  - Develops over days to weeks
- Hypertensive emergency
  - Significantly elevated BP with evidence of secondary organ damage (e.g., encephalopathy or left ventricular failure)
  - Develops over hours
- Essential (primary) hypertension
  - Hypertension in which no underlying disease is discovered
  - Multifactorial causes
  - Increasingly common due to increasing obesity, sedentary lifestyle, and poor diet
  - Diagnosis of exclusion
- Secondary hypertension
  - Result of underlying pathology
  - Many causes: cardiac, endocrine, toxic, renal, CNS

Blood pressure (BP) measurement in pediatrics

- Manual BP with auscultation is ideal
  - If initial BP via automated BP cuff is abnormal, must repeat with manual reading
- Appropriately sized BP cuff
  - Circumference completely encircles arm with overlap
  - Bladder width ~40% of arm circumference
    - Small cuff size can falsely elevate BP readings
- Attempt to obtain when patient is calm and cooperative
  - Crying, fear, pain, anxiety, fever, and hunger can all falsely elevate BP readings
  - If initial BP is elevated and patient shows no sign of end-organ failure, repeat measurement when patient has calmed

Secondary causes of hypertension

- Kidney disease
  - Chronic kidney disease, nephritis, renal artery stenosis, obstructive uropathy, Wilms tumor, etc.
  - More frequent < 6 years of age
- Cardiac disease
  - Coarctation of the aorta (most common)
    - BP in right arm > 20 mmHg above lower extremity BP

  - Others: Abdominal aortic obstruction (abdominal masses), inflammatory arteritis (e.g., Takayasu arteritis, vasculitis)
- Endocrine disease
  - Rare but highly treatable, with many potential causes
  - Examples: Congenital adrenal hyperplasia, familial hyperaldosteronism, hyperthyroidism, hyperparathyroidism, pheochromocytoma, Cushing syndrome, etc.
  - Special note on neurofibromatosis type 1 (NF1)
    - NF1 is particularly known to have multiple potential causes for hypertension
    - Association with renal artery stenosis, coarctation of the aorta, middle aortic syndrome, pheochromocytoma
- Neurologic disease
  - Many causes, including any intracranial process with increased ICP
  - Examples: Familial dysautonomia, Guillain–Barré syndrome, neuroblastoma
- Environmental/drug exposures
  - Many drugs, prescription and otherwise, can elevated BP
  - Common sources: Stimulants (pseudoephedrine, caffeine, cocaine, amphetamines), oral contraceptives, corticosteroids, anabolic steroids
  - Medication withdrawal can also induce hypertension
    - Clonidine withdrawal

Approach to severe hypertension presenting to emergency care

- History and physical to evaluate for secondary causes of hypertension
- Careful attention to signs of end-organ failure
  - Cardiac exam: Signs of congestive heart failure, pulmonary edema, absent or decreased femoral pulses, peripheral edema
  - Abdominal exam: Palpable mass, audible bruit
  - Neurologic exam: Mental status, cerebellar function
  - Ophthalmologic exam: Disc edema, hemorrhage or infarct, visual acuity
- Laboratory investigations
  - Initial investigations should be limited to basic interventions
  - CBC, electrolytes, BUN, serum creatinine, urinalysis and urine culture
  - Four-limb manual BP
  - ECG
  - Further investigations must be targeted to the suspected secondary source of the hypertension
    - Example: Echocardiogram to evaluate for left ventricular hypertrophy and coarctation; Doppler renal ultrasound to evaluate for renal artery stenosis
- Initial interventions
  - Attention to airway, breathing, and circulation
  - Establish IV access
  - Careful selection of a short-acting IV antihypertensive medication
    - The choice of antihypertensive must be tailored to patient need, with consideration of underlying disease process, potential drug–drug interactions, and medication side effects
    - Avoidance of long-acting antihypertensives to avoid overaggressive drop in BP and allow for tighter control of therapy
    - Avoidance of enteral medications due to variable effect and longer half-lives
      - Enteral medications may be considered in some cases of hypertensive urgency
  - Examples of IV pharmacologic options
    - Nicardipine
      - Calcium channel blockade
      - Reduces peripheral vascular resistance

        - Caution with intracranial processes, as can increase ICP
    - Labetalol
        - Alpha-1 and beta-blockade
        - Reduces peripheral vascular resistance
        - Contraindicated in asthma, congestive heart failure, heart block, or in pheochromocytoma or cocaine overdose (unopposed alpha effects)
    - Sodium nitroprusside
        - Potent and direct vasodilator
        - Strong arterial and venous smooth muscle relaxant with instant onset
        - Black box warning: Can cause cyanide toxicity (metabolized to thiocyanate and cyanide), must monitor thiocyanate levels
    - Esmolol
        - Beta-1-blockade
        - Metabolism is independent of liver/kidney
        - Contraindicated in asthma, heart block, congestive heart failure
    - Hydralazine
        - Arterial vasodilator
        - Can cause increased ICP and fluid retention
    - Phentolamine
        - Alpha-adrenergic antagonist
        - Reserved for hypertension from catecholamine excess, e.g., pheochromocytoma or cocaine toxicity
- Goals of therapy
  - Reduction of BP by < 25% in first 6–8 h
    - Cautious approach is warranted due to cerebrovascular autoregulation
    - Overaggressive drop in BP can put patient at risk for brain ischemia
- Further management
  - Patients with hypertensive urgencies typically require admission for further evaluation and management
  - Patients with hypertensive emergencies typically require intensive care monitoring and resuscitation

Table 7.12 Timeline for first hour management of pediatric septic shock

Timeline (min)	Intervention
0–15	ABCs, cardiorespiratory monitoring, supplemental oxygen, frequent blood pressure monitoring, strict intake and output, order intravenous access and labs
5–15	Obtain IV access, escalate to IO if unable to obtain IV
	Labs: Blood culture, venous blood gas, glucose, lactate, electrolytes, complete blood count
0–20	Initial rapid fluid resuscitation of 20 mL/kg normal saline fluid bolus
0–60	Up to 3 fluid boluses with maximum 60 mL/kg, reassessments after each additional bolus for attainment of clinical goals, have vasopressor of choice ready for infusion, monitor for need for intubation and development of pulmonary edema
0–60	Administer intravenous antibiotics within 1 h
60	Initiation of vasopressor of choice if fluid-refractory shock, consideration of need for stress dose steroids, continual reassessments
> 60	Prompt transfer to pediatric ICU within 1 h

SEPSIS AND SHOCK

The first hour management of pediatric sepsis and septic shock. Further details on sepsis and shock can be found in Chap. 8 "Critical Care."

First-hour management of septic shock

- Early recognition and resuscitation is key, although recognition is challenging
- Institutions benefit from implementing a sepsis screening tool and a sepsis intervention protocol (Table 7.12)
- Clinician assessment within 15 min
- Resuscitation begins within 30 min

PEARLS AND PITFALLS

Respiratory distress

- In the search for a localizing problem for respiratory distress, remember to carefully consider disorders external to the lung.

- A significant amount of non-airway disease can cause respiratory distress via derangement of either the respiratory system controls or acid-base status causing a secondary respiratory compensation.
- Be alert for abnormal breathing patterns in the absence of abnormal auscultatory findings.
  - Bradypnea/tachypnea may signify increased ICP or CNS depression, as in hypothermia, narcotic overdose, mass lesion, meningitis, encephalitis, spinal cord injury or neuromuscular disease, or anxiety or pain.
  - Kussmaul respirations: acidosis (diabetic ketoacidosis).
- "Not all that wheezes is asthma."
- For patients with atypical or unexpectedly severe clinical presentations of what appears to be an asthma exacerbation, always consider less common intrathoracic pathology:
  - Intrinsic lung disease (bronchopulmonary dysplasia, cystic fibrosis, pneumonitis, lung malformations), heart failure, mediastinal masses, and GERD.
- Be alert for "red flag" warning signs that can indicate imminent respiratory failure:
  - Upper airway: tripoding, drooling, gurgling, inspiratory and expiratory stridor.
  - Lower airway: grunting, head bobbing, see-saw abdominal retractions.
  - Neurologic: AMS, lethargy, extreme irritability.

The acute abdomen

- See Table 7.4 for Pearls and Pitfalls.

Anaphylaxis

- The absence of skin findings does not rule out anaphylaxis.
  - Many children will have only transient skin changes or rash.
- Anaphylaxis can present with primarily neurologic symptoms such as syncope.
- Prompt administration of intramuscular epinephrine is associated with lower risk of hospitalization and fatality.
- Delayed administration of epinephrine is associated with increased risk of hospitalization and worsened outcomes such as hypoxic-ischemic encephalopathy and death.
- Antihistamines such as diphenhydramine relieve itching through H1-blocker effects but do not help with airway or respiratory symptoms, hypotension, or shock.
- Inhaled bronchodilator therapy with albuterol can reverse bronchospasm but does not help with angioedema, hypotension, or shock.
  - Keep in mind that epinephrine is also a potent bronchodilator and will help relieve acute wheezing from anaphylaxis.

Head trauma

- Infants are at higher risk from mortality and morbidity due to head trauma from nonaccidental trauma and may not have many signs or symptoms due to limited neurologic exams.
- Always maintain a low threshold of suspicion for nonaccidental trauma.

Burns

- Always maintain a low threshold of suspicion for nonaccidental trauma.
- "Red flag" warning signs that should raise suspicion for abuse:
  - "Stocking and glove" distribution of burn: Suggest forceful immersion of extremity in hot liquid.
  - Full thickness burns: Children typically will retract extremity before this degree of injury can occur.

Inhalation injury

- Severe airway injury from smoke inhalation can occur in the absence of external burn findings.

- Risks for smoke inhalation injury include young age and exposure within a closed space.
- Due to risk for CO poisoning, early application of 100% oxygen, blood gas analysis, and carboxyhemoglobin level are important.

Altered mental status

- Broad differential diagnosis can make management of AMS a challenging diagnostic puzzle.
- Careful attention to history and physical clues and low index of suspicion for life-threatening disorders can help guide the differential diagnosis.
- Many of the more common causes of AMS are reversible if discovered promptly
  - Promptly identify and correct hypoglycemia, hypoxia, hypothermia, hypercarbia, and hypotension.

Foreign body ingestion and aspiration

- Unwitnessed foreign bodies within the airway have the potential to masquerade as more common diseases such as croup and bronchiolitis/asthma.
- Esophageal foreign bodies have the potential to cause significant airway compromise.
- Impaction is often to underlying pathology such as eosinophilic esophagitis, GERD, and known prior strictures.

Drowning

- Conduct careful assessment of all end-organ function in drowning victim.
- Underlying disease can be the precipitating cause for or a coexisting risk factor in a drowning event, e.g., toxic ingestion, intentional overdose, recreational drug use, seizure disorder, cardiac arrhythmia, hypoglycemia.
- Prevention of drowning is key.

Hypertensive crisis

- Hypertension in a young child or infant is more likely to represent secondary hypertension with identifiable cause.
- Unless there are signs of acute end-organ dysfunction, treatment of hypertension in pediatric patients is conservative.

Sepsis and shock

- Pediatric sepsis requires prompt recognition and treatment.
- Emphasis on first-hour fluid resuscitation and inotropic therapy with the following clinical goals:
  - Improvement in heart rate.
  - Normalization of BP.
  - Restoration of perfusion and pulses.
  - Reassessments after each bolus for signs of fluid overload.
  - Antibiotic administration within first hour of recognition,
  - Prompt transfer to the intensive care unit for further support.

References

1. Kuppermann N, Holmes JF, Dayan PS, Hoyle JD Jr, Atabaki SM, Holubkov R, Pediatric Emergency Care Applied Research Network (PECARN), et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. Lancet. 2009;374(9696):1160–70.
2. Liang JL, Tiwari T, Moro P, Messonnier NE, Reingold A, Sawyer M, Clark TA. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2018;67(RR-2):1–44.
3. Rupprecht CE, Briggs D, Brown CM, Franka R, Katz SL, Kerr HD, Centers for Disease Control and Prevention (CDC), et al. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the advisory committee on immunization practices. MMWR Recomm Rep. 2010;59(RR-2):1–9.

4. Suguitan M. Rule of nines. CodeHealth, 5 Oct 2017. codehealth.io/library/article-85/rule-of-nines/. Accessed 11 Dec 2018.
5. Hoffman RS, Nelson LS, Goldfrank LR, Flomenbaum N, Howland MA. Goldfrank's toxicologic emergencies. 10th ed. New York: McGraw-Hill Education; 2015.
6. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics. 1975;55(6):871–6.

Suggested Reading

Respiratory Distress

Kämäräinen A. Out-of-hospital cardiac arrests in children. J Emerg Trauma Shock. 2010;3(3):273–5.

Leung AK, Cho H. Diagnosis of stridor in children. Am Fam Physician. 1999;60(8):2289–96. Review.

Weiner DL, Deanehan JK. Respiratory distress. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 451–64.

Young KD, Gausche-Hill M, McClung CD, Lewis RJ. A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. Pediatrics. 2004;114(1):157–64.

Acute Abdomen

Bachur RG. Abdominal emergencies. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 1313–33.

Reust CE, Williams A. Acute abdominal pain in children. Am Fam Physician. 2016;03(10):830–6.

Rothrock SG, Pagane J. Acute appendicitis in children: emergency department diagnosis and management. Ann Emerg Med. 2000;36(1):39–51.

Anaphylaxis

Holmes JF, Lillis K, Monroe D, Borgialli D, Kerrey BT, Mahajan P, Pediatric Emergency Care Applied Research Network (PECARN), et al. Identifying children at very low risk of clinically important blunt abdominal injuries. Ann Emerg Med. 2013;62(2):107–16.e2.

Krishnamoorthy V, Ramaiah R, Bhananker SM. Pediatric burn injuries. Int J Crit Illn Inj Sci. 2012;2(3):128–34.

Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291–307.

Sicherer SH, Simons FER, Section on Allergy and Immunology. Epinephrine for first-aid management of anaphylaxis. Pediatrics. 2017;139(3). pii: e20164006.

Stevenson MD, Ruddy RM. Allergic emergencies. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 616–20.

Trauma and Burns

Holmes JF, Lillis K, Monroe D, Borgialli D, Kerrey BT, Mahajan P, Pediatric Emergency Care Applied Research Network (PECARN), et al. Identifying children at very low risk of clinically important blunt abdominal injuries. Ann Emerg Med. 2013;62(2):107–16.e2.

Krishnamoorthy V, Ramaiah R, Bhananker SM. Pediatric burn injuries. Int J Crit Illn Inj Sci. 2012;2(3):128–34.

Liang JL, Tiwari T, Moro P, Messonnier NE, Reingold A, Sawyer M, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep: Morb Mortal Wkly Rep Recomm Rep. 2018;67(2):1–44.

Menaker J, Blumberg S, Wisner DH, Dayan PS, Tunik M, Garcia M, Intra-abdominal Injury Study Group of the Pediatric Emergency Care Applied

Research Network (PECARN), et al. Use of the focused assessment with sonography for trauma (FAST) examination and its impact on abdominal computed tomography use in hemodynamically stable children with blunt torso trauma. J Trauma Acute Care Surg. 2014;77(3):427–32.

Status Epilepticus

Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16(1):48–61.

Glissmeyer EW, Nelson DS. Coma. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 99–108.

Kimia AA, Chiang VW. Seizures. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 465–71.

Altered Mental Status

Borgialli DA, Mahajan P, Hoyle JD Jr, Powell EC, Nadel FM, Tunik MG, Pediatric Emergency Care Applied Research Network (PECARN), et al. Performance of the pediatric Glasgow coma scale score in the evaluation of children with blunt head trauma. Acad Emerg Med. 2016;23(8):878–84.

Glissmeyer EW, Nelson DS. Coma. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 99–108.

Poisoning and Toxic Exposure

Hoffman RS, Nelson LS, Goldfrank LR, Flomenbaum N, Howland MA. Goldfrank's toxicologic emergencies. 10th ed. New York: McGraw-Hill Education; 2015.

Toce MS, Burns MM. The poisoned pediatric patient. Pediatr Rev. 2017;38(5):207–20.

Foreign Body Aspiration and Ingestion

Kramer RE, Lerner DG, Lin T, Manfredi M, Shah M, Stephen TC, et al. Management of ingested foreign bodies in children: a clinical report of the NASPGHAN Endoscopy Committee. J Pediatr Gastroenterol Nutr. 2015;60(4):562–74.

Diabetic Ketoacidosis

Agus MS, Dorney K. Endocrine emergencies. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 690–717.

Cooke DW, Plotnick L, Cooke DW, Plotnick L. Management of diabetic ketoacidosis in children and adolescents. Pediatr Rev. 2008;29(12):431–6.

Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Medicine Collaborative Research Committee of the American Academy of Pediatrics. New Engl J Med. 2001;(4):264–9.

Rosenbloom AL. The management of diabetic ketoacidosis in children. Diabetes Ther. 2010;1(2):103–20.

Concussion/Head Injury

Iverson GL, Gardner AJ, Terry DP, Ponsford JL, Sills AK, Broshek DK, et al. Predictors of clinical recovery from concussion: a systematic review. Br J Sports Med. 2017;51(12):941–8.

Kuppermann N, Holmes JF, Dayan PS, Hoyle JD Jr, Atabaki SM, Holubkov R, Pediatric Emergency Care Applied Research Network (PECARN), et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. Lancet. 2009;374(9696):1160–70.

Lumba-Brown A, Yeates KO, Sarmiento K, Breiding MJ, Haegerich TM, Gioia GA, et al. Centers for Disease Control and Prevention guideline on the diagnosis and management of mild traumatic brain injury among children. JAMA Pediatr. 2018;172(11):e182853.

Lumba-Brown A, Yeates KO, Sarmiento K, Breiding MJ, Haegerich TM, Gioia GA, et al. Diagnosis and management of mild traumatic brain injury in children: a systematic review. JAMA Pediatr. 2018;172(11):e182847.

O'Brien MJ, Howell DR, Pepin MJ, Meehan WP 3rd. Sport-related concussions: symptom recurrence after return to exercise. Orthop J Sports Med. 2017;5(10):2325967117732516.

Drowning

Brenner RA. Prevention of drowning in infants, children, and adolescents. Pediatrics. 2003;112(2):440–5.

Chandy D, Weinhouse GL. Drowning (submersion injuries). Danzi DF. UpToDate. Waltham: UpToDate. http://www.uptodate.com. Accessed 13 Dec 2018.

Idris AH, Bierens J, Perkins GD, Wenzel V, Nadkarni V, Morley P, et al. 2015 revised Utstein-style recommended guidelines for uniform reporting of data from drowning-related resuscitation: an ILCOR advisory statement. Resuscitation. 2017;118:147–58.

Salomez F, Vincent JL. Drowning: a review of epidemiology, pathophysiology, treatment and prevention. Resuscitation. 2004;63(3):261–8.

Hypertensive Crisis

Constantine E, Merritt C. Hypertension. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 225–32.

Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al; Subcommittee on screening and management of high blood pressure in children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3). pii: e20171904. *Erratum.* Pediatrics. 2018;142(3). pii: e20181739.

Sepsis and Shock

Balamuth F, Potts DA, Funari MK, Lavelle J. Shock. In: Shaw KN, Bachur RG, editors. Fleisher & Ludwig's textbook of pediatric emergency medicine. 7th ed. Philadelphia: Wolters Kluwer; 2016. p. 605–10.

Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, et al. American College of Critical Care Medicine Clinical Practice Parameters for hemodynamic support of pediatric and neonatal septic shock. Crit Care Med. 2017;45(6):1061–93.

Howell MD, Davis AM. Management of sepsis and septic shock. JAMA. 2017;317(8):847–8.

Critical Care

8

Manpreet K. Virk and M. Hossein Tcharmtchi

HISTORY AND PHYSICAL EXAMINATION

The importance of a well-performed history and relatively complete physical examination despite the sophisticated available technology cannot be underscored enough. It can provide valuable information guiding the practitioner to rapid recognition of the disease and its severity.

History

- **Temperature**
  - Hypothermia can frequently be linked to trauma, sepsis, intoxication, and hypothyroidism
  - Fever > 41 °C is frequently associated with invasive bacterial infection
  - Inconsolable crying, poor feeding, not waking up, grunting, seizures, and decreased urine output usually indicate a life-threatening illness like sepsis or meningitis
  - In general, when fever defervesces, patients look better, are more active, and playful
  - Degree of fever, the presence of tachycardia out of proportion to the fever, the presence of tachypnea, and hypotension all suggest serious infection, most likely bacterial
- **Altered mental status**
  - For example, accidental ingestion, encephalitis, shock, or meningitis (fever and headache)
- **Vomiting**
  - For example, bowel obstruction (bilious vomiting is an ominous sign of possible bowel obstruction), hydrocephalus (marked increase in head circumference), incarcerated hernia, inborn errors of metabolism, or increased intracranial pressure
- **Vomiting and/or abdominal pain**
  - For example, appendicitis, intussusception, testicular torsion, lower lobe pneumonia, acute pyelonephritis, gastroenteritis or mesenteric adenitis (tends to improve with time), or volvulus (usually the pain is progressive, abnormal vital signs, lethargy, abdominal distension, or bilious vomiting)
- **Respiratory distress**
  - For example, asthma, pneumonia, bronchiolitis, foreign body inhalation, retropharyngeal abscess, epiglottitis, tracheitis, or croup

Physical examination

- Head, eyes, ears, nose, and throat (HEENT): Examine the head for signs of trauma like scalp defects and laceration; palpate the anterior and posterior fontanelle for fullness
  - Examine the eyes for swelling, redness, proptosis, eye movement limitation, and if

M. K. Virk · M. H. Tcharmtchi (✉)
Department of Pediatrics, Section of Critical Care, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA
e-mail: mhtcharm@texaschildrens.org

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_8

possible visual acuity. Check pupillary size and their reactivity to light, the retina, and optic disk. Check eyes and nose for abnormal drainage (blood, cerebrospinal fluid)

- Lungs: Observe the breathing pattern and respiratory rate; auscultate for inspiratory stridor, grunting, coughing, retractions, nasal flaring, or expiratory wheezing
- Heart: Observe the heart rate, active precordium; auscultate the heart to detect the presence of murmur, pericardial friction rub, and distant heart sound (pericardial effusion)
- Extremities: Palpate the extremities for warmth and swelling. Check the fingers and toes for clubbing. Check distal pulses and capillary refill time
- Abdomen: Palpate and percuss the abdomen for distension, tenderness, and guarding. Auscultate for bowel sounds
- Neurologic: Check the posture and mental status, Glasgow Coma Scale (GCS), deep tendon reflexes, motor strength and tone, and cranial nerves II–XII

Some common constellations of findings on physical examination and potentially associated diseases:

- **Increased intracranial pressure:** Hypertension, bradycardia, and bradypnea (Cushing's triad)
- **Transtentorial herniation—early signs:** Headache, altered mental status, small reactive pupils, decorticate posturing, and Cheyne–Stokes breathing (progressively deeper, and sometimes rapid breathing followed by apnea)
- **Transtentorial herniation—late signs:** Coma, pupils fixed and dilated in midposition, decerebrate posturing, and ataxic breathing (completely irregular breathing with apneic episodes)
- **Uncal herniation:** Unilateral third nerve palsy and unilateral fixed dilated pupils deviating downward and laterally
- **Common signs of shock:** Lethargy, tachycardia, cool or flushed extremities, poor or bounding distal pulses, prolonged or flash capillary refill time, mottled or pale skin
- **Bowel obstruction:** Abdominal distension, tenderness, absent bowel sounds, bilious vomiting
- **Peritoneal irritation seen in appendicitis:** Abdominal tenderness and guarding (ruptured appendix relieves the pain)

MALIGNANT HYPERTHERMIA (MH)

- Occurs in MH-susceptible patient
- MH is a hypermetabolic state when exposed to a volatile anesthetic agent (such as halogenated ethers like isoflurane, desflurane, and sevoflurane) or succinylcholine
- Its cause is due to unregulated passage of calcium from the sarcoplasmic reticulum into the intracellular space
- More commonly observed clinical presentation in children: Sinus tachycardia, hypercarbia, and hyperthermia
- Less commonly observed findings: Masseter muscle rigidity, generalized muscle rigidity, myoglobinuria, hyperkalemia, and EKG changes

Management of malignant hyperthermia

- ABCD evaluation (airway, breathing, circulation, and disability) per Pediatric Advanced Life Support (PALS) recommendations
- Discontinue the triggering agent
- Particularly on intubated patients, sudden hypercarbia may be due to DOPE (displacement, obstruction, pneumothorax, equipment)
- Optimize oxygenation and ventilation
- Treatment: Dantrolene
- Monitor and treat hyperkalemia

HEPATIC FAILURE

- Hepatic dysfunction starts with nonspecific prodromes
  - Nausea and vomiting
  - Abdominal discomfort and/or swelling
  - Malaise with or without fever
  - Symptoms may wax and wane for days to weeks
  - It may not present with jaundice
- Hepatic dysfunction may progress rapidly to hepatic failure
- Acute hepatic failure can start at any age and in any clinical setting
- In two-thirds of the cases that require transplantation, the cause of acute liver failure is unknown
- Signs and symptoms of impending hepatic failure can be suspected by progression of
  - Jaundice
  - Rising liver enzymes, ammonia, and direct or conjugated bilirubin
  - Encephalopathy from stage 0, without any neurological symptoms, to stage IV with coma
  - Decreased synthetic function (factors V and VII have shortest half-lives)
  - Worsening coagulopathy, rising international normalized ratio (INR) and prothrombin time (PT)

Management

- Supportive
- Treat the cause
- Manage complications
- If not reversible—liver transplantation

SPLENIC RUPTURE

- Potentially life-threatening condition
- Spontaneous atraumatic rupture is rare, e.g., infectious mononucleosis and neoplasm
- Most common cause of splenic rupture is blunt abdominal trauma
- Large amounts of blood can be lost leading to hemorrhagic hypovolemic shock
- Management of hemodynamically stable splenic rupture (grades 1–3) is conservative:
  - Observation and monitoring
  - Serial hemoglobin and hematocrit
- Hemodynamically unstable splenic rupture (grades 4–5) requires abdominal exploration
- Management largely depends on the institution

INCREASED INTRACRANIAL PRESSURE (ICP)

- Increase in ICP is most commonly associated with the following conditions:
  - Traumatic brain injury—most common cause of elevated ICP in children
  - Hydrocephalus
  - Brain tumors
  - Infection
  - Hepatic encephalopathy
  - Central nervous system venous outflow impairment
  - Intractable refractory epilepsy
- Chronic slow increase of ICP is usually well tolerated
- Acute increase of ICP is a life-threatening condition requiring emergent intervention
- Early recognition is key for improved neurologic outcome

Clinical presentation

- Headache
- Vomiting
- Altered mental status and coma
- Acute onset of weakness
- Papilledema—it takes several days to develop and can be absent in acute cases

- Hypertension with bradycardia or tachycardia
  - Cushing triad is a late sign of impending herniation: **Hypertension, bradycardia,** and **respiratory depression**
- Less common findings include
  - Seizures
- Normal intracranial pressure in adults is 5–15 mm Hg
  - It is lower in children and infants
  - It is subatmospheric in newborns
- In general, ICP > 20 mm Hg should be treated

Management

- The initial management involves ABCD per PALS recommendations
  - Particular attention to D (disability) for signs of trauma or increased ICP
- The major goal of management is to minimize ICP and maintain adequate cerebral blood flow (CBF)
- Depending on the insult, the autoregulation of blood flow to the brain may be lost
- Cerebral blood flow can be monitored with the cerebral perfusion pressure (CPP)
- CPP = MAP (mean arterial pressure) minus ICP
- If jugular venous pressure (JVP) is higher than ICP, it should be used for calculating CPP
  - All measurements are in mm Hg
- Normal CPP in adults range from 50 to 70 mm Hg
- The CPP is lower in children due to a lower MAP
- There are no established ranges for children
  - Based on age, the normal accepted range is 40–60 mm Hg
- The gold standard for ICP measurement is intraventricular catheter
  - It has the advantage of cerebrospinal fluid (CSF) drainage to treat an acute sudden increase of ICP

Management of patients with increased ICP and decrease in CPP

- Elevation of the head in midline to 15–30° to allow for adequate venous drainage. Higher elevation may decrease CPP
- Normothermia and normal blood sugar
- Maintain PCO2 between 35 and 40 mm Hg and avoid hypoxemia as both high PCO2 and low SpO2 cause vasodilation of cerebral vasculature, leading to increase in CBF and increase in ICP
  - Extreme hypocarbia leads to vasoconstriction of brain vasculature, resulting in a decrease in CBF causing further ischemia
  - Hypoxia or hypercarbia leads to vasodilation of brain vasculature and an increase in CBF and further rise in ICP
- Seizures increase metabolic demand of the brain and as a result increase in ICP
- Prophylactic anticonvulsants should be used for patients at high risk of developing seizures
  - Severe traumatic brain injury
  - Depressed skull fractures
  - Parenchymal injuries
- Adequate pain control is essential
- Prevent hypotension and maintain adequate MAP using 0.9% normal saline maintenance intravenous fluid (IVF) and bolus
  - Avoid hypotonic solutions

Specific measures for intubated patients

- Use lidocaine 1 mg/kg for intubation and when suctioning endotracheal tube (ETT) to diminish cough reflex
  - Cough causes a transient increase in ICP
- Avoid using ketamine and succinylcholine
- Elevate the head 15–30° and keep in midline to allow for adequate venous drainage
- Tape ETT to the face and not around the neck
- Keep positive pressure ventilation (positive end-expiratory pressure) [PEEP] and peak inspiratory pressure [PIP]) to a minimum

while maintaining adequate oxygenation and ventilation (maintain PCO2 between 35 and 40 mm Hg)
- Sedation and potentially neuromuscular blocking to permit adequate ventilation and oxygenation as well as decreasing metabolic demand of the brain

Hyperosmolar therapy
- There is limited evidence comparing mannitol with hypertonic saline for treatment of acute signs of herniation or raised ICP
- Mannitol
  - Rapidly distributed in extracellular space, creating an osmotic gradient between plasma and parenchymal tissue. To produce an equilibrium, water shifts from intracellular space to extracellular space
  - Osmotic diuresis of free water leads to increased serum sodium and osmolality
  - There is a risk of hypovolemia
  - Does not cross an intact blood–brain barrier
  - Monitor serum osmolality; avoid using if more than 320 mOsm/L
- Hypertonic 3% saline
  - There is limited evidence on the optimal dosing and concentration
  - There is less risk of diuresis
  - Can be given as continuous infusion
  - Target serum sodium level 145–155 mEq/L

Hypothermia
- Clinical studies have demonstrated comparable outcomes between therapeutic hypothermia (32–34 °C) and targeted temperature management at 36 °C
- Targeted temperature management is preferable

Hyperventilation
- It is used for treatment of acute sudden rise in ICP or acute signs of brain herniation for a short period of time until other more definitive measures are introduced
  - Barbiturate coma
  - Decompressive craniectomy
  - CSF drainage
- It will cause hypocarbia due to vasoconstriction of brain vasculature and a decrease in CBF causing ischemia

Dexamethasone
- It is only recommended for vasogenic edema caused by mass effect
  - Brain tumors
  - Brain abscess

Clinical findings associated with cerebral edema
- Asphyxial arrest is the most common type of cardiopulmonary arrest in infants and children
- Cerebral edema can be the result of many types of injury to the brain leading to increased ICP. It can be classified into 4 categories:
- **Vasogenic edema** due to disruption of the blood–brain barrier and extravasation of protein
  - Hydrostatic cerebral edema seen in acute malignant hypertension
  - Cerebral edema from brain neoplasms or trauma
  - High-altitude cerebral edema due to fluid leakage from the capillaries
- **Cytotoxic edema** where the blood–brain barrier is intact
  - Disruption in cellular metabolism damages the sodium–potassium pump leading to sodium and water retention
    - Cardiac arrest
    - Severe hypothermia
  - Disruption of sodium–calcium pump leading to retention of calcium and sodium in brain cells

- **Osmotic cerebral edema**
  - Plasma dilution due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), water intoxication, and rapid decrease of glucose (diabetes ketoacidosis, hyperosmolar hyperglycemic state)
  - This creates an abnormal pressure gradient between the brain (higher osmolality) and plasma (lower osmolality) and movement of water into the intracellular space
- **Interstitial edema due to disruption of CSF–brain barrier**
  - Obstructive hydrocephalus with spread of CSF into extracellular space
  - In contrast to vasogenic edema, there is no protein leakage
- **Symptoms of cerebral edema**
  - Headache
  - Slurred speech
  - Ataxia
  - Weakness
  - Disorientation
  - Memory loss
  - Hallucinations or delusions
  - Seizures
  - Bradycardia
  - Coma

BRAIN DEATH

- Clinical criteria required to determine brain death include deep unresponsive coma from irreversible causes, loss of brainstem reflexes, and loss of motor function (excludes spinal reflexes)
  - Any reversible condition that interferes with the interpretation of the examination must be previously excluded
- Close hemodynamic monitoring along with indwelling arterial catheter is necessary in order to assure adequate oxygenation and ventilation as well as for PaCO2 measurements for apnea test
- **Prerequisite conditions to be fulfilled prior to performing a brain death evaluation:**
  - Correction of electrolyte derangements such as potassium, sodium (135–155 mEq/L), calcium, and glucose
  - Correction of hypotension and shock
  - Correction of hypothermia (above 35 °C)
  - Allowing adequate time for sedative, analgesics, and neuromuscular blocking agents to be metabolized
- Brain death evaluation involves evaluation of neurological function, including brain stem reflexes and apnea test
- Two separate examinations are carried out with an interval of 24 h for full-term infants up to 1 month of age; and 12 h apart for infants from 1 month of age to 18 years
- **Absence of brainstem reflexes is defined as the presence of:**
  - Midposition fixed dilated pupils bilaterally
  - Absence of cough, gag, and corneal reflexes
  - Absence of spontaneous eye movements during oculovestibular and oculocephalic testing
  - Absence of any respiratory effort without ventilatory support
- In addition, there should be a flaccid motor tone and lack of any spontaneous movement or response to any tactile, visual, and verbal stimuli
- **An apnea test is to be performed following each neurological evaluation unless medically contraindicated:**
  - Apnea test is performed off ventilator support with supplemental oxygen at fraction of inspired oxygen or FIO2 of 1 = 100% oxygen
  - A positive test is defined as the lack of respiratory effort when off the ventilator and rise in PaCO2 of 20 mm Hg above baseline or above 60 mm Hg
- Death is declared after the second examination confirms brain death
- Apnea test should be aborted in patients requiring high-dose vasoactive agents and those who do not tolerate the test due to hemodynamic instability or hypoxemia

- Radionuclide cerebral blood flow test is a commonly used ancillary study in most ICUs utilizing portable gamma cameras. The study evaluates cerebral blood flow and its uptake into the brain tissue
- Electroencephalogram has also been used to identify the absence of any electrical activity
- **Indications for performing ancillary tests:**
  - When brain death evaluation and apnea test are not able to be completed due to unstable clinical status
  - If medications or medical conditions interfere with brain death evaluation
  - To reduce the interval observation period between the two examinations
  - If there is any concern about the validity of the examination
- If the ancillary test is inconclusive of the absence of cerebral blood flow or if the electroencephalogram (EEG) shows electrical activity, then observation period must be prolonged until the patient meets the criteria for clinical brain death and apnea testing or until another ancillary study can be repeated

Table 8.1 Common features of shock

Cold shock	Warm shock
Cardiac dysfunction	Vasoplegia
Low cardiac output and high SVR	High cardiac output and low SVR
Clinical presentation—common features	
Tachycardia	Tachycardia
Tachypnea	Tachypnea
Hyper- or hypothermia	Hyper- or hypothermia
Poor food intake	Poor food intake
Not playful	Not playful
Irritability	Irritability
Runny nose	Runny nose
Increased SVR	Decreased SVR
Impaired end-organ perfusion:	Impaired end-organ perfusion:
Lethargy	Lethargy
Cool extremities	Warm extremities
Weak distal pulses	Bounding distal pulses
Prolonged capillary refill > 3 s	Flash capillary refill (< 3 s)
Decreased urine output	Decreased urine output
Lactic acidosis	Lactic acidosis
	Widened pulse pressure
Low or normal blood pressure[a]	Low blood pressure[a]

SVR systemic vascular resistance

[a]Late sign due to compensatory mechanisms. It can remain normal even with substantial compromise of the cardiovascular system

COMMON CONDITIONS REQUIRING EMERGENCY CHILD SUPPORT

Shock

Definitions

- Shock is a dynamic and unstable state that can be life-threatening if not recognized in a timely manner. It is an imbalance between oxygen delivery (impaired perfusion) and tissue metabolic demands (Table 8.1)
- Cardiac output is the product of stroke volume (SV) and heart rate (HR): CO (L/min) = SV (L) × HR/min
- Oxygen delivery (DO2) is determined by cardiac output (CO) and the arterial content of oxygen (CaO2) = DO2 × CaO2
- Arterial oxygen content is the amount of oxygen bound to hemoglobin plus the amount of oxygen dissolved in the arterial blood (usually minimal and therefore negligible when calculating)
- Arterial oxygen content = (Hgb × 1.36 × SaO2) + (0.003 × PaO2)
- Hgb g/dL, SaO2 = Percent arterial oxyhemoglobin saturation, PaO2 = arterial oxygen tension (dissolved O2), and 1.36 = the amount of oxygen carried by 1 g of Hgb

Stages of shock

- **Compensated**
  - During this stage of shock, vital organ functions are maintained by a number of compensatory mechanisms like peripheral vasoconstriction (increased systemic vascular resistance, or SVR), leading to increased cardiac output

  - As a result, the blood pressure is usually normal. This can delay the recognition of shock and therefore timely intervention to reverse the process with the goal of restoring normal tissue oxygen delivery
  - Hypotension develops usually late in shock states with the exception of early distributive shock (sepsis) and neurogenic due to peripheral vasodilation (decreased SVR)
  - If unrecognized or undertreated, compensated shock progresses to decompensated shock
- **Decompensated**
  - At this stage, the compensatory mechanisms are not sufficient to maintain the perfusion of the vital organs. It leads to advanced end-organ dysfunction, cellular hypoxia, and irreversible organ damage
  - Outcome is poor despite appropriate resuscitative measures

Common management strategies

- Successful management of shock depends on early recognition and accurate classification based on clinical findings
- ABCD evaluation (airway, breathing, circulation, and disability) per PALS recommendations
- Start oxygen—ideally high-flow nasal cannula in order to titrate FiO2
- In some cases, endotracheal intubation is necessary
  - It decreases the work of breathing and oxygen consumption due to respiratory distress
- Continuous hemodynamic monitoring, including heart and respiratory rate, blood pressure, and oxygen saturation (SpO2)
- Obtain intravascular/intraosseous access per PALS recommendations
  - If intravascular access is unsuccessful after 3 attempts within 5 min, obtain intraosseous access
  - Do not delay treatment while waiting for IV access
  - Intraosseous access is safe, quick, and effective in children, and the frequency of the complications is negligible
  - Ideal intraosseous placement in order of preference
    - Tibial tuberosity (anteromedial surface of proximal tibia)
    - Proximal humerus
    - Femoral
    - Iliac crest
- Except for cardiogenic shock, administer 20 ml/kg of isotonic fluid (0.9% sodium chloride or Ringer's lactate) over the first 5–10 min
- Assess the patient after each bolus for further need of fluid
- Evaluate for fluid overload—examine for rales and hepatomegaly
- Check blood glucose and electrolytes
- Monitor end-organ perfusion
  - Urine output
  - Mental status
- Central venous line, indwelling arterial line and Foley catheter
- Imaging studies
- Close monitoring of response to treatment
- Goal is to restore normal circulation to age-appropriate physiological parameters

Classification of Shock

Hypovolemic Shock

- Most common type of pediatric shock. It is the consequence of extravascular (diarrhea) or intravascular (hemorrhage) fluid loss leading to decreased preload
- Decreased preload in turn leads to a decline in cardiac output
- Clinical findings as outlined in Table 8.1
- Usually cardiac output is low—cold shock

Specific management strategies

- In addition to common management strategies outlined before
- The mainstay of treatment is rapid restoration of plasma volume and oxygen delivery to the tissues

- Multiple boluses of 0.9% sodium chloride or Ringer's lactate 20–100 ml/kg of fluid may be required
- Continuous fluid losses should be taken into account when managing these patients
- Goal is to restore normal circulation to age-appropriate physiological parameters
- For all patients who require more than 40 mL per kilogram of bolus, the need for vasopressor or inotropes should be considered

Cardiogenic Shock

- History of heart disease, poor feeding, excessive sweating, and poor weight gain
- In addition to the common features outlined in Table 8.1
- Gallop rhythm, rales, jugular venous distention, hepatomegaly
- Chest radiography (CXR) may show cardiomegaly
- Failure to meet the tissue oxygen demands due to low cardiac output, inadequate preload, excessive afterload, intrinsic muscle failure, or dysrhythmia
- For example,
  - Depressed myocardial contractility (infection, toxins, severe hypocalcemia or hyperkalemia)
  - Arrhythmias (supraventricular tachycardia)
  - Outflow obstruction from left heart (hypoplastic left heart syndrome, aortic stenosis, and coarctation of the aorta where femoral pulses are usually absent or diminished as well as lower blood pressure in the lower extremities compared with the right upper extremity)
  - Outflow obstruction from right heart (tricuspid atresia, pulmonary atresia, and tetralogy of Fallot. All three are cyanotic congenital lesions that cause obstruction of the right heart outflow)
  - Myocarditis, pericarditis, and congenital cardiomyopathies
  - Coronary ischemia (anomalous left coronary artery from the pulmonary artery (ALCAPA))
  - Congenital lesions resulting in significant left-to-right shunts (ventricular septal defects, truncus arteriosus, ALCAPA). They are typically present between 6 weeks and 3 months of age as pulmonary vascular resistance (PVR) gradually falls after birth
  - Pneumothorax and cardiac tamponade both prevent diastolic filling of the heart

Specific management strategies

- In addition to common management strategies outlined before
- The presentation of the cardiogenic shock may easily be missed or confused with other causes of shock
- Cardiogenic shock should be considered in patients whose condition worsens with fluid therapy as initial management of shock
- Obtain electrocardiogram and echocardiogram with any suspicion of cardiogenic shock
- Routine laboratory investigations plus lactate and B-type natriuretic peptide (BNP)
- Do not delay treatment while waiting for echocardiogram
- Most children with poor cardiac function may be volume depleted. Judicious and slow administration of fluids (5–10 ml/kg) is paramount in these children
- Use of inotropes such as dopamine, epinephrine, or milrinone may be required
- Goal is to restore normal circulation to age-appropriate physiological parameters
- Consider diuretics if volume overload is suspected

Distributive Shock: Septic Shock

- Systemic inflammatory response syndrome (SIRS) criteria. The presence of 2 or more of the following criteria, one of which must be abnormal temperature or white blood cell (WBC) count
  - Elevated or depressed WBC count
  - Fever > 38.5 °C or hypothermia < 36 °C
  - Tachycardia or bradycardia
  - Tachypnea

- Sepsis: SIRS + suspected or proven infection
- Severe sepsis: sepsis + either cardiovascular or respiratory dysfunction; or > 2 other organ systems dysfunction
- Septic shock: Sepsis and cardiovascular organ dysfunction
- In addition to the clinical presentations outlined in Table 8.1
- Septic patients may present with vague symptoms or in overt septic shock
- Can present as warm or cold shock
- The majority of community-acquired septic shock presents as cold shock
- Warm shock is seen in older children and those with a central venous line

Specific management strategies

- In addition to common management strategies outlined before
- Rapid recognition and initiation of treatment to restore normal circulation to age-appropriate physiological parameters
- Early intervention following the guidelines of American College of Critical Care Medicine (ACCM) and PALS in the first 60 min.
- Fundamental features of the guidelines
  - **0 to 5 min**
    - Establish IV access. If unsuccessful, establish an intraosseous (IO) line
  - **5 to 15 min**
    - Isotonic saline bolus 20 ml/kg up to 60 ml/kg within the next 10 min with reassessment after each bolus. Stop boluses if hepatomegaly or rales are present
    - Treat hypoglycemia and hypocalcemia
    - Start antibiotics
    - There is a linear increase in risk of mortality for each hour delay in antibiotic administration
  - **15 to 60 min**
    - Start epinephrine peripheral IV/intraosseous/intramuscular infusion (PIV/IO/IM) at 0.05–0.5 mcg/kg/min for fluid refractory shock
    - Use atropine/ketamine PIV/IO, if needed for central vein or airway access
    - Once central access available, titrate epinephrine to reverse cold shock; if epinephrine is unavailable, titrate central dopamine 5–10 mcg/kg/min. Titrate central norepinephrine 0.05–0.3 mcg/kg/min to reverse warm shock; use central dopamine if norepinephrine is unavailable
    - If shock is catecholamine resistant and if at risk for adrenal insufficiency, start IV hydrocortisone stress dosing at 100 mg/m2 per day divided in 4 doses
  - **Advanced treatments 60 min and beyond**
    - Use central venous pressure, mean arterial pressure, and other additional monitoring devices such as Doppler ultrasound, pulse index contour cardiac output (PiCCO), thermodilution cardiac output to titrate fluid, inotropic, vasopressor, and vasodilator support
    - If hemoglobin is less than 10 g/dL, transfuse packed red blood cells
    - If already on epinephrine and the blood pressure is normal, ScvO2 (central venous oxygen saturation) < 70% treat cold shock with milrinone infusion. Add nitrovasodilators if SVR index is high and/or the skin perfusion is poor. Consider levosimendan if shock persists
    - If already on epinephrine and the blood pressure is low, ScvO2 < 70%, treat cold shock with norepinephrine to obtain normal diastolic blood pressure. Consider dobutamine, enoximone, levosimendan, or milrinone if shock persists
    - If already on norepinephrine and euvolemic and the blood pressure is low, ScvO2 > 70%, treat warm shock with vasopressin, dobutamine, enoximone, and levosimendan
    - If shock persists, treat pericardial effusion and pneumothorax if present
    - If shock remains refractory, consider extracorporeal membrane oxygenation (ECMO)

  - The principles of rapid fluid expansion for septic shock may not apply in all settings, particularly in developing countries
    - The fluid expansion as supportive therapy study (FEAST) [1] showed that the fluid expansion as outlined above may increase harm in a resource-limited settings

Anaphylactic Shock

- In addition to the clinical presentations as outlined in Table 8.1
- Immunoglobulin E (IgE)–mediated
- Exposure to an allergen interacting with IgE
- Potentially life-threatening systemic reaction

Specific management strategies

- In addition to common management strategies outlined before
- Rapid recognition and initiation of treatment to restore normal circulation to age-appropriate physiological parameters
- Injection of IM epinephrine 0.01 mg/kg, maximum 0.5 mg
- If no response, injection can be repeated every 5–10 min
- Occasionally the patient may require epinephrine infusion
- Elevation of the lower extremity in supine position if tolerated
- Due to massive fluid shift, poor perfusion should be treated with isotonic solutions
- Inhaled albuterol for bronchospasms, 0.15 mg/kg and repeat as needed
- H1 antihistamine–diphenhydramine 1 mg/kg IV, maximum dose 40 mg
- H2 antihistamine–ranitidine 1 mg/kg IV, maximum dose 50 mg
- Glucocorticoids–methylprednisolone 1 mg/kg IV, maximum dose 125 mg

Neurogenic Shock

- Rare
- Caused due to acute injury to the spinal cord or central nervous system resulting in loss of sympathetic venous tone
- Clinical presentations as outlined in Table 8.1
- Unlike other forms of shock, neurogenic shock exhibits hypotension with bradycardia

Specific management strategies

- In addition to common management strategies outlined before
- Hypovolemia due to loss of sympathetic venous tone and decreased preload should be treated with 0.9% sodium chloride or Ringer's lactate boluses
- Stabilization of the spine
- Computed tomography (CT) or magnetic resonance imaging (MRI)
- Neurosurgical consultation if trauma is suspected

Obstructive Shock

- Cardiac pump failure due to extracardiac causes
- Often associated with poor right ventricular output
- Pulmonary causes include pulmonary embolism and severe pulmonary hypertension
- Mechanical causes include tension pneumothorax and pericardial tamponade
- In addition to the clinical presentations as outlined in Table 8.1
- Depending upon the cause of obstructive shock, these patients may present with
  - Jugular vein distention
  - Hypotension
  - Pleuritic chest pain
  - Chest pain
  - Tracheal deviation
  - Unilateral breath sounds
  - Muffled heart sounds
  - Pulsus paradoxus

Specific management strategies

- In addition to common management strategies outlined before
- Fluid boluses to preserve preload
- Every attempt should be made to treat the underlying cause
- Pericardiocentesis for cardiac tamponade
- Chest tube placement for pneumothorax

Hemothorax and Flail Chest

- Flail chest is defined as a condition with fractures of 3 or more consecutive ribs or combined fracture of the sternum and ribs creating an unstable injury and could be associated with hemothorax or pneumothorax requiring emergent drainage
- Leads to impaired mechanics of the chest wall wherein one segment of the chest moves inward instead of outward during inspiration
- Usually results from traumatic impact with high energy mechanism and is associated with high morbidity
- There is high incidence of intrathoracic (pulmonary contusions) and extrathoracic injuries (traumatic brain injury)
- Less commonly seen in children compared to adults given the more compliant chest wall

Examination

- On examination, a characteristic paradoxical movement of the chest wall moving inward rather than outward during inspiration and outward instead of inward during exhalation is seen
- CXR and CT scan can identify rib fractures and associated thoracic injuries

Management

- Pain control, pulmonary toilet. Ensure adequate ventilation and oxygenation
- Close cardiorespiratory monitoring is recommended
- Supplemental oxygen along with adequate pain control (regional nerve blocks along with systemic analgesia) is standard of care
- In severe cases with large pulmonary contusions and ARDS, mechanical ventilation is necessary

ARDS

- Clinical entity of dyspnea, cyanosis resistant to supplemental oxygen, and chest infiltrates on chest radiography without cardiac ailment

Pediatric Acute Respiratory Distress Syndrome (PARDS)

- PARDS is defined as an acute respiratory failure occurring within 7 days of a known clinical trigger (direct or indirect)
- New parenchymal infiltrates not fully explained by cardiac failure or fluid overload
- Direct insult to the lung damaging the alveoli
- Indirect injury causes primary destruction of the pulmonary endothelial barrier, resulting in interstitial edema
- Develops in the first 1–6 days after the initial insult
- Results in decreased pulmonary compliance, leading to arterial hypoxemia
- May resolve completely without fibrosis

Causes

- Most common causes of direct injury are pneumonia (most common), aspiration pneumonitis, fat embolism, and submersion injury
- Indirect causes include multisystem trauma, sepsis, SIRS, and transfusion-related acute lung injury (TRALI)

Clinical presentation

- History of exposure to gaseous fumes or hydrocarbon ingestion and potential aspiration
- Dyspnea due to increasing alveolar flooding and decreasing pulmonary compliance
- Cough and fever
- Severe pulmonary edema and abnormal gas exchange due to alveolar damage
- Tachypnea, crackles, wheezing, diminished air entry, mild to severe respiratory distress with accessory muscle use
- Signs of impending respiratory arrest may be noted such as bradypnea, tachycardia, altered mental status, and cardiovascular collapse
- Tachypnea occurs in order to maintain adequate minute ventilation

Investigations

- Arterial blood gas (pH, PCO2, PO2) with lactate

- CXR—Essential for diagnosing ARDS. Radiographic findings immediately after the inciting event may be entirely normal or may show only the primary disease process. As the disease progresses, the lung fields become diffusely and radiographically homogeneously opaque. (ARDS is a non homogeneous disease process; however, this is not distinguishable on the CXR findings)
- Complete blood count (CBC) may reveal leukocytosis
- Chemistry panel
- Coagulation tests such as disseminated intravascular coagulation (DIC) panel
- Liver function tests and renal function tests (blood urea nitrogen [BUN], creatinine) to monitor end-organ injury
- CT scan is often not possible, given the risk of life-threatening decompensation during transport and is unnecessary for the management of PARDS
- Echocardiogram to determine cardiac function and to rule our intracardiac shunts

Management

- Mainly supportive therapy aimed at treating the inciting cause and measures to reduce ventilator-induced lung injury (VILI)
- Noninvasive mechanical ventilation is defined as acute respiratory failure requiring full-face bilevel positive airway pressure (BiPAP) or at least a CPAP of ≥ 5 cm H2O with either a P/F ratio less than 300
- P/F ratio = PaO2/ FIO2
- Endotracheal intubation as well as invasive monitoring is required in severe cases with indwelling arterial catheters, central venous lines, and Foley catheter

Pulmonary

- Early application of noninvasive PPV is recommended in an alert cooperative patient to aid alveolar recruitment
- Endotracheal intubation and mechanical ventilation are required in cases unresponsive to noninvasive PPV
- Arterial hypoxemia is an important feature of PARDS. Goal of PPV is to recruit alveoli by application of modest PEEP to reduce V/Q mismatch, to allow adequate gas exchange and reduce VILI
- Judicious application of PEEP and limiting inflation pressures is paramount to the management of PARDS

Principles of PPV in PARDS

- Different modes have been used to achieve adequate ventilation and oxygenation
  - There is no evidence showing superiority of one mode to another
- Titrate FIO2 and PEEP to maintain oxygen saturation above 88%, PaO 55–80 mm Hg, thus preventing biotrauma from excessive oxygen exposure
- Limit alveolar plateau pressures to less than 30 cm H2O to prevent barotrauma
- Low tidal volumes (~ 4–6 ml/kg) allow permissive hypercapnia while monitoring indices of oxygen delivery and acid base balance
- Adequate PEEP to prevent stress-induced alveolar injury by repetitive opening and closing of alveoli
  - "Ideal PEEP" is where 0.6 FIO2 (to prevent oxygen toxicity) affords adequate saturation (> 88%)
- If conventional mechanical ventilation fails, transition to high-frequency oscillatory ventilation (HFOV) pressures should be considered to limit VILI from high inflation pressures
- Neuromuscular blockade in the first 72 h should be considered along with adequate sedation and analgesia to reduce metabolic demand and improve patient–ventilator synchrony
- If conventional therapies fail, ECMO should be considered in candidates with reversible causes of acute respiratory failure before they develop nonpulmonary organ dysfunction and failure

Cardiovascular complications

- Close monitoring of hemodynamic parameters

- Fluid boluses with crystalloid, colloid, and packed red blood cell transfusions are often required. Vasoactive infusions are often needed to maintain adequate cardiac output

Renal
- Monitor urine output closely
- Early institution of diuretics and renal replacement therapies should be considered to prevent adverse effects of fluid overload on pulmonary compliance (not in the acute phase of volume resuscitation, typically in the first 24–48 h)

Gastrointestinal
- Careful attention should be paid to early institution of parenteral nutrition if enteral route is not feasible
- Stress ulcer prophylaxis

Infectious
- Broad-spectrum antimicrobial therapy
  - Antifungal and antiviral therapy should be considered, particularly in the immunocompromised patient

Others

Prevention of venous thromboembolism and pressure ulcers

Pericardial Tamponade

- Definition: the rapid accumulation of fluid or air in the pericardial space causing elevated pericardial pressure compressing the right atrium and impeding systemic venous return leading to decreased preload resulting in decreased cardiac output
- Life-threatening condition
- Early recognition and prompt management are crucial
- Complications include obstructive shock and cardiac arrest

Causes
- Postcardiac surgery
- Trauma
- Inflammatory conditions causing serositis—Kawasaki disease, systemic lupus erythematosus, acute rheumatic fever
- Lymphatic anomaly causing chylous pericardial effusions
- Severe fluid overload associated with systemic inflammatory response and multiorgan failure

Sign and symptoms
- Tachycardia
- Hypotension
- Wide pulse pressure
- Elevated central venous pressures
- Pulsus paradoxus—exaggeration of systolic blood pressure decline of more than 10 mmHg during inspiration

Diagnosis
- Pericardial tamponade is a clinical diagnosis
- Echocardiogram will reveal pericardial fluid/air collection along with compression of right atrium in diastole

Management
- Close hemodynamic monitoring
- Optimization of preload to augment cardiac output and improve perfusion by administration of 0.9% sodium chloride or Ringer's lactate
- Avoid diuretics, which could further decrease effective arterial blood volume, worsening hypotension
- Avoid sedatives that would cause vasodilation and further drop in cardiac output
- Emergent pericardiocentesis to drain pericardial fluid/air is the definitive therapy

EMERGENCY LIFE SUPPORT

Endotracheal Tubes and Ventilatory Support

- Ventilatory management and selecting the appropriate endotracheal tube (ETT) size in pediatric patients depends largely on the age and size

- ETT intubation selection according to internal diameter (ID):
  - ETT size (uncuffed tubes) in infants: 3–3.5 mm internal diameter
  - ETT size (uncuffed) for 1–2 years of age: 3.5–4.5 mm internal diameter
  - ETT size (uncuffed) for children more than 2 years of age is determined by the formula: (mm ID) = (age in years/4) + 4
  - For example, if the child is 8 years old, ID of ETT = 8/4 + 4 = 6
  - Cuffed ETT size should be half to one size smaller than uncuffed or can use the following formula (mm ID) = (age in years/4) + 3
- When used appropriately, cuffed ETT is as safe as uncuffed ETT
- Backup ETT sizes in a half-size larger and half-size smaller should be readily available
- ETT is typically inserted to the cm marking corresponding to three times the internal diameter of the tube

Unique pediatric considerations

- If ETT is too large, it may cause damage to this area leading to subglottic injury and resulting in stenosis
  - After extubation, it can cause inspiratory stridor and may potentially necessitate reintubation. In extreme cases, a tracheostomy may be needed
- In contrast to adults, the narrowest part of the pediatric trachea is below the glottis at the level of cricoid cartilage and selection of the correct ETT size is important to prevent injury to the mucosa
- If the ETT is too small, it compromises the ability to ventilate and oxygenate due to the "leak"
- Positioning of the ETT is as important as the size selection—see above
- Right main stem intubation leads to total collapse of the left lung, desaturation, and hyperventilation of the right lung
- Intubation of the esophagus
  - Can lead to distension of the stomach and aspiration of gastric content
  - If unrecognized, has life-threatening consequences
- Airway stimulation and activation of vagus nerve can cause increased secretion and bradycardia
  - Premedication with atropine or glycopyrrolate may help to visualize the vocal cords
- Successful ETT placement should be confirmed by colorimetric nonwaveform capnography. Auscultation and fogging of ETT are not adequate measures of confirmation
- Position of ETT should be 2 cm above the carina and below the first rib, usually at the level of the second rib. The position should be confirmed by CXR. The clavicles are not a reliable landmark of placement
- Direct trauma is rare in the hand of the trained specialist
  - Pharyngeal and laryngeal damage
  - Damaged teeth, lips, and gums

Common Indications for Endotracheal Intubation and Ventilatory Support

Respiratory Failure (RF)

- Type I = hypoxemic respiratory failure
- Type 2 = hypercapnic respiratory failure
- Causes for RF:
  - Ventilation abnormalities
    - Respiratory muscle fatigue
    - Chest wall abnormalities
    - Neuromuscular disease
  - Decreased ventilatory drive
  - Increased airway resistance or obstruction
  - Oxygenation abnormalities
    - Refractory hypoxemia
    - Acute lung injury and ARDS
    - Need for PEEP (pulmonary edema or hemorrhage)
    - Excessive work of breathing

Other common indications

- To decrease systemic myocardial oxygen consumption
- To decrease left ventricular afterload

- To improve oxygen supply to meet the demand (shock, cardiac arrest)
- To protect the airway
  - Inability to control secretions
  - Traumatic brain injury
  - GCS score < 8
  - Intoxications causing altered mental status and loss of protective airway reflexes

Common modes of ventilatory support (Table 8.2)

- Mechanical ventilation—invasive positive pressure ventilation (PPV)
- There are several mechanical ventilation modalities. The following is a brief description of the 2 most commonly used modes
- **Pressure control mode:**
  - Delivers preset pressure, rate, and inspiratory time with decelerating inspiratory flow
  - Tidal volume (VT) is determined by preset pressure and the compliance of the respiratory system
  - Minute ventilation (MV) is not guaranteed
  - Frequent assessment is required to assure the desired MV delivery, as any decrease in compliance will decrease VT and MV = hypoventilation
  - Typically, the preset pressure should be kept below 35 cm H2O
- **Volume control mode:**
  - Delivers preset tidal volume, inspiratory time, and rate with constant inspiratory flow
  - VT is determined by preset volume
  - MV is guaranteed
  - PIP varies and depends on the compliance of the respiratory system
  - PIP limit should be set 5–10 cm H2O higher than patient's generated PIP. Frequent assessment is required to monitor PIP; if consistently higher than the limit, consider changing the mode
  - Typically, PIP should be kept below 35 cm H2O

Table 8.2 Modes of mechanical ventilation

Parameter	Pressure control	Volume control
Tidal volume	Variable	Constant
PIP (peak inspiratory pressure)	Limited	Variable
Ti	Preset	Preset
Respiratory rate	Preset	Preset
Flow pattern	Decelerating	Constant (square wave)
Advantages	Decelerating flow allows alveolar recruitment, prevents overdistention, and decreases barotrauma	Decreases volutrauma Guarantees set minute ventilation

Initial approach to setting ventilator parameters (see Table 8.2)

- Choose a familiar mode. Two commonly used modes of conventional mechanical ventilation are:

1. **Volume control synchronized mandatory intermittent ventilation (SIMV)**
   - VT (VT = 6–8 cc/kg, assure proper chest rise, may need more for obese patients)
     - PIP varies and depends on the compliance of the respiratory system
     - Typically, PIP should be kept below 35–40 cm H2O
   - Rate (bpm) depending on the age and the disease process
     - Start at the rate according to the patient age range
     - Lower rate is desired for patients with asthma to allow complete exhalation
   - FIO2—start at 1 (100% oxygen)
   - PEEP (cm H2O), depending on the disease process
     - Intubation results in the loss physiological PEEP by ETT bypassing the larynx. A minimum PEEP is always required to keep alveoli open
     - Usual starting point is 3–5 cm H2O
   - Inspiratory time Ti (s) is age and disease dependent
     - Increasing Ti will increase mean airway pressure and improve oxygenation
     - Remember increasing Ti will decrease expiratory time

  - Pressure support (cm H2O) in addition to PEEP. When taking spontaneous breaths on the ventilator, the pressure support assists to overcome the resistance in the ETT and the ventilator tubing, helping with airflow easing spontaneous respiration.
    - Start at 5–10 cm H2O
  - SIMV allows patient to take spontaneous breaths, maintaining synchrony between the ventilator and the patient

2. **Pressure control SIMV and its variables are the same as above, *except***
  - PIP (starting point 20–25 cm H2O) with close monitoring of the chest rise. Increase as needed to achieve appropriate chest rise
  - VT is determined by the compliance of the respiratory system

Common Special Ventilator Settings and Strategies to Prevent VILI

- **Permissive hypercapnia** is a ventilator strategy in the management of severe acute respiratory failure and ARDS
  - In contrast to hypoxemia, hypercapnia is not life-threatening
  - The tidal volume/pressure is lowered deliberately, resulting in hypoventilation
  - It minimizes lung damage caused by repetitive opening and stretching of the alveoli, preventing barotrauma/volutrauma
  - This strategy results in a lower pH and higher PCO2
  - Over time, the pH improves, as this respiratory acidosis will be compensated by the kidneys
  - For example, in ARDS, with this lung protective strategy, the VT can be decreased to 4–6 cc/kg
  - This is discussed further above in the ARDS section

PEEP and ARDS

- PEEP plays an important role in the lung protective strategy
- Increase in PEEP results in an increase of mean airway pressure, improving oxygenation
  - The key is to keep the alveoli open while preventing overdistention
  - The ideal goal is to keep the respirations on the portion of the loop with the optimal pulmonary compliance–functional residual capacity (FRC)
  - At this point, minimum pressure is needed to expand the lungs
  - In general, the "ideal PEEP" is where 0.6 FIO2 (to prevent oxygen toxicity) affords adequate saturation (> 88%)

CARDIOPULMONARY RESUSCITATION (CPR): AHA GUIDELINES

Chest compression rate

- For infants, children, and adults: 100–120/min
- The recommended sequence per PALS guidelines (2015) is C-A-B-D: circulation–airway–breathing–defibrillate
- Allow the chest wall to recoil completely after each compression to improve venous return to the heart
- The goal of the compressions is to reach a coronary perfusion pressure of 15 mm Hg (adult data)
  - This pressure has been linked to successful return of spontaneous circulation
  - There is no such threshold established for children
  - It requires the presence of arterial and central venous pressure monitoring catheters

Chest compression depth

- Infant
  - At least one-third the depth of the chest
- Newborn
  - At least one-third the depth of the chest

  - About 4 cm
- Child 1 year of age to puberty
  - Lower third of the sternum
  - At least one-third the depth of the chest
  - About 5 cm
- Adolescent (after puberty)
  - Like adults
  - Lower third of the sternum
  - About 5–6 cm

Chest compression techniques

- Infant and newborn—**lone rescuer**
  - 2-finger compression method to compress the newborn and infant sternum just below the intermammary line
- Infant and newborn—**two healthcare providers**
  - 2-thumb-encircling-hands chest compression
  - 2 thumbs are placed together on the sternum to depress the sternum while the other fingers of both hands spread to encircle the thorax
  - The thumbs can be placed side by side or they can overlap
  - This technique provides a better depth of compression and therefore a better coronary perfusion pressure compared to lone rescuer technique
- Child 1 year of age to puberty
  - Use 1 or 2 hands, whichever is preferable to achieve the goal depth
- Adolescent (after puberty)
  - Adult 2-hand technique
  - Heel of the hand on the chest
  - Heel of the other hand on the top of the first hand
  - Keep arms straight and shoulders directly over the hands

Chest compressions to breath ratios

- Lone rescuer 30:2
- Two rescuers 15:2
- When patient is intubated, this ratio does not apply

Automated external defibrillator (AED)—AHA recommendations

- Use AED for children between 1 and 8 years in cardiac arrest
- Mainly for out-of-hospital arrest
- Use pediatric pads and pediatric dose attenuator (for small children) to deliver the correct dose of shock
- If not available, do not delay treatment while waiting for pediatric pads and pediatric dose attenuator, instead use adult pads and AED
- The pads should be placed according to the drawing on the pads
- They should not come in touch or overlap
- For infants, use manual defibrillation to deliver an accurate dose
  - If not available, use pediatric pads and pediatric dose attenuator to deliver the correct dose of shock
  - If not available, do not delay treatment while waiting for pediatric pads and pediatric dose attenuator, instead use adult pads
- Follow the instructions of the AED

PEARLS AND PITFALLS

- Treatment of shock should not be delayed until hypotension (late sign) develops. Do not delay treatment waiting for IV access.
- When measuring CPP: use intracranial pressure or JVP, whichever is higher.
- Do not administer benzodiazepines to patients with hepatic failure.
- Asphyxial arrest is the most common type of cardiopulmonary arrest in infants and children.
- There are four types of cerebral edema: vasogenic, cytotoxic, interstitial, and osmotic.
- Apnea test—Two separate examinations are carried out with an interval of 24 h for full-term infants up to 1 month of age; and 12 h apart for infants from 1 month of age to 18 years.

- There are four types of shock: hypovolemic, cardiogenic, distributive, and obstructive.
- Pericardial tamponade is defined as the rapid accumulation of fluid or air in the pericardial space causing elevated pericardial pressure compressing the right atrium and impeding systemic venous return, leading to decreased cardiac output.
- Cardiac tamponade is a clinical diagnosis.
- Children have higher oxygen consumption compared to adults and are prone to hypoxemia; hence, ensuring adequate oxygenation prior to, during, and after the intubation is crucial.
- For CPR, the recommended sequence per PALS guidelines is C-A-B-D: circulation–airway–breathing–defibrillate.
- In CPR, allow the chest wall to recoil completely after each compression to improve venous return to the heart.

References

1. Maitland K, Kiguli S, Opoka R, Engoru C, Olupot-Olupot P, Akech S, FEAST Trial Group, et al. Mortality after fluid bolus in African children with shock. N Engl J Med. 2011;364:2483–95.

Suggested Reading

Ad Hoc Statement Committee. American Thoracic Society: mechanisms and limits of induced postnatal lung growth. Am J Respir Crit Care Med. 2004;170(3):319–43.

American Heart Association. Web-based integrated guidelines for cardiopulmonary and emergency cardiovascular care – part 12. Pediatric advanced life support. https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/part-12-pediatric-advanced-life-support/. 26 Sep 2018. Accessed 21 Sep 2018.

Bronicki RA, Price J. Cardiogenic shock. In: Kline MW, editor. Rudolph's pediatrics. 23rd ed. New York: McGraw-Hill Education; 2018.

Burri PH, West JB, Crystal RG. Postnatal development and growth. In: Crystal RG, West JB, editors. The lung: scientific foundations, vol. 2. Philadelphia: Lippincott-Raven; 1997. p. 1013–26.

de Caen AR, Berg MD, Chameides L, Gooden CK, Hickey RW, Scott HF, et al. Part 12:Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(18 Suppl 2):S526–42.

Critical Care Review: Pediatric. Mount Prospect, IL; 2018. http://www.sccm.org/Education-Center/Critical-Care-Review-Pediatric. Accessed 15 Sep 2018.

Drutz JE. The pediatric physical examination. In: Post TW, editor. UpToDate. Waltham: UpToDate. http://www.uptodate.com. Accessed 15 Sep 2018.

Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014;42(8):1749–55.

Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5 Suppl 1):S23–40.

Nakagawa TA, Mudit M. The determination of brain death. In: Nichols DG, Shaffner DH, editors. Rogers' textbook of pediatric intensive care. 5th ed. Philadelphia: Wolters Kluwer; 2016. p. 1066–76.

Nelson P, Litman RS. Malignant hyperthermia in children: an analysis of the North American malignant hyperthermia registry. Anesth Analg. 2014;118(2):369–74.

Nguyen TC, Carcillo JA. Pathophysiology of sepsis. In: Kline MW, editor. Rudolph's pediatrics.

23rd ed. New York: McGraw-Hill Education; 2018.

Oliveira CF, Oliveira DSF, Gottschald AFC, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. Intensive Care Med. 2008;34(6):1065–75.

Pomerantz W. Pathophysiology and classification of shock in children. In: Post TW, editor. UpToDate. Waltham: UpToDate. http://www.uptodate.com. Accessed 15 Sep 2018.

Sackett DL, Rennie D. The science of the art of the clinical examination. JAMA. 1992;267(19):2650–2.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.

Tasker R. Elevated intracranial pressure in children. In: Post TW, editor. UpToDate. Waltham: UpToDate. http://www.uptodate.com. Accessed 15 Sep 2018.

Tzelepis GE, McCool FD. The respiratory system and chest wall diseases. In: Murray JF, Nadel JA, Broaddus VC, Mason RJ, Ernst JD, King Jr TE, et al., editors. Murray and Nadel's textbook of respiratory medicine. 6th ed. Philadelphia: Elsevier; 2016. p. 1707–1722.e4.

Ventre KM, Arnold JH. Acute lung injury and acute respiratory distress syndrome. In: Nichols DG, Shaffner DH, editors. Rogers' textbook of pediatric intensive care. 5th ed. Philadelphia: Wolters Kluwer; 2016. p. 766–93.

Waltzman M. Initial evaluation and management of shock in children. In: Post TW, editor. UpToDate. Waltham: UpToDate. http://www.uptodate.com. Accessed 15 Sep 2018.

Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1334–49.

Wesson DE, Cox CS Jr. Thoracic injuries. In: Coran AG, Adzick NS, editors. Pediatric surgery. 7th ed. Philadelphia: Elsevier Mosby; 2012. p. 271–88.

Infectious Diseases

9

Matthew B. Laurens

PUBLIC HEALTH CONSIDERATIONS: PREVENTION OF INFECTIOUS DISEASES

Infection Control and Prevention

Childcare Centers

- Immunization: Required for all enrollees and staff
- Assist children with toileting and hand hygiene
  - Hand washing with soap and water, alcohol-based antiseptic is acceptable if > 24 months old
  - Careful food preparation and diaper changing
  - Disinfecting environmental surfaces prevents diarrheal diseases
  - Respiratory etiquette (sneeze or cough into elbow)
- Exclusion and return policies:
  - Use gloves when contacting body fluids
  - Do not exclude because of lice, ringworm, conjunctivitis without fever or behavior change, rash without fever

Common organisms in childcare centers

- *Shigella* infection
  - Transmitted from infected feces (person-to-person contact)
  - Do: Stool bacterial cultures for any symptomatic contact
  - Know: If *Shigella* infections are confirmed, administer appropriate antibacterial treatment
  - Return to childcare center if diarrhea has resolved and stool culture is negative
- Nontyphoidal *Salmonella* species
  - No antibiotic is required except:
    - Infants younger than 3 months of age
    - Immunocompromised host
  - Infected individuals should be excluded from childcare until symptoms resolve
- *Salmonella* serotype Typhi
  - Treatment is indicated for infected individuals
  - Return to childcare center
    - 5 years of age or younger: 48 h after antibiotic treatment
    - Older than 5 years: 24 h after the diarrhea has resolved
- Other risk of infection: e.g., *Giardia*; rotavirus; cryptosporidiosis; respiratory syncytial virus (RSV); parainfluenza virus; adeno,

M. B. Laurens (✉)
Division of Infectious Diseases and Tropical Pediatrics, Department of Pediatrics, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA
e-mail: mlaurens@som.umaryland.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_9

rhino, and corona viruses; *Haemophilus influenzae*, *pneumococcal*, hepatitis A, and cytomegalovirus infections

Hospital and Office

- Standard precautions are indicated in the care of all patients including:
  - Hand hygiene before and after each patient contact
  - Protective equipment when needed

Preventive methods

- Alcohol-based products preferred because of their superior activity and adherence
- Soap and water are preferred when hands are visibly soiled or exposed to a spore-forming organism (*Clostridium difficile* is the most common), or for norovirus
- Gloves, isolation gowns, masks, and goggles for any exposure to body fluids, contaminated materials, and sharps
- Strict aseptic technique for all invasive procedures and for catheter care
- Separate well and sick children areas in medical offices

Examples of infections and agents requiring transmission-based precautions

- Contact precautions, e.g., RSV, *C. difficile*, other infectious diarrhea, and *Staphylococcus aureus*
  - Gloves and gowns are required when there is direct patient contact
- Droplet precautions, e.g., influenza, *Neisseria meningitidis*, mumps, and *Bordetella pertussis*
  - Use of a surgical mask is required
  - A single room is preferred
  - Remember all office and hospital staff should receive an annual influenza immunization
- Airborne precautions, e.g., *Mycobacterium tuberculosis*, measles, varicella (with contact precautions), severe acute respiratory syndrome (SARS)
  - Negative pressure airborne infection isolation room
  - Room air needs 6–12 changes per hour or recirculation through a high-efficiency particulate air (HEPA) filter
  - Certified N95 fine particle respirator mask or similar sealing mask

Prevention of Infection Through Breastfeeding

- Exclusive breastfeeding for the first 4–6 months is recommended by American Academy of Pediatrics (AAP)
- Interrupt breastfeeding for:
  - Breast abscess or cellulitis with direct contact with infant's mouth; can continue on other side
  - Women with tuberculosis (for first 2 weeks of treatment, then acceptable)
  - Maternal HIV (except in resource-limited settings)
  - Maternal human T cell lymphotropic virus (HTLV) types 1 or 2
- Do not interrupt for maternal hepatitis B

Immunologic characteristics of breast milk

- Postpartum colostrum contains high concentrations of antibodies and other infection-protective elements
- The actual antibodies against specific microbial agents present in an individual woman's milk depends on her exposure and response to the particular agents
- Lactoferrin: Limits bacterial growth by iron chelation
- Lysozyme: Bacterial cell wall lysis
- Lactalbumin: Enhances *Bifidobacterium* growth and modulates immune system
- Casein: Limits adhesion of bacteria and facilitates the growth of *Bifidobacterium*
- Carbohydrates: Enhance the growth of probiotics
- Lipids: Lytic effect on many viruses and are active against *Giardia*

Absolute contraindication of breastfeeding

- Maternal HIV infection (except in resource-limited settings)
- HTLV1 and HTLV2
- Tuberculosis (active, untreated pulmonary tuberculosis, until effective maternal treatment for the initial 2 weeks or the infant is receiving isoniazid)
- Herpes simplex virus (HSV) infection on a breast (until the lesions are cleared)
- Breast abscess or cellulitis with direct contact with infant's mouth; can continue on other side

Prevention of Vector-Borne Disease

- Chemoprophylaxis before traveling to endemic areas, e.g., atovaquone/proguanil for malaria should be given before traveling to endemic areas
- Use mosquito netting (bed-net) during sleep in tropical areas
- Use protective clothing
- Repellents, e.g., DEET (> 20%) applied to children should be used to prevent tick and mosquito bites
  - Insecticide should not be applied to children's hands because of risk of ingestion
- Use of occlusive clothing to prevent mosquito and tick bites is effective
- Remove tick from skin immediately, then wash with soap and water
- Keep pets tick-free
- Immunization against disease (e.g., yellow fever, typhoid, cholera, Japanese encephalitis, meningococcus, rabies if high risk) when traveling to endemic area at least 2 weeks before departure

Recreational Water Use

- Exposure to contaminated water can cause diarrhea and other infections, e.g., swimmer's ear
- *Cryptosporidium* is most common cause of recreational water-associated outbreaks; *Giardi*a is second, also *Shigella* is another cause
- Regularly test home pools for pH, free chlorine, or bromine
- People with diarrhea should not participate in recreational water activities
- Children with diarrhea should avoid swimming for 2 weeks after cessation of diarrhea (for *Cryptosporidium*)
- Avoid water ingestion
- Clean the child with soap and water before swimming
- Change diapers in the bathroom

Antimicrobial Resistance

- Use of antimicrobials is the most important factor that leads to antimicrobial resistance, including in patients and in agriculture
- Diseases for which antibiotics are not appropriate: Nonspecific cough, bronchitis, viral pharyngitis, common cold

Infections in Immunocompromised Hosts

Malnutrition

- Malnutrition increases susceptibility to infections; repeat or chronic infections contribute to malnutrition. A vicious cycle
- Malnutrition increases severity of disease and risk of poor outcomes
- Malnutrition increases risk of bacterial versus viral diarrhea
- Malnutrition increases risk of pneumonia

Central nervous system (CNS) diseases

- Infants have immature hypothalamic thermoregulatory system and lack a central "control" of temperature, making their body temperature more susceptible to environmental temperature
- Infants with CNS infection affecting thermoregulatory system may present with hypothermia

Asplenia

- Example: Sickle cell anemia, congenital or surgical asplenia
- Increased risk for bacteremia and meningitis due to encapsulated organisms like *Streptococcus pneumoniae, H. influenzae* type b (Hib), and *N. meningitidis*
- Consider daily antimicrobial prophylaxis (especially for sickle cell disease)
- Special vaccine consideration for asplenia:
  - Pneumococcal conjugate (PCV13) and polysaccharide (PPSV23) vaccines are indicated
  - Following PCV13 series, PPSV23 should be given at 24 months of age and 5 years later
  - Meningococcal conjugate vaccine (MCV) should be given at 2 months of age (MenACWY-CRM, e.g., Menveo). Revaccinate 3 years later and then every 5 years.
  - (MenACWY-D, e.g., Menactra) cannot be given before 2 years of age

Malignancy

- Fever and neutropenia (absolute neutrophil count [ANC] < 500) increase the risk of bacterial infection. Investigate with blood and urine cultures, consider chest radiograph, and treat with antibiotic for Gram-positive and Gram-negative coverage (cefepime or piperacillin/tazobactam). Consider adding vancomycin if methicillin-resistant *S. aureus* (MRSA) colonized or if skin/soft tissue infection or sepsis present.
- Major infections in patients with cancer include: bacteremia due to intestinal translocation, invasive fungal infections including *Candida* and *Aspergillus*, *Pneumocystis jiroveci* pneumonia.

Burn injury

- Burn wounds are susceptible to infection with Gram-positive and Gram-negative bacteria, yeast, and viruses (HSV, varicella-zoster virus [VZV])

Indwelling central lines

- Central line-associated bloodstream infections (CLABSI) are a common complication. Obtain culture from central line **and** periphery, then begin vancomycin + cefepime or piperacillin/tazobactam
- If MRSA or methicillin-sensitive *S. aureus* (MSSA), remove the line and continue treatment.

VIRAL INFECTIONS

Cytomegalovirus (CMV)

Background

- CMV is a double-stranded DNA virus and a member of the *Herpesviridae* family
- At least 60% of the US population has been exposed to CMV
- CMV usually causes an asymptomatic infection; afterward, it remains latent throughout life and may reactivate

Mode of transmission and period of communicability

- Vertical transmission
  - CMV can be maternally transmitted: (1) transplacentally in utero, (2) at birth through infected maternal genital tract, and (3) postnatally by ingestion of CMV-positive human milk or transfusion
  - Risk decreased by the use of pasteurized human milk or freezing human milk
- Horizontal transmission
  - Exposure to CMV can occur from almost all body fluids, including:
    - Urine, saliva, and tears
    - Genital secretions, blood transfusion, and transplanted organs
  - Toddlers infected postnatally with CMV shed the virus in their urine for a mean of 18 months (range 6–40 months)
  - Healthy adults infected with CMV will shed the virus for up to several weeks

  - Shedding of CMV in toddlers in childcare centers can be as high as 70%
- Transfusion and transplantation
  - Can be eliminated by CMV-negative donors
  - Filtration to remove white blood cells (WBCs)
  - Latent form in tissue and WBCs can be reactivated many years later

Congenital CMV infection
- Microcephaly
- Periventricular calcifications (intracerebral)
- Chorioretinitis, strabismus, microphthalmia, and optic nerve atrophy
- Hypotonia, poor feeding, ventriculomegaly, cerebellar hypoplasia
- Intrauterine growth restriction
- Prematurity
- Jaundice
- Hepatosplenomegaly
- Thrombocytopenia; petechiae and purpura
- Later in childhood 7–15% will develop progressive sensorineural hearing loss
- Developmental delays

Diagnosis
- Perinatally or postnatally:
  - Confirmed by detection of the virus in urine, blood, saliva or CSF by culture or polymerase chain reaction (PCR)
  - Congenital CMV: If diagnosed in first 3 weeks of life
- Immunocompromised host:
  - Test for pp65 antigen (CMV antigenemia assay) or quantitative DNA in blood or plasma

Treatment
- Congenital CMV
  - Treatment modestly improves hearing and neurodevelopmental outcomes for infants
  - CNS disease is treated with oral valganciclovir (or IV ganciclovir) for 6 months
- CMV retinitis in HIV
  - Ganciclovir and valganciclovir are indicated for induction and maintenance therapy
- CMV pneumonitis in bone marrow or stem cell transplant patients
  - Ganciclovir plus CMV immune globulin are used together

Herpes Family Viruses (DNA Viruses)

- Epstein–Barr virus (EBV)
- HSV1, HSV2
- CMV
- VZV
- Human herpesvirus type 6 (HHV-6), aka sixth disease
- Human herpesvirus type 7 (HHV-7)
- HHV-6 and HHV-7 can both cause exanthema subitum, aka roseola
- Human herpesvirus type 8 (HHV-8, aka Kaposi sarcoma-associated herpesvirus)

Epstein–Barr Virus (EBV)

Background
- EBV or human herpesvirus-4 is a gammaherpesvirus that infects more than 95% of the world's population
- Mode of transmission primarily by oral contact with saliva
  - EBV is shed in saliva at high concentrations for more than 6 months following acute infection and intermittently at lower concentrations for life
  - Young children directly or through handling toys
  - Adolescents due to close contact such as kissing

Clinical presentation
- EBV infection in healthy person; infectious mononucleosis (EBV is the most common cause)
  - Fever
  - Exudative pharyngitis (similar to streptococcal pharyngitis but more painful)
  - Cervical lymphadenopathy, commonly anterior, and posterior cervical lymph node (may compromise the airway)

  - Splenomegaly (90%); 2–3 cm below the left costal margin is typical
  - Hepatomegaly (10%)
  - Fatigue and malaise
  - Rash
  - Typically a benign, self-limited illness in healthy persons, but can cause fatal disseminated infection even in healthy hosts
- EBV infection in immunocompromised persons (transplant, HIV)
  - Fatal disseminated infection
  - Nonmalignant EBV-associated proliferations, e.g., virus-associated hemophagocytic syndrome
  - Post-transplant lymphoproliferative disorders
  - X-linked lymphoproliferative syndrome
  - Nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, non-Hodgkin lymphoma, gastric carcinoma

Diagnosis

- Heterophile antibody test (monospot)
  - Not recommended for children younger than 5 years of age as the result is not specific for acute mononucleosis
  - Helpful for older children and adolescents with mono signs and symptoms
- EBV viral capsid antigen (VCA) immunoglobulin (Ig) M and IgG serology to distinguish acute from past infection
  - No previous infection: Negative VCA IgG, negative VCA IgM
  - Acute infection: Positive VCA IgG, positive VCA IgM
  - Recent infection: Positive VCA IgG, +/– VCA IgM, positive early antigen
  - Past infection: Positive IgG, negative VCA IgM, negative early antigen, positive nuclear antigen

Management

- Ampicillin or amoxicillin may cause morbilliform rash
- Decrease immunosuppressive therapy in transplant patients if possible
- Short courses of corticosteroids for fewer than 2 weeks can be given in the following cases:
  - Tonsillar inflammation with impending upper airway obstruction
  - Massive splenomegaly
  - Myocarditis
  - Hemolytic anemia
  - Hemophagocytic lymphohistiocytosis (HLH)

Complications

- Splenomegaly:
  - Avoid strenuous activity and contact sports for 21 days after onset, then limited noncontact aerobic activity if no overt splenomegaly
  - Contact sports allowed 4–6 weeks after onset if no splenomegaly
  - Fatigue may persist for 3–6 months or longer

Herpes Simplex Virus 1 and 2 (HSV1 and HSV2)

- Characterized by neurovirulence, latency, and reactivation in the area supplied by the ganglia in which latency was established
- Reactivation induced by various stimuli (e.g., fever, trauma, emotional stress, sunlight, and menstruation)
- Spread by direct contact with lesions or infective secretions

Epidemiology

- Neonatal:
  - Exposure during passage through birth canal or ascending infection through ruptured or apparently intact membranes

  - Risk greatest with maternal primary infection near time of delivery (25–60%) versus 2% risk if recurrent maternal infection
  - Most neonatal HSV cases born to mothers with no HSV symptoms
- Children and adolescents:
  - Shed virus for > 1 week with primary genital infection (high viral concentration)
  - Shed virus for 3–4 days with recurrent infection
  - Reactivation without symptoms is common
  - Incubation period is 2 days–2 weeks

Clinical manifestations

- Neonatal (3 forms that may overlap):
  - 25%: Disseminated disease affecting mostly liver, lungs, and CNS; "sepsis" clinical picture
  - 30%: CNS disease "meningoencephalitis"
  - 45%: Skin, eye, and mouth (SEM) disease
- Children and adolescents:
  - Most primary HSV is asymptomatic; reactivation is also mostly asymptomatic
  - Gingivostomatitis is the most common clinical manifestation; usually HSV1, associated with fever, irritability, submandibular lymphadenopathy and ulcerative gums and buccal mucosa. May recur as "fever blister" or "cold sore"
  - Genital herpes: Genital vesicles or ulcers of genitalia and/or perineum, HSV1 or HSV2. Immunocompromised may have more recurrence
  - Eczema herpeticum occurs when patients with atopic dermatitis are infected with HSV, having ulcerative and/or vesicular areas on top of eczematous lesions
  - Encephalitis results from primary or recurrent HSV, with fever, altered mental status, seizures. Magnetic resonance imaging (MRI) may show temporal lobe abnormalities. CSF may show increased red blood cells, but not if early in disease course
  - Aseptic meningitis is usually mild and associated with HSV2

Herpetic Whitlow (Fig. 9.1)

- Due to autoinoculation of HSV
- Vesiculoulcerative lesions affect the pulp of the distal phalanx of the finger associated with deep-seated swelling and erythema
- Oral antiviral medications are optional and are used in extensive disease

Herpes Gladiatorum (Fig. 9.2)

- Herpes gladiatorum occurs in contact sports, e.g., wrestling and boxing

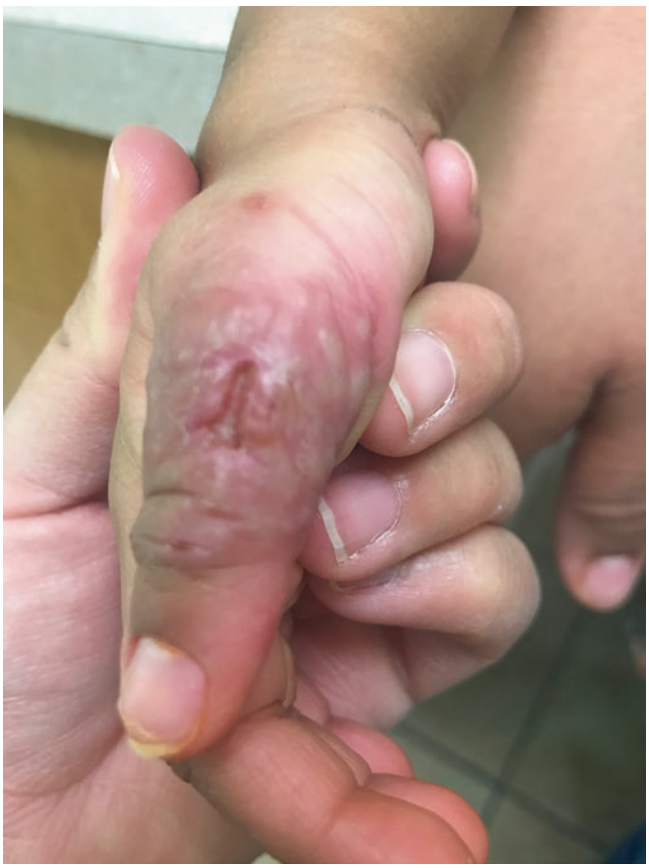


Fig. 9.1 Herpetic whitlow: Herpetic Whitlow infection in a 2-year-old with vesicular lesions, ulcer, and surrounding erythema involving the base of the thumb

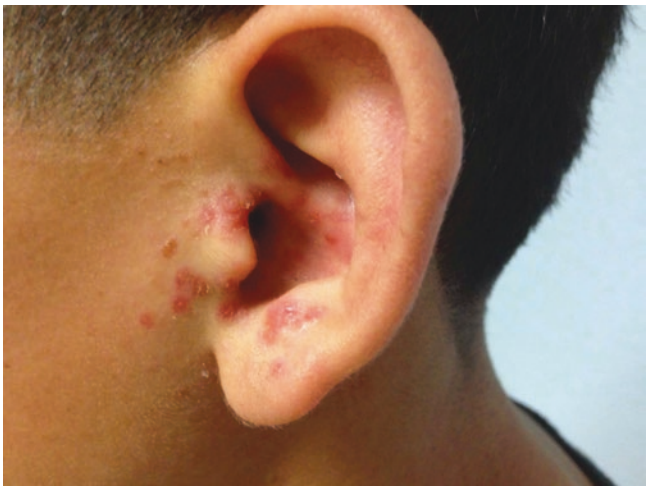


Fig. 9.2 Herpes gladiatorum: 16-year-old boy wrestling player presents with painful blisters in the left ear

- Most commonly affects exposed areas, e.g., face and upper extremities
- Patients should avoid contact sports during outbreaks until the culture or PCR results are negative
- Suppressive therapy is likely to be effective, but data about such therapy are insufficient

Treatment

- Antivirals: Acyclovir, valacyclovir, famciclovir
- Neonatal: IV acyclovir for 14 days (SEM disease) or 21 days (disseminated disease or CNS disease); begin therapy before test results return
  - All infants with any type of HSV should have ophthalmologic assessment
  - Repeat lumbar puncture near end of therapy for HSV CNS disease and continue treatment if positive
  - Oral acyclovir suppressive therapy indicated for 6 months
- Genital, primary: Oral acyclovir for 7–10 days
- Genital, recurrent: Same as primary; can be used routinely or at start of an episode
- Mucocutaneous, immunocompromised: IV acyclovir
- Mucocutaneous, healthy host: May benefit from therapy, oral acyclovir for 5–7 days
- CNS encephalitis: IV acyclovir for 21 days

Varicella-Zoster Virus (VZV): Chickenpox and Shingles

Background and epidemiology

- VZV is herpesvirus family member
- Incubation period is 2 weeks
- Contagious 1–2 days before rash until all lesions are crusted over
- Spreading via airborne or direct contact with mucosa of upper respiratory tract or conjunctiva, and transplacental passage
- VZV is the cause of varicella (chickenpox) and herpes zoster (shingles)
- Varicella is more contagious than zoster
- Immunity to varicella is lifelong; reactivation as zoster infection is possible
- Immunocompromised at higher risk for severe disease and disseminated infection

Clinical presentation

Varicella (Chickenpox)

- The prodrome: low-grade fevers, headaches, and malaise
- Skin lesions initially appear on the face and trunk
- Lesions start as red macules and pass through stages of papules, vesicles with central umbilication, pustules, and then crust over
- The vesicle on the erythematous base of a lesion leads to its description as a "pearl" or "dewdrop on a rose petal"
- Lesions predominate in central skin areas and proximal upper extremities with relative sparing of distal and lower extremities
- Chickenpox generally is a benign self-limited illness, and is more severe in adults, adolescents, and infants compared to older children

- Complications include bacterial superinfection, especially with *Streptococcus pyogenes,* which can progress to cellulitis, myositis, and sepsis
- Pneumonia (major cause of morbidity and mortality), hepatitis, and thrombocytopenia are also possible
- Immunocompromised patients may experience visceral dissemination, encephalitis, hepatitis
- Neonates whose mothers develop varicella 5 days to 2 weeks before delivery have increased risk of death due to diminished maternal antibodies

Herpes zoster (shingles)

- Latency establishes in sensory ganglia infected during primary VZV or vaccination
- Shingles classically is a unilateral rash consisting of grouped vesicles on an erythematous base, covering 1–3 adjacent dermatomes, often accompanied by pain and pruritus (Fig. 9.3)
- Postherpetic neuralgia, pain after rash resolves, is uncommon in pediatrics

Treatment of VZV

- Healthy host: Keep fingernails short, topical calamine for itching, acetaminophen for fever, avoid salicylates due to risk of Reye's syndrome
- Immunocompromised host: IV acyclovir within 24 h of rash onset
- Unvaccinated > 12 years old, chronic skin or lung disorders: Acyclovir or valacyclovir

Prevention in immunocompromised exposure

- VariZIG (varicella-zoster immune globulin) or IVIG within 4 days (ideal) and up to 10 days post-exposure. Isolate for 28 days after exposure
- Alternative is oral acyclovir or valacyclovir starting 7 days after exposure. Isolate for 21 days after exposure

General prevention

- Children can return to school if all lesions are crusted
- Airborne isolation for hospitalized patients with varicella
- Cover skin lesions for patients with herpes zoster
- Immunize all persons who lack evidence of immunity
- Immunize exposed, unvaccinated persons from 3 to 5 days post-exposure

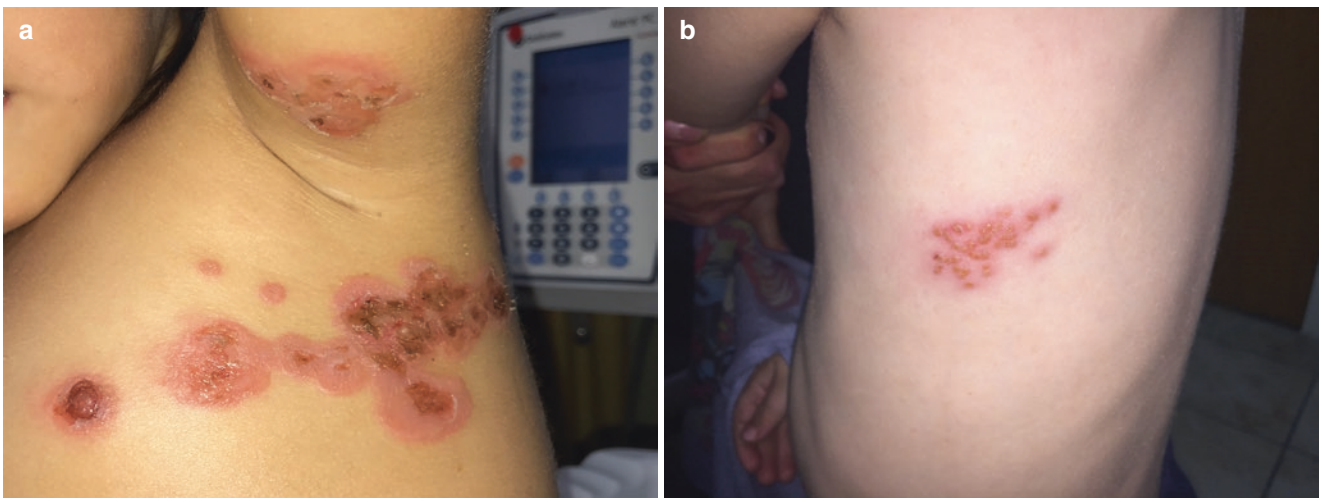


Fig. 9.3 (**a**) 2-year-old girl with painful herpes zoster rash (shingles). (**b**) 4-year-old boy with herpes zoster (shingles)

- Discharge or isolate exposed patients without evidence of immunity
- VariZIG given to the baby born to mother who develops illness from 5 days before until 2 days after birth
- IV acyclovir is indicated for varicella infection in infants born to mothers who experience chickenpox from 5 days before until 2 days after delivery

Human Herpesvirus Type 6 (HHV-6)

Including Roseola Infantum (Exanthem Subitum)

Background

- Commonly affects children ages 6–18 months old

Clinical presentation (Fig. 9.4)

- Typically, a nonspecific febrile illness without rash
- Very high fever for 3–7 days, followed by maculopapular rash in 20% after fever resolves; rash can last hours to days
- They may have lymphadenopathy, vomiting, diarrhea, febrile seizure, or respiratory symptoms

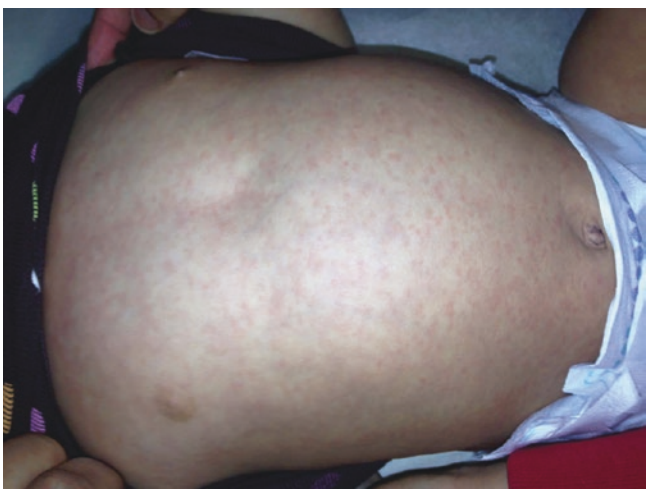


Fig. 9.4 Roseola infantum: 9-month-old boy afebrile presents with small, pale pink papules and blanchable, maculopapular exanthem, had high fever for 3 days before the rash

- 10 to 15% of children with primary HHV-6 will have febrile seizures
- Primary infection establishes latency that may reactivate (all herpes viruses)
- Immunocompromised may develop bone marrow suppression, graft rejection, pneumonia, encephalitis, hepatitis
- Incubation is 9–10 days

Management

- Mainly supportive for healthy host
- For immunocompromised, may consider ganciclovir, valganciclovir, or foscarnet

Human herpesvirus-7 (HHV-7)

- Childhood febrile illness, also causes exanthem subitum (roseola)
- Most infections are asymptomatic
- Like HHV-6, establishes latency that may reactivate
- 85% of healthy adults have evidence of past infection

Human herpesvirus-8 (HHV-8)

- Kaposi sarcoma
- A trigger for hemophagocytic lymphohistiocytosis (HLH)
- Multicentric Castleman disease

Other DNA Viruses

- Parvovirus B19
- Adenovirus

Parvovirus B19

Erythema Infectiosum/Fifth Disease

Background

- Incubation period 4–14 days
- Mode of transmission: Respiratory secretions

Clinical presentation

- *Erythema infectiosum*
  - Mild constitutional symptoms, e.g., fever, malaise, myalgia, and headache

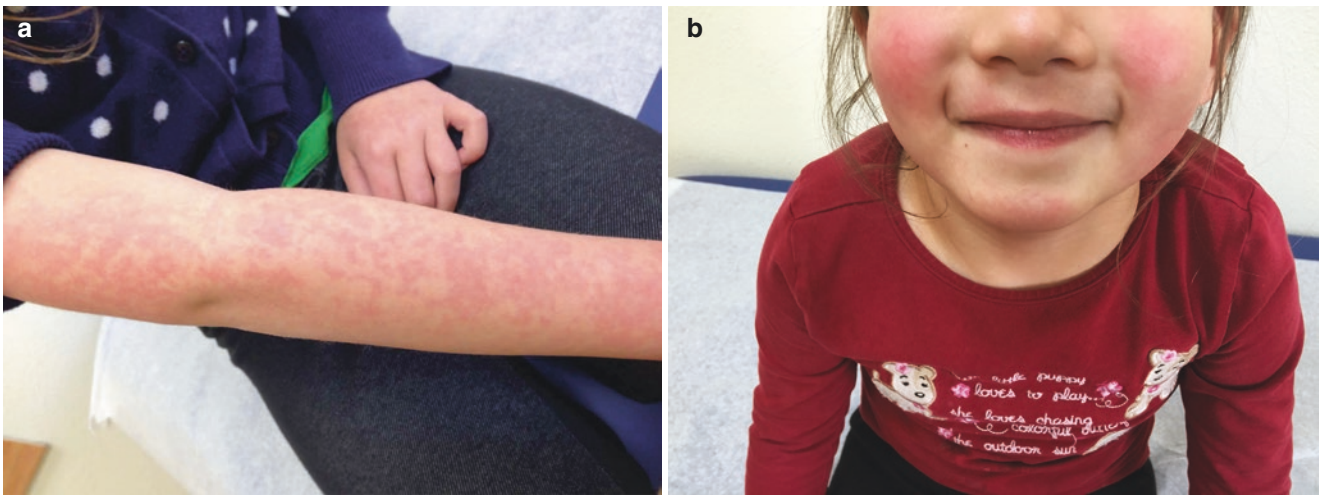


Fig. 9.5 (**a**) *Erythema infectiosum*: Erythematous maculopapular rash on the arm, which fades into a classic lacelike reticular pattern as confluent areas clear. (**b**) Classic slapped-cheek appearance of fifth disease

  - Bright red facial rash (slapped cheek appearance [Fig. 9.5])
  - Circumoral pallor
  - Lacy maculopapular rash lasting for 2–4 days begins on the trunk and moves to extremities (Fig. 9.5)
  - Rash may be pruritic, does not desquamate, and may recur with bathing or exercise
  - Arthritis or arthralgia may occur
- Mild respiratory illness without rash
- Purpuric rash in a gloves and socks distribution
- Polyarthropathy syndrome (mostly adults)
- Chronic erythroid hypoplasia and severe anemia (HIV, immunodeficient)
- Aplastic crisis for 7–10 days
  - Occurs in persons with hemolytic disease such as sickle cell anemia, spherocytosis, and thalassemia
  - Transient low to zero reticulocytes, leukopenia
- Hepatitis and myocarditis (rare)
- Hydrops fetalis
  - 2 to 6% risk of fetal death if occurs during pregnancy; increased risk earlier in pregnancy
- Can be asymptomatic or subclinical

Remember

- Rash is not infectious, and children can go to school without restrictions

Adenovirus

Background

- Mode of transmission:
  - Person to person through contact with conjunctival and respiratory secretions
  - Fecal–oral transmission and via fomites
- Outbreaks usually are concentrated in winter, spring, and early summer; otherwise all year round
- Persist in environment and resist disinfectants
- Incubation period:
  - Respiratory infections from 2 to 14 days
  - GI disease from 3 to 10 days

Clinical presentation

- Upper respiratory tract infection:
  - Nonspecific febrile illness
  - Otitis media
  - Pharyngitis
  - Exudative tonsillitis
  - Pneumonia

- Follicular conjunctivitis (clinically similar to enterovirus conjunctivitis)
- Gastroenteritis
- Hemorrhagic cystitis
- Pharyngoconjunctival fever:
  - Fever, tonsillitis (sometimes suppurative)
  - Follicular conjunctivitis, coryza, and diarrhea
  - Cervical and preauricular lymphadenopathy is common
  - Generalized rash in association with fever, conjunctivitis, and pharyngitis can be mistaken for Kawasaki disease

Laboratory

- PCR (preferred), antigen detection, and viral culture
- Persistent and intermittent shedding complicates diagnostics

Management

- Supportive treatment in healthy host
- Consider cidofovir in immunocompromised with severe disease

Respiratory viruses

- Influenza
- Parainfluenza
- Respiratory syncytial virus
- Human metapneumovirus
- Rhinovirus
- Coronavirus

Influenza Virus

Background and epidemiology

- Influenza is an orthomyxovirus
- Types: A, B, and C. Types A and B are responsible for epidemic disease in humans
  - Influenza A viruses found in humans are H1N1 and H3N2
  - Some strains are more virulent, causing more severe disease than others
  - Frequent antigenic change, or antigenic drift:
    - Point mutations causing minor antigen changes, leads to new influenza virus strains that cause seasonal epidemics in winter
    - Reason for constant reformulation of influenza vaccine to include new virus strains
  - Occasional antigenic shift:
    - Mutations causing major antigen changes, leads to new influenza virus subtypes that contain a new hemagglutinin (HA) or neuraminidase (NA), causing pandemics
    - Most recent pandemic: 2009–2010 caused by influenza A (H1N1)
- Mode of transmission
  - Large-particle respiratory droplet between individuals (cough, sneeze)
  - Contact with contaminated surfaces; fingers then touch face
  - Incubation period is 1–4 days
- Most outbreaks occur in schools
- Hospitalization rates are highest in children < 2 years and elderly > 65 years

Clinical presentation

- Fever, malaise, myalgia, headache, nonproductive cough, sore throat, and rhinitis
- Children may also develop croup or bronchiolitis
- Younger children may have febrile seizures or sepsis-like symptoms
- Uncomplicated influenza disease typically resolves within 3–7 days

Complications

- Primary viral pneumonia
- Secondary bacterial infections such as pneumonia (*S. aureus* and *S. pneumoniae*)
- Sinusitis and otitis media
- Encephalitis
- Underlying medical conditions such as asthma, diabetes, sickle cell, immunosuppression, neurologic disorders, or congenital

heart disease increase risk for complications, including hospitalization

Diagnosis

- Reverse transcription-PCR and multiplex PCR (testing for multiple respiratory viruses at once)
- Rapid antigen-detection tests, immunofluorescence
- Nasopharyngeal (NP) swab specimens have highest yield
- For hospitalized patients with lower respiratory tract disease, obtain endotracheal or bronchoalveolar lavage (BAL) specimen even if NP negative

AAP immunization guidelines

- Annual vaccination of all children ages 6 months through 18 years before the start of influenza season
- Regardless of seasonal epidemiology, children 6 months through 8 years of age who previously have not been immunized against influenza require two doses of trivalent or quadrivalent inactivated influenza vaccine or live-attenuated influenza vaccine (LAIV) administered at least 4 weeks apart to produce a satisfactory antibody response
- Children > 9 years and those who have received two doses in a previous year receive a single dose annually
- Special emphasis for those with underlying medical conditions, including asthma, hemodynamically significant cardiac disease, HIV, persons on aspirin therapy, sickle cell, diabetes, renal disease, pregnancy
- Egg allergy is not a contraindication to influenza vaccine! (but was in the past….)

Treatment

- Prophylaxis with oseltamivir or zanamivir can be given at the same time as immunization and should be considered for immunosuppressed, unimmunized, close contacts of persons at high risk for complications, and for all when seasonal vaccine does not match circulating strains
- Children who have influenza and are at high risk for complications, regardless of the severity of their illness
- Healthy children who have moderate-to-severe illness
- Three antivirals used in pediatrics:
  - Oseltamivir is administered orally, approved for > 2 weeks old; most common adverse effects are nausea and vomiting, although neuropsychiatric events have been reported
  - Zanamivir is inhaled, approved for treatment (age > 7) and prophylaxis (age > 5)
  - Baloxavir in children ≥ 12 years administered as a single oral dose
- Adamantanes (amantadine and rimantadine) no longer recommended due to resistance

Avian Influenza H5N1

Background

- Reported cases were in south Asia, Iraq, Turkey, and Egypt
- Highly pathogenic strain in birds and poultry
- Not a human strain

Mode of transmission

- Humans who have close contact with infected birds or poultry
- Visiting market selling live infected birds

Clinical presentation

- Severe lower respiratory disease in infected persons

Prevention

- H5N1-specific vaccine (developed and approved)
- Avoid visiting markets where live birds are sold
- Thorough cooking inactivates the virus, but avoidance of poultry if there a concern is more appropriate

Parainfluenza Virus (PV)

Background and epidemiology

- Parainfluenza viruses are paramyxoviruses distinct from the influenza family
- Previous infection does not confer immunity, so reinfection can occur
- Transmitted via contact with NP secretions and respiratory droplets and fomites
- Seasonal patterns of transmission: PV1 and PV2 occur in fall, PV3 occurs in spring, and PV4 occurs year-round
- Children shed virus for 1 week before symptoms and for 1–3 weeks after symptoms resolve
- Incubation period is 2–6 days

Clinical manifestation

- May cause clinical syndrome similar to influenza
- Major cause of laryngotracheobronchitis (croup) in children (see "Respiratory" section)
- Can also cause pneumonia, bronchiolitis, and otitis media
- Most parainfluenza infections are self-limited, but immunocompromised can have severe pneumonia and disseminated disease

Treatment

- Supportive care, as most infection is self-limited
- Corticosteroids lessen severity, complications, and need for hospitalization
- Nebulized racemic epinephrine for severe croup with significant inspiratory/expiratory stridor and retractions

Respiratory Syncytial Virus (RSV)

- Infection with RSV, the most common cause of bronchiolitis (See Chap. 20 "Pulmonology")

Prevention

- Palivizumab: Humanized monoclonal immunoglobulin, recombinant DNA technology
  - Reduces risk of lower tract disease in high-risk children
  - Administered every 30 days during RSV season (max 5 doses/season)
  - Considered for first 1–2 years of life
  - Indicated for:
    1. Preterm infants with chronic lung disease
    2. Infants with hemodynamically significant congenital heart disease
    3. Preterm infants < 29 weeks gestational age
    4. Anatomic pulmonary abnormalities or neuromuscular disorder
    5. Profoundly immunocompromised children

Human Metapneumovirus

Background and epidemiology

- Humans are the only source
- Spread via contact with infected secretions
- A leading cause of bronchiolitis in infants
- Overlap with RSV season (winter–spring)

Clinical presentation

- Bronchiolitis indistinguishable from RSV bronchiolitis
- Can also cause pneumonia, croup, upper respiratory infection
- Secondary bacterial infection with *S. pneumoniae* can occur
- Severe disease in immunosuppressed and history of preterm delivery
- Most children have one human metapneumovirus infection before 5 years of age

Treatment

- Supportive

Rhinoviruses

Background and epidemiology

- The most common cause of common cold (25–80% of cases)
- The common cold is an acute respiratory tract infection characterized by mild coryzal symp-

toms, rhinorrhea, nasal obstruction, and sneezing
- The most common viral trigger for asthma exacerbation
- About 200 antigenically distinct viruses from 8 different genera can cause common cold (66–75%)
- Children typically have 2 episodes/year; adults have 1 episode/year

Clinical features
- Pharyngitis, nasal congestion, and discharge that goes from clear to mucopurulent
- Malaise, headache, myalgia, cough, fever
- Symptoms peak at 3–4 days and last 7 days
- Can cause otitis media, bronchiolitis, and pneumonia

Testing
- Not useful clinically
- PCR preferred, usually paired with enterovirus PCR due to genetically conserved regions

GI Viral Infection

- Norovirus (Norwalk virus) and Sapovirus
- Rotavirus

Norovirus and Sapovirus

Background and epidemiology
- Norovirus, formerly referred to as Norwalk virus, is the most common cause of epidemic nonbacterial gastroenteritis in the world
- Norovirus is the leading cause of viral gastroenteritis cases in the USA, after rotavirus vaccine introduction
- Norovirus causes death in young children and the elderly
- Sapoviruses also cause outbreaks
- Outbreaks of both occur in crowded areas (schools, long-term care facilities, cruise ships)
- Transmission is fecal–oral or vomitus–oral, contaminated food/water, contaminated surfaces, airborne transmission of vomitus documented
- Highly resistant to environmental decontamination, including alcohol hand cleansers
- Incubation period is 12–48 h
- Shedding may last 4 weeks in healthy host, and > 6 months in immunocompromised

Clinical presentation
- Abrupt onset of nausea and vomiting (profuse, nonbloody, nonbilious) more common in adults
- Watery diarrhea (non-bloody) may be the only symptom in children
- Abdominal cramps
- Headaches
- Low-grade fever is common
- Myalgias and malaise
- Chronic gastroenteritis in immunocompromised
- Symptoms last 24–48 h, longer in children, immunocompromised, and elderly

Rotavirus

Background and epidemiology
- Causes severe acute gastroenteritis
- Shed in stool days before and after clinical illness
- Transmitted fecal–oral, possibly respiratory
- Late winter to early spring transmission
- Stable in environment for weeks to months
- Rotavirus was most common viral cause of acute gastroenteritis until vaccine introduction that reduced hospitalizations by 75% for children < 5 years

Clinical presentation
- Acute onset vomiting, then 24 h later severe watery diarrhea
- Up to 33% have high fever
- First infection is more severe
- Causes dehydration, electrolyte imbalance, and metabolic acidosis
- Symptoms last 3–7 days

- Immunocompromised may have severe, prolonged, and fatal symptoms

Diagnosis

- Antigen assay testing (enzyme immunoassay, chromatographic immunoassay, latex agglutination)

RNA Viruses

- Enterovirus
- HIV
- Measles
- Mumps
- Rubella
- Rabies
- Arboviruses

Enteroviruses (Non-polio Viruses and Poliomyelitis)

Non-polio Viruses (Echovirus, Coxsackievirus, and Numbered Enteroviruses)

Background and epidemiology

- More common in the summer and fall
- Humans are the only known reservoir for human enteroviruses
- Enteroviruses transmitted by the fecal–oral route and respiratory route
- Survive in environment for long periods
- Outbreaks can occur
- Most severe disease in infants and young children
- Viral shedding in stool (weeks to months) and respiratory secretions (1–3 weeks)

Clinical manifestations

- Meningitis/encephalitis
  - Enterovirus is the most common cause of meningitis in pediatrics (bacterial or viral)
  - Meningitis commonly caused by echovirus
  - Common in older children
  - Fever, headache, photophobia, and nuchal rigidity, CSF pleocytosis
  - Severe complications: Seizure, hemiparesis, hearing loss, and mental deterioration
  - No signs of toxicity (hypotension, hypoperfusion) as in bacterial meningitis
  - Best diagnostic test: CSF enterovirus PCR
- Herpangina
  - Caused by many enteroviruses, including coxsackievirus type A
  - Sudden onset of high fever in children 3–10 years of age, and can be associated with vomiting, malaise, myalgia, and backache
  - Poor intake, drooling, sore throat, dysphagia, and dehydration may occur
  - Oral lesions:
    - One or more small tender papular pinpoint vesicular lesions, on erythematous base on anterior pillars of the fauces, soft palate, uvula, tonsils, and tongue, then ulcerate in 3–4 days
- Hand, foot, and mouth disease (Fig. 9.6)
  - Mostly caused by coxsackie A16 and enterovirus 71
  - Fever (may be present)
  - Oral vesicles and ulcers on buccal mucosa and tongue
  - Painful erythematous vesicles on hands and feet; it may affect the groin and buttocks
  - Usually last for 7–10 days
  - Most common complication is dehydration due to odynophagia
- Acute hemorrhagic conjunctivitis (similar to adenovirus conjunctivitis)
  - Subconjunctival hemorrhage
  - Swelling, redness, and tearing of the eye
  - Resolves spontaneously within 7 days
- Myocarditis/pericarditis
  - Commonly caused by coxsackievirus B or echovirus
  - Common symptoms: Shortness of breath, chest pain, fever, and weakness
- Congenital and neonatal infection
  - Sepsis-like syndrome associated with maternal enterovirus infection and lack of maternal immunity

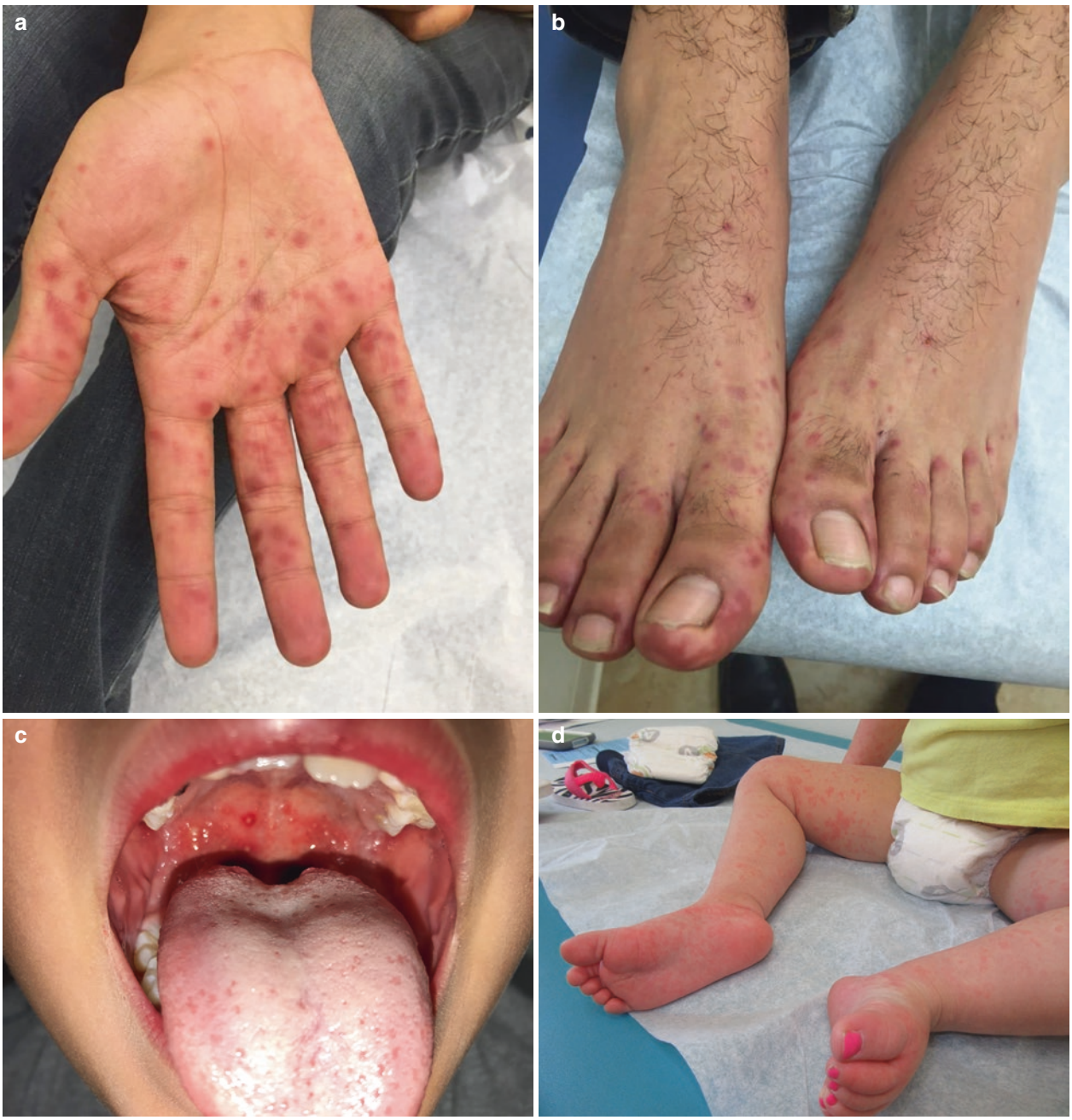


Fig. 9.6 Hand, foot, and mouth disease. (**a**) Tender macules in the hand. (**b**) Tender macules and vesicles in both feet. (**c**) Multiple painful vesicles on the hard palate. (**d**) Erythematous macules all over the body and feet in an 18-month-old who has fever and oral ulcers

  - Can range from mild febrile infection to encephalitis and negative bacterial culture
  - Can cause hepatic necrosis

Diagnosis

- PCR from rectal swab, stool, throat, nasopharynx, conjunctiva, trachea, blood, urine, tissue biopsy, and CSF
- Most respiratory panels with multiplex PCR do not distinguish enterovirus from rhinovirus due to genetic similarity and testing for a shared, conserved region in genome
- Enterovirus 71 often has negative PCR testing

Treatment

- Supportive, and IVIG can be considered for immunocompromised to reduce illness and duration of shedding

Poliomyelitis

Background and epidemiology

- Humans are the only reservoirs
- Three serotypes: Types 1, 2, and 3; type 2 eradicated globally; type 3 not seen since 2012; only type 1 is currently circulating
- Paralytic disease caused by wild type or live, oral vaccine virus
- Stable in liquid environment (pools, ponds, etc.)
- After illness, virus persists in throat (1–2 weeks) and GI tract (3–6 weeks)
- Incubation period 3–6 days; paralysis occurs 1–3 weeks after exposure

Clinical presentation

- Asymptomatic infection in 70%
- Fever and sore throat in 25%
- Aseptic meningitis in 1–5%
- Flaccid paralysis in a descending manner without reflexes in < 1%
  - Follows febrile illness
  - Symmetric paralysis affecting proximal muscles
  - Cranial nerve and diaphragm/intercostal muscle involvement may affect respiration
  - 33% recover
- Affects anterior horn cells in the spinal cord

Diagnosis

- Cell culture of pharynx, stool, and CSF obtained as early as possible

Treatment

- Supportive

Human Immunodeficiency Virus (HIV)

Background

- HIV is RNA virus
- Highest infectivity due to the very high (3–4 weeks) initial viremia
- Nearly all patients seroconvert within 6 months of acquiring the infection

Mode of transmission

- Transmitted by two principal modes in the pediatric age group:
- Mother-to-child
  - Transplacental transfer
  - Exposure to maternal blood, amniotic fluid, and cervicovaginal secretions during delivery
  - Postpartum through breastfeeding
- Behavioral (risk behavior in adolescent either unprotected sex or injection drugs)
- Other transmission modes include needle-stick injury, mucous membrane exposure, and transfusion

Clinical presentation

- During the "window" period:
  - Infected person has a negative HIV antibody test result, but HIV RNA testing results are usually positive
- Acute retroviral syndrome, characterized by:
  - Fever, lymphadenopathy, rash, myalgia, arthralgia, headache, diarrhea, oral ulcers, leukopenia, thrombocytopenia, and transaminitis
- Red flags for HIV infection
  - Thrush in apparently healthy child or adolescent
  - Invasive candidal infections
  - Recurrent severe infections
  - Lymphadenopathy and/or hepatosplenomegaly
  - Failure to thrive

- Parotid enlargement
- Opportunistic infections
  - *Pneumocystis jiroveci* pneumonia
  - *Mycobacterium avium* complex
  - Cytomegalovirus
  - *Toxoplasma gondii*
  - Human viscerotropic leishmaniasis

Diagnosis: Perinatal and postnatal infection

- Preferred overall test in infants and children < 18 months is HIV DNA PCR; highly specific by 2 weeks of age
  - 55% sensitivity at birth that increases to 100% by age 3 months
- Preferred test for HIV-1 infection is HIV RNA PCR because of greater clinical experience
- Some use both to obtain viral load and confirmation
- Maternal antibody transfer can complicate diagnostics
- In HIV exposed, test at delivery, 2–3 weeks, 1–2 months, and 4–6 months
- Presumed negative in children < 18 months if: Two negative HIV DNA or RNA tests from separate specimens at > 2 weeks of age, one negative HIV DNA or RNA test from > 8 weeks of age, or one negative HIV antibody test at > 6 months of age and no clinical or laboratory evidence of infection
- Definitive negative in non-breastfed < 12 months: At least 2 negative HIV DNA or RNA virologic tests from separate specimens at > 1 month and > 4 months, at least 2 negative HIV antibody tests from separate specimens at > 6 months and no clinical or laboratory evidence of infection

Diagnosis: Adult and adolescent infection

- Conduct initial serology, followed by confirmatory serology testing
- For initial serology testing:
  - Antibodies to HIV-1/HIV-2 and HIV-1 p24 antigen (fourth generation)
  - Antibodies to either HIV-1 and HIV-2 (third generation)
- For confirmatory serology testing:
  - Differential antibody testing to HIV-1 and HIV-2
  - HIV-1 Western blot and HIV-1 indirect immunofluorescence assay

Evaluation of HIV positive children

- CD4 percentage and absolute cell counts
- Plasma HIV RNA concentration (viral load)
- HIV genotype to assess for baseline resistance and mutations
- Complete blood count with differential count
- Serum chemistries with liver and renal function tests
- Lipid profile and urinalysis
- For children younger than 5 years of age, CD4 percentage is the preferred test for monitoring immune status
- Screening for hepatitis B, hepatitis C, and tuberculosis is recommended for all HIV positive patients

Treatment of HIV

- Triple-drug combination antiretroviral therapy effectively controls HIV infection

Prevention

- Breastfeeding is contraindicated in HIV positive mothers
- All exposed infants should receive 6 weeks of zidovudine
- Condoms and abstinence are the best forms of preventing sexual transmission of AIDS
- Cesarean delivery and treatment of HIV-positive mothers (especially with high viral load) decreases the risk of transmission of HIV to their infants
- Immunization of infants and children
  - Immunization schedule for HIV-exposed children is the same as for their healthy peers, with only a few exceptions:
    - Patients who have severely symptomatic illness
    - Patient with CD4 percentage of less than 15% or CD4 counts of less than 200 cells/mm^3 should not receive MMR, varicella vaccines, or other live vaccines

- Annual influenza immunization is recommended for all children older than age 6 months, but only the killed vaccine

Measles Virus

Background

- Mode of transmission: Respiratory droplets (airborne)
- Infectious for 3–4 days before the onset of morbilliform rash and 4 days after the exanthem

Diagnosis

- PCR testing, IgM detection, 4-fold rise in IgG serology, cell culture
- IgM detection is preferred test

Clinical presentation

- High fever plus coryza, cough, conjunctivitis
- Rash develops next: Erythematous, morbilliform, maculopapular rash spread from face downward and disappears the same way
- Koplik spots (white spots on oral mucosa) during prodrome
- Complications in young children and immunocompromised include otitis media, bronchopneumonia, croup, diarrhea, and death
- Death is also more common with severe malnutrition
- Severe complication: Acute encephalitis with permanent brain damage

Control and prevention

- Vaccinate non-immunes within 72 h of exposure
- Immune globulin within 6 days of exposure for non-immunes if vaccination not possible, including pregnant women, severe primary immunodeficiency, bone marrow or solid organ transplant recipient, acute lymphoblastic leukemia, HIV AIDS with severe immunosuppression, and infants whose mothers received immunomodulatory drugs during pregnancy
- HIV on antiretroviral therapy and documented measles vaccination × 2: Treat as immune
- Vaccinate all health-care personnel

Mumps

Background

- An acute, self-limited, systemic viral illness characterized by the swelling of one or more of the salivary glands, typically the parotid glands

Mode of transmission

- Contact to respiratory secretions
- Incubation period is 16–18 days

Clinical presentation

- Symptoms in the patient's history consist mostly of fever, headache, and malaise
- Within 24 h, patients may report ear pain localized near the lobe of the ear and aggravated by a chewing movement of the jaw
- Unilateral or bilateral parotid swelling (Fig. 9.7)
- Orchitis may occur after puberty; rarely causes sterility

Complications

- Rare: Arthritis, thyroiditis, glomerulonephritis, myocarditis, transverse myelitis, encephalitis, oophoritis, permanent hearing impairment

Diagnosis (Table 9.1)

- PCR from buccal swabs, throat washings, saliva, or CSF
- Viral cell culture
- Serology

Treatment

- Supportive care only
- School exclusion for 5 days from onset of parotid gland swelling

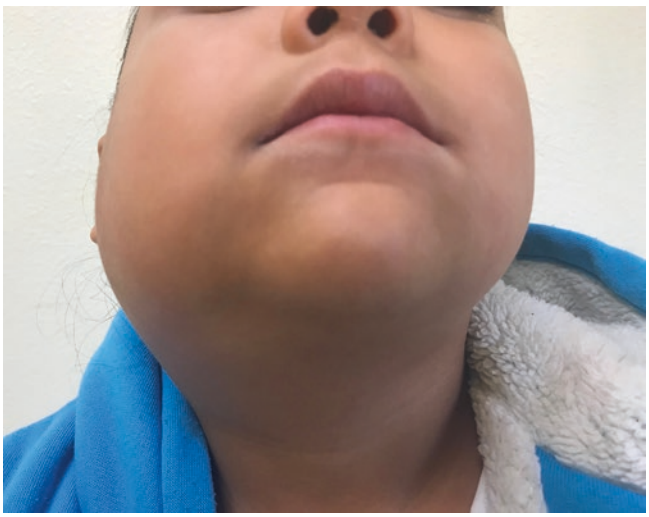


Fig. 9.7 Child with unilateral parotitis

Table 9.1 Differences between viral and bacterial parotitis

Viral parotitis (mumps)	Bacterial parotitis
Well-appearing	Toxic-appearing or ill-looking
No fever or low-grade fever	High fever
Mild tenderness	Moderate or severe tenderness
Normal labs, positive mumps IgM	Leukocytosis, shift to the left, high CRP

IgM Immunoglobulin M, *CRP* C-reactive protein

- Unimmunized children should stay out of school for 26 days after onset of parotitis in the last person with mumps in the affected school.

Rubella Virus

Epidemiology

- Transmitted via direct or droplet contact with respiratory secretions
- Peak incidence from winter to spring
- 25 to 50% asymptomatic
- Lifelong immunity
- Can transmit 3 days before to 7 days after rash appears
- Infants with congenital rubella may shed for 1 year in nasopharyngeal secretions and urine
- The USA has not experienced rubella transmission since 2004; imported cases occur
- The Americas have not experienced rubella transmission since 2009
- Incubation period: 16–18 days

Clinical presentation

- Congenital rubella syndrome
  - Constellation of congenital anomalies
    - Ophthalmologic (cataracts, microphthalmos, congenital glaucoma)
    - Cardiac (patent ductus arteriosus, peripheral pulmonary artery stenosis)
    - Auditory (hearing impairment)
    - Neurologic (meningoencephalitis, microcephaly, mental retardation, autism)
  - Neonates will have growth restriction, interstitial pneumonitis, hepatosplenomegaly, thrombocytopenia, and dermal erythropoiesis that manifests as "blueberry muffin" rash
  - Neonates may also have metaphyseal lucencies (also seen in vitamin D intoxication/hypercalcemia, rickets, scurvy, arsenic and heavy metal poisoning, leukemia, congenital syphilis, sickle cell disease, congenital hypothyroidism)
  - Increased risk of congenital defects if fetal infection occurs early in pregnancy
- Postnatal rubella
  - Subclinical or mild disease
  - Erythematous maculopapular rash
  - Forchheimer spots: Rose-colored spot on soft palate
  - Lymphadenopathy (posterior auricular or suboccipital nodes)
  - Conjunctivitis
  - Adolescent females susceptible to transient arthralgia and arthritis
  - Rare complications: Encephalitis, thrombocytopenia
- Infants with congenital rubella may shed the virus from the nasal mucosa > 1 year to susceptible contact

Rabies Virus

Background

- RNA virus classified in the *Rhabdoviridae* family
- Usually transmitted by bats and carnivores, e.g., raccoons, foxes, and coyotes
- Almost never transmitted by squirrels, chipmunks, rats, mice, rabbits, and guinea pigs

Clinical presentation

- Anxiety
- Dysphagia
- Seizures
- Encephalitis
- In most cases, progress to death

Treatment

- Prompt local flushing and cleaning the wound with soap and water
- Passive and active immunization for:
  - All persons bitten by bats, carnivores, e.g., raccoon, foxes, and coyotes
  - Open wound or scratch contaminated with saliva of infected animals or human
- No prophylaxis if domestic dog, cat or ferret that can be observed for 10 days
- Domestic animals that may be infected should be euthanized and tested
- The need for tetanus and local wound care should be considered

Passive and active immunization should be started as soon as possible

- Human rabies immunoglobulin (passive)
- Rabies vaccine (active)
- Both should be given together
- Human rabies immunoglobulin: As much as possible of the dose should be infiltrated directly to wound, the remainder of the dose should be given intramuscularly (IM)
- Rabies vaccine should be given IM in opposite arm or thigh, the first dose immediately after exposure then repeated at days 3, 7, and 14. Immunocompromised persons get an additional dose at day 28

Arboviruses (Arthropod-Borne Viruses)

- West Nile virus (WNV)
- Dengue fever

West Nile Virus

Background and epidemiology

- The most common neuroinvasive arboviral disease in the USA
- Transmitted to humans by *Culex* mosquitoes
- Transmission occurs from summer to fall
- California, North and South Dakota, Nebraska and Illinois were the most common locations in 2018
- Incubation 2–6 days
- Humans also infected via transfusion and organ transplant

Clinical presentation

- Most cases are asymptomatic (70–80%)
- May present with fever and flu-like symptoms
- Fever, headache, myalgia, arthralgia, vomiting, diarrhea, transient rash
- < 1% have neuroinvasive disease: Meningitis, encephalitis, acute flaccid myelitis
- WNV encephalitis: Altered mental status, seizures, paresis, nerve palsies, or coma in more severe cases
- Most recover completely but can take months

Diagnosis

- Anti-WNV IgM in serum or CSF may take a week to turn positive

Treatment

- Supportive

Dengue Fever

Background and epidemiology

- Arbovirus transmitted by *Aedes* mosquitoes
- History of travel to endemic area

- Endemic in Asia, Africa, Latin America, and Puerto Rico
- Transmission has occurred in Hawaii, Florida, and Texas
- Incubation period is 3–14 days

Clinical presentation

- Can be asymptomatic
- Febrile illness lasting 2–7 days: Pain in muscles, joints and bones, headache; retro-orbital pain, facial erythema, injected oropharynx, macular or maculopapular rash, leukopenia, petechiae
- Critical phase: 24–48 h with plasma leakage
- Convalescent phase: Improvement and stabilization
- Severe dengue (dengue hemorrhagic fever or dengue shock syndrome) occurs in 5% and can be deadly
- Increased risk for severe dengue with subsequent infection

Laboratory

- During febrile phase, diagnose with PCR for viral DNA or immunoassay for nonstructural protein 1 (NS-1)
- From 3 to 5 days after onset, can test for anti-dengue IgM
- Leukopenia, thrombocytopenia, and modest elevation of liver enzymes

Treatment

- Supportive

Human Papillomavirus (HPV)

Background and epidemiology

- Most adults will be infected at some time
- School-age children acquire nongenital hand and foot warts through minor skin trauma
- Genital transmission occurs skin-to-skin
- HPV causes most vulvar, vaginal, penile, and anal cancers; 70% of oropharyngeal cancers
- Rare transmission to infant during delivery
- Incubation period is months to years
- Oncogenic strains 16 and 18 are responsible for two thirds of all cervical cancers
- Nononcogenic HPV type 6 and 11 are responsible for > 90% of anogenital warts

Clinical features

- Most infections are subclinical
- Skin warts are generally painless; plantar warts can be painful
- Anogenital warts (*condylomata acuminata*) have cauliflower-like surface and can occur in groups
- Invasive cancers linked to HPV include the following locations: Oropharynx, penis, anus, cervix, vagina, and vulva
- Squamous intraepithelial lesions can be low or high grade due to persistent HPV
- Cervical intraepithelial neoplasia (CIN) is precancerous and linked to HPV
- Adenocarcinoma in situ is another endocervical precancer

Immunization

- 2 doses before 15th birthday
- Only 9-valent vaccine available in USA since 2017

BACTERIAL PATHOGENS

Gram-Positive Bacteria

S. aureus

Background and epidemiology

- *S. aureus* is the most common cause of skin and soft tissue infection and musculoskeletal infection in healthy children
- Second leading cause of healthcare-associated bacteremia (coagulase-negative staphylococci is first)
- Leading cause of secondary bacterial pneumonia in children
- Most common cause of healthcare-associated surgical site infections
- Coagulase positive
- Grapelike clusters (Fig. 9.8)

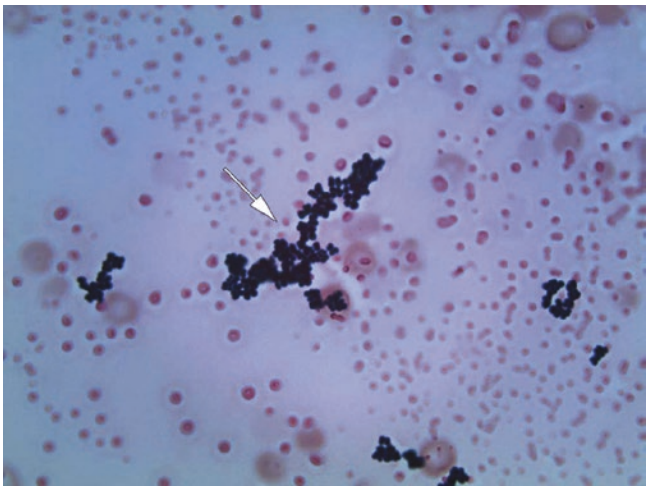


Fig. 9.8 *Staphylococci* in blood culture (Gram stain, original magnification × 1000). The bacteria are Gram-positive cocci and grow in pairs, tetrads, and clusters (*arrow*). (Courtesy of M. Nawar Hakim, MD, Department of Pathology, Texas Tech University Health Sciences Center, El Paso, Texas, USA)

- *S. aureus* colonizes the nares and skin in 30–50% of children
- Transmitted by direct contact and indirectly from other patients in hospital settings
- Can spray short distances into the air
- "Vancomycin-intermediately susceptible *S. aureus*" related to repeat vancomycin use in individuals. Vancomycin-resistant *S. aureus* rare
- Incubation period can be 12 h for postoperative toxic shock syndrome

Common staphylococcal infections

- Bullous and crusted impetigo
- Skin and soft tissue or lymph node infection
- If the organism seeds the bloodstream, dissemination to joints, bones, kidney, liver, muscles, lungs, and heart valves may occur, causing substantial morbidity and potential mortality
- *S. aureus* is the most common cause of osteomyelitis, including sickle cell disease patients (who are also at increased risk for *Salmonella* osteomyelitis)
- Children with cyanotic congenital heart disease are at high risk of staphylococcal brain abscess
- Children who undergo neurosurgical procedures, especially shunt revisions, are at high risk for staphylococcal infection
- Indwelling bloodstream catheters can be associated with staphylococcal infection and must be removed if the patient develops symptoms or positive culture

Folliculitis/Furunculosis/Carbunculosis (Fig. 9.9)

Background

- Folliculitis: Superficial inflammation centered around a follicle
- Furuncles: Bacterial folliculitis of a single follicle that involves a deeper portion of the follicle
- Carbuncle: Bacterial folliculitis that involves the deeper portion of several contiguous follicles
- Bacterial folliculitis most often caused by *S. aureus*.
- Hot tub folliculitis is usually caused by Gram-negative bacteria (most *often P. aeruginosa;* self-limited)
- Usually the child looks healthy and does not appear ill
- Abscess (< 5 cm) drainage alone is curative without antibiotics and should be performed along with a request for culture

Management of skin and soft tissue infections

- Indication for antibiotics
  - The child has high fever or other systemic symptom
  - The abscess is larger than 5 cm
  - Located in a critical location or in an area difficult to drain
  - Signs and symptoms persist following incision and drainage
- Common oral anti-staphylococcal antibiotics
  - Trimethoprim–sulfamethoxazole (TMP-SMX) effective against most MRSA
  - Cephalexin remains a good empiric choice for MSSA and group A *Streptococcus* (GAS) infections

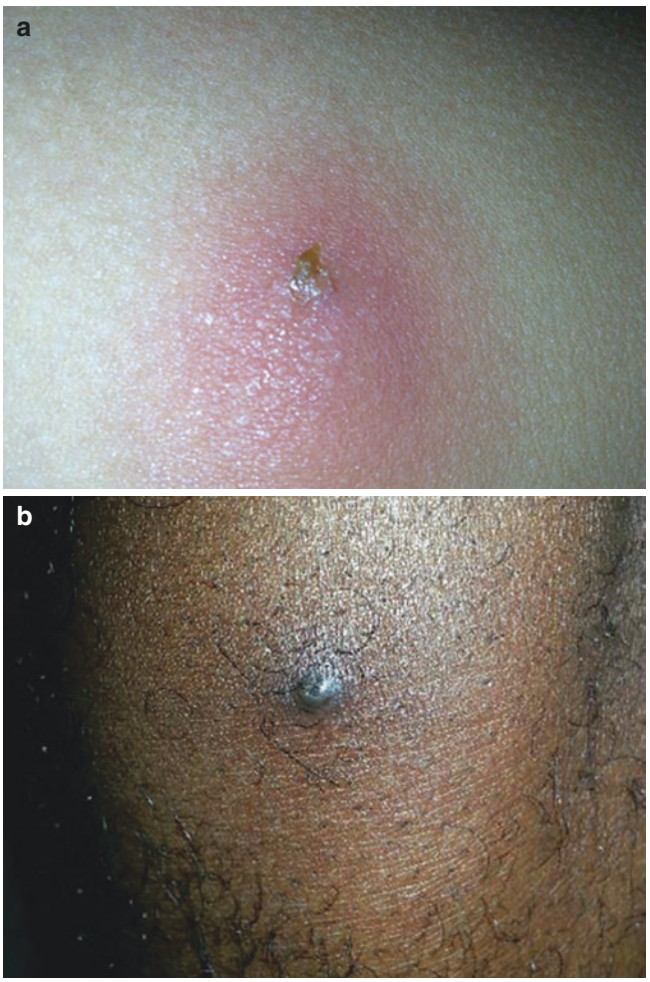


Fig. 9.9 (**a**) Furuncle: Erythematous tender papulonodule with central punctum with point of fluctuant. (**b**) Folliculitis: Superficial inflammation centered around a follicle, tender to touch

  - Clindamycin
  - Doxycycline (in children older than 8 years of age)
  - Linezolid (for resistant MRSA infections not susceptible to TMP-SMX or clindamycin)
- Recurrent staphylococcal skin infections recommendations
  - Enhanced hygiene and environmental cleaning
  - Treatment for anyone in the family who has active disease
  - Nasal and perianal mupirocin
  - Skin decolonization (chlorhexidine and/or bleach baths)
  - Treatment with antibiotic-based decolonization regimens (usually rifampin plus an additional agent) in selected cases

Toxic Shock Syndrome (TSS)

Background

- Production of toxic shock syndrome toxin-1 (TSST-1)
- Can be caused by *S. aureus or S. pyogenes* (aka group A *Streptococcus* or GAS)

Risk factors

- Tampon
- Surgical implants
- Invasive staphylococcal disease, including pneumonia and skeletal infection
- Nasal packing
- Progressive skin infection in cases caused by *S. pyogenes*

Clinical presentation

- Fever
- Vomiting
- Hypotension (abrupt onset)
- Hypocalcemia
- Watery diarrhea
- Myalgia
- Strawberry tongue
- Conjunctival hyperemia
- Rash with hand and foot desquamation
- Blood culture is usually negative if the cause is *S. aureus*
- Blood culture is usually positive if the cause is *S. pyogenes*

Treatment

- Vancomycin + clindamycin (stops toxin production) + nafcillin or oxacillin, pending culture results
- In cases of tampon-associated TSS, must be removed immediately and the recommended length of therapy is 10–14 days
- IV fluids and routine management of shock; consider IVIG for refractory shock

- Do not treat hypocalcemia unless symptomatic or electrocardiogram changes
- Anytime there is a postsurgical toxic shock, any device implanted during surgery must be removed immediately

Staphylococcal Scalded Skin Syndrome (SSSS)

Background

- SSSS (aka Ritter disease of the newborn)
- Ritter disease and staphylococcal epidermal necrolysis encompass a spectrum of superficial blistering skin disorders caused by exfoliative toxins of some strains of *S. aureus*
- SSSS differs from bullous impetigo; the exfoliative toxins are restricted to the area of infection in bullous impetigo, and bacteria can be cultured from the blister contents
- Exfoliative toxins cause separation of the epidermis beneath the granular cell layer. Bullae and diffuse sheetlike desquamation occurs
- Exotoxin is a protein and is classified as either type A or B. Most are type A

Clinical presentation

- Fever, malaise, and irritability
- Most of the patients do not appear severely ill
- Tenderness to palpation
- Dehydration may be present and can be significant
- Nikolsky sign (gentle stroking of the skin causes the skin to separate at the epidermis)
- Bacteremia may or may not present

Diagnosis

- Blood cultures are usually negative in children (but positive in bullous impetigo) and is usually positive in adults
- A chest radiograph should be considered to rule out pneumonia as the original focus of infection
- A biopsy of the affected area will demonstrate separation of the epidermis at the granular layer

Management

- Fluid rehydration is initiated with lactated Ringer solution at 20 mL/kg initial bolus
- Repeat the initial bolus, as clinically indicated, followed by maintenance therapy with consideration for fluid losses from exfoliation of skin being similar to a burn patient
- Prompt treatment with parenteral anti-staphylococcal antibiotics is essential

S. aureus Food Poisoning

Background

- The most common cause of food poisoning in the USA
- Eating contaminated food containing preformed enterotoxin
- Usually associated with meat, baked food filled with cream, and mayonnaise
- Incubation period < 4–6 h

Clinical presentation

- Nausea, vomiting, and abdominal cramps in few hours after exposure to contaminated food
- Fever may be present
- Some children can have severe dehydration

Management

- Hydration
- No antibiotic required

Staphylococcal, Coagulase-Negative

Background

- *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* are examples of coagulase-negative staphylococci

- *S. epidermidis* is methicillin-resistant in most cases
- *S. epidermidis* is the most common cause of catheter-related bacteremia
- Catheter becomes contaminated when passing through the skin
- *S. epidermidis* is a common contaminant in the blood cultures

Common source of infection

- Skin, mucous membrane
- Nosocomial infection
- IV catheter
- Ventriculoperitoneal shunts
- Prosthetic devices, e.g., heart valves, joints, and pacemakers
- Bone marrow transplant
- Premature infants (intravascular catheter)

Management

- Removal of the foreign body may be necessary to clear the infection
- In neonatal intensive care unit (NICU), positive culture must be initially treated if suspicious of infection
- Draw two cultures from two different sites. To be considered positive, both cultures should be positive within 24 h.
- Vancomycin is the drug of choice

Methicillin-Sensitive *S. aureus* (MSSA)

Background

- Most of *S. aureus* strains produce beta-lactamase enzyme and are resistant to penicillin and ampicillin

Drug of choice

- Nafcillin or oxacillin (+ rifampin if indwelling foreign body)
- Treat for 3–4 days for bacteremia

Alternative drugs

- Cefazolin
- Clindamycin
- Vancomycin
- Ampicillin + sulbactam

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Background

- MRSA strains are resistant to all beta-lactamase resistant (BLR) beta-lactam and cephalosporin antimicrobials and other antimicrobial agents

Drug of choice in MRSA cases (oxacillin MIC, 4 ≥ µg/mL)

- Vancomycin ± gentamicin or ± rifampin (multidrug resistance)
- For example, endocarditis, septicemia, and CNS infection (combination therapy is recommended)
- Alternative drugs in MRSA cases (multidrug resistance)
  - Trimethoprim–sulfamethoxazole
  - Linezolid
  - Quinupristin/dalfopristin
  - Daptomycin
  - Treat for 7–9 days for bacteremia

Community (not multidrug resistance)

- Vancomycin ± gentamicin (or ± rifampin) for life-threatening infections, e.g., endocarditis
- Clindamycin (if strain susceptible) for pneumonia, septic arthritis, osteomyelitis, skin, or soft tissue infection
- TMP-SMX for skin or soft tissue infections
- Daptomycin for vancomycin-intermediately susceptible *S. aureus*

S. pneumonia (Pneumococcal Infection)

Background and epidemiology

- *S. pneumoniae* is a Gram-positive, catalase-negative, alpha-hemolytic bacterium
- The bacteria are Gram-positive diplococci (Fig. 9.10)
- Introduction of pneumococcal conjugate vaccines (PCV7 and PCV13) significantly reduce invasive pneumococcal disease in children
- Nasopharyngeal carriage rates are 21% for industrialized countries to 90% in resource-limited settings
- Transmission is person-to-person via respiratory droplets, occurring with viral upper respiratory infections
- More common in winter
- Incubation period is 1–3 days

Risks of invasive pneumococcal disease

- The highest age-specific attack rates occur during the first 2 years of life
- Children who have sickle cell disease
- Children who have asplenia
- Congenital immune deficiencies
- Immunosuppressive medications or bone marrow transplants also are at increased risk
- CSF leaks, e.g., neurosurgical procedures or skull fractures
- Cochlear implants
- Chronic heart or lung disease
- Diabetics

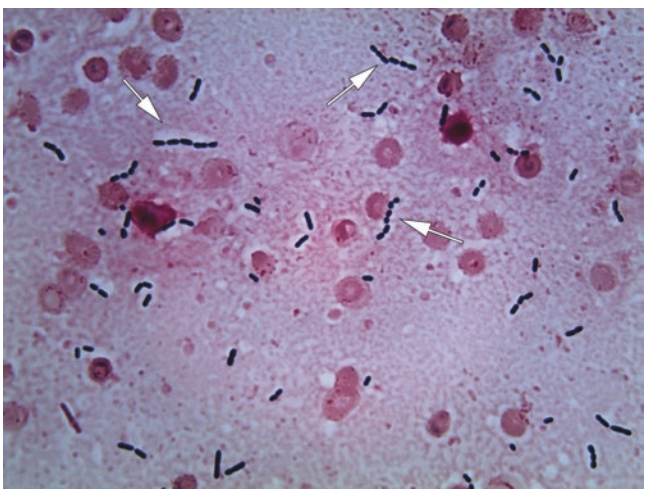


Fig. 9.10 *Streptococcus pneumoniae* (pneumococci) in blood culture (Gram stain, original magnification × 1000). The bacteria are Gram-positive diplococci (*arrows*). They are often lancet-shaped. (Courtesy of M. Nawar Hakim, MD, Department of Pathology, Texas Tech University Health Sciences Center, El Paso, Texas, USA)

Clinical manifestations

- Common pneumococcal infections include:
  - Acute otitis media
  - Sinusitis
  - Pneumonia
  - Bacteremia (most common manifestation of invasive pneumococcal disease)
  - Meningitis (leading cause of meningitis)
- Pneumonia
  - *S. pneumoniae* is the most common bacterial cause of community-acquired pneumonia in both children and adults
  - High fever and ill-appearing
  - Cough and tachypnea
  - Respiratory distress
  - Crackles
  - Diminished breath sounds
  - Lobar consolidation may be noted on chest radiography in older children
  - Know: Infants and young children may have bronchopneumonia with a scattered distribution of parenchymal consolidation
  - Pleural fluid may be evident in some patients

Diagnosis

- Culture from blood or normally sterile body fluids such as CSF, pleural, synovial, or middle ear fluid
- PCR on blood or CSF specimen
- Positive results should have antimicrobial susceptibility testing for penicillin, cefotaxime or ceftriaxone, and clindamycin.

Treatment

- **Outpatient otitis media:** Amoxicillin (80–90 mg/kg/day for < 6 months and 6–23 months with bilateral disease) with watch and wait 48–72 h for older children

and nonsevere disease. Treat 10 days for severe disease. Treat 5–7 days for > 6 years for mild or moderate disease. Alternate therapies include amoxicillin-clavulanate, cefdinir, cefpodoxime or cefuroxime or IM ceftriaxone × 3 doses. Same dosages for sinusitis if bacterial sinusitis diagnosed. If penicillin allergic type I (anaphylaxis), use clindamycin or levofloxacin

- **Outpatient pneumonia:** Amoxicillin (90 mg/kg/day)
- **Inpatient pneumonia**: Parenteral ampicillin. Alternatives: Cefotaxime and ceftriaxone
- **Pneumococcal meningitis:** Due to antibiotic resistance concerns, treatment of proven or suspected cases mandates empiric therapy with **cefotaxime or ceftriaxone plus vancomycin** while awaiting susceptibility results. Discontinue vancomycin if susceptible to penicillin, cefotaxime, or ceftriaxone
- **Other invasive pneumococcal infections, inpatient:** Same as for pneumococcal meningitis

Streptococcus pyogenes

- Group A Streptococcus (GAS) is a Gram-positive bacterium that grows in chains (Fig. 9.11)

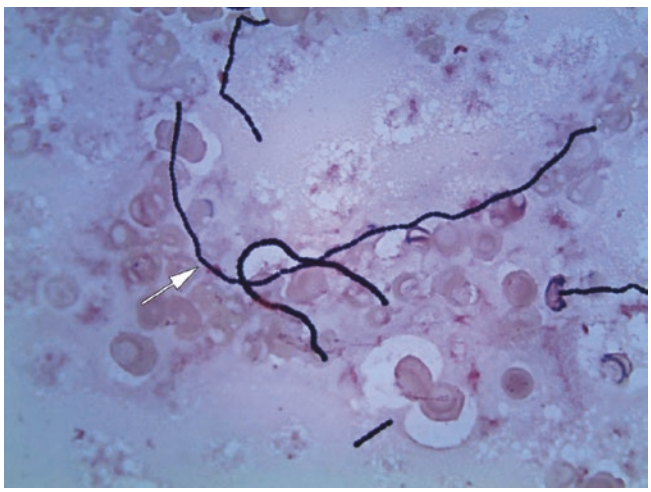


Fig. 9.11 Streptococci in blood culture (Gram stain, original magnification × 1000). The bacteria are Gram-positive cocci and grow in chains (*arrow*). (Courtesy of M. Nawar Hakim, MD, Department of Pathology, Texas Tech University Health Sciences Center, El Paso, Texas, USA)

Group A Beta-Hemolytic Streptococcus (GAS) Pharyngitis

Background and epidemiology

- Causes pharyngitis and impetigo
- Pharyngitis: Transmits via contact with respiratory tract secretions of infected person
- Impetigo: Transmits via direct contact from another person
- Increased risk for pharyngitis and impetigo with crowding
- Most often in schools, childcare centers, contact sports
- Some are chronic pharyngeal carriers
- Increased risk of invasive GAS infection in infants and elderly
- Like *S. aureus*, can cause TSS
- Rheumatic fever can develop in about 3% of untreated patients with GAS pharyngitis
- Incubation period for GAS pharyngitis is 2–5 days; for GAS impetigo is 7–10 days
- For TSS, can occur 14 h after inoculation of organism (e.g., trauma)

Clinical presentation

- Sore throat, fever, headache, and abdominal pain the most classic presentation
- Nausea and vomiting may occur
- Pharyngeal erythema and palatal petechiae (Fig. 9.12)
- Inflammation of the uvula
- Anterior cervical lymphadenopathy
- Tonsillar exudates may or may not be present

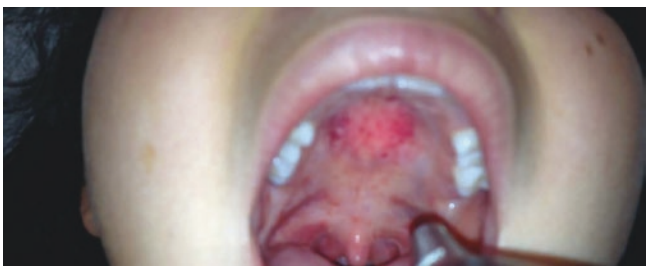


Fig. 9.12 Streptococcal pharyngitis: Palatal petechiae, rapid strep was positive in this patient

Diagnosis

- Rapid antigen detection test is highly recommended to decrease overuse of antibiotics
- Testing of asymptomatic household contacts not recommended except when contacts are at increased risk of developing sequelae of GAS infection, e.g., rheumatic fever, post-streptococcal glomerulonephritis, or TSS
- If rapid antigen detection test (RADT) positive, treat (specificity of 95%)
- If RADT is negative, do throat culture (sensitivity of 65–90%)
- Treatment of GAS sore throat as long as 9 days after the onset of symptoms still effectively prevents rheumatic fever; initiation of antibiotics is seldom of urgent importance

Treatment

- Reduces complications
- Decreases the duration of infection
- Reduces transmission to others
- Oral penicillin VK (250–500 mg twice to three times a day for 10 days) is the antibiotic treatment of choice for GAS pharyngitis
- Amoxicillin (50 mg/kg, maximum 1 g, once daily for 10 days) often is used instead of oral penicillin because of its more palatable liquid formulation
- Cephalosporins or macrolides may be used as first-line therapy in patients allergic to beta-lactam antibiotics but otherwise are not recommended as first-line therapy
- IM benzathine penicillin G 600,000 U for children who weigh < 27 kg and 1.2 million U for heavier children as a single dose (if adherence is a problem but is painful)
- Know: Treatment is indicated if a GAS carrier develops an acute illness consistent with GAS pharyngitis

Treatment to eradicate GAS carriage indications

- History of acute rheumatic fever
- Close contact who has a history of rheumatic fever
- Families experiencing repeated episodes of GAS pharyngitis
- Eradication regimens include clindamycin, cephalosporins, amoxicillin–clavulanate

Scarlet Fever (Scarlatina)

Background

- Syndrome characterized by exudative pharyngitis, fever, and scarlatiniform rash
- Caused by toxin-producing GAS found in secretions and discharge from the nose, ears, throat, and skin

Clinical presentation

- Fever may be present
- Patient usually appears moderately ill
- On day 1 or 2, the tongue is heavily coated with a white membrane through which edematous red papillae protrude (classic appearance of white strawberry tongue) (Fig. 9.13)
- By day 4 or 5, the white membrane sloughs off, revealing a shiny red tongue with prominent papillae (red strawberry tongue)
- Red, edematous, exudative tonsillitis

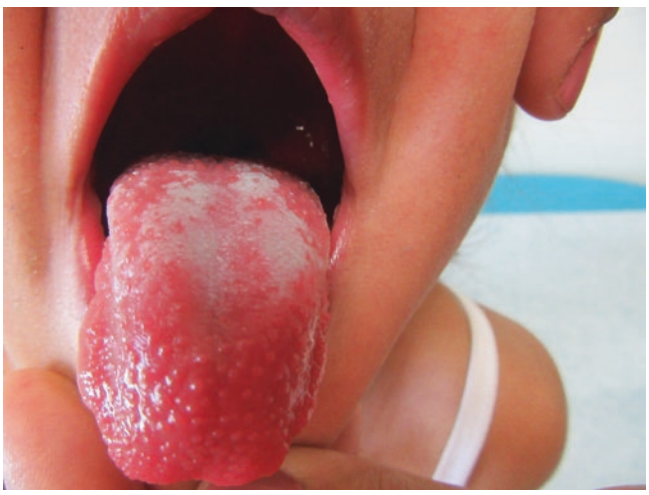


Fig. 9.13 Strawberry tongue with white coat in a child with scarlet fever

- Diffuse, erythematous, blanching, fine papular rash that resembles sandpaper on palpation (Fig. 9.14)
- The rash is prominent especially in the flexor skin creases of the antecubital fossa and axillae (Pastia lines, which are pathognomonic for scarlet fever)
- Circumoral pallor
- Desquamation after the rash starts to fade (usually the rash lasts about 1 week)

Diagnosis

- Throat culture or rapid streptococcal test
- Anti-deoxyribonuclease B and antistreptolysin O titers (anti-DNase B and ASO, antibodies to streptococcal extracellular products)

Management

- Penicillin remains the drug of choice (documented cases of penicillin-resistant group A streptococcal infections still do not exist)
- First-generation cephalosporin may be an effective alternative

Streptococcosis

- Occurs in children younger than 3 years
- Young infants may not present with classic pharyngitis
- Low-grade fever
- Thick purulent nasal discharge
- Poor feeding
- Anterior cervical lymphadenopathy
- Some patients may be toxic with high fever, malaise, headache, and severe pain upon swallowing

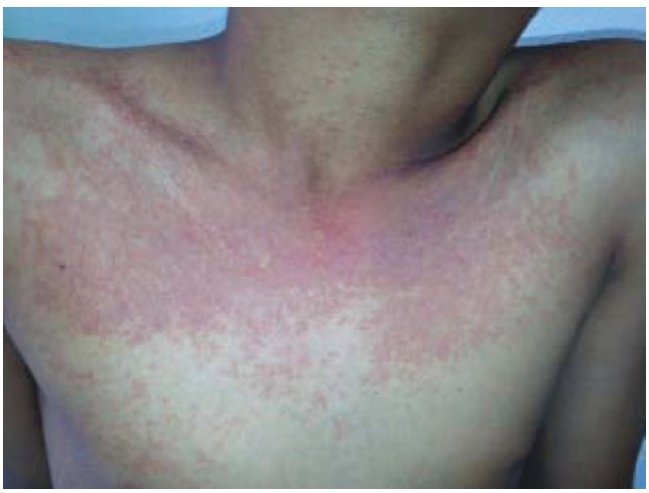


Fig. 9.14 Scarlet fever: Fine erythematous punctate eruption with dry, rough texture to the skin that resembles the feel of coarse sandpaper and scarlet macules overlying the generalized erythema

Impetigo

Background

- GAS impetigo is a superficial bacterial skin infection (small percentage)
- In North America the etiologic agent is primarily *S. aureus*

Clinical presentation

- Common (i.e., crusted or nonbullous) impetigo: Initial lesion is a superficial papulovesicular lesion that ruptures easily
- The lesion becomes purulent and covered with an amber-colored crust (Fig. 9.15)
- Bullous impetigo: Superficial fragile bullae containing serous fluid or pus form and then

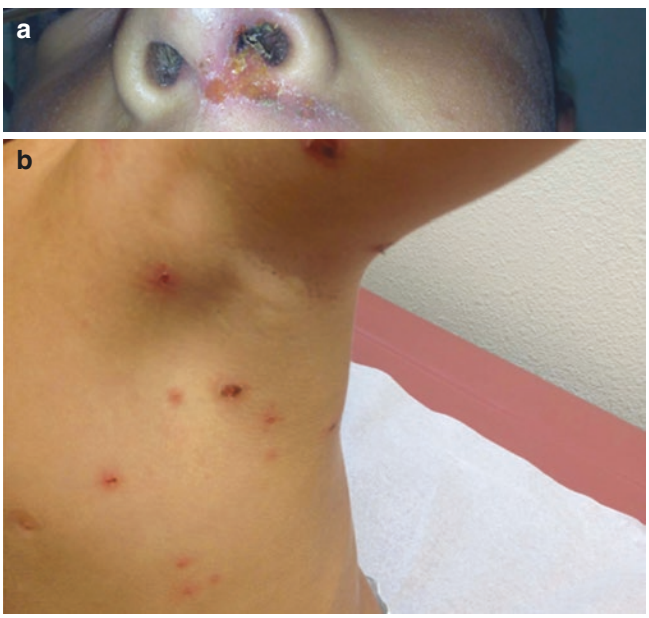


Fig. 9.15 (**a**) Impetigo: Honey-crusted lesions under the nostril and on the cheek. (**b**) Impetigo: Honey-crusted lesions on the arm and trunk

rupture to form round, very erythematous erosions
- The lesions usually located in exposed areas, especially the face and extremities
- Lesions usually often spread due to autoinoculation

Treatment
- Topical mupirocin or retapamulin for localized lesions
- Multiple localized lesions may require systemic treatment such as cephalexin or clindamycin that covers both GAS and staphylococcal infections
- Should not go back to school until at least 12 h after beginning appropriate antimicrobial
- Patient should avoid close contact with other children if possible

Perianal Bacterial Dermatitis (Formerly Called Perianal Streptococcal Dermatitis)

Background
- May be caused by *S. pyogenes* (GAS) or *S. aureus*, occurring in children 6 months–10 years
- Often misdiagnosed and treated inappropriately
- Early antibiotic treatment results in dramatic and rapid improvement in symptoms

Clinical presentation
- Perianal rash, itching, and rectal pain; blood-streaked stools may also be seen in one-third of patients
- Bright red, sharply demarcated rash around the anal area (Fig. 9.16)

Diagnosis
- A rapid streptococcal test of suspicious areas can confirm the diagnosis if etiology is GAS (vast majority of cases)
- Routine skin culture is an alternative diagnostic aid

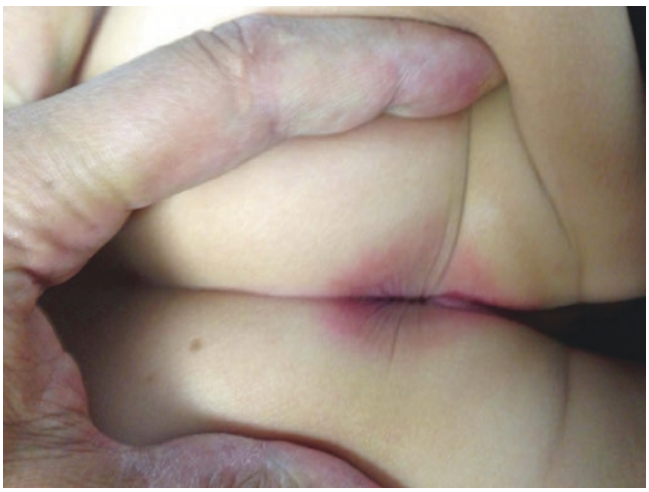


Fig. 9.16 Perianal bacterial dermatitis: 4-year-old presents with rectal pain, itchiness, and discomfort when sitting; physical exam shows bright red, sharply demarcated rash around the anal area. Strep test was positive

Management
- Treatment with empiric oral cephalexin is effective for most staph and strep; if rapid strep is positive, can use oral penicillin or amoxicillin
- Topical mupirocin three times per day for 10 days
- Follow-up is necessary because recurrences are common

Erysipelas GAS

Clinical presentation
- Erythema and edema
- Sharply defined and elevated border tender to palpation
- Systemic signs such as fever are often present
- Lymphangitis may occur

Management
- Systemic antibiotic therapy is required
- Parenteral antibiotics may be needed, especially in immunocompromised patients

Streptococcal Toxic Shock Syndrome

Background

- GAS TSS is a form of invasive GAS disease associated with the acute onset of shock and organ failure

Risk factors

- Injuries resulting in bruising or muscle strain
- Surgical procedures
- Varicella infection
- NSAID use
- Streptococcal exotoxins that act as superantigens cause release of cytokines leading to capillary leak, leading to hypotension and organ damage

Clinical presentation

- Fever
- Abrupt onset of severe pain, often associated with a preceding soft-tissue infection, e.g., cellulitis or osteomyelitis
- Know: Patient may be normotensive initially, but hypotension develops quickly
- Erythroderma, a generalized erythematous macular rash, may develop

Diagnosis

- Leukocytosis with immature neutrophils
- Elevated serum creatinine values
- Hypoalbuminemia
- Hypocalcemia
- Elevated creatine kinase concentration
- Myoglobinuria, hemoglobinuria
- Positive blood cultures
- Diagnosis of GAS TSS requires isolation of GAS, e.g., blood or CSF

Treatment for GAS TSS

- Aggressive fluid replacement is essential to maintain adequate perfusion to prevent end-organ damage
- Vasopressors also may be required
- Immediate surgical exploration and debridement are necessary, and repeated resections may be required
- Empiric therapy with broad-spectrum IV antibiotics to cover both streptococcal and staphylococcal infections, e.g., clindamycin IV plus penicillin G IV
- Immune globulin intravenous (IGIV) also may be used as adjunctive therapy

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus Infections (PANDAS)

Background

- PANDAS describes a group of neuropsychiatric disorders, in particular, obsessive compulsive disorder (OCD), tic disorders, and Tourette syndrome, that are exacerbated by GAS infection
- Diagnostic criteria for PANDAS include:
  - Tourette syndrome; abrupt onset in childhood
  - Relationship between GAS infection and episodic symptoms confirmed by RADT, throat culture, skin culture, or serologic testing
  - Evaluation for GAS infection should be considered in children who present with the abrupt onset of OCD or tic disorder

Management

- Treatment of the GAS infection and neuropsychiatric therapy
- Behavioral therapy and pharmacological therapies, including:
  - Selective serotonin reuptake inhibitors (SSRIs) for OCD
  - Clonidine for tics

Necrotizing Fasciitis

Background

- A form of invasive bacterial disease that is often polymicrobial. This infection is characterized by extensive local necrosis of subcutaneous soft tissues

- Typically caused by GAS and/or mixed aerobic and anaerobic flora, including *Clostridium, Staphylococcus.* Salt water necrotizing fasciitis contains *Vibrio species*. Freshwater necrotizing fasciitis contains *Aeromonas*

Clinical presentation
- Fever, hypotension, malaise, and myalgias
- Rapidly increasing pain; erythematous skin that progresses to blisters, bullae, and crepitus with subcutaneous gas

Laboratory findings
- Leukocytosis with a predominance of neutrophils
- Elevated creatine kinase, lactate, and creatinine values
- Positive wound cultures

Diagnosis
- Diagnosis is clinical and requires a high degree of suspicion because of the rapid progression of infection

Treatment
- Early and aggressive surgical exploration and debridement
- Triple antibiotic therapy with IV penicillin G, clindamycin, and an aminoglycoside is recommended
- Hemodynamic support if GAS TSS is present
- Repeat surgery is necessary until all necrotic tissue has been removed
- Antibiotic therapy should continue for several days after completion of surgical debridement and may include penicillin G, vancomycin, metronidazole, or imipenem/meropenem

Listeria monocytogenes

Background
- Aerobic Gram-positive bacillus
- Rare disease with case fatality of 16–20%
- Mode of transmission is mostly foodborne
  - Unpasteurized milk and soft cheeses
  - Undercooked poultry
  - Deli-style, prepared meats
  - Asymptomatic vagina carrier in pregnant women

Clinical presentation
- Neonatal early onset infection < 7 days causes preterm birth, sepsis, or pneumonia with 14–56% fatality. Characteristic *granulomatosis infantisepticum* rash with papules
- Neonatal late onset infection > 7 days causes meningitis with 25% fatality

Treatment
- Ampicillin and aminoglycoside

Corynebacterium diphtheriae

Background
- Gram-positive pleomorphic bacillus
- Humans are reservoirs
- Rare due to immunization

Clinical presentation
- Low-grade fever
- Sore throat
- Malaise
- Difficulty swallowing
- Bilateral cervical lymphadenopathy ("bull neck")
- Grayish exudates over mucous membrane
- Bleeding after attempting to remove the membrane
- Diphtheria toxins can cause myocarditis, necrosis, and peripheral neuritis

Treatment
- If diphtheria is suspected, antitoxin (equine hyperimmune antiserum IV) should be started immediately to neutralize the toxins. Administer erythromycin for 14 days also.
- Know: Close contacts should receive single IM dose of penicillin G benzathine or oral erythromycin regardless of their immunization status.

Enterococcus

Background
- Gram-positive cocci
- Normal inhabitant of the GI tract
- *Enterococcus faecalis* and *Enterococcus faecium*
- Most neonatal enterococcal infections are nosocomial and occur after 2nd week of life, usually with bacteremia due to line infection or necrotizing enterocolitis (common symptoms in neonates include, fever, bradycardia, apnea, and abdominal distention)

Associated infections
- Bacteremia in neonates
- Catheter-associated bacteremia
- Endocarditis
- Intra-abdominal abscess
- UTI

Antibiotics
- Resistant to all cephalosporins and vancomycin
- *E. faecalis* is susceptible to ampicillin
- *E. faecium* is resistant to ampicillin. Treat with vancomycin pending susceptibility results unless vancomycin-resistant *enterococcus* (VRE), which requires linezolid
- Sensitivity testing is imperative because of resistance
- Sensitive enterococcal sepsis or endocarditis must be treated with penicillin, ampicillin, or vancomycin + gentamicin

Bacillus anthracis

Background
- Large positive rods (bacilli) that cause anthrax
- Types of anthrax: Cutaneous anthrax, pulmonic, and GI
- Inoculation occurs from handling contaminated substance, e.g., wool, and in cases of bioterrorism, via mail

Clinical presentation
- Painless papules and ulcers
- Painless black eschar with painless swelling and induration

Treatment
- Penicillin G or quinolones, e.g., ciprofloxacin

Bacillus cereus

Background
- Soil-dwelling, Gram-positive rods, beta hemolytic bacterium
- Produces GI symptoms due to enterotoxin production in vivo in the GI tract

Clinical presentation
- Vomiting with incubation period 1–6 h (the emetic form is commonly associated with fried rice left at room temperature)
- Diarrhea with incubation period 8–16 h
- Eye infection after traumatic eye injuries in contact lens wearers

Diagnosis
- Usually clinical
- *B. cereus* spores in stool
- Isolated toxins from suspected food items

Treatment
- Self-limited and requires no antibiotics

Arcanobacterium haemolyticum

Background
- *A. haemolyticum* can be mistaken with strep pharyngitis or scarlet fever
- Gram-positive bacillus
- Grows slowly as small colonies with narrow bands of hemolysis on blood-enriched agar
- Growth enhanced by culture on rabbit or human blood with incubation in 5% CO2

Clinical presentation
- Common in teenagers and young adults
- 0.5–3% of acute pharyngitis
- Except for absence of palatal petechiae and strawberry tongue, the disease indistinguishable from that caused by group A *Streptococcus*
- Fever
- Pharyngeal exudates
- Cervical lymphadenopathy
- Scarlatiniform or maculopapular pruritic rash in 50% of cases; usually spares the palms and soles

Treatment
- Macrolides: Erythromycin or azithromycin

ANAEROBES

Clostridium botulinum

Background
- *C. botulinum* is an anaerobic Gram-positive rod that survives in soil and marine sediment by forming spores
- Human botulism is caused by neurotoxins A, B, E, and, occasionally, F

Infant Botulism

- Ingestion of honey or exposure to contaminated soils increases the risk
- Age between 3 weeks and 6 months
- Symptoms develop 3–30 days from the time of exposure

Clinical presentation
- Constipation usually the initial finding
- Feeding difficulty is a common presenting symptom
- Hypotonia
- Increased drooling
- Weak cry
- Truncal weakness
- Cranial nerve palsies
- Generalized weakness with ventilatory failure

Diagnosis
- Stool toxin detection

Treatment
- Botulism immune globulin (BIG) IV should be started as early as possible if clinically suspected
- Antibiotics (gentamicin) can potentiate toxin paralytic effect

Foodborne Botulism

Background
- Most common source is home canned food
- Symptoms develop 12–36 h after toxin ingestion
- Wound botulism is similar, except the incubation period between 4 and 14 days

Clinical presentation
- Initial symptoms: Dry mouth, nausea, and diarrhea
- Bilateral cranial nerve palsies
- Eye diplopia and blurring vision
- Dysphagia
- Upper extremity weakness
- Respiratory dysfunction
- Lower extremity dysfunction

Treatment of botulism in older patients
- Equine trivalent antitoxin (types A, B, and E)
- Wound debridement for wound botulism is recommended

Clostridium perfringens

Background
- Gram-positive, rod- shaped, anaerobic, spore-forming bacterium
- Spores found in raw meat and poultry
- Incubation period 8–12 h

Clinical presentation
- Sudden onset of diarrhea
- Crampy abdominal pain

Management
- Resolves within 24 h
- Rehydration

Clostridium tetani

Background
- *C. tetani,* an obligate anaerobic Gram-positive bacillus, is the pathogen responsible for tetanus
- Nonencapsulated and forms spores that resist heat, desiccation, and disinfectants
- Contaminated deep puncture wounds, open wounds, soil, and animals (wool) containing spores are the most common sources of this bacteria

Neonatal tetanus
- Contaminated umbilical cord is a common source of infection
- Poor feeding (poor suck and swallowing due to muscle spasm)
- Constant crying
- Decreased movement
- Spasm and rigidity

Generalized tetanus
- Trismus (lockjaw)
- Sardonic smile (*risus sardonicus*)
- Severe muscle spasm
- Opisthotonos (severe hyperextension)
- Laryngeal spasm can lead to airway obstruction and death
- Tetanic seizure is severe; tonic contractions with high fever
- Diagnosis is always clinical

Treatment
- Human tetanus immune globulin immediately
- Penicillin G or metronidazole
- Muscle relaxants

Prevention of tetanus
- Routine immunization with DTaP and Tdap

Prevention in wound injuries guideline
- Tetanus vaccine +/− tetanus immunoglobulin (TIG)
  - Dirty wound, immunization is unknown or less than three tetanus shots: Give TIG + tetanus vaccine
  - Dirty wound, immunized > 5 years and < 10 years: Immunize, no TIG
  - Dirty wound, immunized < 5 years: No treatment
  - Clean wound, immunized < 10 years: No treatment
  - Clean wound, immunized > 10 years: Immunize, no TIG

Clostridium difficile

Background
- Gram-positive anaerobes
- Colonization
  - Around 50% of infants younger than 1 year are colonized
  - Carriage decreases by 1–5% by 2 years of age
- Risk factors:
  - Having infected roommate or having symptomatic patient in the same ward
  - Antibiotics, e.g., beta-lactams drugs, clindamycin, and macrolides
  - Underlying bowel disease or surgeries
- Symptomatic disease is due to toxins A and B produced by the organism

Clinical presentation
- Asymptomatic colonization is common in infants and young children
- Watery diarrhea

- Abdominal cramps
- Abdominal tenderness
- In severe cases:
  - Systemic toxicity
  - Bloody diarrhea
  - Toxic megacolon, perforation, or even death are complications of pseudomembranous colitis

Diagnosis

- Documenting toxin A and B in stool using PCR or nucleic acid amplification tests (NAATs) (for toxin genes)
- Endoscopic findings of pseudomembranous enterocolitis
- Young children < 2 years are commonly colonized with *C. difficile*

Treatment

- Initial episode, non-severe: Oral metronidazole
- Oral vancomycin with or without metronidazole can be used in severe cases
- Recurrence: Oral vancomycin can be used alone or with rifaximin, or fecal microbiota transplantation

Prevention

- Hand washing with water and soap
- Know: Alcohol-based product are not effective against the organism
- Diluted bleach solution is the best for decontamination of surfaces
- Limit antibiotic use
- Infected children should be excluded from childcare facility for the duration of diarrhea

GRAM-NEGATIVE BACTERIA

Gram-Negative Anaerobes

- Bacteroides
- Fusobacterium anaerobes
- **Causes a variety of clinical manifestations depending on the location**
  - Head and neck
    - Retropharyngeal abscess
    - Peritonsillar abscess
    - Dental abscess
    - Ludwig angina
  - CNS
    - Brain abscess
    - Subdural and epidural empyema
  - Lung
    - Aspiration pneumonia
    - Lung abscess
    - Pleural empyema
  - Abdomen
    - Peritonitis
    - Appendicitis
    - Intra-abdominal abscess
  - Skin and soft tissue
    - Infected bite wound
    - Necrotizing fasciitis
    - Cellulitis
  - Antibiotics with anaerobic activity
    - Clindamycin
    - Penicillin
    - Ampicillin–sulbactam
    - Amoxicillin–clavulanic acid
    - Metronidazole

Campylobacter Species

Background and epidemiology

- *Campylobacter jejuni* (Gram-negative motile bacilli)
- One of the most common agents associated with bacterial gastroenteritis
- Common sources: Uncooked poultry (chicken and turkey), unpasteurized milk, dogs and cats
- Incubation period: 2–5 days

Clinical presentation

- Bloody diarrhea
- Abdominal pain (may mimic inflammatory bowel disease in severe cases)
- Tenesmus
- Fever

Diagnosis
- Stool culture in a selective media at temperature 42 °C incubated in gas mixture O2 and CO2

Treatment
- Azithromycin and erythromycin shorten illness duration and prevent relapse

Chlamydia pneumoniae

Background and epidemiology
- Transmitted from one person to another via respiratory secretions
- 50% of adults have antibody evidence of exposure

Clinical presentation
- Patient may be asymptomatic or mildly to moderately ill
- Illness is usually prolonged with cough persisting for 2–6 weeks
- Pneumonia and pulmonary rales
- Acute bronchitis and bronchospasm
- Less commonly: Nonexudative pharyngitis, laryngitis, otitis media, and sinusitis

Diagnosis
- Fourfold increase in IgG titer from acute to convalescent
- IgM titer of ≥ 1:16
- Cross-reactivity and persistent antibody makes diagnosis problematic

Treatment
- Macrolides, doxycycline, or tetracycline

Chlamydophila psittaci

Background
- *C. psittaci* is obligate intracellular bacterial pathogen
- Birds are major reservoir of *C. psittaci*, e.g., parakeets and parrots
- Animals such as goats and cows may become infected

Clinical presentation (psittacosis)
- Fever
- Nonproductive cough
- Headache
- Malaise
- Extensive interstitial pneumonia can occur
- Pericarditis, hepatitis, and encephalitis (rare)

Diagnosis
- Serology, nucleic acid amplification tests, PCR

Treatment
- Doxycycline preferred therapy, including children < 8 years
- Macrolides for pregnant women

Conjunctivitis Due to *Chlamydia trachomatis*

Background and epidemiology
- The most frequently identified infectious cause of neonatal conjunctivitis
- Transmitted perinatally from infected mothers

Clinical presentation
- The symptoms typically develop 5–14 days after birth
- Conjunctival edema
- Hyperemia
- Watery-to-mucopurulent discharge
- A pseudomembrane may form and bloody discharge may be present if infection is prolonged

Management
- Oral erythromycin × 14 days or azithromycin × 3 days
- Know: Topical prophylaxis with erythromycin or silver nitrate given to all infants to prevent neonatal gonococcal conjunctivitis is *ineffective* against chlamydial conjunctivitis. Suctioning may increase comfort and improve feeding.

Pneumonia Due to *C. trachomatis*

Background

- Small, Gram-negative, obligate intracellular organisms
- Transmitted to the infant from the birth canal
- Generally presents as a subacute infection 2–19 weeks after birth

Clinical presentation

- Rhinorrhea, congestion, or conjunctivitis
- Tachypnea
- Staccato cough
- Crackles (rales)
- Wheezing (rare)
- Preterm infants may have episodes of apnea

Diagnosis

- Chest radiography reveals infiltrates and hyperinflation
- Laboratory testing may reveal:
  - Peripheral eosinophilia
  - Elevated serum immunoglobulins
- A positive NP direct fluorescent antibody (DFA) test or culture is considered diagnostic

Treatment

- Antibiotic treatment should be started presumptively on clinical grounds
- Same antibiotic regimens as for neonatal conjunctivitis
- If untreated, symptoms can last for months and include persistent hypoxemia
- Remember: Diagnosis of chlamydial pneumonia in an infant necessitates treatment of the infant's mother and her sexual partner

Chlamydia Genitourinary Tract Infection

Background

- Sexual transmission

Clinical presentation

- Females: Vaginitis in prepubertal girls, urethritis, cervicitis, endometritis, salpingitis, proctitis, and perihepatitis (Fitz–Hugh–Curtis syndrome). Can progress to pelvic inflammatory disease
- Males: Urethritis, epididymitis, and proctitis
- Reiter syndrome (arthritis, urethritis, bilateral conjunctivitis)
- *Lymphogranuloma venereum* (LGV): Ulcerative lesion on genitalia followed by tender, unilateral lymphadenopathy

Diagnosis

- NAATs of vaginal, endocervical, and male intraurethral specimens; urine specimens

Treatment

- Doxycycline 100 mg per os BID for 7 days
- Azithromycin single dose 1 g

Trachoma

Background

- Chronic keratoconjunctivitis caused by the obligate intracellular bacterium *C. trachomatis*
- Disease transmission occurs primarily between children and the women who care for them
- Trachoma is the most common infectious cause of blindness worldwide

Clinical presentation

- Chronic follicular keratoconjunctivitis with corneal neovascularization resulting from untreated or chronic infection
- Blindness occurs in up to 15% of those infected
- Trachoma rarely occurs in the USA

Diagnosis

- Clinical diagnosis and NAATs can confirm the causative agent
- The cicatricial phase has unique clinical features (eyelid scarring, eyelid buckling, lashes

rubbing on eye), which lead to definitive diagnosis in most cases

Treatment
- Azithromycin single dose 20 mg/kg

Neisseria gonorrhoeae (Gonococcal Infections)

Background
- *N. gonorrhoeae* is a Gram-negative diplococcus
- Gonococcal infection is the second most common bacterial disease in the USA classified as nationally reportable and notifiable
- Highest prevalence in youth, especially females between 15 and 19 years of age
- The incubation period is 2–7 days
- A child abuse evaluation must be performed in any prepubertal case

Neonatal conjunctivitis
- Conjunctivitis due to mucosal transmission during vaginal delivery
- Topical antibiotics (erythromycin, silver nitrate, or tetracycline) to the eyes of a newborn within 1 h of birth can prevent the infection
- Treatment is ceftriaxone 125 mg IM × 1

Gonococcal pharyngitis
- Genital–oral activity is the major risk
- Infection is asymptomatic in most cases
- Patients who have gonococcal pharyngitis have a significant public health impact
- Gonococcal pharyngitis patients at risk for developing disseminated gonococcal infection (DGI)
- Pharyngeal infection clears spontaneously within 12 weeks
- Treatment is ceftriaxone 250 mg IM × 1

Gonococcal urethritis
- Dysuria and a mucopurulent penile discharge
- May be coinfected with other sexually transmitted organisms, most commonly, *C. trachomatis*
- Positive leukocyte esterase usually seen in urine specimen
- Diagnosis of gonococcal urethritis with NAATs
- Presence of intracellular diplococci in urethral discharge
- Treatment is ceftriaxone 250 mg IM × 1 plus azithromycin 1 g × 1

Epididymitis (gonococcus)
- Dysuria and a mucopurulent discharge
- Scrotal edema with scrotal, inguinal, or flank pain
- Urinalysis may demonstrate WBCs
- In most cases this infection is transmitted sexually and may be an extension of urethritis

Gonococcal proctitis
- Most cases of proctitis due to *N. gonorrhoeae* occur in homosexual males
- Clinical presentation
  - Anal discharge
  - Rectal bleeding
  - Anorectal pain
  - Tenesmus
  - Constipation

Disseminated gonococcal infection (DGI)
- DGI infection occurs in 0.5–3% of people infected with *N. gonorrhoeae*
- DGI usually causes an asymptomatic genital infection
- Migratory arthritis (wrist, ankle, and knee) are the most common locations
- Dermatitis
- Tenosynovitis
- Fever and chills may occur
- Elevated WBC count
- DGI occurs more commonly in females

Screening methods for infection *N. gonorrhoeae* and *Chlamydia*

- Culture is the gold standard for diagnosing *C. trachomatis*
- Standard collection sites include the endocervix, male and female urethra, nasopharynx, conjunctiva, vagina, and rectum
- NAATs amplify nucleic acid sequences specific for the organism of interest
- The ease of urine collection, together with the high sensitivity of NAATs, has made these tests the preferred method for screening
- The presence of Gram-negative intracellular diplococci on microscopy suggests the diagnosis of gonococcal infection

N. meningitidis (Meningococcal Infections)

Background

- Aerobic Gram-negative diplococcus *N. meningitidis*
- Natural commensal organism living in the nasopharynx of humans
- Children younger than 2 years of age have a nearly fivefold greater risk of contracting meningococcal disease than the general adult population
- Risk of transmission: Crowded living conditions, e.g., college dormitories, military barracks

Clues to investigate for invasive meningococcal infection

- Rash
  - Any rash appearing in the context of a sudden febrile illness should raise concern
  - Meningococcal rash is typically present within 24 h of any symptomatology
  - Petechiae may be intraoral or conjunctival or be hidden in skinfolds
  - Early rash may not be petechial
- True rigors
  - Shaking chills that cannot be stopped voluntarily
  - Prolonged (10–20 min)
- Neck pain
  - Severe pain in the neck, back, or extremities
  - May manifest in younger children as refusal to walk
  - Meningismus: In patients older than 3 years, the classic signs of Kernig and Brudzinski may be elicited
- Vomiting
  - May be associated with headache or abdominal pain without diarrhea
- Cushing triad:
  - Bradycardia
  - Hypertension
  - Respiratory depression
- Purpura fulminans (meningococcemia)
  - Aggressive spread of purpura to large areas with ischemic necrosis
  - Sudden drops in blood pressure
  - Acute adrenal hemorrhage (Waterhouse–Friderichsen syndrome)

Diagnosis

- Culture of the organism from a normally sterile site is the gold standard for bacteriological diagnosis
- CSF study:
  - CSF WBC counts are elevated in most patients who have meningitis
  - CSF WBC counts are low or even normal if the disease is severe and rapidly progressive
  - Markedly low glucose and elevated protein values are associated with the diagnosis of meningitis
- All patients with meningococcal disease or meningitis must be tested for CH50 or CH100 assay (20% of children with meningococcal disease will end having a complement deficiency)

Management

- Know: Antibiotics and fluids should not be delayed
- Penicillin is effective treatment for both severe meningococcal septicemia (SMS) and meningococcal meningitis if the diagnosis is certain
- Broad-spectrum antibiotics effective against *N. meningitidis* and other potential pathogens are indicated (e.g., ceftriaxone, cefotaxime, and vancomycin)
- Emergency care evaluation and preferably transported via emergency medical services to allow for prompt delivery of IV fluids and airway management if the condition is suspected
- Large isotonic fluid boluses (20 mL/kg) over the first 5 min
- Inotropic/vasoactive agent such as dopamine or dobutamine
- Hydrocortisone may be beneficial in children respond poorly to vasopressors

Prevention and indications for meningococcal vaccines

- MenACWY vaccine is routinely recommended at 11–12 years of age; 2 vaccines licensed for children and adults, 1 dose
  - Can give as young as 2 months as a 4-dose series for high risk (complement deficiency, asplenia, HIV, travel to endemic area)
- MenB vaccine is optional and preferred for 16–18 years of age, 2-dose series
  - Can give as young as 10 years for high risk (complement deficiency, asplenia, outbreak, lab workers); 2- or 3-dose series for high risk
- Antibiotic prophylaxis, e.g., rifampin, ciprofloxacin, azithromycin, or ceftriaxone should be used for contacts:
  - Childcare contact
  - Direct exposure to oral secretions of individuals with meningococcal disease (such as personnel providing mouth-to-mouth resuscitation)

Haemophilus influenzae

Background

- Pleomorphic Gram-negative coccobacillus spread via respiratory tract secretions
- Formerly the most common cause of meningitis and serious bacteremia in children
- Introduction of the *H. influenzae* vaccine quickly reduced the incidence of encapsulated *H. influenzae* type b
- Nontypeable strains are still responsible for a large number of mucosal infections, including conjunctivitis, otitis media, sinusitis, and bronchitis

Bacterial meningitis

- Peak age is less than 1 year
- Mortality rate around 5%
- Common complications include: Subdural empyema, brain infarct, cerebritis, ventriculitis, brain abscess, and hydrocephalus
- Long-term sequelae occur in 15–30% of survivors with sensorineural hearing loss; others include language disorders, intellectual disability, and developmental delay
- Dexamethasone before or with antibiotics such as ceftriaxone or cefotaxime to prevent hearing loss and neurologic sequelae

Epiglottitis

- Hib was the predominant organism (> 90%) in pediatric epiglottitis before vaccine introduction. Since that time, other bacteria, including *S. pneumoniae*, GAS, *S. aureus*, and *Moraxella catarrhalis,* can cause epiglottitis
- Occurs primarily in children aged 2–7 years.
- The clinical triad of drooling, dysphagia, and distress is the classic presentation
- Fever with associated respiratory distress or air hunger occurs in most patients
- Treatment in patients with epiglottitis is directed toward relieving the airway obstruction and eradicating the infectious agent

- Optimally, initial treatment is provided by a pediatric anesthesiologist and either a pediatric surgeon or a pediatric otolaryngologist

Buccal infections

- Buccal cellulitis previously was always caused by *H. influenzae* infection before the vaccine
- Always associated with bacteremia if present
- Present with palpable cellulitis on both checks, purplish in color, and child looks very toxic

Periorbital cellulitis

- Previously *H. influenzae* was a common cause, now *S. pneumoniae* bacteria is the most common etiology associated with sinusitis
- Minor trauma or insect bite of the eyelid usually associated with preseptal cellulitis due to *S. aureus* or a Group A *Streptococcus*

Pyogenic arthritis

- *H. influenzae* was the most common cause of septic arthritis in children less than 2 years of age before Hib vaccine

Occult bacteremia

- Occult bacteremia with *H. influenzae* will result in in 30–50% developing meningitis or other deep or focal infection from occult bacteremia
- All occult bacteremia from *H. influenzae* has to be treated immediately

Pneumonia

- Pneumonia from *H. influenzae* used to cause about one-third of bacterial pneumonia before Hib vaccine and was associated with pleural effusion and positive blood culture in most cases

Treatment (in patient with life-threatening illness)

- Remember: The organism produces beta lactamase, which makes amoxicillin ineffective
- Cefotaxime or ceftriaxone is the antimicrobial of choice
- Meropenem or chloramphenicol is another option
- Amoxicillin is the drug of choice for noninvasive diseases such as otitis media or sinusitis; if amoxicillin fails, uses antibiotics against beta-lactamase-producing strains, e.g., nontypeable *H. influenzae* including amoxicillin/clavulanate, TMP-SMX, azithromycin, cefuroxime axetil, cefixime, and cefpodoxime.

Rifampin antibiotic prophylaxis for contact with invasive Hib infection

- All members of household who did not receive immunization
- Less than 4 years with incomplete immunization
- Younger than 12 months who did not complete primary Hib immunization
- Immunocompromised child
- Nursery school and childcare center if two or more cases within 60 days (outbreak)

Mycoplasma pneumonia

Background

- *M. pneumoniae* is the leading cause of pneumonia in school age children and young adults
- Infection is prevalent in persons living in group setting
- Incubation period is 2–3 weeks

Clinical presentation

- Pulmonary manifestations
  - Nonproductive cough
  - Chills
  - Scattered rales
  - Skin rash
  - Bilateral infiltrate on chest radiograph
- Extrapulmonary manifestations
  - Pharyngitis
  - Rash
  - Stevens–Johnson syndrome

- Hemolytic anemia
- Arthritis
- CNS disease (encephalitis; cranial nerve palsy, especially CN III)

Testing for mycoplasma

- Mycoplasma DNA PCR nasal washing
- IgG and IgM serology or cold agglutinin

Treatment

- Mycoplasma lacks the cell wall and beta lactams are not effective
- Azithromycin is the drug of choice

Pasteurella multocida

Background

- Small Gram-negative coccobacilli; normal oral flora in animals, e.g., dogs and cats
- Dog or cat bite is a common risk

Clinical presentation

- Erythema, tenderness, and edema usually develop rapidly within 24 h
- Regional lymphadenopathy and fever may occur
- Infection that occurs days after the bite is usually caused by *S. aureus*

Treatment

- Clean wound with soap and water
- Treatment should cover potential pathogens, e.g., *P. multocida, S. aureus*, and anaerobes
- Administration of antibiotic within 8–12 h of injury may decrease the risk of infection
- Penicillin is the drug of choice for *P. multocida* alone
- Amoxicillin–clavulanate is the drug of choice for suspected polymicrobial wounds, including cat bites
- Clindamycin + TMP-SMX is appropriate for children allergic to penicillin

Bordetella pertussis

Background

- Small Gram-negative coccobacillus that infects only humans
- Spreads by aerosol droplets expelled while coughing or sneezing in proximity to others
- Incubation period of 7–10 days

Clinical presentation

- Catarrhal phase
  - Lasts from 1 to 2 weeks
  - Mild fever
  - Cough
  - The cough worsens as the patient progresses to the paroxysmal phase
- Paroxysmal phase
  - Lasts from 2 to 6 weeks
  - Rapid fire or staccato cough
  - 5 to 10 uninterrupted coughs occur in succession, followed by a "whoop" as the patient rapidly draws in a breath
  - May occur several times per hour
  - Can be associated with cyanosis, salivation, lacrimation, and post tussive emesis
  - Despite the severe spells, patients often appear relatively well between episodes
  - Whoop is usually absent in infants less than 6 months of age
  - Gasping, gagging, and apnea can occur
- Convalescent phase
  - Decreasing frequency and severity of the coughing episodes
  - Lasts from weeks to months

Complications of pertussis

- Pertussis is most severe in infants < 6 months
- Apnea
- Pneumonia
- Seizures
- Encephalopathy
- Death

Thoracic pressure-related complications
- Pneumothorax or pneumomediastinum
- Subcutaneous emphysema
- Superficial petechial hemorrhage
- Rib fracture
- Rectal prolapse
- Intracranial hemorrhage

Diagnosis
- PCR of NP specimen collected with Dacron swab is diagnostic test of choice
- PCR remains positive late in the course of the illness
- Leukocytosis as high as 60,000 can be seen due to absolute lymphocytosis

Management
- Infants afflicted with pertussis often require hospitalization for fluid, nutritional, and respiratory support
- If left untreated, most individuals will clear *B. pertussis* spontaneously from the nasopharynx within 2 to 4 weeks of infection
- Antibiotics can shorten the course and attenuate the severity of pertussis if started early and can shorten the period of contagiousness
- Once the paroxysmal phase begins, antibiotics are not effective in altering the course of the disease
- Excluded from school for 21 days if untreated, or for 5 days while taking antibiotic
- Azithromycin is the drug of choice:
  - Infant less than 6 months: 10 mg/kg per day as a single dose for 5 days
  - Older infants and children: 10 mg/kg as a single dose on day 1 then 5 mg/kg per day as a single dose on days 2–5

Prophylaxis to close contacts is the same as the treatment
- Infants less than 1 year
- Pregnant women
- Immunocompromised
- Underlying lung disease

Immunization
- Because immunity to pertussis from the DTaP series wanes over time, a booster dose is recommended at age 11–12 years

Brucellosis

Background
- Brucellosis is a zoonotic infection caused by the bacterial genus *Brucella*
- Brucellosis caused by Gram-negative bacillus
- The bacteria are transmitted from animals to humans by ingestion of unpasteurized milk or cheese, direct contact with an infected animal, or inhalation of aerosols
  - *B. melitensis* (from sheep; highest pathogenicity)
  - *B. suis* (from pigs; high pathogenicity)
  - *B. abortus* (from cattle; moderate pathogenicity)
  - *B. canis* (from dogs; moderate pathogenicity)

Clues to *Brucella* infection
- Fever of unknown origin
- Culture negative endocarditis
- Individuals at greatest risk for brucellosis are those exposed to goats, sheep, cows, camels, pigs, reindeer, rabbits, or hares, both in areas of endemic disease and in areas where the disease is not endemic
- Bone/joint inflammation
- Orchitis
- Hepatic abscess
- CNS symptoms

Diagnosis
- Elevated liver enzymes is a common finding
- Blood culture (alert laboratory if suspecting *Brucella*, as lab staff easily infected)
- Serology is most commonly used
- PCR in development

Treatment

- Children > 8: doxycycline + rifampin for 6 weeks
- Children < 8: TMP/SMX + rifampin for 6 weeks
- Add gentamicin for serious infection or complications

Bartonella henselae

Cat-Scratch Disease

Background

- *B. henselae* is Gram-negative rod or bacilli with a polar flagellum
- Kittens or cats less than 1 year old are most common source, also dogs
- Transmission can occur by petting alone with subsequent self-inoculation via a mucous membrane, skin break, or conjunctiva
- Clue for the diagnosis: Contact with cats and lymphadenopathy

Clinical presentation

- Regional lymphadenopathy (cervical and axillary are common locations) (Fig. 9.17)
  - Usually large and may be tender, warm, and erythematous
  - Suppuration can occur in 30% of cases
  - Node may remain enlarged for several months
  - Papule at the site of scratch may precede the development of lymphadenopathy
- Parinaud oculoglandular syndrome:
  - Painless nonpurulent conjunctivitis
  - Ipsilateral preauricular lymphadenopathy
- Other clinical presentations
  - Fever of unknown origin
  - Hepatic splenic microabscesses
  - Painful osteolytic lesions
- Patients may recall being scratched, licked, or bitten by a cat in the previous 2–8 weeks
- Fever, anorexia, headache, sore throat, or arthralgia may occur

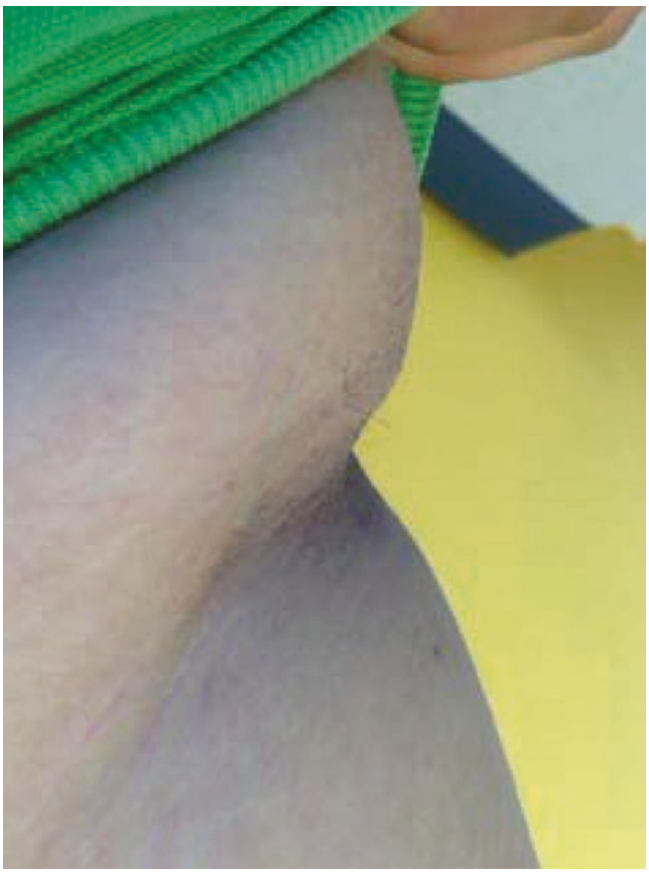


Fig. 9.17 14-year-old female with large tender axillary lymphadenopathy, she has kittens at home

- Lymphadenopathy remains regional and typically resolves within 2–4 months but may last up to 6–12 months

Diagnosis

- Indirect fluorescence assay (IFA) testing and enzyme-linked immunoassay (ELISA) are used to detect serum antibody to *B. henselae*
- An antibody titer that exceeds 1:64 suggests recent *Bartonella* infection
- Lymph node biopsy generally is not indicated in typical cases

Treatment

- Cat-scratch disease is self-limited
- Use of azithromycin can decrease lymph node size faster than natural course

- Doxycycline or rifampin may also treat
- Immunocompromised should receive antibiotics

Surgical treatment

- Remember: Incision and drainage are not recommended (risk of sinus tract and persistent drainage)
- Aspiration will be diagnostic and therapeutic; repeated aspirations may be performed if pus reaccumulates and pain recurs

Citrobacter

- Cause brain abscess in neonates
- Order computed tomography (CT) or MRI if CSF grow
- *Citrobacter* otherwise is very rare disease

Klebsiella

- A rare cause of pneumonia and meningitis
- Can cause UTIs but is less common than *E. coli*
- Most *Klebsiella* are resistant to ampicillin

Pseudomonas Species

Background

- Gram-negative organism
- Found in the soil and freshwater
- Gains entry through hair follicles or via skin breaks

Risk factors

- Cystic fibrosis (see Chap. 20 "Pulmonology")
- Associated with progressive deterioration of pulmonary function
- Associated with hot tub folliculitis
- Ocular infection from contaminated lenses
- Puncture wound osteomyelitis
- In immunocompromised patients, e.g., ecthyma gangrenosum
- Hospitalized and debilitated patients
- Burn wounds
- Ventilator-associated pneumonia

Clinical presentation according to the site of infection

- *Pseudomonas* keywords
  - Nail-puncture wound through tennis shoes
  - IV drug abuse, with endocarditis or osteomyelitis
  - Diabetes with otitis media
  - Leukemia with ecthyma gangrenosum
- Hot tub folliculitis
  - Clinical presentation:
    - The rash onset is usually 8 h to 5 days after exposure to contaminated water
    - Erythematous pruritic macules that progress to papules and pustules
    - Rash usually spares face, neck, soles, and palms
    - Usually confused with insect bites (history is important)
    - Rash clears spontaneously within 2–10 days
  - Self-limited, require no antibiotics
  - Acetic acid 5% compresses for 20 min twice a day for 4 days for symptomatic relief

Antimicrobial therapy

- Piperacillin/tazobactam (Zosyn)
- Ceftazidime (third generation)
- Cefepime (fourth generation)
- Carbapenems (meropenem, imipenem)
- Aminoglycosides (gentamicin)
- Aztreonam
- Certain fluoroquinolones (ciprofloxacin, levofloxacin)

Nontyphoidal Salmonellosis

Background

- Gram-negative bacilli that are usually motile bacteria
- A common cause of diarrhea
- Incubation period 6–72 h

Mode of transmission
- Contaminated poultry, beef, eggs, fruits, vegetables, bakery, and dairy products
- Turtles, iguana, and exotic reptiles

Clinical presentation
- Can be asymptomatic
- Most common presentation is gastroenteritis
- Abrupt onset of fever, nausea, and vomiting
- Abdominal cramps
- Moderate-to-severe watery diarrhea most common manifestation

Diagnosis
- Stool may show leukocytes, mucus, and blood
- CBC; leukocytosis and shift to the left
- After symptoms the patient can be a carrier for 4–5 weeks

Indication of antibiotic therapy
- In infants less than 3 months
- Infant < 12 months with temperature > 39 °C
- Hemoglobinopathies, e.g., sickle cell anemia, HIV, and neoplastic diseases
- Immunocompromised patients at any age

Typhoid Fever

Background
- *Salmonella enterica* serovar Typhi (*S.* Typhi)
- Mode of transmission
  - Poor sanitation and overcrowding
  - Spread by fecal–oral contamination of food or water by individuals who are carriers for *S.* Typhi in either stool or urine
  - Typhoid is endemic in many developing areas

Clinical presentation
- Fever "can exceed 104 °F (40 °C)"
- Malaise
- Chills
- Headache, anorexia, myalgias, and dry cough may be seen
- Abdominal pain is common
- Diarrhea is more likely in children
- Abdominal tenderness, hepatosplenomegaly, and a coated tongue
- Rose spots (pink, blanchable maculopapular lesions that are 2–4 mm in diameter) are seen on the torso and abdomen
- Know: Neonatal typhoid generally presents within 3 days of birth with fever, emesis, diarrhea, abdominal distention, pronounced hepatomegaly, jaundice, and (sometimes) seizures
- Know: Absence of abdominal or intestinal changes is not typical of typhoid

Diagnosis
- Blood cultures are the mainstay of diagnosis, positive in 50% of those with the disease
- Stool culture may increase yield

Treatment
- Treatment includes:
  - Hydration and correction of fluid–electrolyte imbalance
  - Antipyretics and antibiotics
- The choice of antibiotic, route, and duration depends on the host, site of infection, and sensitivities of the organism
- IV cefotaxime or ceftriaxone for 14 days is appropriate
- Multidrug resistant (MDR) strains, including resistance to ampicillin, TMP-SMX, cephalosporins, carbapenems, and fluoroquinolones have emerged mostly from Asia. Only azithromycin works for these MDR strains
- For severe typhoid with obtundation, stupor, coma, or shock:
  - Two-day course of IV dexamethasone may be life-saving

Shigella

Background
- *Shigella* is a Gram-negative bacillus
- *S. dysenteriae and S. flexneri* usually cause bloody diarrhea

- *S. sonnei and S. boydii* usually cause watery diarrhea
- Ingestion of as few as 10 organisms can cause diarrhea
- Incubation period is 2–4 days
- Outbreak can occur in childcare centers

Mode of transmission
- Person to person
- Fecal–oral
- Anal–oral
- House flies
- Contaminated fomites

Clinical presentation
- Ranges from mild diarrhea to life-threatening dysentery
- Fever
- Abdominal camps
- High-volume watery stools
- Small-volume bloody stool may follow 24–48 h later
- Blood-mucoid stool is a common presentation
- Rectal prolapse occurs in 5–8%

Complications
- Hemolytic-uremic syndrome
- Seizures
- Colonic perforation
- Toxic encephalopathy

Diagnosis
- Stool culture is diagnostic
- Stool study with large number of neutrophils is suggestive but not specific
- Peripheral WBCs are usually elevated; bandemia is very common

Treatment
- Most infections with *S. sonnei* are self-limited and do not warrant antibiotics
- Antimicrobial therapy is recommended for immunocompromised patients with shigellosis
- Antimicrobial therapy for 5 days will shorten the duration and eradicate the organism from stool
- Antimicrobial resistance testing guides therapy
- Empiric ceftriaxone, ciprofloxacin or azithromycin are usually effective
- If there is an alternative to ciprofloxacin, it is not recommended for those less than 18 years

Childcare center
- Once *Shigella* is identified in a childcare center or household, all symptomatic individuals in these environments should be cultured for *Shigella*
- Anyone found to have *Shigella* cannot return to the care center until the diarrhea has stopped and stool culture test is negative

Escherichia coli

Background
- *E. coli* is a Gram-negative, lactose fermenting, motile rod, belonging to the *Enterobacteriaceae*
- *E. coli* is one of the most frequent causes of many common bacterial infections, including cholecystitis, bacteremia, cholangitis, UTI, and traveler's diarrhea; and other clinical infections such as neonatal meningitis and pneumonia

Acute bacterial meningitis
- The vast majority of neonatal meningitis cases are caused by *E. coli* and group B streptococcal infections
- Pregnant women are at a higher risk of colonization with the K1 capsular antigen strain of *E. coli*, which is commonly observed in neonatal sepsis
- Low-birth weight and a positive CSF culture result portend a poor outcome
- Most survivors have subsequent neurologic or developmental abnormalities

Pneumonia

- *E. coli* respiratory tract infections are uncommon and are almost always associated with *E. coli* UTI

Intra-abdominal infections

- *E. coli* intra-abdominal infections often result from a perforated viscus (e.g., appendix, diverticulum) or may be associated with intra-abdominal abscess, cholecystitis, and ascending cholangitis
- They can be observed in the postoperative period after anastomotic disruption. Abscesses are often polymicrobial
- *E. coli* is one of the more common Gram-negative bacilli observed together with anaerobes

Enteric infections

- Enterotoxigenic *E. coli* (ETEC) is a cause of traveler's diarrhea; azithromycin is the drug of choice; infants < 3 months can receive a third generation cephalosporin
- Enteropathogenic *E. coli* (EPEC) is a cause of childhood diarrhea; can be treated with TMP-SMX
- *Enteroinvasive E. coli* (EIEC) causes a *Shigella*-like dysentery
- Enteroaggregative *E. coli* (EAEC) is primarily associated with persistent diarrhea in children in developing countries, and enteroadherent *E. coli* (EAEC) is a cause of childhood diarrhea and traveler's diarrhea in Mexico and North Africa
- Enterohemorrhagic *E. coli* (EHEC) causes hemorrhagic colitis or hemolytic-uremic syndrome (HUS)
- Strains of STEC serotype O157:H7 have caused numerous outbreaks and sporadic cases of bloody diarrhea and HUS

Urinary tract infections

- The urinary tract is the most common site of *E. coli* infection, and more than 90% of all uncomplicated UTIs are caused by *E. coli* infection
- The recurrence rate after a first *E. coli* infection is 44% over 12 months
- *E. coli* UTIs are caused by uropathogenic strains of *E. coli*
- *E. coli* causes a wide range of UTIs, including uncomplicated urethritis, cystitis, pyelonephritis, and urosepsis

Other miscellaneous *E. coli* infections

- Septic arthritis
- Endocarditis
- Soft tissue infections especially in patients with diabetes

E. coli (O157:H7)

Background

- Gram-negative rods
- Occurs in all ages
- Transmitted via ingestion of contaminated food (e.g., ground beef) or infected feces
- The disease linked to eating undercooked beef and unpasteurized milk or apple juice
- Produces Shiga toxins; the most virulent strain
- The incidence of *E. coli* O157:H7 > *Shigella*

Clinical presentation

- Usually begins as nonbloody diarrhea then becomes bloody
- Severe abdominal pain is common
- Fever in one-third of the cases
- May progress to hemorrhagic colitis in severe cases
- HUS may occur

Management

- No antibiotic is proven effective, and antibiotic use may increase risk of HUS
- Do not treat with antibiotics in most cases
- Do not use antimotility agents

Yersinia enterocolitica

Background
- Small Gram-negative coccobacillus
- It produces entero and endotoxins
- Pigs are commonly infected
- Ingestion of raw or improperly prepared food, such as pork (pork intestine or chitterlings), contaminated unpasteurized milk, and water

Clinical presentation
- Blood and mucus in stool
- Fever
- Right lower quadrant pain
- Leukocytosis
- Mimics appendicitis

Treatment
- No treatment for isolated intestinal infection
- If < 6 months old, extraintestinal manifestation, sepsis, or immunocompromised, then antibiotic is indicated
- Cefotaxime or ceftriaxone

Francisella tularensis

Background
- Gram-negative pleomorphic bacillus that causes tularemia or "rabbit fever"
- Found in many animals, especially rabbits
- Transmitted by ticks and blood-sucking flies
- Organism can be ingested or inhaled
- Prevalent in the Southwest desert; Arkansas, Missouri, and Oklahoma

Clinical presentation
- Fever, chills, myalgias, and arthralgias
- Irregular ulcers at the site of inoculation
- Lymphadenopathy that suppurates and forms an ulcer
- Oculoglandular tularemia (unilateral conjunctivitis, corneal ulceration)
- Pneumonic tularemia (dry cough, dyspnea, and pleuritic-type chest pain)
- Typhoidal tularemia (fever, chills, myalgias, malaise, and weight loss)

Diagnosis
- Serology, e.g., ELISA or PCR

Treatment
- Gentamicin or streptomycin for 10 days

Prevention
- Avoid tick-infested areas, check clothing for ticks, and use tick repellents
- Avoid exposure to dead or wild mammals and wear gloves if such exposure is necessary; hands should be thoroughly washed afterward

Rocky Mountain Spotted Fever (RMSF)

Background and epidemiology
- Tickborne rickettsial disease
- Transmitted by the American dog tick (*Dermacentor variabilis*) east of the Rocky Mountains and Pacific coast
- Spread by Rocky Mountain wood tick (*D. andersoni*) in Rocky Mountain region
- Spread by Brown dog tick (*Rhipicephalus sanguineus*) worldwide
- Caused *by Rickettsia rickettsii*
- Peak transmission in summer

Clinical features
- Early illness (days 1–4)
  - Fever
  - Malaise
  - Headache
  - Abdominal pain
  - Myalgias
  - Rash appears 2–4 days after fever; 10–15% do not have rash
  - Maculopapular rash starts at the wrists and ankles, spreads centrally to palms and soles
  - Rash becomes petechial and purpuric

- Late illness
  - Altered mental status
  - Pulmonary edema, acute respiratory distress syndrome (ARDS)
  - Multiorgan failure (CNS, kidney)

Laboratory

- Serology testing: Indirect fluorescent antibody (IFA) for IgG at presentation and 2–4 weeks later. Frequently negative during 1st week of illness
- PCR blood may be helpful if positive but does not rule out infection, as the organism is intracellular

Treatment

- Start treatment before testing results return; can be fatal within days
- Doxycycline is the treatment of choice even in children < 8 years
- Antibiotic is given for at least 5–7 days and at least 3 days after fever resolves
- Best outcome when treatment started within 5 days of illness

Complications

- Vasculitis
- Disseminated intravascular coagulation (DIC)
- Death

Ehrlichiosis

Background and epidemiology

- Gram-negative cocci
- Transmitted by:
  - Lone star tick (*Amblyomma americanum*) in South Central and Eastern United States. Also transmits for tularemia and southern tick associated rash illness (STARI)
  - Blacklegged tick (*Ixodes scapularis*) in Eastern United States. Also transmits for anaplasmosis, Lyme disease, and babesiosis
- Can transmit via blood transfusion and organ transplantation
- Peak transmission in summer
- Incubation period is 5–14 days

Clinical presentation

- Similar to RMSF with early and late illness (Table 9.2)
- Maculopapular rash sparing the face that may spread to palms/soles; appears in 60% of children 5 days after fever begins

Laboratory findings

- Leukopenia
- Neutropenia
- Thrombocytopenia
- Hyponatremia
- Elevated liver enzymes

Treatment

- Drug of choice is doxycycline, including children < 8 years

Borrelia burgdorferi

Lyme Disease

Background

- Tick-borne infection caused by spirochete *B. burgdorferi*
- Transmitted by *Ixodes* species ticks in the nymphal stage
- Commonly seen in spring and summer

Table 9.2 Difference between Rocky Mountain spotted fever and ehrlichiosis

Difference	Rocky Mountain spotted fever	Ehrlichiosis
Mode of transmission	Tick	Tick
Rash	Very common, including on palms and soles	60% of children
Neutropenia	Less common	More common
Thrombocytopenia	Yes	Yes
Anemia	Present in ~15%	Occurs in 50% later in illness
Hyponatremia	Yes	Yes
Liver enzymes	May be elevated	Usually elevated
Treatment	Doxycycline	Doxycycline

- Common regions in the USA: Northeast to Mid-Atlantic (> 90%), upper Midwest (Wisconsin and Minnesota), West Coast (California)
- Incubation period: 11 days

Early localized disease stage I

- Erythema migrans (pathognomonic skin lesion) either bullseye or clear center
- Myalgia
- Arthralgia
- Mild fever

Early disseminated disease stage II (weeks to months later)

- Multiple erythema migrans lesions
- Meningitis (lymphocytic)
- Cranial nerve palsies, e.g., Bell palsy
- Peripheral neuropathy, e.g., foot drop
- Heart block: first, second, or third degree

Late disseminated disease stage III

- Arthritis
- Oligo-migratory arthritis
- Remember: Lyme disease can be confused with juvenile idiopathic arthritis (JIA)

Diagnosis

- Erythema migrans is pathognomonic and is an early lesion; antibodies not developed yet
  - No need to test. Treat based on clinical diagnosis
- Serologic testing indicated to confirm early and late disseminated disease. Two-tiered testing:
  - Initial test is highly sensitive enzyme immunoassay assay (EIA). If positive, then
  - Western blot test, considered positive if *either*
    - 2 IgM bands positive, *or*
    - 5 IgG bands positive

Treatment

- Early localized: Doxycycline for 10 days (amoxicillin for 14 days if < 8 years)
- Isolated facial palsy: Doxycycline for 14 days
- AV block or meningitis: Doxycycline or ceftriaxone for 14 days
- Arthritis: Doxycycline for 28 days (amoxicillin for 28 days if < 8 years)

Treponema pallidum

Background

- *T. pallidum* is spirochete mobile bacteria
- Mode of transmission:
  - Sexual contact
  - Transplacental (congenital)
  - Exposure to infected blood or tissue

Clinical presentation

- Congenital syphilis
  - Stillbirth, hydrops, preterm, or asymptomatic
  - Hepatosplenomegaly
  - Snuffles (nasal secretions)
  - Lymphadenopathy
  - Mucocutaneous lesions
  - Pneumonia
  - Bone findings: Osteochondritis and periostitis
  - Maculopapular rash prominent on hands and feet that are highly infective
  - Late manifestations: Interstitial keratitis, deafness, Hutchinson teeth (peg-shaped incisors), anterior bowing of shins, frontal bossing, mulberry molars, saddle nose
- Primary syphilis
  - Genital chancre 3 weeks after exposure
  - Painless papule that then become painless ulcer, which is very contagious
- Secondary syphilis 2–10 weeks after the chancre heals
  - Maculopapular rash involving palms and soles
  - *Condyloma lata* (wart-like plaques around the anus or the vagina confused with *condyloma acuminata* seen in HPV)
  - Generalized lymphadenopathy
- Tertiary syphilis (symptomatic late syphilis 15–30 years after initial infection)
  - Cardiovascular, CNS, gummatous lesions

Diagnosis and treatment

- Screening methods:
  - Rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL) test correlate with disease activity
  - Other infections and autoimmune diseases can cause false positive RPR or VDRL
- Fluorescent treponemal antibody absorption (FTA-ABS) test confirms the diagnosis, and this test remains positive for life
- Congenital syphilis:
  - Unlikely: No evaluation or treatment. Maternal titer low/negative and history of adequate treatment, normal infant physical exam, and infant titer < 4-fold the maternal titer
  - Less likely: Benzathine penicillin G single dose, no evaluation. Maternal history of adequate treatment > 4 weeks before delivery, normal infant physical exam, and infant titer < 4-fold the maternal titer
  - Possible: Aqueous crystalline penicillin G for 10 days; analysis of CSF, CBC, long bone radiographs: Mother not treated adequately or treated < 4 weeks before delivery, normal infant physical exam, and infant titer < 4-fold the maternal titer
  - Proven/highly probable: Aqueous crystalline penicillin G for 10 days; analysis of CSF, CBC, chest and long bone radiographs; transaminase; neuroimaging; ophthalmologic exam. Mother not treated adequately or treated < 4 weeks before delivery, or abnormal infant physical exam, or infant titer 4-fold higher than maternal titer
- Treatment with penicillin for acquired syphilis, with doxycycline or tetracycline if allergic to penicillin

Mycobacterium tuberculosis

Background

- *M. tuberculosis*, a tubercle bacillus, is the causative agent of tuberculosis (TB)
- Mycobacteria, such as *M. tuberculosis,* are aerobic, non-spore-forming, non-motile, facultative, curved intracellular rods measuring 0.2–0.5 μm by 2–4 μm
- Retains many stains after decolorization with acid-alcohol, which is the basis of the acid-fast stains used for pathologic identification
- TB spreads most commonly via airborne transmission
- TB is unlikely to spread from child < 4 years of age due to limited tussive force
- TB is likely to spread from infected adults to children (usually household or childcare center)

Risk factors

- Foreign-born individuals in the USA have TB rates 9.5 times higher than those of persons born in the USA
- HIV infection, treatment with TNF-alpha antagonists such as infliximab and etanercept, and other immunocompromising conditions
- Recent latent tuberculosis infection (LTBI)
- IV drug use
- Certain medical conditions such as diabetes and renal failure
- Incubation period from exposure to positive test is 2–10 weeks

Clinical presentation

- Only 5–10% of children older than 3 years of age who have untreated LTBI progress to disease
- Most LTBI progress to disease within 1–2 years of initial infection
- The most common site of infection is the lung (up to 80%)
- **Pulmonary disease**
  - Infants and adolescents are more likely to be symptomatic than 5 to 10-year-old children
  - Cough (usually last 3 weeks or longer)
  - Hemoptysis
  - Low-grade fever
  - Weight loss (rare)
  - Night sweats

  - Loss of appetite
  - Hilar or mediastinal adenopathy may be seen
  - Cavity lesions
- **Superficial lymphadenopathy**
  - The most common extrapulmonary form of TB
  - Children who have TB lymphadenopathy tend to be older than those who have non-tuberculous mycobacterial lymphadenopathy
  - Common locations: Anterior cervical, followed by posterior triangle, submandibular, and supraclavicular
  - Lymph nodes usually measure 2–4 cm and lack the classic inflammatory findings of pyogenic nodes
  - There may be overlying violaceous skin discoloration
  - Surgical node excision is not curative but may be necessary to establish the diagnosis
  - Most children respond well to a 6-month course of multidrug therapy, but occasionally therapy must be extended to 9 months, based on clinical response
- **CNS disease**
  - Tuberculomas, occurring in 5% of children who have CNS TB, appear as single rim-enhancing lesions ranging from 1 to 5 cm
  - In TB meningitis, CSF analysis typically demonstrates lymphocytes, a low-glucose concentration, and a high-protein value
  - The most common findings on CNS imaging:
    - Hydrocephalus and basilar enhancement
    - Vascular lesions involving the basal ganglia and midbrain also are common
  - TB should be considered in cases of childhood stroke
- **Pleural TB**
  - Seen more in older child and adolescent
  - Can occur in isolation or concomitantly with pulmonary parenchymal disease
  - Symptoms include chest pain, fever, cough, dyspnea, and anorexia. Auscultatory findings mimic those of bacterial pneumonia
  - Most children have positive tuberculin skin test (TST) results
  - Effusions are more common on the right and rarely bilateral
  - The pleural fluid is exudative and lymphocytic
  - A 6-month course of therapy is recommended
- **Miliary tuberculosis**
  - Due to lymphohematogenous spread, it is a disease of the young or immunocompromised children
  - Miliary disease can present shortly after primary infection
  - Multiorgan involvement is common
  - Clinical presentation:
    - Pyrexia
    - Hepatomegaly and splenomegaly
  - TST is insensitive because disseminated disease can produce TST anergy
  - AFB culture from gastric aspirates can have a yield as high as 50%
  - A prolonged course of therapy (9–12 months) should be administered to patients who have disseminated disease
- **Skeletal TB**
  - The most common manifestations of skeletal disease are:
    - Spondylitis
    - Arthritis
    - Osteomyelitis
  - Most patients are in the second decade of life
  - Spinal involvement (Pott disease), which can affect even young children
  - Skeletal lesions can develop more than 10 years after initial infection
  - MRI is the preferred imaging choice because it can demonstrate lesions months before plain radiographs
  - Chest radiographs are positive in 50% of children who have skeletal TB
  - TST results are usually positive
- **Other forms of TB include:**
  - Abdominal
  - Renal
  - Cutaneous disease

TB testing

- Cultures can be obtained by sequential sputum sampling or by gastric aspiration of early morning secretions in the younger child
- The bacillus grows slowly
  - 6 to 8 weeks to grow on Lowenstein–Jensen media
  - 2 to 3 weeks to grow in liquid media
- AFB stains include Kinyoun, auramine–rhodamine (Truant), and Ziehl–Neelsen
- Tuberculin skin test (TST) (Table 9.3)
  - Measured in millimeters of induration (not erythema)
  - Reading is 48–72 h after placement
  - Preferred for children < 2 years
  - Know: If a child returns for TST interpretation after 72 h and has induration meeting the criteria for positivity, the test is considered positive.

Table 9.3 Positive tuberculin test reaction results in infants, children, and adolescents

Induration of 5 mm or more	Induration 10 mm or more	Induration more than 15 mm
Children in close contact with known or suspected contagious people with tuberculosis	Children < 4 years of age	Children 4 years of age or older without any risk
Children with suspected tuberculosis either clinically or on chest radiograph	Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes, renal failure, malnutrition	
Children receiving immunosuppressive therapy or with immunosuppressive conditions, including HIV	Children born in, or who travel to, high-prevalence countries	
	Children exposed to adults in high-risk categories	

  - A negative result never eliminates the possibility of TB disease because many disseminated forms of TB, including TB meningitis, can induce TST anergy
- False-negative TST results:
  - Recent measles infection or vaccination
  - High-dose corticosteroid treatment, irradiation
  - Immunosuppressive therapy
  - Immunocompromising medical conditions
  - Disseminated tuberculosis
- False-positive TST result:
  - Primarily in children exposed to nontuberculous (environmental) mycobacteria
  - Children recently received a bacillus Calmette–Guérin vaccine
  - A boosting phenomenon: Children received multiple sequential TSTs
  - First screen for exposure risk by history before testing. Do not test all children routinely
- Bacillus Calmette–Guérin (BCG) vaccine
  - TST can be interpreted normally in a child who received a single dose of BCG vaccine as a young child
  - Having received BCG as an infant may not explain a positive skin test result later in life
  - The assumption that BCG receipt is the cause of a positive TST could lead to a lack of treatment for high-risk children who potentially could benefit from LTBI therapy
- Whole blood interferon-gamma release assays (IGRAs) have several potential advantages:
  - Only one office visit is required
  - There is no risk of the boosting phenomenon
  - More specificity for LTBI because the antigens in the IGRAs is shared less commonly with nontuberculous mycobacteria and are not found on BCG
- Chest radiographs
  - Children who have LTBI usually have normal-appearing chest radiographs

  - An isolated calcified lesion in a child who has a positive TST result can be treated as LTBI
  - The most common abnormal radiographic finding is hilar or mediastinal adenopathy
  - Other findings can include infiltrates, atelectasis, pleural effusions, cavities, or miliary disease
- TB exposure:
  - Children younger than 4 years of age and immunocompromised children
  - Should begin isoniazid (INH), pending results of repeat testing
  - If the second test result is negative, medication can be discontinued
  - Children experiencing TB exposure who are older than age 4 years and immunocompetent can be observed off medications, pending the second test result in 2–3 months

Latent TB infection (LTBI)

- The child demonstrating a positive skin test result should be treated for LTBI to decrease the risk of disease progression later in life
- The mainstay of therapy for LTBI is 12 weeks of daily INH and weekly rifampin
- An alternative is 4 months of daily rifampin (for INH intolerant or resistance)

Treatment of TB

- The standard initial regimen for pulmonary and extrapulmonary TB:
  - INH, rifampin, pyrazinamide (PZA), and ethambutol
  - INH and rifampin are administered for 6 months, and PZA and ethambutol are stopped after the first 2 months
- Exceptions: Treating children who have TB meningitis, where treatment courses of 7–12 months often are used

Side effects of antituberculous medications

- INH, rifampin, and PZA are all hepatotoxic
- Ethambutol can rarely cause optic neuritis (decreased color perception is the first sign of deterioration)
- Pyridoxine supplementation indicated for exclusively breastfed infants, nutritional deficiencies, symptomatic HIV, and pregnant females

Challenging clinical scenarios

- Adult in the household has infectious TB
  - All children in the household should have chest radiographs and TSTs performed
  - Children younger than 4 years of age should be started empirically on INH and rifampin until the TST is repeated in 2–3 months
  - If the second TST result is negative and the child is immunocompetent, medication can be discontinued
  - If the TST result is positive or the child is immunocompromised, INH and rifampin should be continued
- Infant whose mother has TB
  - The TST is helpful only if the result is positive, which is very rare
  - If the mother has a positive TST result and negative chest radiograph (LTBI), the child needs no evaluation
  - If the mother has radiographic features consistent with TB, the neonate requires evaluation for congenital TB
  - If the infant does not have congenital TB, he or she should be separated from the mother until the infant is receiving INH and pyridoxine (if the mother is breastfeeding) and the mother is receiving appropriate multidrug therapy
  - Once the infant is receiving INH, separation is unnecessary, and breastfeeding should be encouraged unless INH resistance is suspected
- Health-care workers (HCWs)
  - If positive TST results, they should receive chest radiographs

  - If the chest radiograph is negative, the HCW may be offered therapy for LTBI after weighing the risks and benefits of latent TB treatment in adults
  - If the chest radiograph is positive, the HCW needs to be evaluated further

Follow-up

- Children who have TB disease should be seen monthly while receiving therapy to document medication tolerance and adherence, weight gain, and achievement of appropriate milestones

Mycobacterium Avium-Intracellulare

Background

- Mycobacterium avium-intracellulare complex is the most common cause of nontuberculous disease in children
- Caused by two types of bacteria: *Mycobacterium avium* and *Mycobacterium intracellulare*
- Usually occurs in children with impaired cell immunity, including very young children < 5 years old
- Organisms are ubiquitous in soil

Clinical presentation

- Cervical lymphadenitis
  - Overlying skin is usually pink to violaceous
  - Usually unilateral
  - Increase in size over several weeks
- Cutaneous infections
- Ear infections
- Disseminated and pulmonary infections (high fever, night sweats, weight loss, lymphadenopathy, abdominal pain, diarrhea, and anemia) can occur in immunocompromised

Management

- Complete resection of infected lymph node is diagnostic and curative. Antibiotics are not necessary!
- Azithromycin or clarithromycin in combination with ethambutol or rifampin if cannot be resected

FUNGAL INFECTIONS

Candida Species

- *Candida albicans* is the most commonly isolated species, and causes infections (Candidiasis or thrush)
- Systemic infections of the bloodstream and major organs (invasive candidiasis or candidemia, particularly in immunocompromised patients)
- *Candida* appears as budding yeast cells and pseudohyphae (Fig. 9.18)

Oral Thrush

Background

- Common in the first 6 postnatal months
- Possibly due to infants' immunologic immaturity

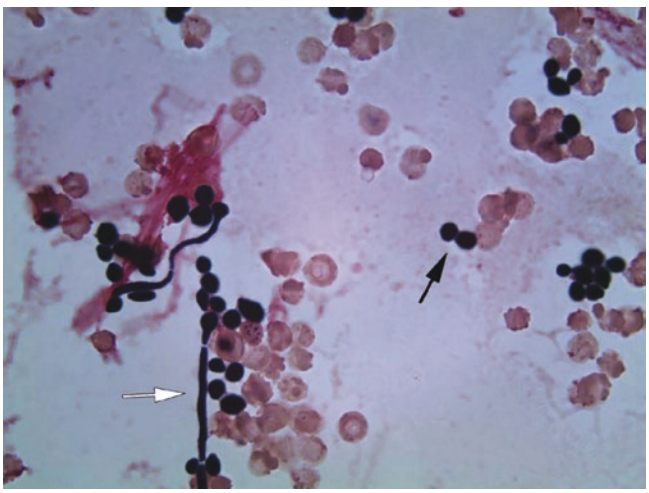


Fig. 9.18 *Candida albicans* in blood culture (Gram stain, original magnification × 1000). Budding yeast cells (blastoconidia, *black arrow*) and pseudohyphae (*white arrow*). (Courtesy of M. Nawar Hakim, MD, Department of Pathology, Texas Tech University Health Sciences Center, El Paso, Texas, USA)

Infection sources

- Contaminated bottle nipples, pacifier, or dropper, e.g., vitamin dropper
- Infected mother's nipples (although the incidence is high in formula fed infants)
- Maternal vaginal colonization with *Candida*

Recognize

- Recurrent or persistent oral thrush beyond 6–12 months raises the concern of immunodeficiency, especially if associated with failure to thrive or hepatosplenomegaly

Risk of infection

- Use of inhaled steroid without adequate rinsing afterward or oral antibiotics can cause oral thrush
- Poorly controlled diabetes in adults can cause *Candida* infection; however, it is not associated with gestational diabetes

Clinical presentation

- Infants may have trouble feeding in severe cases
- Tiny focal white area that enlarge to white patches on oral mucosa (Fig. 9.19)
- If scraped with a tongue blade, lesions are difficult to remove and leave behind an inflamed base that may be painful and may bleed
- Examine the patient with diaper dermatitis for oral lesions

Treatment

- Oral nystatin
- Once-daily oral fluconazole is superior to oral nystatin for resistant thrush

Candidal Diaper Dermatitis

Clinical presentation

- Lesions consist of beefy-red plaques, often with scalloped borders
- Satellite papules and pustules may be observed surrounding the plaques (Fig. 9.20)
- Maceration is often present, especially in intertriginous areas

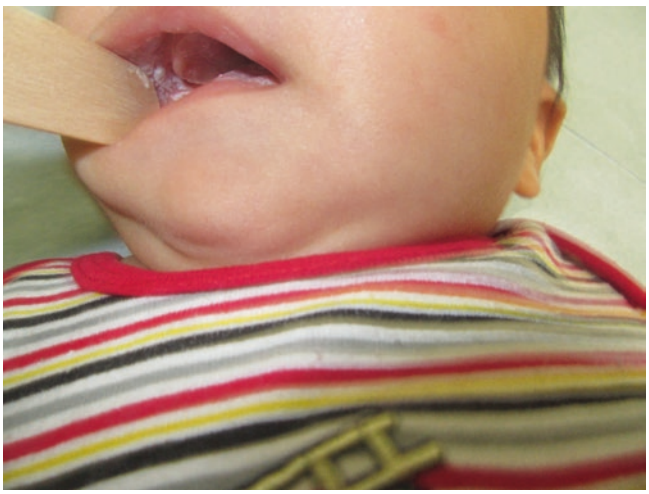


Fig. 9.19 Thrush: Tiny focal white areas that enlarge to white patches on oral mucosa; it was difficult to remove the white spots with the tongue blade

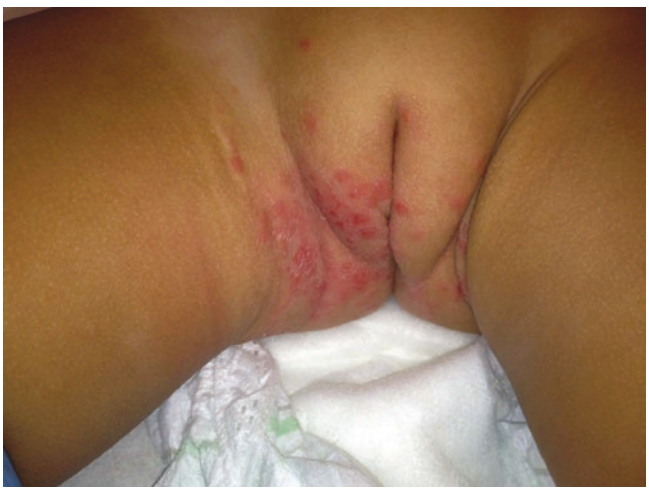


Fig. 9.20 Candidal diaper rash: Lesions consist of beefy-red plaques with satellite papules

Treatment

- Topical nystatin, miconazole, clotrimazole

Vulvovaginitis

Background

- Common in pubertal and adolescent girls
- Risk factors
  - Oral antibiotics
  - Oral contraceptive
  - Pregnancy
  - Poor hygiene
  - Diabetes

Clinical presentation
- Vulvar/vaginal erythema and itching
- White, cottage cheese-like vaginal discharge

Treatment
- Topical nystatin or clotrimazole
- Single dose of oral fluconazole for recurrent or refractory cases

Candidal Infections in Neonates

Background
- Very low-birth-weight and premature infants
- Central line-associated bloodstream infection (CLABSI): Obtain blood culture from periphery and catheter

Treatment
- Remove the catheter if CLABSI
- Parenteral micafungin or amphotericin, pending identification and sensitivity testing

Aspergillus

Background
- *Aspergillus* species consist of ubiquitous molds found in organic matter
- Most common species affecting humans are *A. fumigatus* and *A. niger*

Mode of transmission
- Inhalation of fungus spores
- Outbreaks can occur during hospital construction

Clinical presentation
- Invasive aspergillosis: Immunocompromised (neutropenia, graft-versus-host disease)
- Pulmonary, sinus, skin, intracranial
- Invasion of vasculature with erosion and hemorrhage
- Aspergillomas and otomycosis: Colonization in immunocompetent children
- Growth in cavities or cysts without invasion
- Underlying cystic fibrosis and TB
- Allergic bronchopulmonary aspergillosis: Hypersensitivity
- Wheezing, mucous plugging, fever, eosinophilia, transient lung infiltrates
- Underlying asthma or cystic fibrosis
- Allergic sinusitis
- Nasal polyps or sinus surgery
- Dark nasal discharge

Diagnosis
- Branched and septate hyphae seen on tissue or BAL
- Molecular testing is definitive
- Galactomannan assay from BAL specimen and serum

Treatment
- Invasive aspergillosis: Voriconazole
- Allergic bronchopulmonary aspergillosis: Corticosteroids

Malassezia furfur

Overview
- Can cause tinea versicolor (see Chap. 26 "Dermatology")
- Can cause neonatal infection in NICU babies receiving total parenteral nutrition (TPN) with lipids
- NICU babies with *M. furfur* may present with fever, bilateral interstitial infiltrates, and increased WBCs
- *M. furfur* requires olive oil overlay to grow

Management of infection in neonates
- Removal of catheters
- Stop lipid infusion
- Start amphotericin B or fluconazole

Histoplasmosis

Background
- Endemic areas: Ohio, Missouri, and Mississippi River valleys
- Mode of transmission
  - Inhalation of spores from bird excreta or contaminated soil
  - No person-to-person transmission

Clinical presentation
- Flu-like symptoms
- Pulmonary infiltrates
- Hilar lymphadenopathy with or without calcifications
- Erythema nodosum
- In younger children may develop progressive disseminated histoplasmosis

Treatment
- Not indicated for immunocompetent children with mild/moderate disease
- Severe or disseminated infection, especially in immunocompromised, treated with amphotericin B + steroids

Coccidioides

Coccidioidomycosis

Background
- Endemic areas
  - California, Arizona, New Mexico, and Texas
- Mode of transmission
  - Inhalation of airborne spores

Clinical presentation
- Most cases are asymptomatic
- Fever
- Cough
- Weight loss (common)
- Fatigue
- Shortness of breath
- Chills
- Erythema nodosum
- Night sweats
- Mild respiratory distress or respiratory failure in severe cases

Diagnosis
- Serology: The appearance of IgM or precipitin antibody against *Coccidioide*s is the most sensitive serologic indication of early infection
- Culture and DNA probe is the most definitive method for the diagnosis
- High index of suspicion is important in patient who travelled or underlying medical conditions
- Elevated erythrocyte sedimentation rate (ESR)
- Lymphocytosis and monocytosis
- Eosinophilia > 5%
- Chest radiograph may show consolidations and hilar lymphadenopathy

Treatment
- Not indicated for immunocompetent children with mild/moderate disease
- Severe or disseminated infection, especially in immunocompromised, treated with fluconazole or itraconazole
- High dose fluconazole for CNS infections

Blastomyces
- *Blastomyce*s causes illness similar to *Histoplasma* and *Coccidioides*
- Seen in Arkansas and Wisconsin hunters and loggers
- Outbreak occurred in children visiting Wisconsin lodge and beaver dam
- B*lastomyces* may disseminate to the skin and cause crusted skin lesions
- Bone lesions more common with blastomycosis
- Itraconazole (mild disease) or amphotericin B (severe disease) are the treatments of choice

Sporothrix schenckii
- Common in florists, as thorny plants are implicated
- Symptoms appear from 7 to 30 days after inoculation
- Present with painless papule at the site of inoculation, then ulcerates
- Secondary lesions follow along the lymphatic chain proximally
- Extracutaneous manifestation may occur, especially in immunocompromised
- Treat with itraconazole for 2–4 weeks

PROTOZOA

Giardia lamblia

Giardiasis

Background
- Giardiasis is an infection of the small intestine caused by the flagellated protozoan *Giardia intestinalis*
- Mode of transmission
  - Travelers and hikers who drink water contaminated with stool from infected animals such as beavers, muskrats, and sheep
  - Outbreaks also may occur from sewage contamination of water supplies
  - Unprotected anal sex also is a source of transmission
  - Childcare centers from fecal–oral transmission
  - Food-associated outbreaks may occur

Clinical presentation
- Most infections remain asymptomatic
- Watery diarrhea with abdominal cramping
- Nausea
- Vomiting
- Weight loss
- Flatulence

Diagnosed
- Microscopic examination of the stool for cysts or by antigen detection

Treatment
- Indicated for all symptomatic patients
- Metronidazole, a single dose of tinidazole, or nitazoxanide for 3 days
- Immunocompromised patients at increased risk for chronic giardiasis and treatment failure

Entamoeba histolytica

Background
- Amebiasis is caused by pathogenic species of Entamoeba
- Mode of transmission
  - Fecal–oral route
  - Travel to high-risk areas with poor sanitation and hygiene

Clinical presentation
- Can be asymptomatic
- Amebic dysentery or colitis
  - Bloody diarrhea with mucus
  - Tenesmus
- Hepatic abscess
  - Fever
  - Abdominal pain
  - Tender enlarged liver
  - Elevated liver enzymes
  - Elevated ESR

Diagnosis
- Serum antibody (95% detectable in invasive amebiasis)
- Stool microscopic examination
- Stool antigen
- Ultrasound if liver abscess is suspected

Treatment
- Symptomatic cases with systemic symptoms
  - Metronidazole followed by paromomycin or iodoquinol to eradicate colonization
- Asymptomatic amebiasis in nonendemic areas should be treated with a luminal agent (iodoquinol, paromomycin, or diloxanide furoate) to eradicate infection
- Amebic liver abscess cured by medical therapy without drainage

Cryptosporidiosis

Background
- Cryptosporidiosis, caused by *Cryptosporidium protozoa*
- Transmitted via fecal–oral route; childcare centers and swimming pools

Clinical presentation
- Nonbloody, watery diarrhea
- Chronic diarrhea in immunodeficient patients

- Test using DFA in stool; routine ova and parasite testing insufficient

Treatment
- Many immunocompetent patients who have cryptosporidiosis have self-limited disease and do not require therapy
- A 3-day course of nitazoxanide:
  - To reduce duration and transmission of diarrhea in children older than 1 year of age
- No swimming pool for at least 2 weeks after diarrhea ends

Toxoplasma gondii

Toxoplasmosis

Background
- Obligate intracellular protozoa
- Mode of transmission
  - Ingestion of contaminated raw or uncooked meat
  - Cat excreta
  - Organ transplants
  - Transplacental to fetus causes congenital toxoplasmosis (see Chap. 2 "Neonatology")

Clinical presentation
- Most cases are asymptomatic
- Fever
- Malaise
- Rash
- Myalgia
- Cervical lymphadenopathy (most common sign)
- Brain abscess (test for HIV)
- Chorioretinitis usually present years later (mostly congenital)

Diagnosis
- Head CT: Ring-enhanced lesion, intracerebral calcifications
- Toxoplasma IgM antibodies
- PCR

Treatment
- Infants with congenital toxoplasmosis: Pyrimethamine plus sulfadiazine and folic acid
- Pregnant females: Spiramycin

Pneumocystis jiroveci

Pneumocystis Pneumonia

Background
- Unicellular fungi that do not respond to antifungal treatment
- Mode of transmission is unknown
- Commonly seen in immunocompromised patients, e.g., HIV patients

Clinical presentation
- Subacute diffuse pneumonitis
- Dyspnea
- Tachycardia
- Hypoxemia that is exaggerated with exertion
- Nonproductive cough
- Fever

Diagnosis
- Chest radiography
  - Bilateral diffuse interstitial disease
- Low CD4
- BAL
- Lung biopsy

Treatment
- TMP-SMX
- IV pentamidine in severe cases
- Prophylaxis in immunocompromised patients
  - TMP-SMX

Plasmodium

Malaria

Background
- Intracellular protozoa
- Transmitted by mosquito bites in endemic areas of the tropics

Plasmodium falciparum

- Most severe, causing death within 48 h if untreated
- Symptoms develop 10 days after mosquito bite, longer if taking prophylaxis
- Complications
  - Cerebral malaria
  - Pulmonary edema
  - Severe anemia
  - Renal failure
  - Shock
- Treatment
  - Chloroquine sensitive (rare)
    - Chloroquine
  - Chloroquine resistant
    - Artemether–lumefantrine
    - Quinine plus doxycycline or clindamycin
    - Atovaquone–proguanil
  - Severe cases
    - IV artesunate (available from Centers for Disease Control and Prevention [CDC] only; not yet FDA-approved)
    - Quinidine gluconate IV (no longer produced for the US market as of 2019) plus doxycycline or clindamycin

P. malariae, P. vivax, and P. ovale

- Periodicity of symptoms
- Nephrotic syndrome – *P. malariae* (most benign form)
- Hypersplenism and splenic rupture – *P. vivax* and *P. ovale*
- Treatment
  - Chloroquine plus primaquine for *P. vivax,* and *P. ovale*
  - Chloroquine for *P. malariae*

Clinical presentation of malaria

- History of traveling to endemic area
- Paroxysmal fever, sweat, and rigors
- Pallor and jaundice
- Headache and myalgia
- Abdominal pain
- Vomiting and diarrhea
- In severe cases
  - Altered mental status
  - Hepatosplenomegaly
  - Anemia
  - Thrombocytopenia
  - Hypotension
  - Hypoglycemia
  - Hyperkalemia
  - Respiratory distress

Diagnosis

- Rapid diagnostic test (immunochromatographic test)
- Thick blood smear
- PCR available, but results are delayed

Prevention

- Traveling to chloroquine resistant areas, e.g., most tropical areas with malaria
  - Atovaquone–proguanil 1–2 days before and 7 days after travel, *or*
  - Doxycycline (> 8 years old) 1 week before until 4 weeks after travel
- Traveling to chloroquine sensitive areas, e.g., Central America
  - Chloroquine 1–2 weeks before and 4 weeks after, *or*
  - Atovaquone–proguanil 1–2 days before and 7 days after travel

HELMINTHIC ORGANISM

Enterobius vermicularis

Pinworm

Mode of transmission

- Person-to-person via fecal–oral route
- Eggs survive up to 3 weeks and are ingested from finger nails, bedding, and toys
- Autoinfection

Clinical presentation
- Anal and vulvar itching (more at night)
- Enuresis

Diagnosis
- Visualizing the adult worm at night on the perineum
- Transparent tape collected over three consecutive mornings under microscope low power

Treatment
- Pyrantel pamoate (over-the-counter), albendazole, mebendazole

Ascaris lumbricoides

Ascariasis

Mode of transmission
- Ingestion of eggs from contaminated soil (fecal–oral)

Clinical presentation
- Most patients are asymptomatic
- Nonspecific abdominal pain or discomfort
- Intestinal obstruction (large number of worms)
- Due to larvae migration to the liver and lung:
  - Obstructive jaundice
  - Peritonitis
  - Cough (Loeffler syndrome)

Diagnosis
- Seeing the ova on microscopic stool examination
- Seeing the adult worm itself

Treatment
- Pyrantel pamoate (over-the-counter), albendazole, mebendazole

Necator americanus

Ancylostoma duodenale

Hookworm

Background
- Found in rural, tropical, and subtropical locales
- Mode of transmission
  - Skin penetration of larvae from soil contaminated by human feces
  - Ingestion

Clinical presentation (blood sucker worms from the intestine)
- Itchiness and burning sensation
- Pharyngitis and gastroenteritis
- Failure to thrive
- Short stature
- Anemia due to chronic blood loss

Diagnosis
- Visualization of eggs in stool (may take 5–10 weeks after infection)

Treatment
- Pyrantel pamoate (over-the-counter), albendazole, mebendazole

Trichuriasis

Whipworm
- Due to infection of large intestine with *Trichuris trichiura*
- More common in the Southern United States
- Transmitted to humans by ingesting eggs
- Usually asymptomatic if only few worms
- Can cause fever, abdominal pain, weight loss, blood in stool, and rectal prolapse
- Presence of eggs in stool is diagnostic
- Treatment is with albendazole, mebendazole, or ivermectin

Trichinella spiralis

Trichinellosis

- *T. spiralis* is usually found in pork
- Symptoms depend on the worm location
- After ingestion the eggs hatch, larvae invade the duodenum and cause abdominal symptoms
- Larvae penetrate, reach bloodstream, end in muscular tissue and cause muscle pain
- If the larvae reach the heart, can cause myocarditis
- Ocular involvement: Presence of chemosis, periorbital edema, and eosinophilia usually suggest the diagnosis
- Diagnosis is confirmed by rising titers
- Treatment is with albendazole or mebendazole

Strongyloides stercoralis

Strongyloidiasis

- *S. stercoralis* is common in certain areas (Kentucky and Tennessee) of the USA
- The only helminthic organism that replicates in the body with autoinfection, and the infection may persist for decades
- Can cause pulmonary symptoms with eosinophilia and GI symptoms
- Potentially fatal in immunosuppressed patients
- Diagnosis of serial stool studies for larvae not the eggs
- Treatment: Ivermectin or albendazole

Toxocariasis

- *Toxocara canis* and *Toxocara cati* can cause visceral larva migrans
- Transmitted to humans by ingesting soil contaminated with dog or cat excreta
- In humans larvae do not develop into adult worms but rather migrate through the host tissue, causing eosinophilia
- Treatment: Albendazole or mebendazole

Cestodes (Platyhelminthes)

- Platyhelminthes include cestodes (tapeworms) and trematodes (flukes)
- Cestodes are flatworms (tapeworms)
- The pork tapeworm *Taenia solium*, present in two different ways
  - If the cysticerci are ingested, taeniasis develops and tape worm grows in the intestine
  - If contaminated food with eggs is ingested, the patient will develop cysticercosis
- Cysticerci live in CNS and the eyes and do nothing until they die
- Diagnosis of neurocysticercosis must be considered in patients with new onset seizures and history of traveling to or immigration from Mexico, Central, or South America, or who are from a household in these areas
- Treatment: Albendazole or praziquantel

Trematodes (Platyhelminthes)

- Trematodes or flukes
- *Clonorchis sinensis* is the Chinese liver fluke
- *Schistosoma haematobium* infects the bladder and causes urinary symptoms
- *Schistosoma mansoni* is a fluke found in Africa, the Middle East, and South America
- *Schistosoma japonicum* is found in Asia
- Most serious complications of Schistosomiasis is cirrhosis with esophageal varices
- Treatment: Praziquantel

FEVER

Fever Without Focus

Febrile Neonate

Background

- Difficult to distinguish between a serious bacterial infection and self-limited viral illness in this age group
- Neonates who have fever and do not appear ill have a 7% risk of having a serious bacterial infection
- Serious bacterial infections include occult bacteremia, meningitis, pneumonia, osteomyelitis, septic arthritis, enteritis, and UTI
- Late onset neonatal bacterial diseases, e.g., group B *Streptococci, E. coli*, and *Listeria monocytogenes* and perinatal herpes (HSV) infection
- If the neonate has fever recorded at home by reliable parents, the patient should be treated as febrile neonate
- If excessive clothing and blanket falsely elevate the temperature, the excessive covering should be removed and retake the temperature in 15–30 min

Management

- All febrile neonates must be hospitalized
- Full sepsis evaluation including blood, urine; CSF should be cultured
- CSF studies should include cell count, glucose, and protein level, Gram stain, cultures; HSV, and enterovirus PCR should be considered
- Blood and urine cultures warranted
- Chest radiograph may be included
- Child should receive empiric antibiotics such as cefotaxime or gentamicin + ampicillin
- Acyclovir should be included if HSV infection is suspected

Fever in 1–3-Month-Old Infants

Background

- Large majority of children with fever without localizing signs in 1–3 months age group likely viral syndrome
- Most viral diseases have distinct seasonal pattern, unlike bacteria, e.g., respiratory syncytial virus, and influenza more common during winter and enterovirus infection more common during summer and fall

Management

- Ill-appearing (toxic) febrile infants ≤ 3 months:
  - Require prompt hospitalization, immediate parenteral antibiotics after blood and CSF cultures are obtained
- Well-appearing infants 1–3 months previously healthy with no evidence of focus of infection:
  - WBCs count of 5000–15,000 cells/μL, an absolute band count of ≤ 1500 cells/μL, normal urinalysis, and negative culture (blood and urine) results are unlikely to have a serious bacterial infection
- The decision to obtain CSF studies in the well-appearing 1–3 months old infant depends on the decision to administer empiric antibiotics
- If close observation without antibiotics planned, a lumbar puncture may be deferred

Fever in 3–36 Months of Age

Background

- Approximately 30% of febrile children in the 3–36 months age group have no localizing signs of infection
- Viral infections cause most fevers in this population
- Risk factors indicating probability of occult bacteremia: Temperature ≥ 39 °C, WBC count ≥ 15,000/μL, elevated absolute neutro-

phil count, bands, ESR and C-reactive protein (CRP)
- The risk of bacteremia and/or pneumonia or pyelonephritis among infants 3–36 months of age increases as temperature (especially > 40 °C) and WBC count (especially > 25,000) increase

Management
- Toxic-appearing febrile children 3–36 months of age who do not have focal infection should be hospitalized, with prompt institution of parenteral antibiotics after blood, urine, and CSF cultures are obtained (full sepsis evaluation)
- For nontoxic-appearing infants who have temperature < 39 °C: Can be observed as outpatient with no diagnostic test or antibiotics
- For nontoxic infants who have rectal temperature ≥ 39 °C, options include obtaining a blood culture and administering empiric antibiotic therapy (ceftriaxone, a single dose 50 mg/kg not to exceed 1 g); or blood culture with no antibiotic and observing the patient within 24 h as outpatient. (Careful observation without empiric antibiotics is generally prudent)

Fever of Unknown Origin (FUO)

Background
- FUO was defined as:
  - More than 8 days' duration of illness. Temperature greater than 38.3 °C (101 °F) on several occasions
  - Failure to reach a diagnosis despite 1 week of investigation
- Patients with undiagnosed FUO (5–15% of cases) generally have a benign long-term course, especially when the fever is not accompanied by substantial weight loss or other signs of a serious underlying disease
- FUO lasting > 6 months is uncommon in children and suggests granulomatous or autoimmune disease (Table 9.4)

Table 9.4 Differential diagnosis of fever of unknown origin

Fever type	Differential diagnosis
Infectious	Viral: EBV, CMV, hepatitis, HIV, parvovirus B19
	Bacterial: tuberculosis, cat scratch, *Brucella*, *Salmonella*, meningococcemia
	Common: otitis media, sinusitis, pneumonia, UTI, osteomyelitis, septic arthritis, meningitis
	Less common: malaria, Lyme disease, endocarditis
Rheumatologic	Juvenile idiopathic arthritis, SLE, dermatomyositis
Oncologic	Leukemia, lymphoma, neuroblastoma, Ewing sarcoma, hemophagocytic lymphohistiocytosis
Autoimmune	Inflammatory bowel disease, macrophage activation syndrome
Drug related	Penicillin, cephalosporins, sulfonamides, acetaminophen
Other	Kawasaki disease, thyrotoxicosis, factitious fever

EBV Epstein-Barr virus, *CMV* cytomegalovirus, *UTI* urinary tract infection, *SLE* Systemic lupus erythematosus

Approach
- Age of the patient is helpful:
  - Children > 6 years of age often have respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JIA, or (rarely) leukemia
  - Adolescent patients more likely to have TB, inflammatory bowel disease, autoimmune process, or lymphoma in addition to the causes of FUO in younger children
- Exposure to wild or domestic animals, and zoonotic infection
- History of pica should be elicited; ingestion of dirt is particularly important due to infection with *T. canis* or *T. gondii*
- Physical examination is essential to find any physical clues to underlying diagnosis, e.g., lymphadenopathy, rash, joint swelling, etc.
- Laboratory determined on case-by-case basis
- ESR > 30 mm/h indicates inflammation and needs further evaluation

- ESR > 100 mm/h suggests tuberculosis, Kawasaki disease, malignancy or autoimmune disease
- Low ESR does not eliminate the possibility of infection
- CRP is another acute phase reactant that is elevated and returns to normal more rapidly than ESR
- Cultures, serologic studies, imaging studies, and biopsies, depending on the individual case

Treatment

- The ultimate treatment of FUO is tailored to the underlying diagnosis
- Empiric trials of antimicrobial agents may be dangerous and obscure the diagnosis of infective endocarditis, meningitis, parameningeal infection, and osteomyelitis
- Antipyretics for fever and relief of symptoms

CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS

Encephalitis

Definition

- Inflammation of the brain

Causes

- Viral, e.g., West Nile virus and herpesvirus (most common)
- Bacteria, e.g., mycoplasma, tertiary syphilis
- Noninfectious, e.g., autoimmune
- Prion protein
- Parasitic
- Fungal
- Acute cerebellar ataxia
  - Ataxia
  - Nystagmus
  - Cerebellar dysarthria

Epidemiology

- WNV remains the most commonly encountered arboviral encephalitis agent
- California encephalitis viruses cause the greatest proportion of symptomatic pediatric infections
- Eastern equine encephalitis has the highest overall mortality rate
- The importance of local epidemiological information and seasonality cannot be ignored
- Enteroviruses are most often seen in spring and summer; arthropod-borne illnesses in the summer and fall

Clinical presentation

- Altered mental status
- Seizures
- Weakness
- Sensory disturbances
- Nonepileptic movement disorders
- Young children in absence of identifiable cause may present with:
  - Somnolence
  - Disinterest in feeding
  - Weak suck and irritability
  - Loss of head control
  - Abnormal eye movements
- Further clinical clues:
  - Fever (either acutely or in the 1–4 weeks interval before the onset of symptoms)
  - Meningeal irritation
  - Any child presenting with uncharacteristic behavior that is persistent and disproportionate to environmental and situational factors

Initial evaluation of the patient includes

- Seasonal presentation
- History of immunosuppression
- Travel history
- Recent local epidemiological information
- Presence of focal neurologic symptoms or deficits.

Investigation

- CBC
- Complete metabolic panel
- Urinalysis
- MRI or CT scan for intracranial pressure (ICP)
- Electroencephalogram (EEG)

- Enteroviral infections can produce a sepsis-like syndrome with more remarkable hematologic abnormalities
- Neonatal HSV infections sometimes produce hepatic function abnormalities and disseminated intravascular coagulation
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Lumbar puncture if normal pressure
- Cerebrospinal spinal fluid study:
  - The lumbar puncture is the single most utilized test for the diagnosis of encephalitis
  - Increased opening pressure
  - Normal or elevated protein concentration
  - Normal glucose level
  - Pleocytosis, polymorphonuclear leukocytes; then converts to lymphocytic in many viral cases
  - Monocytic; predominance may show with progression of the disease
  - Hemorrhagic pleocytosis with HSV
  - Atypical lymphocytes with EBV
  - Mononuclear leukocytes with echovirus or varicella-zoster infection
  - PCR amplification of viral DNA
  - Pleocytosis tends to be less dramatic in parainfectious encephalitis or acute cerebellar ataxia
  - Fourfold rise in titer, especially IgM, against a suspected agent is most often considered diagnostic
- IV acyclovir while waiting for lumbar puncture, or while waiting for laboratory results, including HSV PCR
- Intracranial hypertension conservative measures
  - Head elevation
  - Hyperventilation
  - Fluid restriction
  - Mannitol is used on a limited basis

Treatment of seizure

- Benzodiazepines (midazolam, lorazepam, diazepam) in the beginning followed by loading dose of fosphenytoin, or phenobarbital II

Meningitis

Neonatal Streptococcal Meningitis

- Guillain–Barré syndrome remains the predominant neonatal meningitis pathogen
- Early-onset disease: Infants typically manifest with signs suggestive of sepsis, often with pneumonia, but less commonly with meningitis
- Late-onset disease: Infants typically are 3–4 weeks of age and present with meningitis or bacteremia

Neonatal Gram-negative meningitis

- Gram-negative bacillary meningitis is rare, *E. coli* being the most commonly isolated pathogen
- Other Gram-negative neonatal meningitis pathogens such as *Citrobacter koseri, Enterobacter sakazakii,* and *Serratia marcescens*

Neonatal herpes simplex (HSV) infection

- HSV in the newborn can present as isolated skin or mucous membrane lesions, encephalitis, or disseminated process
- HSV infection occurs most commonly in infants born to mothers who have active primary infection
- Frequently no maternal history or clinical evidence is available to alert the practitioner to this diagnosis
- The incubation period is 2 days to 2 weeks, and most infants who develop HSV CNS infection are 2–3 weeks of age

Neonatal meningitis due to Listeria

- Common sources:
  - Unpasteurized milk
  - Soft cheese
  - Prepared ready-to-eat meats
  - Undercooked poultry
  - Unwashed raw vegetables
- Can precipitate abortion and preterm delivery
- Septic appearance in the neonate is typical in cases of early onset
- Papular truncal rash has been identified

S. pneumoniae

- Pneumococcus is the leading pathogen causing bacterial meningitis in infants and young children in developed countries

N. meningitidis

- Meningococcal disease generally occurs in otherwise healthy individuals and often has a fulminant presentation with high fatality rates

Aseptic meningitis

- Enterovirus is the most common etiology
- *B. burgdorferi* in mid-Atlantic states (Lyme)
- Vasculitis in the setting of systemic lupus erythematosus or Kawasaki disease.
- Drug-induced such as ibuprofen, and IV immunoglobulin

Other causes of meningitis

- *M. tuberculosis*
- *B. burgdorferi*
- *R. rickettsii*

Clinical manifestations

- Infants younger than 1 month of age who have viral or bacterial meningitis
  - Fever
  - Hypothermia
  - Lethargy
  - Irritability
  - Poor feeding
- Signs and symptoms of increased ICP and meningeal inflammation
  - Vomiting
  - Apnea
  - Seizures can also occur
- Older children and adolescents often experience
  - Malaise
  - Myalgia
  - Headache
  - Photophobia
  - Neck stiffness
  - Anorexia
  - Nausea

Physical examination

- Altered levels of consciousness can present as irritability, somnolence, lethargy, or coma
- ICP include:
  - Papilledema
  - Diplopia
  - Unilateral or bilateral dilated pupils
  - Poorly reactive pupils
  - Bulging fontanelle in infants
  - Head circumference should always be obtained, especially in those who have an open fontanelle
- Meningismus is suggestive of meningeal irritation
- Kernig sign:
  - The patient lies supine and the thigh is flexed at a right angle to the trunk. If knee extension from this position elicits pain, the Kernig sign is positive
- Brudzinski sign:
  - The patient lies supine and flexes his or her neck
  - A positive sign occurs if the patient also reflexively flexes the lower extremities, typically at the knees
- Absence of Kernig and Brudzinski signs does not exclude meningitis
- Exanthems typical for enterovirus, borreliosis (erythema migrans), and invasive meningococcal or pneumococcal disease (petechiae and purpura) may be present

Diagnosis

- All children who are suspected of having meningitis should have their CSF examined unless lumbar puncture is contraindicated
- Contraindications of lumbar puncture include:
  - Focal neurologic deficits
  - Signs of increased ICP
  - Uncorrected coagulopathy
  - Cardiopulmonary compromise
- CT scan is performed before lumbar puncture if any sign of ICP present
- CSF findings in bacterial meningitis (Table 9.5)

Table 9.5 Cerebrospinal fluid analysis

Type of infection	White blood cells	Protein	Glucose
Bacterial meningitis	> 1000/μL	High	Low (less than half of serum)
Viral meningitis (viral)	< 500/μL	Normal	Usually normal
Tuberculosis	< 500/μL (predominant lymphocyte)	Very high	Low (less than half of serum)

  - Glucose concentration is usually less than one half of the measured serum value
  - Protein value often is greater than 100 mg/dL
  - WBC often greater than 1000/mcL, with a predominance of polymorphonuclear leukocytes
  - Gram stain is extremely helpful if positive
  - CSF culture remains the gold standard for diagnosing bacterial meningitis
- CSF finding viral meningitis
  - WBC count of 50–500/mcL
  - Neutrophil predominance is common early in the course of infection, shifting to lymphocytic predominance quickly during the illness
  - Glucose and protein concentrations frequently are normal, although the protein value can be slightly elevated. Gram stain is universally negative
  - In cases of enteroviral meningitis, enteroviral PCR can confirm the diagnosis
- Tuberculous meningitis, epidemiologic clue, high protein, and lymphocytosis
- SIADH and hyponatremia commonly occur in bacterial meningitis
- Leukopenia, thrombocytopenia, and coagulopathy may be present in meningococcal and rickettsial infections

Management

- Therapy should not be delayed if CNS infection is suspected
- Appropriate antimicrobials are required in bacterial meningitis, HSV encephalitis, Lyme meningitis, tuberculous meningitis, and rickettsial infection; in all cases, timely diagnosis and correct antimicrobial choice are critical
- If the practitioner cannot perform a lumbar puncture or there are contraindications to CSF examination, a blood culture should be obtained and antibiotics administered promptly

Drug choice and duration

- For infants
  - Ampicillin (300 mg/kg/day divided every 6 h) and cefotaxime (300 mg/kg/day divided every 6 h) is appropriate. Gentamicin can be used instead of cefotaxime
  - Acyclovir (60 mg/kg/day divided every 8 h) should be added if HSV infection is a concern
  - Vancomycin (60 mg/kg/day given every 6 h) should be added, if the Gram stain suggests pneumococcus
- Children older than 1–2 months of age
  - Vancomycin (60 mg/kg/day divided every 6 h) plus ceftriaxone (100 mg/kg/day given in one dose or divided into two doses) or cefotaxime (200–300 mg/kg/day divided every 6 h) should be used for empiric coverage
  - Once culture and susceptibility data are available, definitive therapy can be selected
- HSV meningitis
  - Neonatal HSV CNS infection typically is treated with IV acyclovir (60 mg/kg/day divided every 8 h) for 21 days
  - The dosing for non-neonates is 30 mg/kg/day divided every 8 h IV for 14–21 days
  - Follow-up CSF HSV DNA PCR should be evaluated at day 21 and the course of therapy extended if the result is still positive

Corticosteroids in bacterial meningitis

- Adjunctive treatment has reduced rates of mortality, severe hearing loss, and neurologic sequelae, significantly in adults who have community-acquired bacterial meningitis
- For children beyond the neonatal age groups, available data suggest that the use of adjunctive corticosteroids may be beneficial for Hib meningitis and could be considered in cases of pneumococcal meningitis
- The dose of dexamethasone for bacterial meningitis is 0.6 mg/kg/day divided into four doses and administered IV for 4 days. The first dose should be given before or concurrently with antibiotics

Care of the child exposed to meningitis

- Meningococcal and Hib disease create an increased risk for secondary infection in contacts
- Rifampin generally is the drug of choice for chemoprophylaxis in children

Prognosis for meningitis

- Intellectual deficits (intelligence quotient < 70), hydrocephalus, spasticity, blindness, and severe hearing loss are the most common sequelae
- Hearing loss occurs in approximately 30% of patients, can be unilateral or bilateral, and is more common in pneumococcal than meningococcal meningitis

Brain Abscess

Causes

- Chronic otitis media
- Paranasal sinus infection
- Otogenic infections, poor dental hygiene/complications from dental procedures
- Mastoiditis
- Metastatic spread, e.g., endocarditis
- Right-to-left cardiac or pulmonary shunts, especially in the presence of cyanotic congenital heart disease
- Neurosurgical procedures (VP shunt)
- Penetrating skull injury, congenital head and neck lesions
- Immunosuppression
- Commonly identified microorganisms: *Streptococci* and *Staphylococci*

Clinical presentation

- Triad of fever, headache, and focal neurologic deficit
- Headache (most common)
  - May be throbbing
  - Worsens with changes in posture or Valsalva maneuver
- Vomiting
- Drowsiness
- Confusion
- Coma
- Hemiparesis
- Papilledema

Frontal lobe abscesses

- Apathy, memory deficits
- Personality change
- Mental slowing

Cerebellar abscesses

- Nystagmus
- Defective conjugate eye movements to that side
- Ataxia
- Hypotonia

Laboratory diagnosis

- Little in the laboratory investigation of patients who have brain abscesses is specific to the diagnosis except for culture of the purulent material and antibiotic sensitivity of the responsible organism

Neuroimaging

- CT scan of the brain
  - Ill-defined
  - Low-density change within the parenchyma
  - Enhancement occurs following administration of contrast material

  - Classic ring-enhancing lesion with surrounding edema
  - Calcification is common in abscesses in neonates
- MRI

Antimicrobial therapy

- For abscesses arising as a result of sinusitis in which *Streptococci* are the most likely organisms, penicillin or cefotaxime and metronidazole
- Chronic otitis media or mastoiditis often is associated with *P. aeruginosa* and *Enterobacteriaceae*, antibiotics to treat abscesses secondary to these infections should include penicillin, metronidazole, and a third-generation cephalosporin
- Metastatic abscesses require a regimen based on the likely site of primary infection
- *S. aureus* is commonly isolated in abscess following trauma

Surgical intervention

- Provide a specimen of purulent material for bacteriologic analysis and antibiotic sensitivity testing
- Remove purulent material, thereby lowering ICP and decreasing the mass effect of the abscess
- Decompress and irrigate the ventricular system and debride the abscess in the event of its rupture into the ventricular system

Prognosis

- Brain abscess is a destructive lesion
- Neurologic sequelae: Epilepsy, motor deficits, visual field cuts, learning disability, hydrocephalus requiring VP shunt placement

PEARLS AND PITFALLS

- Monospot testing for acute mononucleosis is not indicated for children < 5 years of age because results are not reliable in young children.
- For children with multiple ulcerations of buccal mucosa and conjunctival involvement (mucous membranes) with skin rash, think erythema multiforme major (Stevens–Johnson syndrome).
- For children with ulcerations of posterior pharynx and painful papules on palms and soles, think enterovirus (especially Coxsackie virus) causing hand, foot, and mouth disease
- For a child with pharyngitis and redness of skin creases of anterior cubital fossae (Pastia lines, also called Thompson sign), think Group A Strep (strep throat).
- Egg allergy, including anaphylaxis, is not a contraindication to influenza vaccination. Only persons with a previous severe allergic reaction to flu vaccine should not receive flu vaccine.
- For returning travelers with fever, obtain malaria testing immediately and begin appropriate therapy (artemether–lumefantrine or atovaquone–proguanil for *P. falciparum*) if positive. Do not delay!
- Children < 2 years old can be colonized with *C. difficile* and may test positive for the organism. Only patients with *C. difficile* toxin production should be considered for treatment with first-line oral metronidazole.
- Patients with a classic bull's eye rash at the site of a tick bite do not require diagnostic testing. Treat for early localized Lyme disease with doxycycline (amoxicillin or cefuroxime for children < 8 years old).
- A positive blood culture for *Candid*a should be acted upon, including repeat blood culture and IV antifungal therapy with central line removal (if associated). A positive sputum culture for *Candida* may represent colonization and should be taken in the clinical context.
- Rash that begins on wrists and ankles, spreading centrally to palms/soles, is likely Rocky Mountain spotted fever. Treat with doxycycline no matter what age.
- Children who return from travel to the Middle East or Central America with ulcerative skin lesions and no systemic symptoms may have cutaneous Leishmaniasis.

- *Kingella kingae* is an etiologic agent of indolent septic arthritis or osteomyelitis in a young child. Can also cause bacteremia in infants and endocarditis in older children.
- Uncommon causes of fever in pediatrics include osteomyelitis, intraabdominal abscess, deep venous thrombosis, Still disease, recurrent fever syndromes (periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA), and familial Mediterranean fever).
- CNS complications of HIV include infection (cryptococcal meningitis, toxoplasmosis, CMV encephalitis, neurocysticercosis), lymphoma, progressive multifocal leukoencephalopathy (PML), peripheral neuropathy, and HIV encephalopathy.
- Nontuberculous mycobacteria can cause unilateral submandibular lymphadenitis with a violaceous hue in young children. Primary treatment is surgical excision, not antibiotics. Excision prevents fistula formation.
- Most mild community-acquired pneumonia can be treated as outpatient with oral amoxicillin as first-line therapy in patients who can tolerate oral fluids.
- The most common etiology for osteomyelitis *and* septic arthritis is *S. aureus*. Persons with sickle cell disease are at higher risk for *Salmonella.*
- For post-exposure rabies prophylaxis, administer rabies immune globulin at the bite site and rabies vaccine at a contralateral site on days 0, 3, 7, and 14 (four total doses of vaccine). For immunocompromised persons (HIV), a fifth dose of rabies vaccine is given on day 28.
- To avoid botulism in the 1st year of life, avoid giving infants prepared cereals that contain honey, as these may also be a potential source.
- For TB testing, can use an interferon gamma release assay (IGRA) for children > 2 years of age. Use skin testing for younger children.

Suggested Reading

American Academy of Pediatrics. *Bartonella henselae* (cat-scratch disease). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2018–2021 report of the committee on infectious diseases. 31st ed. Itasca: American Academy of Pediatrics; 2018a. p. 244–7.

American Academy of Pediatrics. Chlamydial infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2018–2021 report of the committee on infectious diseases. 31st ed. Itasca: American Academy of Pediatrics; 2018b. p. 273–83.

American Academy of Pediatrics. Cytomegalovirus infection, varicella-zoster virus infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2018–2021 report of the committee on infectious diseases. 31st ed. Itasca: American Academy of Pediatrics; 2018c. p. 310–7. and 869–83.

American Academy of Pediatrics. Gonococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2018–2021 report of the committee on infectious diseases. 31st ed. Itasca: American Academy of Pediatrics; 2018d. p. 355–65.

American Academy of Pediatrics. Group A streptococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2018–2021 report of the committee on infectious diseases. 31st ed. Itasca: American Academy of Pediatrics; 2018e. p. 616–28.

American Academy of Pediatrics. Human immunodeficiency virus infection. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2018–2021 report of the committee on infectious diseases. 31st ed. Itasca: American Academy of Pediatrics; 2018f. p. 459–76.

American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red book: 2018–2021 report of the committee on infectious diseases. 31st ed. Itasca: American Academy of Pediatrics; 2018g. p. 829–53.

American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. Pediatrics. 2008;122(5):1127–34.

American Academy of Pediatrics, American Public Health Association, National Resource Center for Health and Safety in Child Care and Early Education. CFOC standards online database. www.nrckids.org/CFOC. Aurora: National Resource Center for Health and Safety in Child Care and Early Education; 2019. Accessed 31 Jan 2019.

Amren DP, Anderson AS, Wannamaker LW. Perianal cellulitis associated with group A streptococci. Am J Dis Child. 1966;112(6):546–52.

Chayavichitsilp P, Buckwalter JV, Krakowski AC, Friedlander SF. Herpes simplex. Pediatr Rev. 2009;30(4):119–30.

Duong M, Markwell S, Peter J, Barenkamp S. Randomized, controlled trial of antibiotics in the management of community-acquired skin abscesses in the pediatric patient. Ann Emerg Med. 2010;55(5):401–7.

Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. J Am Acad Dermatol. 2007;57(5):737–63.

Khazaeni LM. Ocular complications of congenital infections. NeoReviews. 2017;18(2):e100–4.

Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics. 2014;134(5):21):e1474–502.

Hematology/Oncology

10

Arpan A. Sinha, Scott Moerdler, Ellen Fraint, Adit Tal, Nora E. Rahmani, and Kerry Morrone

RED BLOOD CELL DISORDERS

Anemias: Introduction

- Anemia is a reduction of red blood cell (RBC) volume or hemoglobin concentration below normal, which leads to a decrease in the capacity of blood to carry oxygen
- The body compensates by increasing cardiac output, increased 2,3-diphosphoglycerate (DPG) in RBCs, oxygen dissociation curve shift to right, increased erythropoietin (EPO)
- Bone marrow starts producing more RBCs—reticulocytosis
- Normal hemoglobin values vary with age, sex, race, and ethnicity
- Prevalence of anemia in different age groups (Fig. 10.1)

Anemia of Newborn (Fig. 10.2) [1]

- In utero hemoglobin increases with advancing gestational age
- At term: Cord blood hemoglobin is ~16.8 g/dL
- Hemoglobin values are lower in premature infants
- Physiologic nadir: After birth, hemoglobin starts decreasing and a nadir is reached at 8–12 weeks in term infants (nadir hemoglobin ~9 to 11 g/dL) and earlier around 6 weeks in premature infants (nadir hemoglobin ~7 to 10 g/dL)
- Normal process
- Does not result in signs of illness and does not require any treatment
- Related to increased tissue oxygenation experienced at birth, shortened RBC life span, and low EPO levels.
- Transplacental hemorrhage: Bleeding from fetal into the maternal circulation sometimes can be severe and cause clinically apparent anemia
- Diagnosis made by Kleihauer–Betke (KB) test, which detects fetal cells in maternal blood, or flow cytometry

Hemolytic Disease of the Newborn (Erythroblastosis)

- Transplacental passage of maternal antibodies active against paternal RBC antigens of the infant

A. A. Sinha
Jimmy Everest Center of Pediatric Hematology and Oncology, Department of Pediatrics, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

S. Moerdler
Pediatric Hematology/Oncology Program, Department of Pediatrics, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ, USA

E. Fraint · A. Tal · N. E. Rahmani · K. Morrone (✉)
Division of Pediatric Hematology, Oncology, Marrow and Blood Cell Transplantation, Department of Pediatrics, Children's Hospital at Montefiore, Bronx, NY, USA
e-mail: kmorrone@montefiore.org

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_10

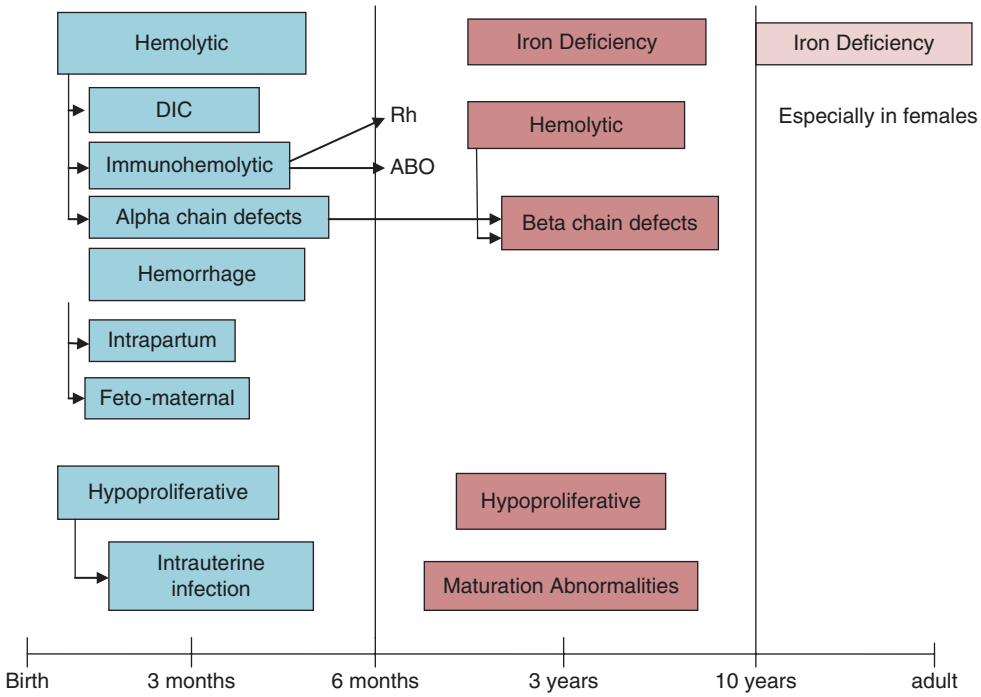


Fig. 10.1 Prevalence of anemia in different age groups

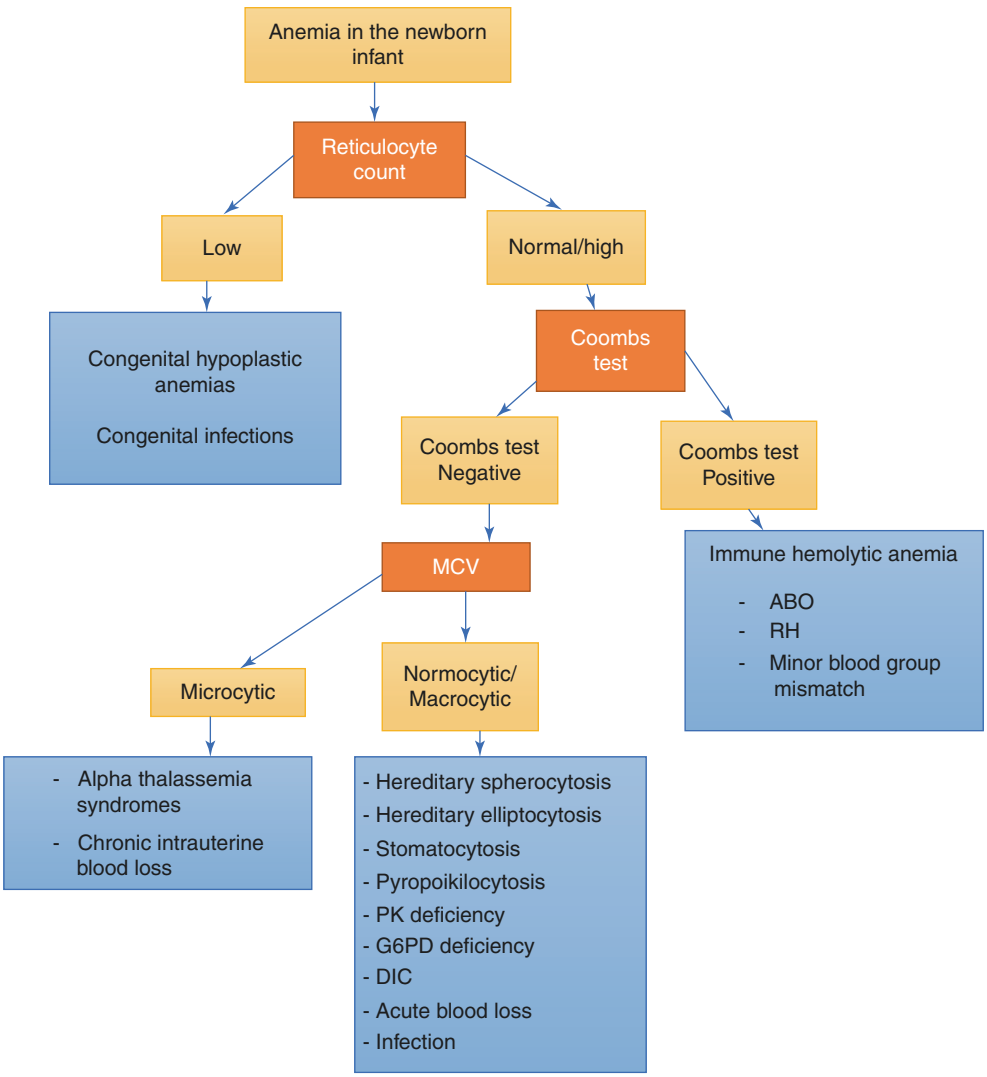


Fig. 10.2 An approach to the diagnosis of anemia in the newborn infant. *MCV* mean corpuscular volume, *PK* pyruvate kinase, *G6PD* glucose-6-phosphate dehydrogenase, *DIC* disseminated intravascular coagulation. (Adapted from Kliegman et al. [1], with permission)

- Important cause of anemia and jaundice in newborn infants
- More than 60 different RBC antigens are capable of eliciting an antibody response
- Significant disease is associated with the D antigen of the Rh group and with ABO incompatibility
- Hemolytic disease may be caused by other RBC antigens

RH Incompatibility

Pathogenesis

- Rh-negative mother develops antibodies by Rh-positive blood from Rh-positive fetus during pregnancy or delivery
- Initial rise in immunoglobulin M (IgM) and, later, IgG, which can cross the placenta to cause hemolytic manifestations
- Hemolytic disease rarely occurs during a first pregnancy but can be more severe in subsequent pregnancies

Clinical presentation

- Wide spectrum of hemolytic disease
- Jaundice evident within the first 6 h after birth
- Ranges from mild hemolysis to severe anemia
- Profound anemia, pallor, signs of cardiac decompensation, massive anasarca, and circulatory collapse
- Risk of bilirubin encephalopathy
- Hydrops fetalis

Laboratory

- Anemia
- Direct antiglobulin test (DAT), or Coombs test, is positive
- Reticulocyte count is increased
- The blood smear typically shows polychromasia and a marked increase in nucleated RBCs
- White blood cell (WBC) count may be normal or elevated; thrombocytopenia may develop in severe cases
- Indirect-reacting bilirubin content rises rapidly to high levels in the first 6 h of life

Antenatal diagnosis

- Antenatal diagnosis is very important
- Important history: History of previous transfusions, abortion, or pregnancy
- Fetal Rh status should be determined, and maternal titers should be monitored

Treatment

- Treatment of an unborn infant: Intravascular (umbilical vein) transfusion of packed RBCs
- Treatment of a liveborn infant: Blood transfusion, intravenous immunoglobulin, exchange transfusion

Prevention of Rh sensitization

- Prevent initial sensitization of Rh-negative mothers by Rho(D) immune globulin (human) within 72 h of delivery of an Rh-positive infant, ectopic pregnancy, abdominal trauma in pregnancy, amniocentesis, chorionic villus biopsy, or abortion

ABO Incompatibility

Introduction

- Most common cause of hemolytic disease of the newborn, generally results in milder disease than Rh incompatibility
- Usually, the mother is type O and the infant is type A or B
- Although ABO incompatibility occurs in 20–25% of pregnancies, hemolytic disease develops in only 10% of the offspring in such pregnancies

Clinical presentation

- Most cases are mild, with jaundice being the only clinical manifestation, which usually appears during the 1st 24 h
- Hydrops fetalis is extremely rare
- The liver and spleen are not greatly enlarged

- Rarely, it may be severe and symptoms and signs of kernicterus develop rapidly

Diagnosis

- Presence of ABO incompatibility
- A weakly to moderately positive DAT (Coombs test) result
- Spherocytes in the blood smear
- Indirect hyperbilirubinemia
- The hemoglobin is usually normal, but may be as low as 10–12 g/dL
- Reticulocytosis with polychromasia and increased numbers of nucleated RBCs
- In 10–20% of affected infants, the unconjugated serum bilirubin level may reach 20 mg/dL or more unless phototherapy is administered

Treatment

- Phototherapy
- In severe cases, intravenous immunoglobulin (IVIG) administration can reduce the need for exchange transfusion
- Exchange transfusions may be needed in some cases to correct dangerous degrees of anemia or hyperbilirubinemia

Clinical approach to a child with anemia

- Thorough history and physical exam
- Initial laboratory testing should include hemoglobin (Hgb)/hematocrit (Hct), RBC indices, WBC count and differential, platelet count, reticulocyte count, and examination of the peripheral blood smear
- Further systematic evaluation based on initial tests (follow flow chart below) (Fig. 10.3) [1]

Key classification markers

- Size of RBC mean corpuscular volume (MCV) can be classified as
  - ***Microcytic*** (MCV < 70 + age)
  - ***Macrocytic*** (MCV > 100)
  - ***Normocytic*** (MCV > 70 + age and < 100)
- Reticulocyte count
  - Reticulocytosis indicates bone marrow response to anemia
  - If bone marrow is overwhelmed, or anemia is secondary to a primary bone marrow (production) problem, then low/inadequate reticulocyte count may be seen

MICROCYTIC ANEMIA

Iron-Deficiency Anemia (IDA)

- Most common type of anemia in infancy and childhood

Etiology

- Blood loss
  - Gastrointestinal (GI) bleed (ulcer, gastritis, drug induced with NSAIDs, steroids, etc.)
  - Intravascular hemolysis and hemoglobinuria
  - Menstruation
  - GI lesions: Meckel diverticulum, vascular malformations
  - Cow's milk allergy
  - Goodpasture syndrome
  - Hemosiderosis
  - Parasitic infections
- Nutritional
  - High cow's milk consumption (> 32 oz/day)
  - Malnutrition
  - Insufficient intake (vegan or vegetarian, iron-poor diet)
- Physiologic
  - Low birth weight
  - Rapid growth
  - Pregnancy
- Impaired absorption
  - Malabsorption syndrome (celiac disease, inflammatory bowel disease [IBD])
  - Gastrectomy

Clinical presentation

- Weakness
- Fatigue
- Difficulty concentrating
- Headaches

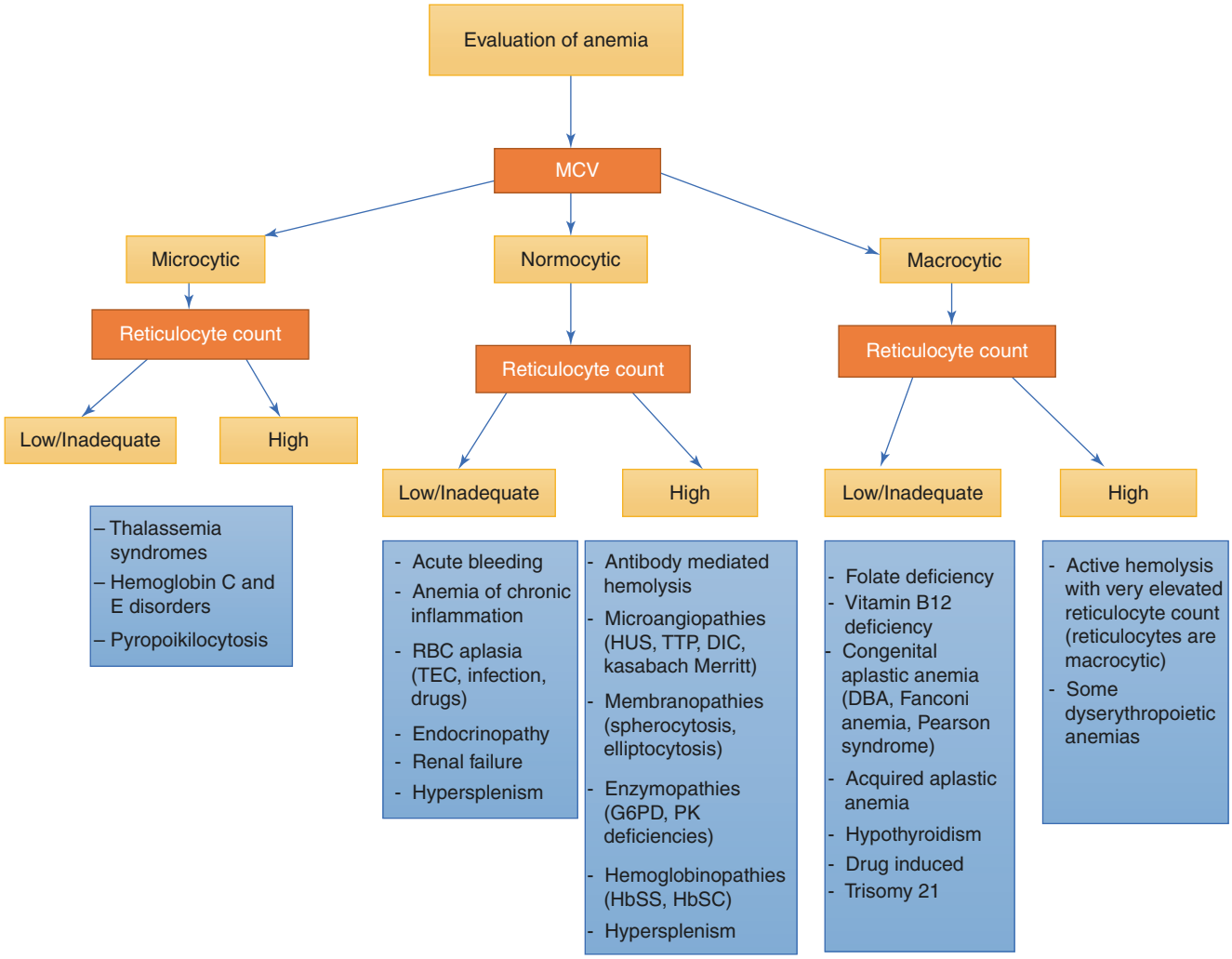


Fig. 10.3 Approach to anemia in older children based on mean corpuscular volume. *MCV* mean corpuscular volume, *RBC* red blood cell, *TEC* transient erythroblastopenia of childhood, *HUS* hemolytic uremic syndrome, *TTP* thrombotic thrombocytopenic purpura, *DIC* disseminated intravascular coagulation, *G6PD* glucose-6-phosphate dehydrogenase, *PK* pyruvate kinase, *DBA* Diamond–Blackfan anemia. (Adapted from Kliegman et al. [1], with permission)

- Pallor
- Pica
- If severe (Hgb < 5 g/dL)
  - Tachycardia, palpitations
  - Irritability
  - Systolic murmur

Laboratory

- Low iron level
- Low reticulocyte count
- Low ferritin (< 10 ug/L)—most sensitive and specific test
- Low transferrin saturation
- High total iron-binding capacity (TIBC)
- RBCs become more microcytic and hypochromic (Fig. 10.4)
- Increased poikilocytosis
- Low MCV
- Increased red blood cell distribution width (RDW)
- Thrombocytosis (can reach up to 1 million/mm^3)
- Mentzer index > 13 (MCV/RBCs)

Treatment

- Dietary change
  - Avoid excessive cow's milk (less than 16 ounces per day)

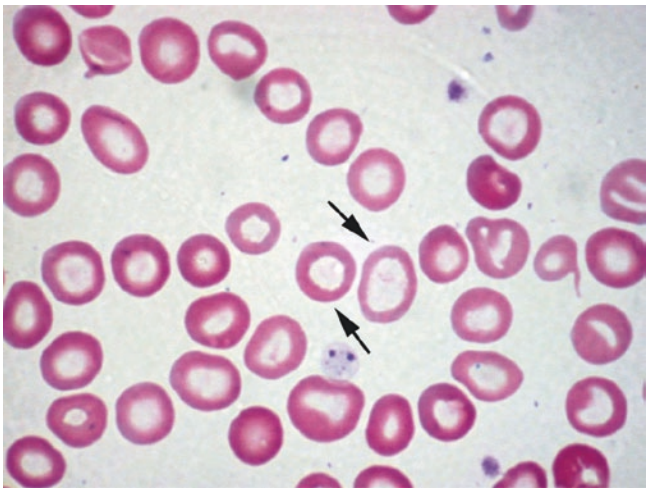


Fig. 10.4 Peripheral blood smear example of hypochromic/microcytic anemia. Notice the variability in the sizes of red blood cells. The *arrows* point to hypochromic erythrocytes with large central hollow. (Courtesy of M. Nawar Hakim, MD, Department of Pathology, Texas Tech University Health Sciences Center, El Paso, Texas)

  - Iron-fortified formula and rice cereal in infants
  - Meat and other iron- and vitamin C-rich foods
- Oral iron therapy—ferrous sulfate, gluconate, fumarate
  - Convenient, inexpensive, and effective
  - 3 to 6 mg/kg of elemental iron in two to three divided doses daily
  - Continue for 3 months to replenish iron stores
  - Improved absorption with vitamin C, worse absorption with milk
  - Side effects include nausea, vomiting, constipation, and metallic taste
  - Changes after treatment with oral iron:
    - Within 12–24 h: Irritability decreases, increased appetite
    - 36 to 48 h: Initial bone marrow response with erythroid hyperplasia
    - 48 to 72 h: Reticulocytosis, peaks at 5–7 days
    - 1 to 3 months: Repletion of stores
    - Recheck hemoglobin 4 weeks after initiation of treatment
      - Hgb should rise at least 1 g/dL within 4 weeks
- Parenteral iron therapy
  - Circumvents absorption problems
  - Indications:
    - Malabsorption
    - IBD
    - Chronic blood loss
    - Chronic kidney disease
  - Increases hemoglobin levels more quickly than oral iron
  - More expensive than oral therapy
  - Side effects include hypersensitivity reactions, headache, flushing, nausea, back and chest pain, arthralgia
    - Resolves within 48 h
- Blood transfusion
  - Appropriate for children with Hgb < 5 g/dL or with clinical signs and symptoms such as respiratory distress, lethargy, significant tachycardia
  - If Hgb < 5 g/dL, transfuse slowly and with caution or avoid fluid overload or congestive heart failure
    - 5 ml/kg over 4 h

Anemia of Chronic Disease

- Associated with chronic inflammatory states
  - Pyogenic infections
  - Systemic diseases—HIV, malignancy
  - Autoimmune diseases, e.g., systemic lupus erythematosus, rheumatoid arthritis

Etiology

- Renal production of EPO suppressed by inflammatory cytokines (IL-1, IL-6, TNF-alpha), resulting in decreased RBC production
- Hepcidin, an acute phase reactant, decreases intestinal iron absorption and prevents release of iron from macrophages
  - Lack of iron availability for developing RBCs

Laboratory

- Usually normocytic and normochromic, rarely microcytic

- Anemia can be mild (Hgb 10–11 g/dL) or severe (Hgb < 9 g/dL)
- Low serum iron
- Low transferrin saturation
- Elevated serum ferritin
- Normal-to-low TIBC

Treatment

- Correct the underlying disorder
- Red blood cell transfusions or EPO may be necessary in severe, symptomatic anemia

THALASSEMIAS

Alpha-Thalassemia

- Healthy individuals have 4 alpha-globin genes, 2 on each chromosome 16
- Typically caused by gene deletions in one or more of these genes
  - Alpha-globin production is reduced to absent
  - Severity of phenotype increases with loss of one, two, three, or four functioning alpha-globin alleles
- Geographic regions: Southeast Asia, Mediterranean (more severe), Africa
- Diagnosis: Clinically or with alpha-globin chain analysis
- Excess beta chains lead to beta 4 chains (HbH)
- Excess gamma chains lead to a tetramer of gamma-globin (Hb Barts)

Alpha-Thalassemia Syndromes

Silent Carrier

- Deletion or dysfunction of one gene
- Asymptomatic
- Normal complete blood count (CBC)
- Normal Hgb electrophoresis

Alpha-Thalassemia Trait/Minor

- Deletion or dysfunction of two genes
  - Heterozygosity (aa/--), more common in Asian ancestry
  - Homozygosity (a-/a-), more common in African ancestry
- Mild hypochromic microcytic anemia

Laboratory

- Mentzer index < 13
- Hgb > 9 g/dL
- Normal Hgb electrophoresis or Hb Barts (3–8%)
- Diagnosed incidentally or misdiagnosed as IDA

Hemoglobin H Disease

- Deletion of three genes
- Mild to moderate hypochromic microcytic anemia
- Symptomatic at birth with mild anemia (Hgb 9–11 g/dL), neonatal jaundice
- Anemia exaggerated by infection, exposure to oxidizing drugs, pregnancy
- May develop splenomegaly, jaundice, and cholelithiasis
- Up to 30% HbH on electrophoresis

Alpha-Thalassemia Major

- Deletion of four genes
- Severe microcytic anemia with hydrops fetalis
- Usually fatal in utero
- Hb Barts on electrophoresis, no HbF, HbA, HbA2
  - Hb Barts cannot deliver oxygen to tissues because of its affinity for oxygen is too high

Beta-Thalassemia

- Healthy individuals have 2 beta-globin genes, 1 on each chromosome 11
- Beta-globin production is reduced to absent
- Multiple possible genetic mutations/deletions

- Geographic regions: Southeast Asia, Mediterranean, Africa (milder)
- Accumulation of excess alpha-globin chains on the RBCs causes increased reactive oxygen species and damage to cellular proteins → shortened RBC survival
- Clinical manifestations caused by ineffective erythropoiesis, chronic hemolytic anemia, and iron overload
- Diagnosed by hemoglobin electrophoresis or beta-globin chain analysis

Beta-Thalassemia Syndromes

Beta-Thalassemia Minor (Trait)

- Heterozygous β0 or β+
- Asymptomatic
- May have microcytic anemia, hypochromia, target cells on peripheral smear
- Hgb electrophoresis with slightly elevated HgbA2

Beta-Thalassemia Intermedia

- Variable symptoms, but more symptomatic than minor
- Results from diverse genetic explanations due to beta gene mutations

Laboratory

- Hgb between 7 and 10 g/dL
- Smear shows microcytosis, hypochromia, target cells, and basophilic stippling
- Hgb electrophoresis with elevated HgbA2 and HbF
- Serum iron, ferritin, and transferrin saturation may be increased
- Mentzer index < 13

Clinical presentation

- Varied
- Can present with pallor, jaundice, anemia, splenomegaly, or skeletal deformities during childhood or later
- Hypercoagulable state, extramedullary hematopoiesis, pulmonary hypertension
- Usually does not require regular transfusions, but may require more transfusions over time

Beta-Thalassemia Major (Cooley Anemia)

- Most severe form of beta-thalassemia and presents at 6–12 months of age
- Minimal to no beta-globin chain production, little to no HbA
- Caused by homozygosity or compound heterozygosity for β0 mutations or β+ variants
- Excess alpha-globin chains result in increased RBC destruction and ineffective erythropoiesis

Laboratory

- Severe, transfusion-dependent microcytic hypochromic anemia
- Reticulocytopenia with elevated RBC count
- Nucleated RBCs
- Target cells on smear
- Elevated LDH, indirect bilirubin, low haptoglobin—indicates hemolysis
- Iron overload, elevated ferritin
- Hgb electrophoresis with elevated HgbA2 and HbF

Clinical presentation

- Pallor, jaundice, fatigue
- Gallstones
- Hepatosplenomegaly
- May be less severe with increased HbF
- Extramedullary hematopoiesis—skeletal deformities
  - Maxillary hypoplasia, flat nasal bridge, frontal bossing
  - Osteopenia/osteoporosis—pathologic bone fractures
- Endocrinopathies from iron overload
  - Hypothyroidism
  - Hypoparathyroidism
  - Diabetes mellitus
  - Growth impairment
  - Hypogonadism

- Cardiovascular from iron overload
  - Congestive heart failure
  - Cardiac arrhythmias
  - Pulmonary hypertension

Treatment

- Chronic hypertransfusion therapy once diagnosis is confirmed
- Iron chelation therapy
  - Deferoxamine—parenteral agent
  - Deferasirox and deferiprone (oral agent more tolerable)
- Monitoring with ferritin level, cardiac, and liver magnetic resonance imaging (MRI) for iron load in critical organs
- Splenectomy may be indicated with severe anemia and increase in transfusion requirements, growth retardation, hypersplenism with other cytopenias, splenic infarction, splenic vein thrombosis, or symptomatic
- Allogeneic hematopoietic stem cell transplant

OTHER MICROCYTIC ANEMIAS

Lead Poisoning

- Young children (< 6 years) more susceptible to toxic effects of lead
- Typically, exposure is through ingestion or inhalation (paint chips, water, pottery)
- Can lead to permanent neurocognitive deficits, acute encephalopathy at extremely high levels, chronic interstitial nephritis
- Anemia—lead inhibits heme synthesis and induces hemolysis
- Elevated blood erythrocyte protoporphyrin or zinc protoporphyrin (heme precursors), high serum lead level
- Smear shows basophilic stippling of RBCs, ringed sideroblasts in bone marrow

Sideroblastic Anemia

- Heritable or acquired erythropoietic disorders due to abnormalities in heme synthesis and mitochondrial function
- Often associated with syndromes
- Variable severity of anemia
- Presence of ringed sideroblasts (RBC precursors with iron-containing granules) in bone marrow aspirate [2]
- Anisocytosis, poikilocytosis, target cells, Pappenheimer bodies on blood smear
- May have microcytic anemia in the absence of iron deficiency or thalassemia, low reticulocyte count
- Splenectomy contraindicated for treatment

METHEMOGLOBINEMIA (CONGENITAL OR ACQUIRED)

- Iron molecule in hemoglobin is oxidized from ferrous (Fe2+) to ferric (Fe3+) state, resulting in methemoglobin (MHg), which cannot transport oxygen
- This leads to decreased oxygen-carrying capacity of blood and cyanosis with significant MHg levels
- Increase in MHg can be *acquired* (from exposure to toxic substances) or *congenital* (absence of reductive pathways, e.g., NADH cytochrome b5 reductase deficiency)
- *Acquired* more common, with infants particularly more vulnerable
- May be seen in infants who ingested foods and water high in nitrates (well water), infants exposed to aniline teething gels or other chemicals, infants with severe gastroenteritis and acidosis
- MHg of 15% associated with visible cyanosis, MHg of 70% is lethal
- MHg colors the blood brown

Treatment

- IV methylene blue

MACROCYTIC ANEMIA

Folic Acid Deficiency

- Folic acid is necessary to form biologically active folates
- Folates are essential for DNA replication and cellular proliferation
- Humans cannot synthesize folate and depend on dietary sources
- Folate supplementation is recommended during pregnancy to prevent neural tube defects in fetus

Etiology

1. **Inadequate intake**
   - Especially during times of increased requirement—seen in pregnancy, growth spurts in children, and in chronic hemolytic anemias
   - Malnutrition is the most common cause of folate deficiency in older children
   - Dietary sources include green vegetables, fruits, and animal organs like liver and kidneys
   - Body stores for folic acid are limited; 2–3 months on folate-free diet
   - Goat's milk is deficient, and supplementation must be given if goat's milk is the main food
   - Powdered milk may also be a poor source of folic acid, unless supplemented
2. **Decreased folic acid absorption**
   - Chronic diarrhea, removal of ileum or IBD, celiac disease
   - Certain anticonvulsant medication, e.g., phenytoin and primidone, can impair absorption
3. **Congenital abnormalities in folate transport and metabolism**
   - Hereditary folate malabsorption
   - Functional methionine synthase deficiency
   - Dihydrofolate reductase deficiency
4. **Drug-induced abnormal metabolism**
   - Methotrexate, pyrimethamine, trimethoprim

Clinical presentation

- Clinical features associated with anemia
- Irritability, chronic diarrhea, poor weight gain
- Hemorrhage from thrombocytopenia in severe cases

Laboratory

- Macrocytic anemia (MCV > 100 fl)
- Variations in RBC shape and size
- Low reticulocyte count, nucleated RBCs
- Megaloblastic changes, including hypersegmented neutrophils (> 5 lobes)
- Elevated LDH (marker of ineffective erythropoiesis)
- Neutropenia and thrombocytopenia may be present in severe deficiency
- Hypercellular bone marrow with megaloblastic changes

Treatment

- Rule out concomitant B12 deficiency before starting folic acid therapy, as folic acid treatment can correct the anemia of B12 deficiency; however, it can aggravate associated neurologic abnormalities
- Treat with folic acid at 0.5–1 mg/day oral/parenteral for 3–4 weeks until a definite hematologic response is seen followed by maintenance dose therapy with a multivitamin (containing 0.2 mg of folate) daily
- Hematologic response can occur within 72 h (can be used as a diagnostic test as well, if diagnosis is unclear)

Vitamin B12 Deficiency

- Active metabolites of cobalamin (vitamin B12) are essential cofactors in two metabolic reactions—methylation of homocysteine to methionine and conversion of methylmalonyl-coenzyme A (CoA) to succinyl CoA. These reactions are critical to DNA, RNA, and protein synthesis
- Cobalamin is synthesized exclusively by microorganisms, and humans rely on dietary

sources (animal products, including meat, eggs, fish, and milk) for their needs
- Vitamin B12 stores last for 3–5 years
- In young infants born to mothers with low vitamin B12 stores, clinical signs of cobalamin deficiency can become apparent in the first 6–18 months of life

Etiology

1. **Inadequate B12 intake**
   - In infants, mostly nutritional due to decreased vitamin B12 levels in breast milk of B12-deficient mothers
   - In children and adults, strict vegetarian or vegan diet
2. **Impaired absorption**
   - Secondary to gastric surgery or medications that impair gastric acid secretion may result in intrinsic factor (IF) deficiency, leading to decreased vitamin B12 absorption
   - Pancreatic insufficiency
   - History of neonatal necrotizing enterocolitis, IBD, celiac disease, or surgical removal of the terminal ileum can result in impaired absorption of vitamin B12
   - Fish tapeworm *Diphyllobothrium latum* infestation
   - Hereditary intrinsic factor deficiency (HIFD)—rare autosomal recessive disorder due to mutations in the IF gene, which leads to lack of gastric IF or a functionally abnormal IF
   - Imerslund–Gräsbeck syndrome—rare, autosomal recessive, clinically apparent by age six
     - Selective vitamin B12 malabsorption in the ileum, and consequent vitamin B12 deficiency
     - Presents with megaloblastic anemia, possible neurologic defects and/or proteinuria
     - Fatal if it remains untreated
   - Classic pernicious anemia (autoimmune gastritis)—can rarely affect children during adolescence. Presence of IF antibodies or anti-parietal cell antibodies. Can have associated immunologic abnormalities, candidiasis, hypoparathyroidism, other endocrine deficiencies
3. **Absence of vitamin B12 transport protein**
4. **Inborn errors of cobalamin metabolism**

Clinical presentation

- May have nonspecific manifestations such as weakness, fatigue, failure to thrive, and irritability
- Can also have pallor, glossitis, vomiting, diarrhea, and icterus
- Neurologic symptoms can include sensory and motor deficits, seizures, developmental delay, developmental regression, and neuropsychiatric changes
- Neurologic problems can occur in the absence of any hematologic abnormalities

Laboratory

- Macrocytic anemia (MCV > 100) (Fig. 10.5)
- Low reticulocyte count for degree of anemia
- Megaloblastic changes, including hypersegmented neutrophils (> 5 lobes)

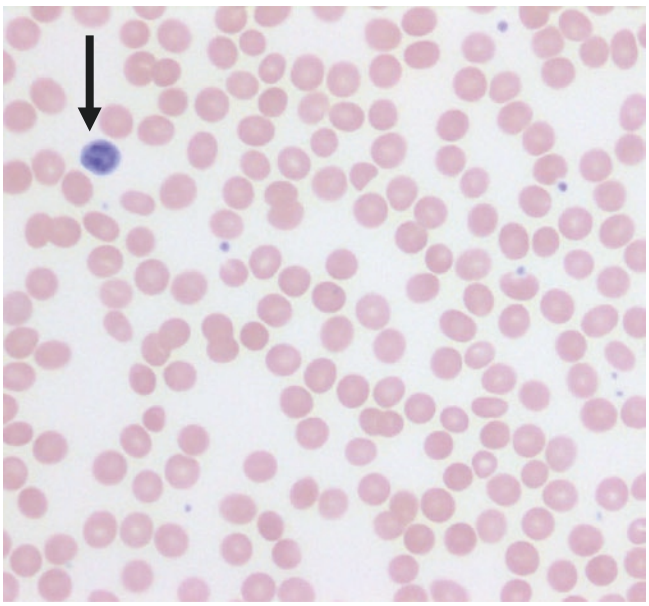


Fig. 10.5 Red cells are usually approximately the size of a small lymphocyte nucleus (arrow). In this case, the red cells are slightly larger than the lymphocyte nucleus on average. Macrocytic anemia is most often a result of folate or vitamin B12 deficiency

- Elevated LDH
- Normal iron and folic acid levels
- Increased methylmalonic acid and total homocysteine levels
- Excessive excretion of methylmalonic acid in the urine is also a sensitive index of vitamin B12 deficiency. Serum homocysteine, on the other hand, is also elevated in folate deficiency, homocystinuria, and renal failure
- Anti-IF antibodies and anti-parietal cell antibodies—useful for the diagnosis of pernicious anemia. Classic Schilling test is no longer regarded as the diagnostic test

Treatment

- Initial correction with parenteral administration of vitamin B12. Goal is to correct deficiency, consolidate response, replete stores, and prevent relapse
- Treat underlying cause
- Duration of treatment dependent on underlying cause. May require lifelong supplementation if underlying cause irreversible, e.g., pernicious anemia

Pearson Marrow–Pancreas Syndrome

- A form of congenital hypoplastic anemia
- Signs of marrow failure in the neonatal period, characterized by macrocytic anemia and, occasionally, neutropenia and thrombocytopenia
- Fetal hemoglobin is elevated
- Bone marrow shows vacuolated erythroblasts and myeloblasts
- Associated clinical features are failure to thrive, pancreatic fibrosis with insulin-dependent diabetes, muscle and neurologic impairment, early death
- Caused by mitochondrial DNA defect, variable clinical course
- Supportive care includes RBC transfusions as needed for anemia and granulocyte-colony stimulating factor (G-CSF) for severe neutropenia

Diamond–Blackfan Anemia (Congenital Hypoplastic Anemia)

Etiology

- Rare, congenital bone marrow failure syndrome
- 90% of cases are recognized in the first year of life
- Mostly autosomal dominant
- Primary defect in the erythroid progenitors

Clinical presentation (Tables 10.1 and 10.2)

- Profound anemia manifested by 2–6 months of age
- More than 50% have associated congenital anomalies
- Craniofacial abnormalities (hypertelorism, snub nose, and high arched palate) are most common—50% cases
- Skeletal anomalies, mostly upper limb and hand (e.g., thumb abnormalities, absent radial pulse—30% cases)
- Short stature
- Genitourinary, cardiac, ophthalmologic, and musculoskeletal anomalies may also be seen

Laboratory

- Macrocytic RBCs with no hypersegmentation of neutrophils
- Normal B12 and folate

Table 10.1 Clinical findings of Fanconi anemia and Diamond–Blackfan syndrome

Fanconi anemia	Diamond–Blackfan anemia
All bone marrow cells are affected (aplastic anemia)	Pure red cell aplasia (normal WBCs and platelets)
Normal adenosine deaminase enzyme (ADA)	High adenosine deaminase enzyme (ADA)
Macrocytic	Macrocytic
Elevated fetal hemoglobin (HbF)	Elevated fetal hemoglobin (HbF)
Thumb anomalies	Thumb anomalies
Short stature	Short stature
Skin changes are common	Not common

WBC White blood cells

Table 10.2 Clinical findings of Diamond–Blackfan syndrome and transient erythroblastopenia of childhood

Transient erythroblastopenia of childhood	Diamond–Blackfan anemia
Pure red cell aplasia (acquired)	Pure red cell aplasia (congenital)
1–3 years of age (most common)	2–3 months of age
Common	Extremely rare
No congenital anomalies	Thumb anomalies, SS, craniofacial anomalies, urogenital anomalies
Normocytic (normal MCV)	Macrocytic
Normal fetal hemoglobin	Elevated fetal hemoglobin (HbF)
Normal serum iron	High serum iron
Normal adenosine deaminase enzyme (ADA)	High adenosine deaminase enzyme (ADA)
Transfusion rarely required	Transfusion and steroids are always required

MCV mean corpuscular volume, *SS* short stature

- Increased adenosine deaminase activity in most patients (useful test to differentiate it from transient erythroblastopenia of childhood [TEC])
- Reticulocyte percentages are characteristically very low despite severe anemia
- Thrombocytosis or, rarely, thrombocytopenia, and occasionally neutropenia, may also be present
- Decreased RBC precursors in bone marrow
- Elevated serum iron
- Normal bone marrow chromosomal studies
- Negative parvovirus B19 titers

Treatment

- Corticosteroids are the mainstay of therapy
- Chronic transfusions initially for 1 year; delaying steroids may also be considered to prevent steroid side effects on growth and development in early infancy
- Iron-chelating agents (if transfusion-dependent)
- Stem cell transplantation for nonrespondents to corticosteroids, and after several years of RBC transfusions

Prognosis

- Cancer predisposition syndrome
- Increased risk for myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), colon carcinoma, osteosarcoma, and female genital cancers
- Survival around 75% at age 40

Fanconi Anemia

Genetics

- Mostly autosomal recessive, rarely can be X-linked recessive

Clinical presentation (Table 10.1)

- Skin abnormalities ~55% of cases (most common)
  - Hyperpigmentation of the trunk and intertriginous areas, *café-au-lait* spots, vitiligo
- Short stature ~50% of cases
- Upper limb anomalies ~43% of cases
  - Absent thumbs, triphalangeal thumbs
- Hypogonadal and genital changes (mostly male) ~35% of cases
  - Underdeveloped penis, undescended testes, hypogonadism, malformation of vagina, uterus
- Fanconi anemia "facies" ~23% of cases
  - Microcephaly, small eyes, epicanthal folds, abnormally shaped or absent ears
- Renal malformations ~21%
  - Horseshoe kidney, absent or duplicate kidney
- Cardiovascular, GI malformations ~11%
- Other skeletal findings like congenital hip dysplasia
- Intellectual disability (ID)

Laboratory

- Marrow failure usually starts in the first decade of life
- Initial findings—macrocytosis and thrombocytopenia followed by granulocytopenia and then anemia

- Variable progression to full-blown pancytopenia due to aplasia
- Diagnostic testing by diepoxybutane (DEB) or mitomycin C assay to detect increased chromosome fragility

Complications
- In addition to bone marrow failure and physical anomalies, this is a cancer predisposition syndrome
- Can lead to carcinoma of the head and neck, and upper esophagus, gynecological cancers
- Can also lead to advanced MDS and acute leukemia

Treatment
- Supportive care and close observation if not transfusion-dependent
- Androgens may produce a response in 50% of patients. Side effects—liver injury, peliosis hepatis, liver tumors
- Hematopoietic stem cell transplantation (HSCT) as a curative option

Shwachman–Diamond Syndrome

Genetics
- Autosomal recessive

Clinical presentation
- Recurrent bacterial infections (secondary to neutropenia)
- Exocrine pancreatic insufficiency → fat malabsorption (absence of steatorrhea does not exclude Shwachman–Diamond syndrome) → failure to thrive
- Skeletal abnormalities: Short stature (metaphyseal chondrodysplasia); abnormal digits (syndactyly, clinodactyly, or supernumerary metatarsals)
- Others: Abnormal facies (bifid uvula, cleft palate, dental dysplasia, hypertelorism, microcephaly), retinitis pigmentosa

Laboratory/workup
- Neutropenia
- Abnormal pancreatic enzymes and steatorrhea
- Bone marrow showing myeloid hypoplasia
- Pancytopenia—60%
- Abdominal imaging/GI consult for evaluation of exocrine pancreatic insufficiency

Diagnosis
- *SBDS* mutation analysis is definitive in 90%

Complications—increase with age, usually after 10 years of age
- Aplastic anemia
- MDS
- Acute myelogenous leukemia

Treatment
- Androgen with low-dose prednisone

NORMOCYTIC ANEMIA

- Approach to normocytic anemia (Fig. 10.6)

Transient Erythroblastopenia of Childhood

- Most common acquired RBC aplasia in childhood
- Temporary, self-limited in otherwise healthy child

Etiology
- Suppression of RBC production
- May be seen after viral infection

Clinical presentation (Table 10.2)
- Can occur from 1 month to 6 years (more common at ages 1–4 years)
- Males more affected than females

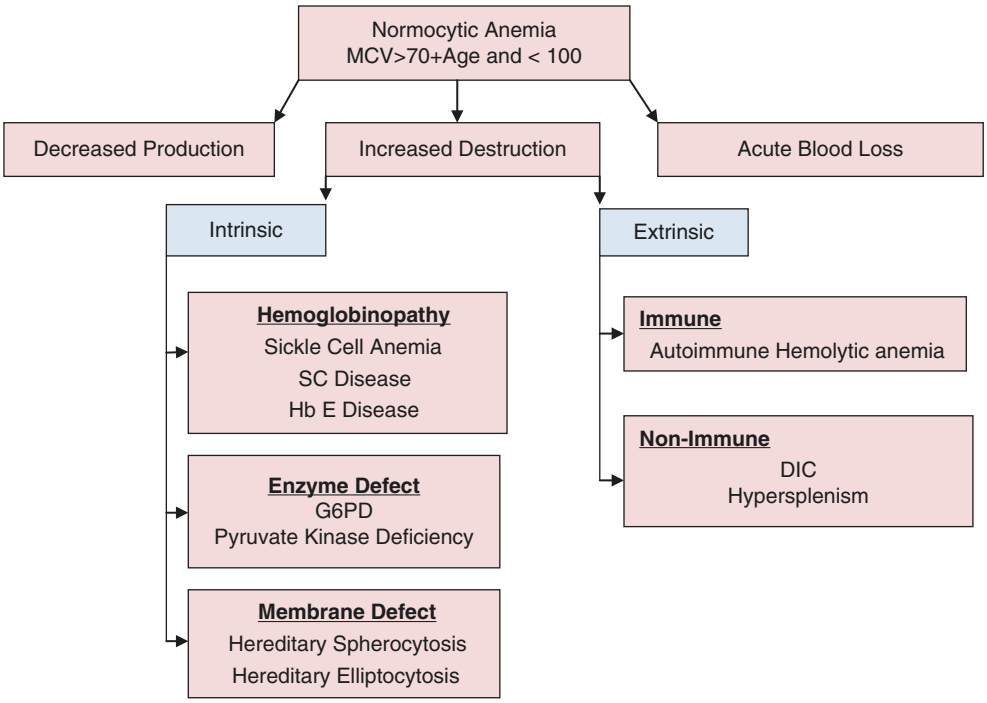


Fig. 10.6 Approach to normocytic anemia. *MCV* mean corpuscular volume, *G6PD* glucose-6-phosphate dehydrogenase, *DIC* disseminated intravascular coagulation

Laboratory

- Hgb usually 6–8 g/dL
- Low reticulocyte count
- MCV normal for age
- May have mild neutropenia
- Bone marrow biopsy rarely required
- Normal adenosine deaminase (ADA)

Treatment

- Reassurance
- Complete recovery in 1–2 months
- Transfusion required only if symptomatic and interfering with quality of life

HEMOLYTIC ANEMIA

Hereditary Spherocytosis

Background

- Most common erythrocyte membrane defect
- Autosomal-dominant inheritance
- Less frequently may be autosomal recessive
- 30% have no family history and considered sporadic

Etiology

- Molecular defects in membrane proteins of the RBC cytoskeleton, most commonly spectrin or ankyrin
- Reduction in surface-to-volume ratio causes spherocytes that are osmotically fragile and trapped by the spleen

Clinical presentation

- Neonatal period: Jaundice and hyperbilirubinemia sufficient to require exchange transfusion
- Variably symptomatic based on severity
- Anemia
  - Pallor, fatigue, exercise intolerance
- Splenomegaly
- Pigment gallstones at a young age
- Susceptible to aplastic crisis as a result of parvovirus B19 infections
  - Erythroid marrow failure may result rapidly in profound anemia, high cardiac output failure, hypoxia, cardiovascular collapse; may have thrombocytopenia

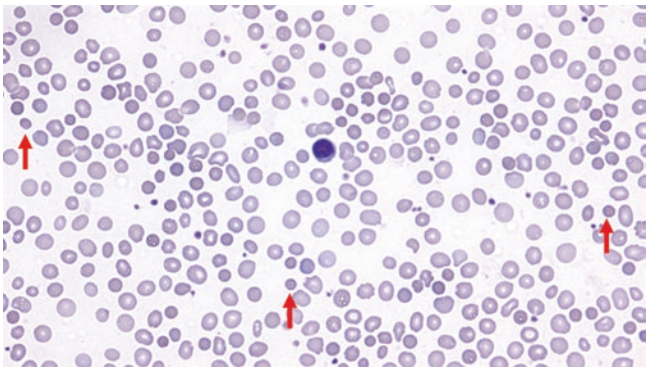


Fig. 10.7 Red cells should be similar in size to 1/3 of central pallor. In hereditary spherocytosis, the red cells lack central pallor and are hyperchromatic (40×). Red arrows point out a few of the examples in this field

Laboratory

- Normocytic anemia (Fig. 10.7)
- Elevated mean corpuscular hemoglobin concentration (MCHC)
- Reticulocytosis
- Elevated LDH
- Low haptoglobin
- Indirect hyperbilirubinemia
- Spherocytes on peripheral smear
- Increased osmotic fragility
  - Not reliable in neonatal period
- Can also be diagnosed with flow cytometry (eosin-5′-maleimide [EMA] binding test)

Treatment

- Folic acid supplementation to prevent deficiency
- Indications for splenectomy
  - Severe disease
  - Low Hgb with frequent need for transfusions
  - Aplastic crises
  - Poor growth
  - End-organ damage—cardiomegaly
- Partial splenectomy can improve transfusion-dependent children with severe case, while theoretically preserving some splenic function and protection against sepsis
- Vaccination for encapsulated organism *Haemophilus influenzae*, meningococcus, pneumococcus should be given before splenectomy, then prophylactic penicillin V 125 mg twice a day < 5 years and 250 twice a day for > 5 years

Hereditary Elliptocytosis

- Also classified as a membrane defect of RBCs, but less common than hereditary spherocytosis
- Autosomal dominant
- Clinical presentation similar as in hereditary spherocytosis

Laboratory

- Elongated, oval, or elliptically shaped RBCs on peripheral smear
  - May also see poikilocytes, spherocytes, microcytosis, and fragmentation on smear

Treatment

- No specific therapy if asymptomatic and minimal hemolysis
- Otherwise similar to hereditary spherocytosis

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Etiology

- Originates from an acquired genetic mutation in *PIGA* in hematopoietic cell membrane
  - *PIGA* involved in synthesis of a membrane anchor that links cell surface proteins to the plasma membrane on hematopoietic cells
- Lack of complement inhibitors CD55 and CD59 on the RBC surface (no anchor)
- Cells become destroyed by complement-mediated lysis

- Severity of illness correlates with the size of the PNH clone

Clinical presentation

- Aplastic anemia may precede the diagnosis of PNH
- Nocturnal or morning hemoglobinuria (sign of intravascular hemolysis)
- Hemolytic anemia
  - Fatigue, jaundice
- Thrombosis and thromboembolic phenomena may occur and can be severe—leading cause of death

Laboratory

- Anemia
- Reticulocytosis
- Negative DAT (Coombs test)
- Indirect hyperbilirubinemia
- Low LDH
- Decreased haptoglobin
- Free serum hemoglobin
- Flow cytometry for CD55 and CD59

Treatment

- Acute
  - RBC transfusions for severe anemia (Hgb < 7 g/dL)
- Chronic
  - Eculizumab—anticomplement therapy (binds to C5 and prevents its cleavage, thereby inhibiting the formation of the membrane attack complex [MAC], decreasing susceptibility to cell destruction)
    - Reduces hemolysis, decreases need for transfusions, reduces risk of thrombosis, and improves quality of life
  - Anticoagulation treatment for thrombosis
    - No preventative anticoagulation indicated unless high risk (hospitalized with illness, postsurgical)
  - Allogeneic hematopoietic stem cell transplant is the only curative treatment

Sickle Cell Disease

Background

- Hemoglobin S is the result of a mutation in the beta-globin chain, with a substitution of valine for glutamic acid at the sixth position
- Autosomal recessive
- Complications arise from vascular–endothelial dysfunction, nitric oxide deficiency, inflammation, oxidative stress and reperfusion injury, hypercoagulability, increased neutrophil adhesiveness, and platelet activation

Clinical presentation

- Can be diagnosed on neonatal screen
- Manifestations begin around 6 months of age, when adult Hgb becomes dominant and Hgb F decreases
- Functional asplenia by around 5 years of age
  - High susceptibility to infections
  - Encapsulated organisms most common
- Large-vessel vasculopathy
  - Cerebrovascular disease
  - Pulmonary hypertension
  - Priapism
  - Retinopathy
- Progressive ischemic organ damage
  - Hyposplenism
  - Renal failure
  - Bone disease
  - Liver damage

Laboratory

- Normocytic anemia
- Sickle cells on smear (Fig. 10.8)
- Hemoglobin electrophoresis shows Hgb S (SS, SC, S-beta-thalassemia)
- May have elevated WBC count

General considerations

- Hydroxyurea (HU) as preventative management
  - Increases level of hemoglobin F and total hemoglobin

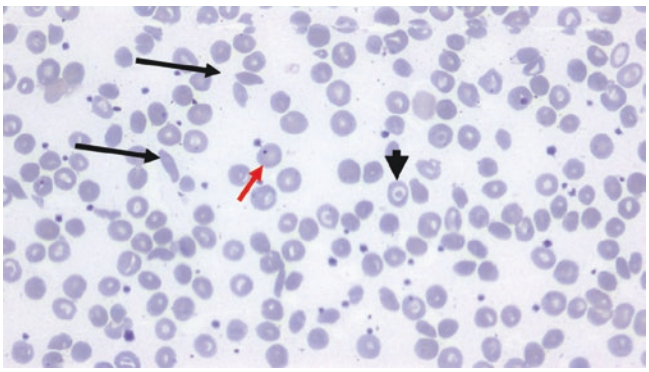


Fig. 10.8 Peripheral smear (40×) from a patient with sickle cell disease showing sickle cells (black arrows), target cells (arrowhead), and a Howell–Jolly body (red arrow)

  - Decreases the pain crises by 50%; prevents splenic dysfunction, cerebral artery damage, and stroke
  - If begun in infancy, may preserve the splenic function and decrease acute chest syndrome (ACS)
  - Initial dose is 20 mg/kg, increase gradually by 2.5–5 mg/kg up to a max of 35 mg/kg/day
  - Monitor for toxicity—mainly myelosuppression
  - Glutamine (Endari) can be given with HU for prevention of morbidities
- Fever
  - Medical emergency—increased risk of bacteremia, sepsis, meningitis, pneumonia/ACS
  - Draw blood culture and perform chest radiograph
  - Initiate parenteral third-generation cephalosporin (i.e., ceftriaxone) × 2 doses and treat other causes if identified

Infection

- Due to functional hyposplenism
- Infectious prophylaxis
  - Penicillin V potassium (VK)
    - Orally from birth until 5 years of age
    - 125 mg orally twice a day 0–3 years
    - 250 mg orally twice a day 3–5 years
  - Continue prophylaxis for life if there is a history of severe infection with encapsulated organisms, splenectomy
- Osteomyelitis
  - Staph or salmonella
  - Treat with prolonged parenteral antibiotics per infectious guidelines

Acute Chest Syndrome

- Occurs in as many as 50% of sickle cell disease (SCD) patients, major cause of hospitalization and mortality

Etiology

- Infection
  - Most commonly *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*
- Vaso-occlusion
- Hypoventilation secondary to pain (pain crisis commonly precedes development of ACS)
- Atelectasis
- Thromboembolism

Clinical presentation

- Fever
- Chest pain
- Hypoxemia
- Respiratory distress
- New infiltrate on chest radiograph

Treatment

- Antibiotic coverage
  - Macrolide
  - Third generation cephalosporin
- Pain management
- Simple RBC transfusion for hypoxemia
- Exchange transfusion indications
  - Continued hypoxemia and worsening respiratory distress in the setting of Hgb > 10 g/dL
- Can lead to risk of pulmonary hypertension—leading cause of mortality in adults with EPO

Vaso-occlusive *Crisis*

- Disruption of blood flow in microvasculature by sickle cells, which have reduction in deformability and increased adhesion to endothelial cells
- Risk factors include increased activity, exposure to cold, infection, hypoxia, and acidosis

- Presents as pain most often in the chest, back, abdomen, and extremities

Treatment
- IV hydration
- Anti-inflammatory medications—NSAIDs, acetaminophen
- Often requires opioids and hospitalization for severe pain crises

Prevention
- Hematologists offer HU to all patients over the age of 9 months with SS or Sβ 0 thalassemia, and Endari (glutamine) to all children with SCD over the age of 5 years

Dactylitis
- Pain and swelling of the hands and feet
- Often the first presentation of pain in toddlers with SCD
- Occurs in 50% of children by 2 years of age
- Differential diagnosis may include osteomyelitis if unilateral
- Treatment with anti-inflammatory pain medications, including acetaminophen and NSAIDs

Priapism
- Prolonged penile erection in the absence of stimulation
- May lead to irreversible changes—tissue necrosis, fibrosis, erectile dysfunction
- If < 2–4 h, treatment with hydration, oral pain management
- If > 4 h, medical emergency
  - IV hydration
  - IV analgesics
  - Aspiration of blood from the corpus cavernosum followed by injection of an alpha-adrenergic agonist

Splenic Sequestration
- Caused by vaso-occlusion in the spleen—pooling of RBCs
- May occur in up to 30% of children with SCD

Clinical presentation
- Rapidly enlarging spleen
- Acute drop in hemoglobin (at least 2 g/dL from baseline) with reticulocytosis
- Can lead to hypovolemic shock and death

Treatment
- IV hydration for hemodynamic stability
- RBC transfusion

Prognosis
- Parents should be taught to palpate spleen
- Repeat episodes are common
- Mortality rate is as high as 10–15%

Aplastic Crisis

Etiology
- Arrest of erythropoiesis, leading to profound and acute drop in hemoglobin
- Occurs most commonly secondary to infection
  - Parvovirus B19
  - May also be caused by bacterial and other viral infections

Clinical presentation
- Pallor
- Fatigue
- Decreased activity
- Poor feeding
- Altered mentation

Laboratory
- Severe anemia
- Reticulocytopenia
- May have thrombocytopenia

Treatment
- Transient with recovery of reticulocytes within 2–14 days
- RBC transfusion support until reticulocyte recovery

Neurologic Complications
- Up to 11% of patients with SCD will have clinically apparent stroke by the age of 20 years

- Ischemic stroke more common in children
- Can also have silent infarctions and transient ischemic attacks (TIAs), which cause neurocognitive and behavioral defects
  - Poor learning in school, academic failure

Clinical presentation

- Headache
- Focal weakness
- Altered mental status
- Seizures
- Posterior reversible encephalopathy syndrome (PRES)
- Cerebral venous sinus thrombosis

Imaging

- Overt stroke means presence of focal neurological deficit > 24 h and or cerebral infarct by T2-weighted MRI
- Silent stroke means absence of focal neurological lesions > 24 h with cerebral infarct on T2-weighted MRI

Treatment

- Immediate (STAT) computed tomography (CT)/MRI
- Initially simple RBC transfusion to raise Hgb to 10 g/dL
- Exchange transfusion
  - Goal is to decrease HbS to < 30%
  - Requires placement of apheresis catheter

Primary prevention of stroke

- Transcranial Doppler (TCD) to measure blood velocity
  - If > 200 cm/s, prophylactic transfusion indicated to decrease Hgb S to < 30%

Secondary prevention of stroke

- Initiation of RBC transfusion therapy after first stroke to prevent recurrent episodes to keep Hgb S < 30%
- Cessation of transfusion associated with recurrence
- Risk of iron overload
  - Treat with iron-chelating agents
  - Deferoxamine (IV), deferasirox (orally), deferiprone (orally)

Renal Disease

- Renal infarction and papillary necrosis
- Proteinuria
- Hematuria
- Diminished concentrating ability (hyposthenuria)
- Renal tubular acidosis
- Urinary tract infections, pyelonephritis
- Hypertension
- Treatment
  - IV hydration with gross hematuria
  - ACE inhibitors in chronic kidney disease and hypertension
    - Lower protein excretion by > 50%

Other Complications

- Delayed puberty
- Impaired growth
- Avascular necrosis
  - Most often femoral and humeral heads
  - Progressive joint destruction seen on MRI
  - Treatment with pain management, surgical core decompression, may progress to require hip replacements in adult life
- Retinopathy
  - Due to retinal artery occlusion and ischemia
  - Can progress to retinal detachment
  - Annual ophthalmologic examination for early detection

Pyruvate Kinase Deficiency

Introduction

- PK deficiency is an inherited autosomal-recessive RBC enzyme disorder that causes chronic hemolysis
- PK is an active enzyme in Embden–Meyerhof–Parnas pathway (glycolytic pathway)
- Deficiency leads to defective RBC glycolysis and decreased adenosine triphosphate (ATP) production, leading to rigid and deformed RBCs with decreased RBC survival
- Unlike *G6PD* deficiency, the hemolysis is present at all times and is not precipitated by exposure to drugs

Clinical presentation

- Clinical course can vary. Can cause severe neonatal hemolytic anemia leading to jaundice and kernicterus or can be mild like well-compensated hemolysis first noted in adulthood
- Signs and symptoms of hemolytic anemia may be present: Pallor, icterus, splenomegaly, gallstones, leg ulcers, etc.

Laboratory

- Significant reticulocytosis; becomes more pronounced after splenectomy
- Smear shows polychromasia and mild macrocytosis to reflect the elevated reticulocyte count
- Pyknocytes may be seen

Treatment

- Phototherapy and exchange transfusions for hyperbilirubinemia in newborns
- RBC transfusion for severe anemia as necessary
- Splenectomy should be performed after the child is 5–6 years of age, if requiring frequent transfusions
- Folate supplementation

Glucose-6-Phosphate Dehydrogenase Deficiency

Introduction

- G6PD is an enzyme involved in the hexose monophosphate pathway, essential for glucose metabolism in RBCs, with a vital role in prevention of cellular damage from reactive oxygen species (ROS)
- G6PD deficiency affects more than 400 million people worldwide, overall 4.9% global prevalence
- Global distribution parallels that of malaria
- Clinically presents with two clinical syndromes:
  - Episodic hemolytic anemia (more common)
  - Chronic nonspherocytic hemolytic anemia

Pathophysiology

- G6PD catalyzes conversion of glucose 6-phosphate to 6-phosphogluconic acid, which produces NADPH, which keeps glutathione (GSH) in the reduced functional state
- Reduced GSH is necessary for protection against oxidant threats from certain drugs and infections
- G6PD activity falls rapidly as RBC ages, which leads to decreased glucose metabolism and impaired elimination of oxidants and subsequent loss of RBC membrane integrity
- Severity of hemolysis depends on the quantity and type of G6PD deficiency and nature of hemolytic agent (usually an oxidation mediator)

Genetics

- X-linked recessive
- Variable intermediate expression shown by heterozygous females due to variable X-inactivation (lyonization)
- More common in African American, Mediterranean, Middle Eastern, and Asian ethnic groups

Clinical presentation

- Most individuals are asymptomatic, unless hemolysis triggered
- Episodes of hemolysis are produced by infection, drugs, and ingestion of fava beans
- Hemolysis ensues usually about 24–48 h after exposure
- Drugs causing hemolysis include antioxidant drugs like aspirin, sulfonamides, antimalarials, and rasburicase
- Ingestion of fava beans can cause acute life-threatening hemolytic syndrome
- G6PD deficiency can also cause severe neonatal jaundice, even leading to kernicterus in some types
- In patients with chronic nonspherocytic hemolytic anemia, patients can have chronic hemolysis and splenomegaly and may require frequent blood transfusions

Laboratory

- Normocytic anemia
- Reticulocytosis with polychromasia may be seen
- Low haptoglobin, hemoglobinuria in severe episodes
- RBCs with Heinz bodies due to hemoglobin precipitation (need supravital stain), bite cells may be seen
- Diagnosis demonstrated by reduced G6PD activity in RBCs
- Immediately after a hemolytic episode, reticulocytes and young RBCs predominate. These young cells have significantly higher enzyme activity than do older cells, so G6PD testing may be falsely negative for G6PD deficiency. Test should be repeated a few weeks after the hemolytic episode

Treatment

- Prevention of hemolysis
- Special consideration given while prescribing the known oxidant drugs in patients (especially males belonging to ethnic groups with high incidence of G6PD deficiency)
- If hemolysis has occurred, discontinue the oxidant agent
- Blood transfusion as needed for severe hemolysis

Other Enzyme Deficiencies

Background

- Sole energy source of erythrocytes is the glycolytic production of ATP. Thus, any defect in the various enzymes in the glycolytic pathway can lead to hemolytic anemia
- Mostly transmitted as autosomal recessive, except:
  - Phosphoglycerate kinase (PGK) deficiency-X-linked abnormality
  - Adenosine deaminase (ADA) overproduction is an autosomal dominant disorder

Clinical presentation

- Manifestations of hemolysis or, if the enzymopathy is present in other tissues, may involve other organ systems

Enzyme deficiencies

- Hexokinase deficiency
- Glucose phosphate isomerase deficiency
- Aldolase deficiency
- Diphosphoglycerate deficiency
- Enolase deficiency
- Phosphofructokinase deficiency
  - Myopathy
  - Associated with type VII glycogen storage disease
  - Common in Ashkenazi Jews
- Triose phosphate isomerase deficiency
  - Cardiac anomalies
  - Recurrent infections
  - Progressive neuromuscular disease with generalized spasticity
- Phosphoglycerate kinase deficiency
  - First ATP-generating enzyme
  - Sex-linked recessive
  - ID
  - Seizures
  - Behavioral disorders

Autoimmune Hemolytic Anemia

Introduction

- Antibodies are formed against antigens on RBC surface, which destroys the RBC, leading to hemolysis
- Hallmark is positive DAT (Coombs test), which detects a coating of immunoglobulin/complement on the RBC surface

Etiology

- Antibodies may be produced as an inappropriate immune response to an RBC antigen (Ag) or to another epitope similar to an RBC Ag (molecular mimicry)

- An infectious agent may alter the RBC membrane so that it become antigenic
- Drugs ~20% of cases, e.g., penicillin and cephalosporins, etc.
- IgM cold antibodies usually associated with infections, e.g., mycoplasma and Epstein–Barr virus (EBV)

Two types of *autoimmune hemolytic anemia (AIHA)*

1. ***Warm AIHA***
   - Antibodies are active at 35–40 °C ("warm" antibodies)
   - Most often belong to the IgG class. They do not require complement for activity
2. ***Cold AIHA (cold agglutinin disease)***
   - Cold antibodies agglutinate RBCs at temperatures < 37 °C (98.6 °F)
   - They are primarily of the IgM class and require complement for hemolytic activity

1. ***Warm AIHA***
   - Clinical presentation
     - Can be acute or chronic
     - Acute transient type lasting 3–6 months, mainly in children 2–12 years—70–80% of patients. Frequently preceded by an infection
     - Spleen is usually enlarged and is the primary site of destruction of antibody-coated RBCs
     - This form characterized by a consistent response to steroids, a low mortality rate, and full recovery
     - Other clinical patterns have a prolonged and chronic course, more frequent in infants and in children > 12 years. Hemolysis may continue for many months or years
   - Laboratory
     - Profound anemia
     - Considerable reticulocytosis, spherocytosis, and polychromasia. (in some cases, a low reticulocyte count may be seen, particularly early in the episode)
     - Leukocytosis
     - Platelet count is usually normal, but concomitant immune thrombocytopenic purpura sometimes occurs—Evans syndrome)
     - The direct antiglobulin test is strongly positive
   - Treatment
     - Supportive treatment for mild cases
     - Corticosteroids for IgG-mediated disease
     - Blood transfusion (blood unit with the least reaction by the Coombs technique)—transient benefit, lifesaving in severe anemia
     - IVIG
     - Splenectomy in persistent cases

2. ***Cold Agglutinin Disease***
   - Cold antibodies usually have specificity for the oligosaccharide antigens of the I/i blood group system
   - They may occur in primary or idiopathic cold agglutinin disease, secondary to infections such as those from *Mycoplasma pneumoniae* and EBV or secondary to lymphoproliferative disorders
   - Cold agglutinin disease is less common in children than in adults
   - More frequently results in an acute, self-limited episode of hemolysis
   - Glucocorticoids not effective
   - Patients should avoid exposure to cold and should be treated for underlying disease
   - If severe, treatment includes immunosuppression and plasmapheresis
   - Splenectomy is not useful in cold agglutinin disease

Paroxysmal Cold Hemoglobinuria

- Mediated by the Donath–Landsteiner (D-L) antibody
- An IgG cold-reactive autoantibody with anti-P specificity
- In vitro, the D-L antibody binds to RBCs in the cold, and the RBCs are lysed by complement as the temperature is increased to 37 °C
- Most reported cases are self-limited
- Most cases are associated with nonspecific viral infections

- Previously congenital or acquired syphilis used to be the most common underlying cause of paroxysmal cold hemoglobinuria
- Accounts for 30% of immune hemolytic episodes among children
- Treatment includes transfusion for severe anemia and avoidance of cold ambient temperatures

WHITE BLOOD CELL DISORDERS

Neutropenia

Acute

- Viral infection: EBV, respiratory syncytial virus, influenza A and B, parvovirus, hepatitis, human herpesvirus 6 (HHV6) infections, measles, rubella
- Bacterial infection
- Hypersplenism
- Drug-induced—recovery after medication cessation
  - Antimicrobials: Sulfonamides, penicillin
  - Antirheumatics: Gold, phenylbutazone, penicillamine
  - Anticonvulsants: Phenothiazine
  - Analgesic and anti-inflammatory: Ibuprofen

Chronic

Cyclic Neutropenia

Clinical presentation

- Approximately 2-day cycles with changing neutrophil counts with neutropenia spanning 3–6 days
- Nadir may be in severe range
- During nadir, the following can develop: Fever, oral ulceration, gingivitis, pharyngitis, skin infections, and occasionally serious infections (pneumonia, necrotizing enterocolitis with peritonitis, and *Escherichia coli (E. coli) or Clostridium* sepsis)

Laboratory

- Counts 2–3/week for 6 weeks, genetic testing

Treatment

- Prophylactic G-CSF during nadir in some cases
- Immediate attention to fevers

Chronic Benign Neutropenia

- No specific underlying etiology found
- No serious infections

Ethnic Neutropenia/Benign Familial Neutropenia

- Seen in patients of African American, Mexican, and Mediterranean descent: No treatment

Congenital Neutropenia

Kostmann Syndrome (Severe Congenital Neutropenia)

- Autosomal recessive

Clinical presentation

- Skin infections and abscesses—most common
- Pneumonia and deep tissue abscesses—often life-threatening
- Mouth ulcers, gingivitis
- Otitis media
- Mild hepatosplenomegaly (HSM)
- Bone marrow arrest
- Progress to MDS/AML

Treatment

- G-CSF
- Stem cell transplant for MDS/AML

Fanconi Anemia

Cartilage Hair Hypoplasia

Chediak–Higashi Syndrome

Immune

- Autoimmune neutropenia
- Neonatal alloimmune neutropenia
- Dysgammaglobulinemia
- Hyper IgM syndrome
- HIV
- PNH

Nutritional

- B12 and folic acid deficiency—Ineffective erythropoiesis with possible associated neutropenia

Bone Marrow Infiltration

Malignancy
- MDS
- Lymphoproliferative disorders

Pancytopenia

- Reduction in the number of RBCs, WBCs, and platelets below age-adjusted lower limit of normal
  – Anemia, leukopenia, thrombocytopenia

Results from: (Table 10.3)
- Decreased production of blood cells or bone marrow failure
- Immune-mediated destruction
- Non-immune-mediated sequestration in periphery

Table 10.3 Differential diagnosis of pancytopenia

	Congenital/inherited	Acquired	
Mechanism	Decreased bone marrow production	Decreased bone marrow production	Increased destruction/sequestration
Common causes	Fanconi anemia	Chemotherapy	Liver disease
	Gaucher disease	Radiation therapy	Portal hypertension
		Megaloblastic anemia	
		Bone marrow infiltration	
		Myelodysplasia	
		Myelofibrosis	
		Aplastic anemia	
		Connective tissue disorders	
		(Rheumatoid arthritis, SLE)	
		Acute viral infections (CMV, EBV)	
		HIV	
		Mycobacterial infection	
Uncommon causes	Bone marrow failure syndromes	Paroxysmal nocturnal hemoglobinuria	Hypersplenism secondary to myelo- and lymphoproliferative disorders
	Dyskeratosis congenita	Anorexia nervosa	Hemophagocytic syndromes
	Congenital amegakaryocytic thrombocytopenia	GVHD	Drug-induced immune pancytopenia
	Shwachman syndrome	Heavy-metal poisoning Infection (parvovirus, HHV6, or CMV in transplant recipients, legionnaires' disease)	Evans syndrome with tricytopenia Infection (brucellosis, visceral leishmaniasis)

SLE systemic lupus erythematosus, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *GVHD* graft-versus-host disease, *HHV6* human herpesvirus 6

Signs and symptoms

- Weakness
- Fatigue
- Easy bruising and bleeding
- Pallor
- Tachycardia
- Shortness of breath
- Infections

Management and treatment

- Depends on etiology
- Treat underlying cause
- Immunosuppression
- Drugs to stimulate bone marrow
- Bone marrow transplant
- Supportive care
  - Blood transfusions

Aplastic Anemia

- Decreased production of mature blood cells
  - Due to reduction in the number or function of progenitor cells
- Characterized by pancytopenia and hypocellular bone marrow
- Injury or loss of pluripotent hematopoietic cells in the absence of infiltrative disease of the bone marrow
- Acquired and inherited causes (Table 10.4)
- Most cases are idiopathic with no identifiable underlying cause
- Vital to distinguish inherited vs. acquired in order to guide management and treatment
- Diagnosis made by bone marrow aspiration and biopsy (aplastic anemia Fig. 10.9) [3] (normal bone marrow Fig. 10.10) [4]
  - Profoundly hypocellular bone marrow with decrease in all elements
  - Marrow space composed of fat cells and marrow stroma
  - Residual hematopoietic cells are normal

Table 10.4 Causes of aplastic anemia

Acquired	Inherited
Secondary	Fanconi anemia
Radiation	Dyskeratosis congenita
Drugs	Shwachman–Diamond syndrome
Chemotherapy	Amegakaryocytic thrombocytopenia
Antiepileptics	Diamond–Blackfan anemia
Anti-inflammatory	Familial aplastic anemias
Antithyroid	
Toxic chemicals	
Benzene	
Solvents	
Viruses	
EBV	
Hepatitis (non-A, B, C, E, or G)	
HIV	
Immune diseases	
Eosinophilic fasciitis	
SLE (uncommon)	
GVHD	
Paroxysmal nocturnal hemoglobinuria	
Pregnancy	
Myelodysplasia	
Idiopathic	

EBV Epstein–Barr virus, *SLE* systemic lupus erythematosus, *GVHD* graft-versus-host disease

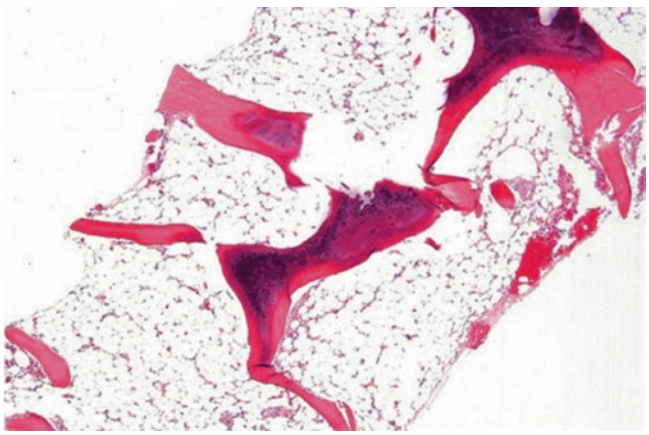


Fig. 10.9 Aplastic anemia: Bone marrow biopsy of a teenage girl with aplastic anemia whose marrow is strikingly hypocellular for age. (From Rogers [3], with permission)

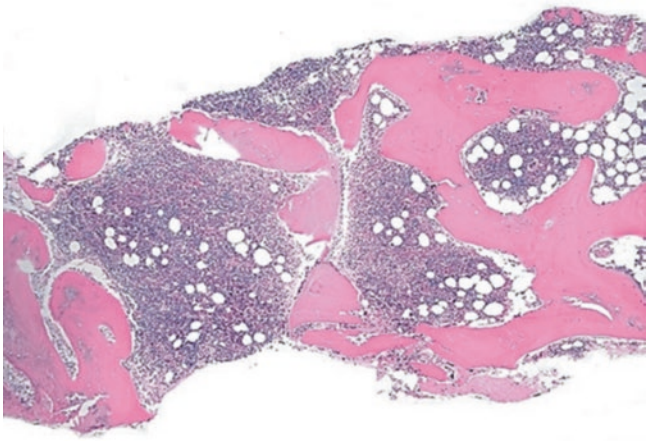


Fig. 10.10 Normal bone marrow biopsy of a 4-year-old boy. Marrow cellularity is estimated by the percentage of hematopoietic cells in the total volume of marrow space. Marrow cellularity declines with age, with the highest cellularity in infants and young children and the lowest cellularity in the elderly (estimated cellularity = 100 minus age). The current biopsy has approximately 90–96% cellularity (100–4 = 96). (From Schafernak and Calvo [4], with permission)

PLATELET DISORDERS

- Approach to platelet disorders (Fig. 10.11)

Thrombocytopenia

Diagnosis

- Normal platelet count 150,000–450,000
- Low platelet count may be due to clumping in the tube and can be ruled out on blood smear or pseudothrombocytopenia screen
- Differential guided by platelet count, platelet size, the presence of other cytopenias, and cause from low production or excessive consumption

Increased Consumption

Kasabach–Merritt Syndrome

- Platelet destruction due to high-velocity turbulent blood flow through venous malformation
- May also be associated with abnormal coagulation profile
- Urgent venous malformation treatment and supportive care required

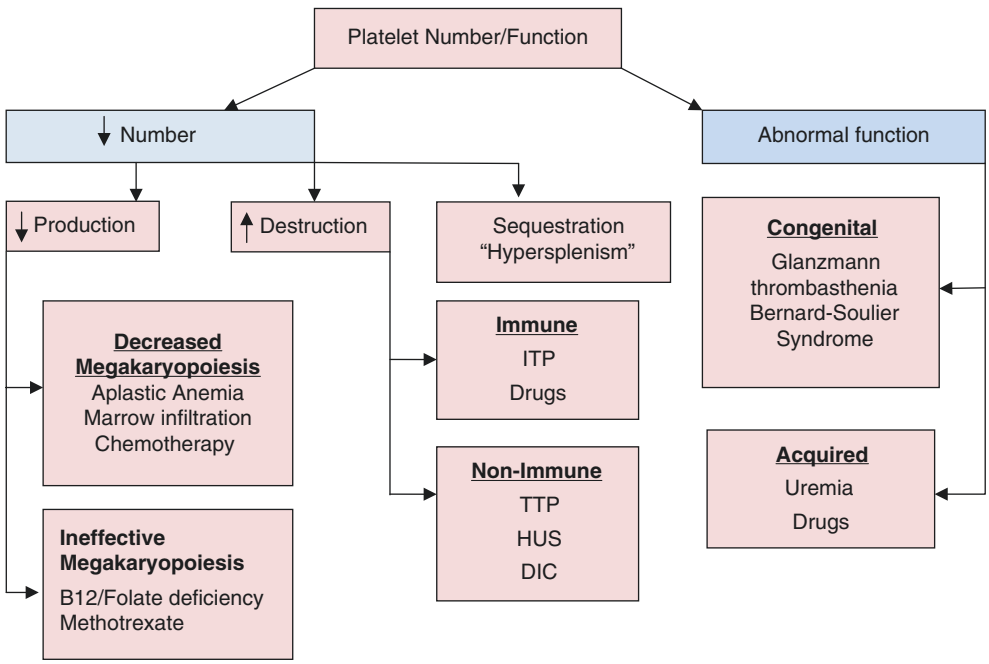


Fig. 10.11 Approach to platelet disorders. *ITP* immune thrombocytopenic purpura, *TTP* thrombotic thrombocytopenic purpura, *HUS* hemolytic uremic syndrome, *DIC* disseminated intravascular coagulation

Immune Thrombocytopenic Purpura (ITP)

- Autoimmune destruction of platelets
- Large platelet size indicates rapid production and release of new platelets from the marrow
- Often associated with a preceding viral illness
- Typically self-limited, resolving within several weeks
- Chronic ITP if lasting > 6 months, and more likely to be associated with a rheumatologic condition
- Intracranial or mucosal bleeding are the most severe complications
- Observation is typically sufficient. Treatment with IVIG or steroids is indicated with significant bleeding

Hemolytic Uremic Syndrome

- Thrombocytopenia associated with microangiopathic hemolytic anemia and kidney failure
- Clinical symptoms include bloody diarrhea, fever, vomiting, and decreased urine output
- Renal failure, thrombocytopenia, and hemolytic anemia usually present 5–10 days after initial symptoms and diarrhea has already resolved
- Blood smear demonstrates schistocytes, indicating intravascular destruction of RBCs (Fig. 10.12)

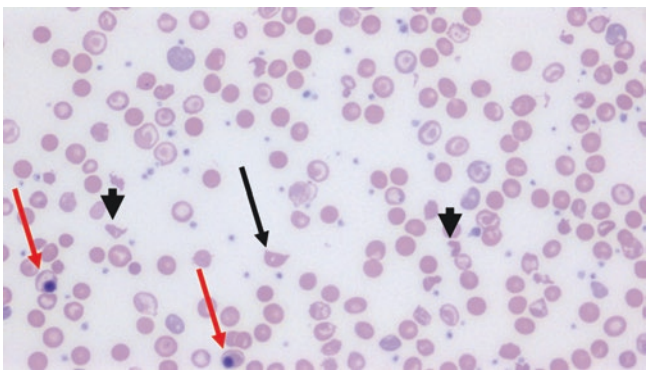


Fig. 10.12 Peripheral smear (40×) from a patient with hemolytic anemia showing a schistocyte (*black arrow*) as well as fragmented cells (*arrowheads*). Note the presence of nucleated red cells (*red arrows*)

- High LDH, high indirect bilirubin, anemia, thrombocytopenia, elevated creatinine, positive Shiga toxin
- Typically associated with hemorrhagic diarrhea due to Shiga toxin produced by *E. coli* O157
- Aggressive supportive care needed for kidney failure, and anemia

Thrombotic Thrombocytopenic Purpura

- Dysfunction of *ADAMTS13* due to acquired autoantibody/inhibitor or congenital mutation
- Lack of *ADAMTS13* function leads to failure to cleave large von Willebrand multimers
- Intravascular shearing on large vWF multimers; causes hemolytic anemia and thrombocytopenia, kidney failure, encephalopathy, and multisystem organ dysfunction

Decreased Production

Marrow Suppression

- Medication effect
- Marrow suppression due to infection, typically viral

Neonatal Thrombocytopenia

- Severe thrombocytopenia in the neonatal period can be dangerous due to the risk of intracranial hemorrhage
- Neonatal alloimmune thrombocytopenia (NAIT): Profound thrombocytopenia due to maternal antibodies against infant's platelets
- Family history of other siblings with neonatal thrombocytopenia should raise concern for an inherited disorder of platelet production

Amegakaryocytic Thrombocytopenia

- Autosomal recessive disorder of failure of bone marrow to make megakaryocytes, and in turn, platelets
- Associated with other congenital malformations including cardiac, kidney, and musculoskeletal

Thrombocytopenia Absent Radii Syndrome (TAR)

- Thrombocytopenia and lack of development of radii
- Associated with congenital heart disease
- May require platelet transfusion support
- Platelet count typically improves over time

Abnormal Function

Glanzmann Thrombasthenia

- Severe platelet dysfunction due to genetic mutation affecting glycoprotein IIb/IIIa
- Normal platelet count, but excessive bleeding due to lack of function
- Diagnosed via platelet aggregation studies

Wiskott–Aldrich Syndrome

- Thrombocytopenia
- Small platelet size
- Eczema
- Recurrent or severe infections due to immunodeficiency
- X-linked mutation in *WAS* gene

Bernard–Soulier Syndrome

- Severe platelet dysfunction due to autosomal-recessive mutation affecting glycoprotein Ib, making platelets unable to bind von Willebrand factor
- Large platelets; may be normal in number

COAGULATION DISORDERS

Bleeding Disorders

1. Suspect bleeding disorder if recurrent or severe bleeding or bruising, frequent/prolonged epistaxis, severe bleeding with procedures or dental extractions, or a family history
2. Workup includes PT/INR, PTT, platelet count, fibrinogen, von Willebrand panel, and potentially specific factor levels
3. Petechiae indicate thrombocytopenia. Purpura typically indicates a more profound diffuse systemic illness, including disseminated intravascular coagulation (DIC), sepsis, or vasculitis

Acquired Bleeding Disorders

Vitamin K Deficiency

- Vitamin K-dependent factors: II, VII, IX, X, C, S
- Vitamin K deficiency can occur due to prolonged antimicrobial use or liver failure
- PT will be prolonged before change is seen in PTT, as factor VII has the shortest half-life
- Replace with vitamin K if mild, or FFP to replace clotting factors if severe bleeding

Hemorrhagic Disease of the Newborn

- Newborns are vitamin K-deficient at birth due to lack of placental transfer of vitamin K and lack of mature gut flora at birth. Prophylactic intramuscular vitamin K given at birth
- If vitamin K is not given, newborn will not have adequate clotting factors and is at risk for hemorrhage
- Classical form of hemorrhagic disease of the newborn includes mucosal or subcutaneous bleeding, bleeding at venipuncture or procedure sites within the first week of life
- Delayed form includes breastfed infants within the first 4 weeks of life and can include intracranial hemorrhage

Disseminated Intravascular Coagulopathy

- Severe systemic process of coagulation factor and platelet consumption, with diffuse clotting and bleeding. High mortality rate
- Detected by thrombocytopenia, elevated PT/PTT, and decreased fibrinogen
- Caused by severe sepsis, malignancy, trauma, burns, or severe multisystem illness

Inherited Bleeding Disorders

Hemophilia A and B

- Suspect if prolonged bleeding with circumcision, joint bleed, or muscle bleed

- May be detected with prolonged PTT and confirmed with factor VIII or factor IX level. Platelet count and PT are normal
- Hemophilia A = congenital deficiency of factor VIII, about 85% of patients
- Hemophilia B = congenital deficiency of factor IX, about 15% of patients
- Both forms are X-linked
- Severity depends on the level of deficient factor: Severe (< 1%), moderate (1–5%), or mild (> 5%)
- With suspicion for intracranial hemorrhage such as vomiting, altered mental status, headache, or history of head trauma, treat immediately with factor and then obtain imaging
- With suspicion for joint bleed or deep muscle bleeding, treat with factor VIII (FVIII) immediately. Repeated joint bleeds lead to destruction of the joint capsule and progressive arthritis

Von Willebrand Disease

- Suspect if prolonged mucosal bleeding, including epistaxis or menorrhagia
- Most common inherited bleeding disorder
- Normal coagulation profile. Detected via von Willebrand panel assessing antigen level and activity level of von Willebrand proteins
- Multiple types of von Willebrand disease:
  - Type 1—Quantitative defect and most common
  - Type 2 A—Defective von Willebrand factors cannot coalesce and form large vWF multimers
  - Type 2B—Overbinding of glycoprotein I b on platelets to von Willebrand proteins causes rapid clearance of platelets and large multimers
  - Type 2M and 2N—Qualitative defects with all sizes of von Willebrand proteins
- Treatment for bleeding in von Willebrand disease is patient- and type-dependent but may include desmopressin or factor VIII/vWF concentrate (Humate-P, CSL Behring)

ERYTHROCYTOSIS

Definition

- Increase in erythrocyte count, hemoglobin, and hematocrit above the age, sex, race, and altitude-adjusted reference range
- Absolute erythrocytosis: Increase in total red cell *mass*
- Relative erythrocytosis: Secondary to severe plasma volume reduction

Clinical presentation

- Hypertension, headache, shortness of breath, neurologic symptoms; thrombocytosis may cause hemorrhage and thrombosis

Primary

- Low EPO concentration
- Acquired

Polycythemia Vera

- Major criteria
  - Hgb > 16.5 g/dL (men) and > 16.0 g/dL (women) or
  - VHct > 49% (men) and > 48% (women) or
  - RBC mass > 25% above mean
  - Bone marrow biopsy showing hypercellularity and trilineage growth with mature megakaryocytes
  - Presence of JAK2 mutation

Secondary

- High EPO concentration

Clinical presentation

- Hyperviscosity, hypertension, headache
  - **Congenital**
    - Hgb variants with high oxygen affinity/hemoglobinopathy
    - 2,3-biphosphoglycerate deficiency
    - Familial erythrocytosis types 2–4

- **Acquired**
  - Hypoxia
  - Altitude
  - Cardiac disease
  - Lung disease
  - Central hypoventilation

Other
- Endocrine tumor (e.g., pheochromocytoma)
- Tumor/cysts (e.g., nephroblastoma, renal cell carcinoma)
- Renal artery stenosis
- Neonatal (trisomies, infant of a diabetic mother, congenital adrenal hyperplasia)

Treatment
- Periodic phlebotomy
- Goal: To reduce risk of thrombosis without increasing bleeding tendency

NEOPLASTIC DISORDERS

Acute Leukemia

Epidemiology
- Most common malignancy in children (30% of pediatric malignancy)
- Five times more common than acute myeloid leukemia (AML)

Acute Lymphoblastic Leukemia (ALL)

Epidemiology
- 3.4 cases per 100,000 per year in the United States
- Incidence higher in Whites and Hispanics than in African Americans
- Peak incidence: 2–5 years of age
- More common in boys

Clinical presentation
- Fever
- Pallor
- Ecchymoses, petechiae
- Bone and joint pain, particularly in lower extremities
  - Patients may present with refusal to bear weight
- Fatigue
- Anorexia
- Extramedullary spread
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Headache
    - Chills/fever: Central nervous system (CNS) disease
    - Rarely: Patient with cranial nerve palsies
  - Testicular enlargement
  - Orthopnea, cough
    - Mediastinal mass
  - Skin lesions
  - Gingival hypertrophy

Peripheral blood abnormalities
- Anemia
- Thrombocytopenia
- WBC abnormalities
  - Neutropenia
  - Elevated WBC
    - 20% with WBC > 50,000 on presentation
  - Lymphoblasts on peripheral smear—peripheral blood usually shows leukocytosis with a population of large mononuclear cells (Fig. 10.13)
- Flow cytometry diagnosis
- Evaluate for tumor lysis

Diagnostic evaluation
- Flow cytometry
  - 70 to 80% pre-B ALL
  - 15 to 17% T-cell ALL
- Bone marrow aspirate and biopsy (Fig. 10.14) [5]
- Lumbar puncture to evaluate for CNS disease

Treatment
- Per local or national chemotherapy protocols

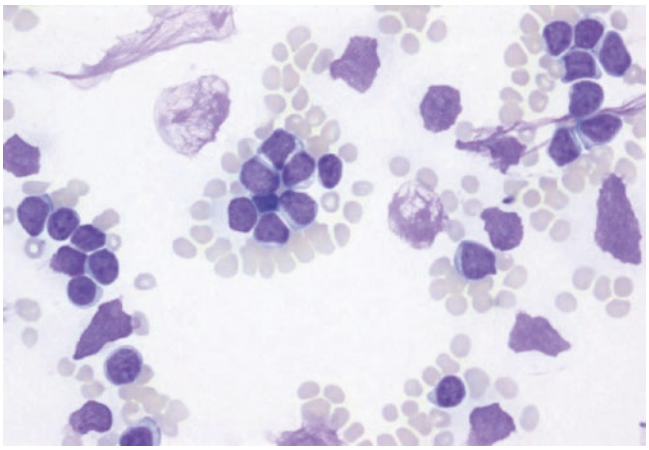


Fig. 10.13 Peripheral blood showing leukocytosis with a population of large mononuclear cells with high nuclear-cytoplasmic ratio, scant *blue* cytoplasm, and fine chromatin with occasional nucleoli. These are features of lymphoblasts. Note scattered smudge cells, another feature often seen in peripheral smears with leukemia

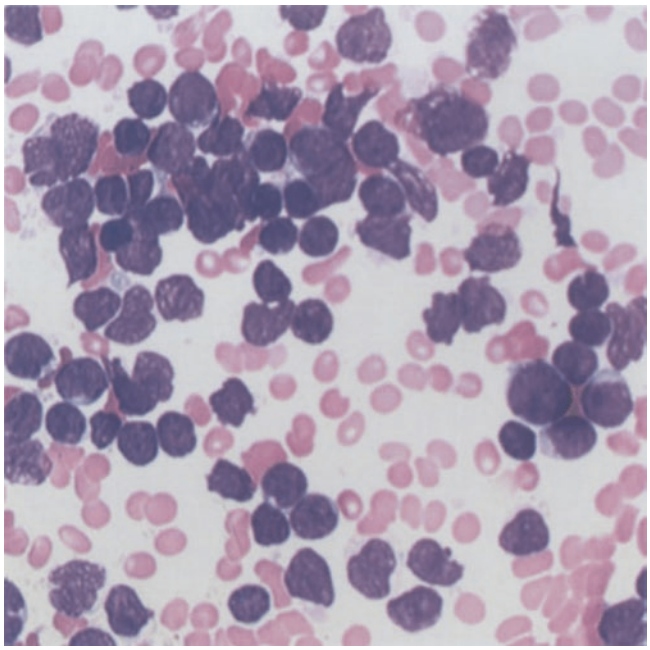


Fig. 10.14 Bone marrow biopsy of B-cell acute lymphoblastic leukemia demonstrating replacement of normal hematopoietic cells with lymphoblasts with round or slightly irregular nuclei with condensed chromatic, without nucleoli. (From Penchansky [5], with permission)

Associated Syndromes/Risk Factors

Trisomy 21

- Predisposed to developing acute leukemia
  - 10 to 20% higher risk of developing leukemia than general population
- Worse outcome compared to non-trisomy 21 patients
  - Higher treatment-related mortality
  - Higher relapse rate
- Leukemia in trisomy 21 differs in clinical features, timing of occurrence, and response to therapy
- AML occurs earlier compared to general population (1.8 vs 7.5 years); ALL has similar age distribution
- Ratio of AML to ALL is roughly equal in children with trisomy 21 vs 1:4 in children without trisomy 21
  - Ratio approaches general population above age 5 years
- 10 to 30% of infants with trisomy 21 develop a transient myeloproliferative disorder or transient leukemia
  - Detected on routine screening
  - Most patients are asymptomatic
  - Spontaneous resolution by 2–3 months of age
  - 20% of patients later develop AML

Bloom syndrome

- Autosomal-recessive disorder; genomic instability with DNA repair defects
- Growth retardation, inflammatory skin changes due to hypersensitivity to UV light, telangiectatic skin
- Predisposition to malignancy, especially leukemia, lymphoma, and GI tract tumors

Ataxia telangiectasia

- Increased risk of developing malignancy, particularly leukemia (ALL) and lymphoma

Fanconi anemia
- Inherited bone marrow failure syndrome
- Chromosome fragility/breakage
- Pancytopenia, radial bone abnormalities, kidney, skin, or GI abnormalities
- Increased risk of leukemia

Acute Myeloid Leukemia (AML)

Epidemiology
- 15% of childhood leukemia; less common than ALL
- Overall survival 65–70%; remains lower than children with ALL

Clinical presentation
- Similar to ALL: Fever, malaise, musculoskeletal pains, lymphadenopathy, hepatosplenomegaly, bleeding
- Reflective of leukemic burden

Peripheral blood abnormalities
- Anemia
- Thrombocytopenia
- WBC
  - Decreased, normal, or increased
  - Leukemic myeloblasts noted on peripheral smear (Fig. 10.15)
- Flow cytometry diagnosis

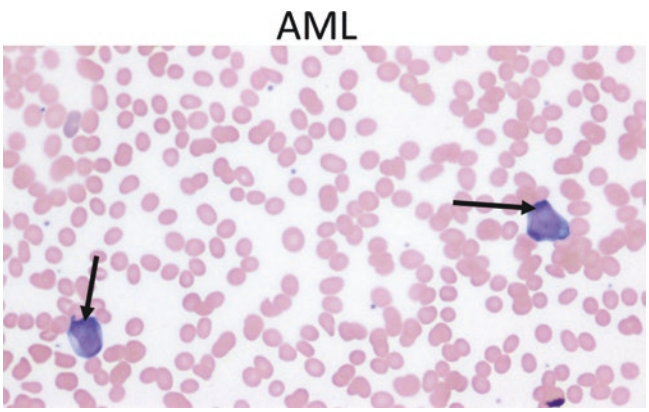


Fig. 10.15 Peripheral blood showing two myeloblasts with a high ratio of nucleus to cytoplasm, finely dispersed chromatin and one or more large nucleoli (*arrows*). Acute myeloid leukemia represents only 20% of childhood leukemia

- Evaluate for tumor lysis
- May have DIC

Diagnostic evaluation
- Flow cytometry
- Bone marrow aspirate and biopsy
  - Morphologic and immunophenotypic assessment
- Lumbar puncture to evaluate CNS for disease

Treatment
- Per local or national protocols
- Two courses of intensive induction chemotherapy followed by either cytarabine-based consolidation or hematopoietic cell transplantation

Associated Syndromes/Risk Factors

- Ionizing radiation
- Organic solvents
- **Paroxysmal nocturnal hemoglobinuria**
- **Trisomy 21**
- **Bloom syndrome**
- **Fanconi anemia**
- **Kostmann syndrome**
  - Severe congenital neutropenia
  - Risk of progression to AML
  - Significantly improved survival with G-CSF
- **Shwachman–Diamond syndrome**
  - Bone marrow dysfunction, most commonly neutropenia
  - Metaphyseal chondrodysplasia
  - Exocrine pancreatic deficiency
- **Diamond–Blackfan syndrome**
  - Congenital pure red aplasia with resultant anemia
    - Other cell lines often normal
  - Short stature
  - Thumb malformations
  - Other congenital anomalies
- **Neurofibromatosis type 1**
  - Bone marrow failure
  - Predisposition to cancers, especially AML and neuroblastoma

Chronic Myelogenous Leukemia (CML)

- Rare among children and adolescents; median age of diagnosis 60–65 years
- Rate of CML increases in the 15–19 years age interval
- Associated with fusion of two genes: *BCR* (on chromosome 22) and *ABL1* (on chromosome 9) resulting in *BCR-ABL1* fusion gene
- BCR-ABL1 fusion results from specific translocation known as Philadelphia chromosome t(9;22)
- Treated with tyrosine kinase inhibitor

Chronic Lymphocytic Leukemia (CLL)

- Rare disease in childhood
- Mature B-cell neoplasm
- 5 to 10% presenting with typical "B" symptoms
- Most patients are asymptomatic with absolute lymphocytosis noted on routine CBC
- Lymphadenopathy
- Hepatosplenomegaly
- Skin involvement
  - Most commonly recognized, nonlymphoid tissue involved
- Other organs may be involved as well

Lymphadenopathy

Causes of lymphadenopathy according to location

- **Cervical**
  - Oropharyngeal infections
  - Mycobacterial lymphadenitis
  - Cat scratch disease
  - Kawasaki disease
- **Supraclavicular**
  - Right side—Malignancy or infection from mediastinum
  - Left side—Malignancy or infection from abdomen
  - Lymphoma
  - Tuberculosis
- **Hilar**
  - Tuberculosis
  - Histoplasmosis
  - Leukemia
  - Lymphoma
  - Sarcoidosis
- **Axillary**
  - Cat scratch disease
  - Arm or chest infection
  - Leukemia
  - Lymphoma
- **Abdominal**
  - Malignancy
  - Mesenteric adenitis
  - Infection
- **Occipital**
  - Scalp infections (tinea capitis, lice)
  - Seborrhea

Clinical approach to lymphadenopathy

- **History**
  - Associated systemic symptoms
- **Age**
  - Lymph node enlargement in children less than 5 years of age most likely infectious
  - Histiocytosis can cause lymphadenopathy in children less than 3 years
  - Large lymph node in neonate most likely related to congenital infection
  - Likelihood of malignant lymphoma increases in adolescents
- **Location**
  - Supraclavicular lymphadenopathy is always abnormal, and the chances of malignancy are high
- **Size**
  - Size of enlarged lymph node aids in determining the need for further evaluation
  - Normal size of lymph node depends on the lymph node region and age of child
  - Normal lymph node size based on age and size:
    - < 1 month of age: < 1 cm

- > 1 month of age:
  - Most regions: < 1 cm
  - Epitrochlear region: < 0.5 cm
  - Inguinal region: < 1.5 cm
- Risk of malignancy increased in lymph nodes > 2 cm
- Malignancy can occur in smaller nodes

- **Characteristics**
  - Consistency
    - Fluctuance indicates infection
    - Hard, fibrotic nodes are due to malignancy or previous inflammation
    - Firm, rubbery nodes may indicate lymphoma or leukemia
      - Nodes in acute leukemia tend to be softer
  - Fixation
    - Normal lymph nodes are freely mobile
    - Abnormal lymph nodes become fixed/nonmobile
  - Tenderness
    - Suggest recent, rapid enlargement, resulting in tension in pain receptors in capsule
    - Occurs with inflammatory processes, immunologic stimulation, and malignancy

Biopsy criteria

- **Size**
  - 2 cm
  - Increasing over 2 weeks
  - No decrease after 4 weeks
- **Location**
  - Supraclavicular
- **Consistency**
  - Hard
  - Matted
  - Rubbery
- **Associated features**
  - Abnormal chest x-ray
  - Fever
  - Weight loss
  - Hepatosplenomegaly

Hodgkin Lymphoma

- Malignant lymphoma
- 7% of childhood cancers
- 1% of childhood cancer deaths
- Incidence varies by age
  - 1 per million for 0–4 years
  - 3.5 per million for 5–9 years
  - 10 per million for 10–14 years
  - 29 per million for 15–19 years
- Bimodal peaks of incidence from 15 to 34 years and older than 55 years
- Infectious agents may be involved
  - EBV
  - HHV6
  - Cytomegalovirus
- Reed–Sternberg cell is the hallmark of HL (Fig. 10.16)

Clinical presentation

- Painless lymphadenopathy
  - Cervical, supraclavicular, axillary, or inguinal

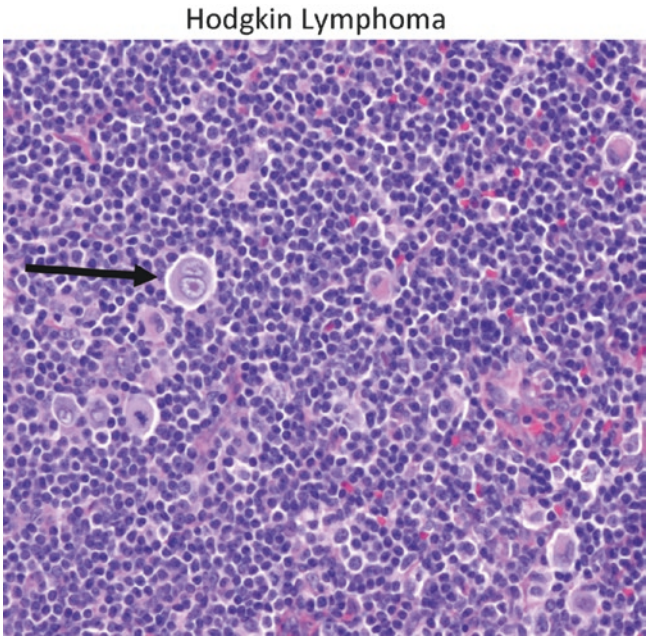


Fig. 10.16 Hodgkin lymphoma presents as a localized or regional lymphadenopathy. The characteristic cell is the Reed–Sternberg cell (*arrow*)

- Mediastinal mass
  - May result in dysphagia, dyspnea, cough, stridor, airway obstruction, or superior vena cava (SVC) syndrome
- Pleural effusion
- Pericardial effusion
- Hepatosplenomegaly
- Bone marrow infiltration
- Systemic symptoms/B symptoms
  - Fever
  - Unintentional weight loss > 10% of body weight within 6 months prior to diagnosis
  - Night sweats

Diagnosis

- Chest radiograph
- CT chest, abdomen, and pelvis
- Positron emission tomography (PET) scan
- Excisional biopsy of lymph node
- CBC, comprehensive metabolic panel (CMP), liver function test (LFT), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR)
- Bone marrow aspirate and biopsy only for patients with advanced stage disease, B symptoms, or CBC concerning for bone marrow involvement

Treatment

- Chemotherapy and radiation therapy are very effective
- Chemotherapy regimens
  - COPP (cyclophosphamide vincristine, procarbazine, and prednisone)
  - ABVD (Adriamycin [generic: doxorubicin], bleomycin, vinblastine, and dacarbazine)

Prognosis

- Early-stage disease has event-free survival of 85–90% and overall survival at 5 years of 95%
- Poor prognostic factors
  - Bulky tumor
  - Advanced stage at diagnosis
  - B symptoms
- Patients who relapse > 12 months after chemotherapy alone or combined modality have good retrieval response

Non-Hodgkin Lymphoma

- 60% of all lymphomas in children
- Median age at diagnosis is 10 years
  - Incidence increases with age
- Burkitt lymphoma is the most common
- Most children have de novo disease with no underlying condition
- Related diseases
  - Severe combined immunodeficiency (SCID)
  - Wiskott–Aldrich syndrome
  - Ataxia telangiectasia
  - Bloom syndrome
  - HIV
  - EBV

Clinical presentation

- Rapidly growing tumors with symptoms based on size and location
- Burkitt lymphoma of the abdomen (sporadic type) more common in the United States
- Burkitt lymphoma of the head and neck (endemic type) more common in Africa
- SVC syndrome—chest involvement
- Intestinal obstruction—abdominal mass
- Paraplegia with spinal cord involvement
- Tumor lysis syndrome
  - Hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia

Diagnosis

- Chest radiograph
- CT abdomen and pelvis
- CBC, CMP, Mg, Phos, uric acid, LDH
- EBV

Biopsy

- Classic "starry sky" appearance of Burkitt lymphoma (Fig. 10.17)

Treatment

- Chemotherapy

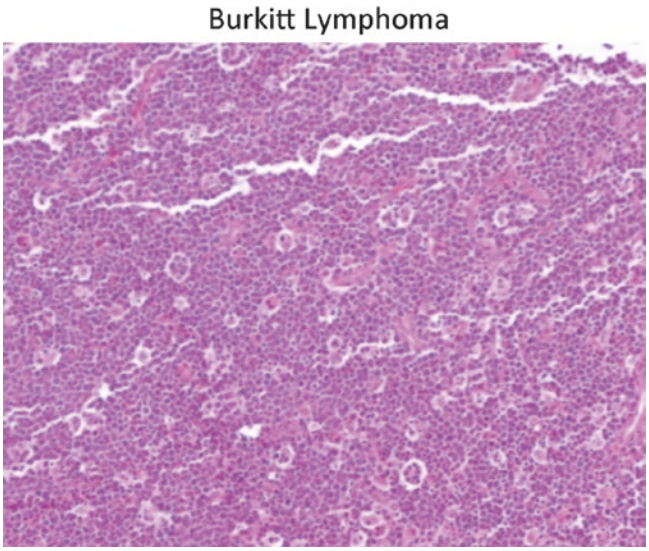


Fig. 10.17 Classic "starry sky" appearance of Burkitt lymphoma. The stars are actually macrophages that are phagocytosing apoptotic Burkitt cells. This example presented as a colonic mass with intussusception

Prognosis
- Excellent in most children
- 90 to 100% survival rate with localized disease

Langerhans Cell Histiocytosis

- Rare histiocytic disorder
- Characterized by single or multiple osteolytic bone lesions with histiocytic infiltration
- Most common in children ages 1–3 years

Clinical presentation
- Varies based on location and extent of involvement
- Limited to one organ in over half of patients
  - Remainder of patients with multisystem disease
- Areas of involvement in order of *decreasing* frequency
  - Bone
  - Skin
  - Lymph node
  - Liver
  - Spleen
  - Oral mucosa
  - Lung
  - CNS
- Common symptoms
  - Bone pain
  - Soft tissue swelling
  - Skin rash
- Less common presentation
  - Diabetes insipidus
  - Respiratory insufficiency
  - Cytopenia
  - Lymphadenopathy
  - Liver dysfunction
  - Organomegaly

Diagnosis
- Biopsy
- Skeletal survey
- Chest radiograph
- CBC, CMP, LFT, ESR, coagulation studies
- Abdominal ultrasound
  - Assess size and structure of liver and spleen
  - Abdominal lymph nodes

Additional testing based on clinical presentation
- Polyuria and polydipsia
  - Early morning urine specific gravity (SG) and osmolality
  - MRI brain
  - Water deprivation test
- Craniofacial bone involvement
  - MRI head
- Vertebral lesions
  - MRI spine
- Diarrhea, failure to thrive, or malabsorption
  - Endoscopy

Treatment
- Based on clinical findings
- Observation
- Surgery
- Chemotherapy

Prognosis
- Excellent for patients with localized disease

Table 10.5 Chemotherapeutic agents and side effects

Chemotherapeutic agent	Side effect
Cyclophosphamide	Hemorrhagic cystitis
Ifosfamide	Myelosuppression
Cisplatin	Hearing loss
Carboplatin	Peripheral neuropathy
Bleomycin	Pulmonary fibrosis
Doxorubicin	Cardiac toxicity
Vincristine/vinblastine	Peripheral neuropathy
Methotrexate	Myelosuppression
	Mucositis
Fluorouracil	Myelosuppression
Mercaptopurine	Myelosuppression
Etoposide	Infusional hypotension
	Secondary malignancy

- Significant morbidity and mortality for patients with multisystem disease

Chemotherapeutic agents and side effects (Table 10.5)

ONCOLOGIC EMERGENCIES

Spinal Cord Compression

- Tumor in or around spinal cord
- Neurologic symptoms
- Bowel or bladder dysfunction
- Treat with steroids and/or radiation

Mediastinal Mass

- Respiratory distress
  - Particularly when supine
- Cannot intubate because airway compression is below the vocal cords
- Cannot maintain oxygenation and ventilation when anesthetized
- Obtain chest radiograph with suspicion/diagnosis of malignancy to evaluate for mediastinal mass
- Tumors associated with mediastinal mass – "four T's"
  - Thymoma
  - Teratoma
  - Thyroid carcinoma
  - (Terrible) lymphoma
- Treatment
  - Treat underlying condition
  - Steroids and radiation in emergency setting

Superior Vena Cava Syndrome

- Due to extrinsic compression of SVC by anterior mediastinal mass
- Signs and symptoms:
  - Plethora/red face
  - Facial swelling
  - Upper extremity edema
  - Distended neck veins
  - Neurologic symptoms (when severe)

Tumor Lysis Syndrome

- Secondary to rapid lysis of tumor cells with high tumor burden
- Most common with:
  - Initiation of chemotherapy
  - Large tumors
  - Lymphoma
  - Leukemia

Laboratory

- Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia

Complications

- Cardiac dysrhythmia
- Sudden death
- Seizure
- Neuromuscular irritability
- Acute kidney injury and failure

Treatment

- Hydration
- Allopurinol
- Rasburicase
  - High uric acid burden
- Continuous venovenous hemofiltration (CVVH)
  - Acute kidney failure

BRAIN TUMORS

- Account for almost 20% of all pediatric cancers
- Peak age 0–4 years

Clinical presentation

- Based on location, size, growth rate, and age
- Increased intracranial pressure
  - Headache
    - Persistent vomiting (often mornings)
  - Mental changes, irritability
  - Visual disturbances
    - Diplopia
    - Papilledema
    - Parinaud syndrome (often associated with pineoblastoma)
  - Gait disturbances and ataxia
- Failure to thrive
- Cranial nerve abnormalities
- Focal neurologic deficits
- Seizures
- Declining school performance
- Loss of developmental milestones

Pathologic diagnosis = Based on cell of origin Can occur at multiple locations in the CNS

- Infratentorial/posterior fossa—60%
  - Pilocytic astrocytoma
  - Medulloblastoma
  - Ependymoma
  - Atypical teratoid /rhabdoid tumor (AT/RT)
  - Diffuse intrinsic pontine gliomas (DIPG)
- Supratentorial—40%
  - Low-grade glioma
  - High-grade glioma
  - CNS embryonal tumor and variants ("PNET")
  - AT/RT
  - Ependymoma
  - Choroid plexus tumors

Pilocytic Astrocytoma

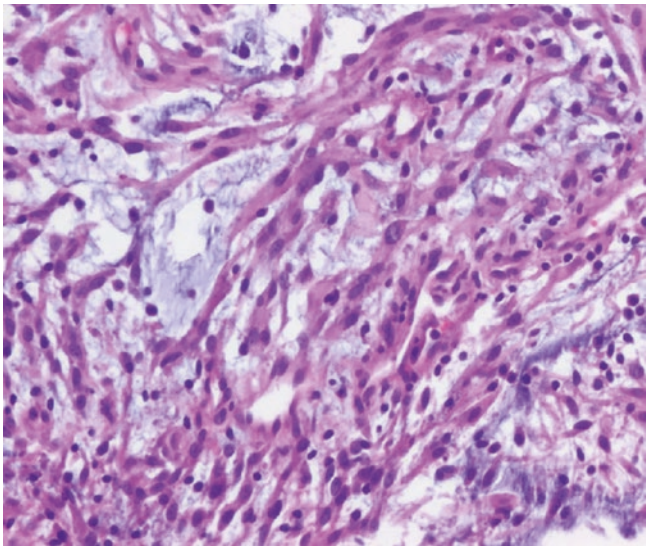


Fig. 10.18 Pilocytic astrocytoma is composed of bipolar cells with frequent microcystic spaces. Juvenile pilocytic astrocytoma is the most common childhood primary brain tumor

Astrocytoma

- Accounts for 40% of all CNS tumors
- Juvenile pilocytic astrocytoma (JPA)—most common subtype in children (Fig. 10.18)

Location = Posterior fossa

- Classic site for JPA is cerebellum but can occur anywhere in CNS

Treatment

- Surgery—primary treatment
- Chemotherapy
- Radiation therapy

Medulloblastoma

- The most common malignant brain tumor in children
- Accounts for 20% of all brain tumors (second most common)
- 90% of embryonal tumors

Location = Arises in cerebellum and fourth ventricle

- May metastasize down the spinal cord and rarely outside CNS

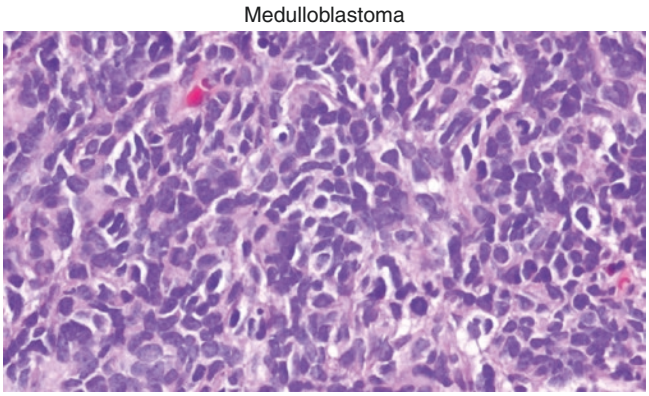


Fig. 10.19 Medulloblastoma (40×) is a so-called "small round blue" cell tumor of childhood. Medulloblastoma is a posterior fossa tumor and the second most common brain tumor of childhood

Histology = Cell type similar to primitive neuroectodermal tumor (PNET) (Fig. 10.19)

Treatment

- Surgery—prognosis based on extent of resection
- Chemotherapy
- Radiation therapy

Ependymoma

- Derived from the ependymal lining of the ventricles

Location = 70% occur in the posterior fossa
Treatment

- Maximally safe surgical resection
- Radiation

Craniopharyngioma

- Account for 7–10% of childhood brain tumors (most common benign brain tumor in children)
- Associated with panhypopituitarism and visual loss (both due to the tumor itself and treatment-related)

Location = Suprasellar

Imaging = Solid and cystic components

Pineoblastoma

- PNET

Syndromes Associated with Brain Tumors

- **Neurofibromatosis (NF) type 1**: Optic glioma, astrocytoma, neurofibroma, malignant nerve sheath tumor
- **NF type 2:** Vestibular schwannomas, meningiomas, spinal cord ependymoma, spinal cord astrocytoma
- **Tuberous sclerosis**
- **Von Hippel–Lindau:** Hemangioblastoma, angiomatosis, pheochromocytoma, renal cell carcinoma, pancreatic cyst
- **Li–Fraumeni:** Association with p53 mutation, astrocytoma, breast cancer, leukemias, brain tumors
- **Cowden syndrome:** Multiple hamartomas including the brain; dysplastic gangliocytoma of the cerebellum
- **Turcot syndrome:** Medulloblastoma and colon polyps

OTHER TUMORS

Hepatoblastoma

- Children < 3 years
- Can be congenital
- 90% occur by age of 5 years, 70% by age 2 years
- Male predominance
- Prevalence 1 per 1 million children

Associated syndromes/risk factors

- Familial adenomatous polyposis and Gardner syndrome (APC gene mutations)

- Glycogen storage disease
- Beckwith–Wiedemann syndrome
- Hemihypertrophy syndromes
- Li–Fraumeni syndrome (TP53)
- Wilms tumor
- Low birth weight infants

Clinical presentation
- Large asymptomatic mass
- Weight loss, anorexia, vomiting, or abdominal pain
- Right lobe more common
- Metastasis most commonly to lungs

Diagnosis
- Laboratory:
  - Elevated alpha-fetoprotein (AFP)
  - Anemia and thrombocytosis are common
  - Bilirubin and liver enzymes are usually normal
  - Hepatitis B and C serologies (usually negative)
- Imaging: Ultrasound, Abdominal X-ray (KUB), CT, and/or MRI
- Biopsy
- Staging based on radiographic criteria (PRETEXT grouping and grade) and surgical resection

Treatment
- Chemotherapy
- Tumor resection
- Liver transplant for unresectable disease

Germ Cell Tumors

- Bimodal age distribution (< 3 and adolescent)
- Types based on histology:
  - Germinoma
    - Dysgerminoma
    - Seminoma
  - Yolk sac tumor
  - Mixed germ cell tumor
  - Teratoma (benign)

Clinical presentation
- Ovarian = Abdominal pain, palpable mass
- Testicular = Irregular, nontender mass
- Extragonadal = Depending on location

Diagnosis
- CT/MRI, metastatic workup (bone scan, chest CT)

Laboratory
- AFP and/or human chorionic gonadotropin (hCG)

Treatment
- Surgery +/− chemotherapy depending on risk group and staging

Neuroblastoma

Malignancy originating from neural crest cells of the sympathetic nervous system

Epidemiology
- Third most common pediatric cancer overall
- Most common extracranial solid tumor in children
- 8% of childhood malignancy
- Most commonly diagnosed neoplasm in infants (28–39% of neonatal malignancies)
- Mean age is 2 years

Clinical presentation
- Symptoms based on mass location
- Most cases arise in abdomen
  - Abdominal pain
  - Distended abdomen, palpable mass
  - Hypertension (due to renal artery compression and catecholamine release)
  - Urinary tract infections (due to the obstructing abdominal mass)
  - Neck mass
  - Thoracic tumors
    - Horner syndrome
  - Spinal tumors
    - Paraplegias

  - Metastatic disease
    - Bone pain (bone metastases)
    - Cytopenias (bone marrow infiltrate)
    - Orbital proptosis and ecchymosis—"raccoon eyes" (retro-orbital soft tissue infiltrate)
    - Bluish subcutaneous nodules (skin infiltrate)
    - Fever/irritability
    - Failure to thrive
- Paraneoplastic symptoms
  - Secretory diarrhea
  - Increased sweating
  - Opsoclonus, myoclonus ("dancing eyes and dancing feet")

Diagnosis (Fig. 10.20)
- CT/MRI (often see calcifications)
- MIBG imaging
- Bone marrow biopsy
- Tumor markers
  - Elevated urine homovanillic acid (HVA), vanillylmandelic acid (VMA)
- Biopsy
  - Poor prognostic factors on pathology:
    - N-myc proto-oncogene (MYCN) amplification

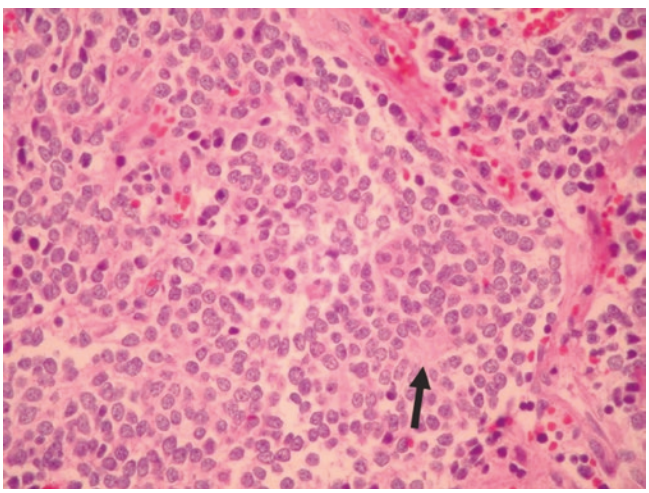


Fig. 10.20 Neuroblastoma is one of the "small round blue" cell tumors of childhood. A majority are at least poorly differentiated with the presence of some neuropil (*black arrow*) often in association with Homer-Wright rosettes (10×)

    - DNA hyperdiploidy (if less than 1 year of age)

Treatment
- Observation only for some low-risk groups
- Surgery
- Chemotherapy
- Radiation therapy
- Stem cell transplant
- New vaccines/antibodies
- Retinoic acid

Wilms Tumor (Nephroblastoma)

WT-1 gene located on 11p13

Epidemiology
- Peak incidence 2–5 years of age, and more common in African American children
- 7 cases/million children

Clinical presentation
- Abdominal mass often noted first by parents
- Abdominal pain, vomiting, hematuria in 12–25%
- Hypertension
- Hematuria
- Anomalies and syndromes associated with Wilms tumor
  - Beckwith–Wiedemann syndrome (hemihypertrophy, organomegaly, macroglossia, omphalocele), loss of imprinting at 11p15
  - WAGR (Wilms, aniridia, genitourinary abnormalities, mental retardation), del 11p13
  - Denys–Drash syndrome (early-onset renal failure with renal mesangial sclerosis, male pseudohermaphroditism), germline *WT1* mutation
  - Perlman syndrome (fetal gigantism, macrocephaly and macrosomia, renal hamartomas)

Diagnosis (Fig. 10.21)
- US, KUB, CT, and/or MRI

- Urinalysis
- Pathology

Treatment

- Surgery (upfront vs. after neoadjuvant chemotherapy)
- Chemotherapy and radiotherapy, depending on the histology and staging
- Overall cure rate for nephroblastoma is approximately 90%; it varies with the clinical and pathological features of the disease
- Poor prognostic factors:
  - Large tumor > 500 g
  - Unfavorable histologic type (anaplasia)
  - Advanced stage (III or IV)

Wilms' Tumor

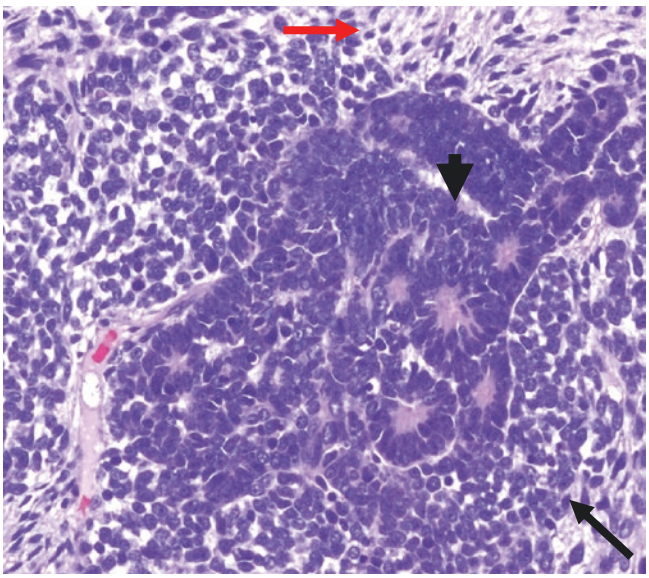


Fig. 10.21 Wilms tumor is a triphasic tumor composed of blastemal (*black arrow*), epithelial (*arrowhead*), and mesenchymal components (*red arrow*). Most are diagnosed before 6 years of age

Rhabdomyosarcoma

Epidemiology

- Most common soft tissue sarcoma
- Increased frequency with neurofibromatosis
- Peak incidence 1–5 years and 15–19 years
- 10% occur in the first year of life
- 70% appear within the first decade

Clinical presentation

- Anatomic distribution
  - Head and neck—40%
  - Genitourinary—20%
  - Trunk—10%
  - Retroperitoneal and others
    - Metastases to lung, bone marrow, lymph nodes, and bone. Metastases to brain and liver more common in relapse setting
- Specific histologic types:
  - Embryonal: 60%, intermediate prognosis
  - Alveolar type: 15%, most in the trunk and extremities; poor prognosis (Fig. 10.22)
  - Botryoid type: 6%, "bunch of grapes"; most in the vagina, uterus, bladder, nasopharynx, and middle ear; good prognosis
  - Pleomorphic form: 1%, adult type

Rhabdomyosarcoma

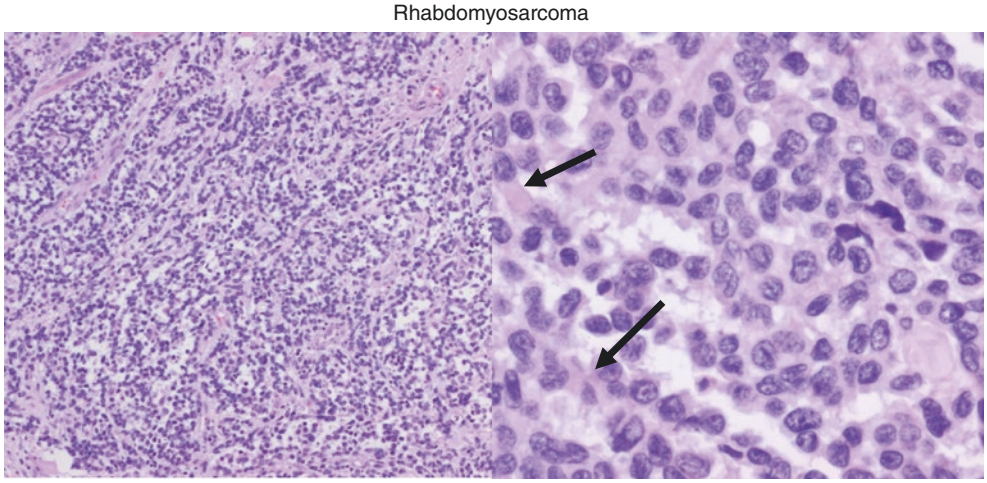


Fig. 10.22 At low power (10×), alveolar rhabdomyosarcoma has a vaguely alveolar growth pattern with neoplastic cells lining thin fibrous septae. At higher power, pink cytoplasmic material is evident (*arrows*) showing early myogenic differentiation

Treatment

- Surgery, chemotherapy, and radiation

PEARLS AND PITFALLS

- If a patient is iron deficient, electrophoresis may not demonstrate if they also have a thalassemia trait (high A2). If there is a concern, it is recommended that hemoglobin electrophoresis should be repeated once the patient is no longer iron deficient.
- All patients with SCD should be followed by a hematologist, and their medication management (hydroxyurea, glutamine) should be guided by the hematologist.
- Pancytopenia can occur with any viral syndrome, especially in a young child, but would still warrant an evaluation by a hematologist/oncologist.
- Children who have significant and unexplained bleeding after surgeries or dental extractions and who require more treatment than is usual for such procedures (nasal packing, repeat surgeries), or who develop acute anemia, should be assessed for an underlying bleeding disorder.
- Male patients who have swelling of their joints when starting to ambulate should have a factor deficiency high on the differential and be referred to a hematologist.
- Consultation with a hematologist regarding how to administer vaccines is recommended in those patients with a known bleeding disorder.
- ITP is a very common disorder; patients who have ITP caused by vaccines should still be rechallenged with those vaccines in the future.
- Children that present with acute and severe shortness of breath without a history of atopy, asthma, or allergies should not be given prednisone without considering the possibility of a mediastinal mass. While it is necessary to stabilize the airway, a hematology/oncology consult should be considered, and appropriate imaging performed in conjunction with respiratory care.
- Oncologic emergencies are true emergencies and cannot wait until the next day or the next week.
- *Within a few hours* of recognizing that a child could have a condition resulting in an oncologic emergency (severe pancytopenia, significant leukocytosis with thrombocytopenia or anemia), the child should be referred to an oncologic specialist or an appropriate emergency room.
- Malignancy should be in the differential for children who are not achieving their appropriate milestones or who are not gaining weight, because some children with brain tumors present mainly with a delay in achieving milestones.
- Significant back pain or continued leg or extremity pain in a child is not normal and should be evaluated by an oncologist. It is not advised to place children on neuropathic agents or prolonged opioids prior to a full evaluation by oncology specialists.

Acknowledgment The authors gratefully acknowledge the contributions of Staci Bryson, MD, and Arlynn F. Mulne, MD, Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas, USA, to the 1st edition of this chapter, from which some images and tables have been incorporated into this edition as well.

References

1. Kliegman R, Stanton B, St. Geme JW III, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. Philadelphia: Elsevier; 2016.
2. Loghavi S, Hasserjian RP. Cytopenias: reactive and neoplastic. In: Wang SA, Hasserjian RP, editors. Diagnosis of blood and bone marrow disorders. Cham: Springer International. p. 17–80.

3. Rogers HJ. Normal bone marrow. In: George TI, Arber DA, editors. Atlas of bone marrow pathology. New York: Science+Business Media; 2018.
4. Schafernak KT, Calvo KR. Constitutional, metabolic, and related disorders. In: George TI, Arber DA, editors. Atlas of bone marrow pathology. New York: Science+Business Media; 2018. p. 33–66.
5. Penanchansky L. Pediatric bone marrow. Berlin: Springer; 2004.

Suggested Reading

Adams M, Jenney M, Lazarou L, White R, Birdsall S, Staab T, et al. Acute myeloid leukaemia after treatment for acute lymphoblastic leukaemia in girl with Bloomsyndrome. J Genet Syndr Gene Ther. 2013;4(8). pii: 1000177.

Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339(1):5–11.

Adams RJ, Brambilla D, Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial Investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med. 2005;353(26):2769–78.

Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339(1):5–11.

Bain B. Diagnosis from the blood smear. N Engl J Med. 2005;353(5):498–507.

Bolton-Maggs PH, Langer JC, Iolascon A, Tittensor P, King MJ, General Haematology Task Force of the British Committee for Standards in Haematology. Guidelines for the diagnosis and management of hereditary spherocytosis – 2011 update. Br J Haematol. 2012;156(1):37–49.

Buitenkamp TD, Izraeli S, Zimmermann M, Forestier E, Heerema NA, van den Heuvel-Eibrink MM, et al. Acute lymphoblastic leukemia in children with Down Syndrome: a retrospective analysis from the Ponte Di Legno study group. Blood. 2014;123(1):70–7.

Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372(19):1832–43.

DeLoughery T. Microcytic anemia. New Engl J Med. 2014;371(14):1324–31.

Haupt R, Minkov M, Astigarraga I, Schäfer E, Nanduri V, Jubran R, Euro Histio Network, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013;60(2):175–84.

Horton TM, Steuber CP, Aster JC. Park JR, editor. Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children. Waltham: UpToDate. http://www.uptodate.com. Accessed 24 Dec 2018.

Karimi M. Guidelines for diagnosis and management of Beta-thalassemia intermedia. Pediatr Hematol Oncol. 2014–10;31:583–96.

Kliegman R, Stanton B, St. Geme JW III, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. Philadelphia: Elsevier; 2016.

Levin TL, Mäkitie O, Berdon WE, Lachman RS. Shwachman–Bodian–Diamond Syndrome: metaphyseal chondrodysplasia in children with pancreatic insufficiency and neutropenia. Pediatr Radiol. 2015;45(7):1066–71. Review.

Lipton JM. Evaluation of pancytopenia. BMJ Best Practice (database). 2018. https://bestpractice.bmj.com/topics/en-us/1024. Accessed 24 Dec 2018.

McClain KL. Kaplan SL, Mahoney Jr DH, Drutz JE, editors. Peripheral lymphadenopathy in children: evaluation and diagnostic approach. Waltham: UpToDate. http://www.uptodate.com. Accessed 24 Dec 2018.

Medeiros LJ, Greiner TC. Hodgkin's disease. Cancer. 1995;75(1 Suppl):357–69.

Nathan DG, Oski FA, Orkin SH, editors. Nathan and Oski's hematology and oncology of infancy

and childhood, vol. 2. Philadelphia: Elsevier Saunders; 2015.

Rabin KR, Whitlock JA. Malignancy in children with trisomy 21. Oncologist. 2009;14(2):164–73.

Rai KR, Stilgenbauer S, Aster JC. Larson RA, editor. Clinical features and diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma. Waltham: UpToDate Inc. http://www.uptodate.com. Accessed 24 Dec 2018.

Schrier SL. Mahoney Jr DH, editor. Acquired aplastic anemia in children and adolescents. Waltham: UpToDate. http://www.uptodate.com (Accessed 24 Dec 2018

Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2017;92(1):94–108.

Van Etten RA. Larson RA, editor. Clinical manifestations and diagnosis of chronic myeloid leukemia. Waltham: UpToDate. http://www.uptodate.com. Accessed 24 Dec 2018

Vannucchi AM. How I treat polycythemia vera. Blood. 2014;124(22):3212–20.

Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, BABY HUG Investigators, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet. 2011;377(9778):1663–72.

Allergy and Immunology

11

Maria I. Garcia Lloret and Caroline Y. Kuo

ALLERGY

Introduction

- Allergic disorders are very common in children and include a variety of conditions such as asthma, allergic rhinitis, atopic dermatitis, and food allergies
- There is a strong familial predisposition for allergic disease, but environmental exposures (i.e., air pollution, cigarette smoke), diet, and concomitant infection also play an important role in the incidence and severity of atopy in children
- Respiratory and food allergies are by far the most prevalent allergic disorders in the pediatric age, but children can also suffer from drug and insect venom hypersensitivity

Allergy or type 1 hypersensitivity is mediated by immunoglobulin E (IgE)

- Sensitization, that is, the ability to make IgE in response to a particular allergen, is the prerequisite for the development of allergic disease
- Yet, sensitization does not always lead to clinical manifestations. In other words, one may be able to detect IgE to peanuts in individuals who eat peanuts regularly with no problems

M. I. Garcia Lloret (✉) · C. Y. Kuo
Division of Pediatric Allergy/Immunology and Rheumatology, Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA, USA
e-mail: migarcia@mednet.ucla.edu

Types of hypersensitivity (Table 11.1)

Allergic Rhinitis (AR)

Background

- Allergic rhinitis (AR) is the most common chronic disease in children
- Often mistaken for recurrent episodes of the common cold
- At difference to the common cold, AR usually does not present with low-grade fevers or malaise. Nasal and eye pruritus also distinguish AR from viral upper respiratory infections
- AR is one of the major reasons for visits to pediatricians and is associated with a number of significant comorbidities, including asthma, sinusitis, and ear infections

Implicated allergens

- Pollens, molds, dust mites, and animal dander are the most common causative allergens
- Tree pollens are highest in the spring, grass pollens in the early summer, and weeds in the fall—all important causes of seasonal or outdoor allergies.
- Molds are high all year round and may cause persistent allergies or indoor allergies, e.g., *Alternaria* and *Cladosporium* in warmer seasons and *Penicillium* and *Aspergillus* in the colder seasons. Molds are an important cause of asthma exacerbations

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_11

Table 11.1 Types of hypersensitivity

Types of hypersensitivity	Examples	Mediators	Description
Type I: allergy (immediate)	Anaphylaxis	IgE	Reaction occurs in minutes
	Allergic rhinoconjunctivitis		Antigens cross-link the IgE on mast cells and basophils → release of histamine and other mediators
			Testing: Skin test for specific IgE
Type II: cytotoxic, antibody-dependent	Drug-induced hemolytic anemia	IgM or IgG	Antibody (IgM or IgG) binds to cell surface antigens → complement fixation → cellular destruction via the MAC
		Complement	Testing: direct and indirect Coombs test
		MAC	
Type III: immune complex disease	Serum sickness	IgG	Circulating immune complexes → deposit in postcapillary venules → local inflammatory reaction
	Lupus	Complement	
	PSGN	Neutrophils	
Type IV: delayed-type hypersensitivity	Contact dermatitis	T-cell	Mediated by T-cells rather than by antibodies
	TB skin test		Cellular response usually appears 48–72 h after antigen exposure
	Chronic transplant rejection		

IgE immunoglobulin E, *MAC* membrane attack complex, *PSGN* poststreptococcal glomerulonephritis, *TB* tuberculosis

- Dog and cat dander are abundant in indoor settings and a common cause of perennial allergic rhinitis and asthma
- Dust mites are another prevalent indoor allergen, is a very important trigger of perennial asthma and allergies

Classification

- **Intermittent** disease with symptoms < 4 days/week or for a duration of < 4 weeks, usually related to outdoor allergens, e.g., pollens
- **Persistent** disease with symptoms > 4 days/week and are present for > 4 weeks, usually related to indoor allergens, e.g., molds

Clinical presentation

- Nasal congestion may be reported by parents as mouth breathing, snoring, or a nasal voice
- Paroxysmal sneezing, nasal and palatal pruritus, nose blowing, sniffing, snorting, and occasional coughing
- Nasal pruritus often produces the classic sign of the allergic salute
- Itchy eyes and postnasal drip
- Seasonality, progression of symptoms, identifiable triggers, alleviating factors, and responsiveness to allergy medication
- Comorbid conditions such as headaches, sleep disturbance, fatigue, and impaired concentration and attentiveness at school
- Nasal turbinates may appear edematous, with a pale to bluish hue
- Cobblestoning from lymphoid hyperplasia may be seen on the posterior oropharynx
- Dark discolorations underneath the eyes, "allergic shiners," are due to venous engorgement and suborbital edema
- Dennie–Morgan lines are folds under the eyes due to edema
- A transverse nasal crease is seen across the bridge of the nose in children who chronically push their palms upward under their noses ("allergic salute"; Fig. 11.1)
- Tonsils and adenoids are frequently enlarged in young patients with chronic rhinitis and can be an additional cause of mouth breathing, snoring, and, in severe cases, sleep apnea
- Chronic mouth breathing from nasal obstruction may cause allergic facies, with an open mouth, receding chin, overbite, elongated face, and arched hard palate
- Allergic conjunctivitis usually presents with excessive tearing, conjunctival injection, and rubbing of the eyes

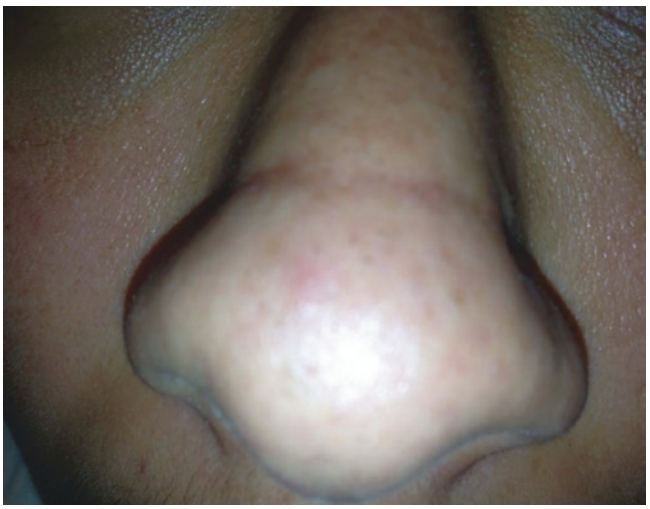


Fig. 11.1 Child with allergic rhinitis showing the transverse nasal crease across the bridge of the nose

Diagnosis

- History and physical examination are key to diagnosis
- Percutaneous (prick or puncture) skin testing remains the most specific and cost-effective diagnostic modality
- Serum detection of allergen-specific IgE by enzyme-linked immunosorbent assay (ELISA) also may be used
- These tests can help to identify the offending allergen, and specific avoidance can be recommended
- Nasal smear for eosinophils with eosinophil count of greater than 4% in children may help distinguish AR from viral infections and non-allergic rhinitis

Management

- Allergen avoidance, whenever possible
- Intermittent disease (outdoor environmental control)
  - Staying inside (5–10 a.m.)
  - Keep air-conditioning on during the spring, fall, and pollen seasons
- Persistent disease (indoor environmental control)
  - Avoiding molds includes humidity control < 51% in the home by using a dehumidifier
  - Use dust mite covers on the bed and pillows
  - Use hypoallergenic pillows and comforters
  - Wash linens in hot water to denature dust mite allergen
  - If allergic to pets, getting rid of them entirely or removing them from the bedroom may help decrease exposure to pet danders
  - A size-appropriate HEPA filter placed in the bedroom may also help decrease exposure to cat dander while removing indoor air pollutants
- Intranasal corticosteroids (INS)
  - The first-line treatment and most effective
  - Onset of action has been shown to be within 12 h
  - Can be used as needed, but far more effective if used long term
  - Epistaxis is the most common side effect
  - Generally have no effect on growth over 1 year of treatment in pediatric patients
- H1 antihistamine
  - The most popular
  - Decreases sneezing, itching, and rhinorrhea, but oral antihistamines are notoriously ineffective in treating nasal congestion
  - Adverse effects include sedation, which can lead to reduced school and cognitive performance
  - Sedation effect can be avoided by using second-generation antihistamines that have low or no sedation effect
- Decongestants
  - Long-term use of oral decongestants, in general, is not recommended because of potential side effects that include palpitations, tachycardia, and insomnia
  - Prolonged use of topical decongestant can lead to rhinitis medicamentosa (rebound nasal congestion)
- Leukotriene receptor antagonists (LTRA) such as montelukast can be used

- Allergy immunotherapy
  - It is not used routinely for management of mild-to-moderate AR that is responsive to medical treatment
  - Reserved for more severe cases and in those in which allergen avoidance is not desired or possible (e.g., pet ownership)
- Comorbidities
  - AR also is one of the risk factors associated with otitis media
  - 20% of children with AR have otitis media with effusion; 50% of the children who have chronic otitis media with effusion have AR
  - Poorly controlled rhinitis symptoms may exacerbate coexisting asthma and is an important cofactor in asthma exacerbations
  - AR may increase the risk of developing sinusitis

URTICARIA

Background

- Urticaria is a rash that consists of pruritic, blanching, erythematous, circumscribed, or (often) coalescent wheals
- Acute urticaria < 6 weeks
- Chronic urticaria 6 weeks or more

Causes

- Common allergens include food, medications, insects, pollens, and animal dander
- Physical factors such as cold, pressure, heat, and light can trigger urticaria
- Another common cause of urticaria in children is infectious illness, especially from viruses

Clinical presentation

- Wheals: Pruritic, blanching, erythematous, circumscribed, or (often) coalescent wheals (Fig. 11.2)

Differential diagnosis

- *Papular urticaria*
  - Common cause of papular, pruritic skin eruptions

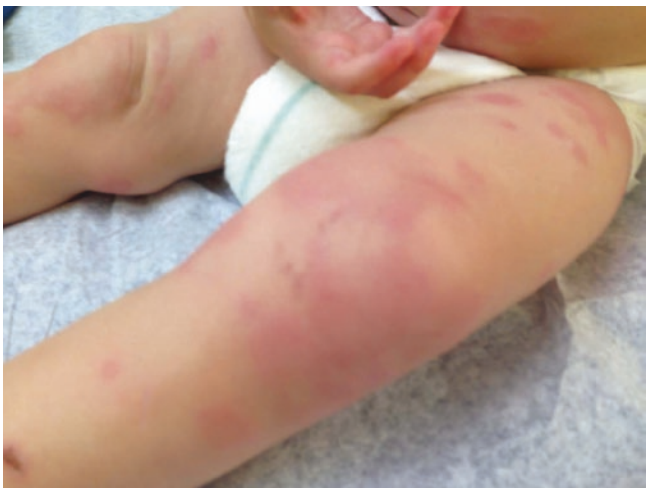


Fig. 11.2 18-month-old child with pruritic circumscribed and coalescent wheals

  - Caused primarily by insect bite-induced hypersensitivity
  - Clusters on exposed areas of skin, sparing the genital, perianal, and axillary regions
  - Prevalence of papular urticaria peaks in children from the ages of 2–10 years
- *Erythema multiforme*
  - Lesions may resemble urticaria and may be triggered by the same etiologic agents such as infections and medications
  - *Erythema multiforme is* distinguished from urticaria by the targetoid appearance of the lesions
  - Patients who have *erythema multiforme* are at risk for developing mucosal and systemic involvement
- *Urticaria pigmentosa* (UP)

Treatment

- Identify and avoid the offending agent
- First-generation antihistamines (diphenhydramine, hydroxyzine) are very effective but can lead to excessive sedation
- Second-generation antihistamines (loratadine, cetirizine, and fexofenadine) are also effective in controlling symptoms
- Use of glucocorticosteroids should be reserved for children not responsive to H1- and H2-antihistamines or children afflicted with severe cases that involve significant angioedema

- Another alternative medication for the treatment of acute urticaria is leukotriene modifiers such as montelukast, but with limited efficacy
- If anaphylaxis, such as laryngeal angioedema, respiratory, or gastrointestinal (GI) symptoms, a self-injectable epinephrine pen should be provided

Chronic Urticaria

Causes

- Defined by urticarial lesions persisting or recurring for more than 6 weeks
- Physical factors are common triggers for chronic urticaria and can act alone or with urticaria of other causes
- The main types of physical urticaria are dermatographic, cholinergic, cold, pressure, solar, vibratory, and exercise-induced
- Chronic infections, thyroid, and autoimmune disease are rare causes of chronic urticaria
- Allergies rarely play a causal role and allergy testing in general is not indicated

Differential diagnosis

- *Urticaria pigmentosa* (UP)
  - A form of cutaneous mastocytosis, usually benign; can be associated with systemic mast cell activation
  - Lesions of UP are reddish brown macules that wheal like a hive when stroked (positive Darier sign)
- Urticarial vasculitis
  - Rare in children but typically presents with fever, arthralgia, and painful fixed urticarial and petechial lesions that last longer than 24 h
  - Urticaria vasculitis is differentiated from typical chronic urticaria by the presence of nonpruritic, painful lesions with systemic symptoms

Diagnosis

- Infection may be the cause for the urticaria
- Positive serologic findings for *Chlamydia pneumoniae* and *Helicobacter pylori* can be found for these illnesses even in asymptomatic patients
- Other reported infectious causes are viral infections, urinary tract infections, and parasitic infections
- Autoimmune diseases that have been associated with chronic urticaria are thyroid disease, celiac disease, type 1 diabetes mellitus, inflammatory bowel disease, juvenile idiopathic arthritis, and systemic lupus erythematosus
- The most common specific autoimmune association with chronic urticaria is autoimmune thyroid disease
- If evidence of vasculitis, referral for skin biopsy may be indicated

Treatment

- Very similar to acute urticaria
- Specialists may use other therapies for children with chronic urticaria that has been refractory to standard therapies
- Examples of these medications include hydroxychloroquine, sulfasalazine, dapsone, omalizumab, colchicine, mycophenolate mofetil, and cyclosporine
- These medications require close monitoring for adverse effects and should be used only by specialists experienced in prescribing these immune-modulating medications

MASTOCYTOSIS

Background

- Disorder characterized by mast cell proliferation and accumulation within various organs, most commonly the skin
- **Cutaneous** mastocytosis
  - Urticaria pigmentosa
- **Systemic** mastocytosis

Clinical presentation

- Most patients have pruritic cutaneous lesions
- Macules, papules, nodules, plaques, blisters, and bullae (Fig. 11.3)

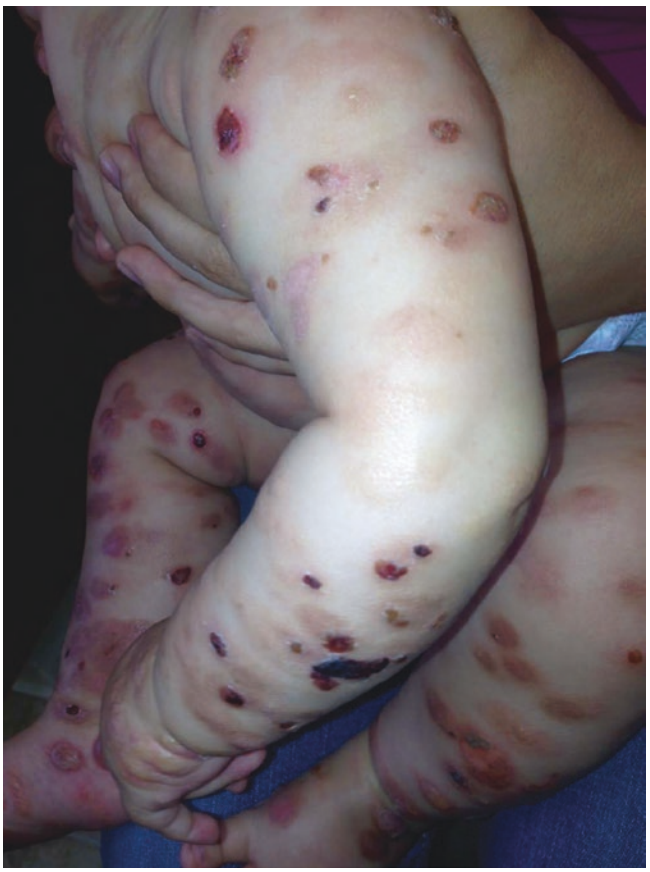


Fig. 11.3 8-month-old girl with severe mastocytosis cutaneous type (urticaria pigmentosa) showing pruritic macules, papules, blisters, and crusts all over the body

- Face tends to be less affected
- Darier sign: Wheal and surrounding erythema develop in a lesion after rubbing it
- Some patients, especially those with extensive cutaneous disease, experience acute systemic symptoms exacerbated by certain activities or ingestion of certain drugs or foods
- Possible systemic symptoms include flushing, headache, dyspnea, wheezing, rhinorrhea, nausea, vomiting, diarrhea, and syncope
- Anaphylactic reactions to Hymenoptera stings may be the first sign of mastocytosis

Diagnosis

- Complete blood count (CBC) in systemic mastocytosis may reveal anemia, thrombocytopenia, thrombocytosis, leukocytosis, and eosinophilia
- Plasma or urinary histamine level
- Elevated tryptase level

Treatment

- H1 and H2 antihistamines decrease pruritus, flushing, and GI symptoms
- Cromolyn is a mast cell stabilizer that improves diarrhea, flushing, headaches, vomiting, urticaria, abdominal pain, nausea, and itching in some patients
- Epinephrine pens for cases of anaphylaxis
- Avoid triggers

Prognosis

- Most patients with urticaria pigmentosa (UP) exhibit onset before age 2 years, which is associated with an excellent prognosis, often resolved by puberty
- Cutaneous mastocytosis onset after age 10 years portends a poorer prognosis, which is associated more often with systemic disease, and carries a higher risk of malignant transformation

HEREDITARY ANGIOEDEMA (HAE)

Background

- HAE usually presents in childhood or adolescence with a mean age at onset between 8 and 12 years
- Type 1 is secondary to insufficient levels of C1 inhibitor
- Type 2 is associated with normal levels but dysfunctional C1 inhibitor
- Type 3 has normal functional levels of C1 inhibitor; this type is nonexistent in children and adolescents

Clinical presentation

- Recurrent, episodic, nonpruritic swelling of the skin and mucosal tissues

- Laryngeal edema that may lead to death by asphyxiation
- Severe abdominal attacks manifested by intestinal edema
- The swelling can occur anywhere on the body, including lips, eyelids, hands, feet, and genitals
- The swelling usually develops over the course of 24 h and then resolves spontaneously in the next 24–36 h
- Can be triggered by minor injury, dental work, infection, stress, or menstruation
- The frequency of the swelling is patient-specific, occurring as frequently as once per week or as rarely as once per year
- The disease is inherited, commonly in an autosomal-dominant fashion
- If a diagnosis of HAE is made, testing of first-degree relatives is recommended

Diagnosis

- The abdominal attacks may be mistaken for an acute abdominal condition such as appendicitis or mechanical obstruction
- The angioedema of HAE occurs without pruritus or urticaria, develops more gradually over several hours, and is poorly responsive to antihistamines, corticosteroids, or epinephrine
- The diagnosis of HAE is made by confirming a deficiency in the C1 inhibitor, either quantitatively or qualitatively

Treatment

- Begins with immediate management of the patient's airway if compromised
- Intubation may be necessary for the protection of the airway if laryngeal edema is present
- In children with severe or frequent attacks occurring more than once per month, long-term prophylaxis should be considered
  - Complement C1 esterase inhibitor can be used as an acute treatment, short or long-term prophylaxis
  - Attenuated androgens, such as danazol or oxandrolone, and antifibrinolytics, such as tranexamic acid

ANAPHYLAXIS

Background

- Anaphylaxis is an acute, life-threatening systemic reaction that results from the sudden release of mediators from mast cells and basophils
- Prompt recognition of the signs and symptoms of anaphylaxis is critical to providing rapid and effective treatment
- Epinephrine is the most important medication for treating anaphylaxis, and earlier administration portends a better prognosis

Causes

- Food
  - The most common cause of anaphylaxis in the outpatient setting is food
  - Foods most commonly implicated are peanuts, tree nuts, fish, shellfish, cow's milk, soy, egg, soy, and seeds
- Medications
  - Medications are the second most common cause of anaphylaxis in children
  - The two most frequent culprits are antibiotics, particularly β-lactam antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Radiographic contrast
  - Anaphylactoid reactions associated with radiographic contrast material occur in approximately 1% of patients
  - Pretreatment with oral corticosteroids and antihistamines can reduce the risk of anaphylactoid reactions from radiographic contrast material
- Stinging insects
  - Hymenoptera: Stings by bees, vespids (yellow jackets, hornets, and wasps), and

stinging fire ants can cause anaphylaxis and can be fatal
  - Cutaneous symptoms can be treated symptomatically with cold compresses, oral antihistamines, and oral analgesics
  - Systemic symptoms should prompt immediate administration of epinephrine and immediate evaluation in a local emergency department
- Latex
  - Natural rubber latex is an emerging cause of anaphylaxis
  - Common in certain patients, e.g., patients with spina bifida and bladder exstrophy due to frequent exposure and sensitization
- Vaccination
  - Anaphylaxis to vaccines is an exceedingly rare but important cause of a life-threatening allergic reaction
  - A vaccine containing gelatin, egg, chicken, yeast, and neomycin can cause anaphylaxis
  - Patients can undergo skin testing to the components of the vaccine, such as gelatin, and to the vaccine itself
- Exercise
  - Exercise and physical exertion can lead to systemic mast cell mediator release, resulting in anaphylaxis
  - A few minutes of exercise can cause flushing, pruritus, diffuse warmth, urticaria, and fatigue
  - It may progress to angioedema, laryngeal edema, GI symptoms, hypotension, or collapse if exercise is continued
  - Eating specific food 4–6 h before exercise is a common co-trigger, as are alcohol or NSAIDs
  - Taking medication before exercise by up to 24 h may prevent food-exercise-induced anaphylaxis or medication-exercise-induced anaphylaxis
- Immunotherapy
  - Subcutaneous allergen immunotherapy (allergy shots) is another potential cause of anaphylaxis
- Idiopathic

Clinical presentation

- Flushing, urticaria, pruritus, angioedema, cough, wheezing, stridor, dyspnea, abdominal cramping, vomiting, diarrhea, dizziness, and syncope
- Absence of cutaneous symptoms argues against anaphylaxis but cannot completely rule it out
- IgE-mediated allergic reactions triggered by foods typically occur rapidly and usually within 1 h of ingestion
- Other adverse food reactions, such as food poisoning, occur more slowly and may be delayed by as much as 24 h from ingestion
- 80% to 90% of cases of food-induced anaphylaxis present with cutaneous findings of hives, angioedema, or both
- Cutaneous findings are uncommon in food poisoning
- A careful history from the patient, parent, caregiver, or other witness is helpful in determining a potential trigger

Differential diagnosis

- Vasovagal or neurogenic syncope
- Vocal cord dysfunction
- Asthma exacerbation
- Panic attack
- Isolated angioedema
- Food poisoning and other causes of shock
- Sepsis
- Cardiogenic shock

Management

- A serum tryptase level taken within 6 h of a suspected anaphylactic reaction may help confirm the diagnosis in many cases

- Referral to an allergist is warranted so that skin tests, specific IgE in vitro testing, can be done
- Challenge tests may be considered for more definitive diagnosis, especially in difficult cases
- Epinephrine
  - The mainstay of short-term treatment for anaphylaxis
  - Aqueous epinephrine in a 1:1000 dilution (0.01 mg/kg in children; maximum, 0.3 mg)
  - Should be administered intramuscularly in the outer aspect of the thigh every 5 min as needed to control symptoms
- Epinephrine pens
  - Self-administration epinephrine pens must be carried for all patients at risk for anaphylaxis
  - For children under 30 kg, the dose is 0.15 mg
  - For children greater than or equal to 30 kg, the dose is 0.3 mg
- Diphenhydramine
  - Second-line therapy
  - 1 to 2 mg/kg every 6 h as needed
- Ranitidine
  - Histamine-2 (H2)-receptor antagonists may be considered
  - 1 to 2 mg/kg
- Inhaled beta-2 agonist, e.g., albuterol if bronchospasm
- Glucocorticosteroids
  - It may not be helpful for short-term treatment but can be considered for prevention of recurrent or protracted anaphylaxis
  - Oxygen therapy and intravenous (IV) fluid
  - If hypoxia or hypotension
- Prevention
  - Avoid triggers or allergens
  - Penicillin reaction non-IgE-mediated
    - For example, vomiting, diarrhea, headache, or a nonurticarial, nonpruritic rash
    - These cases can be given cephalosporin with no problem
  - Penicillin reaction IgE-mediated
    - Anaphylaxis
    - Urticarial rash
    - First-generation cephalosporins in penicillin-allergic patients is 3–7%, whereas the increased risk is negligible for third-generation cephalosporins
  - Stevens–Johnson syndrome or toxic epidermal necrolysis associated with a particular medication
    - Same drug and structurally related drugs should be strictly avoided in the future

FOOD ALLERGIES

Mechanism of food allergies

- IgE-mediated
  - The most common form, affecting about 8% of children in the United States
- Non-IgE-mediated
  - Not so rare, includes disorders such as eosinophilic esophagitis (EoE), cow's milk protein allergy, and food protein-induced enterocolitis (FPIES)
- Most common triggers
  - Eggs, cow's milk, peanuts, tree nuts, fish, shellfish, soy, and wheat

Clinical presentation

- Skin reactions, urticaria, or angioedema (80%)
- Atopic dermatitis (AD) is a frequent comorbidity in patients with IgE-mediated food allergy
- Nasal congestion, rhinorrhea, cough, wheeze
- Abdominal pain, emesis, diarrhea
- Anaphylaxis
- In IgE-mediated food allergy, the onset of reaction is usually quick, from minutes to up to 2 h

- Non-IgE-mediated reactions develop over time and can present as dysphagia (EoE), delayed and protracted emesis (FPIES), and failure to thrive
- Cow's milk protein allergy characteristically presents in breastfed infants with bloody stools, fussiness, and occasionally failure to thrive

Diagnosis
- Skin testing
- ELISA
- Oral food challenge (the gold standard)
- Food allergy may play a causative role in a select group of children with severe atopic dermatitis; diagnosis in these cases may require the implementation of an elimination diet with the subsequent monitoring of skin manifestations

Treatment
- Avoidance is the mainstay of treatment
- Oral and epicutaneous immunotherapy are novel therapeutic modalities in development

Prognosis
- Allergies to peanuts, tree nuts, fish, and shellfish tend to be lifelong
- Most infants and children outgrow allergies to egg, milk, and soy protein
- Cow's milk protein allergy usually resolves in the second year of life

ADVERSE DRUG REACTIONS

- Many drug reactions are idiosyncratic (nonimmune)
- Drug overdose
- Drug-drug interaction
- Drug side effects
- Some drug reactions are triggered by an immune response to the drug. All types of hypersensitivity (Table 11.1) have been implicated in these immune-mediated drug reactions

Immune responses
- Specific IgE hypersensitivity
- IgG-predominant response resulting in serum sickness
- Antibody-mediated hemolysis by binding of the drug to the surface of red blood cells
- Drug-induced, delayed-type hypersensitivity reaction mediated by T-lymphocyte and monocytes

Timing of reaction
- If the drug given IV and an immediate reaction occurs within an hour, an IgE-mediated (type 1) process is likely
- If the reaction is delayed up to 72 h, a non-IgE-mediated reaction is more likely
- Steven–Johnson syndrome, toxic epidermal necrolysis, fixed drug reactions, and photosensitivity usually appear more than 72 h after exposure to drugs

Specific drug reaction
- Penicillin is composed of benzylpenicillin, which is the major determinant of penicillin allergies
- Minor determinants, e.g., benzylpenicilloate, are responsible for most anaphylaxis

Cross-reactivity
- Penicillin cross-reacts with cephalosporin at a rate of 3–7%
- Penicillin has a high rate of cross-reactivity with imipenem
- Penicillin has no cross-reactivity with aztreonam, per current reporting

Desensitization
- Desensitization is necessary if the medication is the only clinically effective therapy
- For example, a pregnant woman with syphilis or a person with neurosyphilis requiring definitive penicillin therapy; both require desensitization and use of IV penicillin
- Subsequent administration down the road may require repeat desensitization

SERUM SICKNESS

Background

- Serum sickness is a type III hypersensitivity reaction that results from the injection of heterologous or foreign protein or serum
- Immune complex causes vascular injury and influx of neutrophils and eventual tissue injury or death
- Reactions secondary to the administration of nonprotein drugs are clinically similar to serum sickness reactions
- Serum sickness does not require prior exposure to an antigen (prior sensitization) and can occur on initial exposure
- The most common cause of serum sickness today is antibiotics, e.g., cefaclor and penicillin
- Stings from Hymenoptera (bees, wasps, and some ants) can induce serum sickness

Clinical presentation

- It may take 6–12 days for the reaction to develop, but can take up to 3 weeks
- If previous exposure has occurred, a reaction may occur as quickly as 1–3 days post-exposure
- Fever/malaise
- Skin rash: Urticarial (92%) and/or serpiginous, the rash typically starts on the anterior lower trunk or the periumbilical or axillary regions and spreads to the back, upper trunk, and extremities
- Arthritis is usually in the metacarpophalangeal and knee joints and usually symmetrical
- Edema may occur, particularly the face and neck
- Renal manifestations include proteinuria, microscopic hematuria, and oliguria
- GI complaints
- Headaches
- Myalgias
- Blurred vision
- Dyspnea/wheezing
- Lymphadenopathy
- Neurologic manifestation, e.g., peripheral neuropathy

Management

- Stop the offending agent
- NSAIDs can help for fever and muscle/bone pain
- Diphenhydramine or hydroxyzine will help to relieve urticaria and itching
- Prednisone 1–2 mg/kg/day can be given if other interventions are not helpful

ALLERGIC REACTIONS TO INSECTS

- Insect stings usually result in site-limited transient pain, itching, and swelling
- Allergic reactions of varying severity can occur in previously sensitized patients and can be life-threatening
- Recurrent systemic reactions to venom tend to be similar in severity to the initial reaction in an individual patient

Clinical presentation

- There are three common types of allergic reactions to the venom of Hymenoptera (includes bees, yellow jackets, wasps, hornets, and fire ants):
  1. **Anaphylactic reactions** (i.e., involving multiple organ systems)
  2. **Systemic cutaneous reactions** (widespread) include widespread pruritus, hives, erythema, and/or angioedema developing shortly after the sting. Can be dangerous if they involve edema of the lips, tongue, or structures near the airway. They may take several days to resolve fully
  3. **Large local reactions** (contiguous to the site) usually result in delayed and prolonged local inflammation that

increases over 24–48 h. Take 3–4 days to resolve

Diagnosis

- History of insect sting and symptoms consistent with an allergic reaction
- Presence of positive skin test and/or elevated serum levels of venom-specific immunoglobulin
- Testing can be done as soon as 1 week following the sting, but if negative and the history is convincing, it should be repeated 5–6 weeks later (transient anergy)

Management

- **Anaphylactic reactions**
  - Epinephrine
  - Other medications as per standard management of anaphylaxis
  - Prescribe epinephrine autoinjector
  - Refer to an allergist for venom immunotherapy
- **Systemic cutaneous reactions**
  - Antihistamines
  - Consider corticosteroids
  - Consider prescribing an epinephrine autoinjector to patients with a history of moderate-to-severe systemic cutaneous reactions
  - Consider referral to an allergist for venom immunotherapy
- **Large local reactions**
  - Ice pack
  - NSAIDs
  - Antihistamines
  - Consider corticosteroids
- **Venom immunotherapy**
  - Effective in reducing the severity of allergic reactions
  - Minimum 5-year duration
  - Indicated in all patients with a history of anaphylactic reaction to an insect sting and positive venom skin test or elevated serum levels of venom-specific IgE
  - Considered in selected patients with a history of moderate-to-severe cutaneous systemic reaction
  - Offered to very selected patients with a history of repeated large local reactions

SKIN TESTING

Background

- Skin prick tests are the most common screening tests for patients suspected to have allergies. Both environmental and food allergies can be tested this way
- Skin testing is highly sensitive and safe even in very young children
- These tests provide useful and reproducible clinical information in a short period (i.e., 15–20 min), with minimal expense and negligible risk to the patient

Indications

- Identification of aeroallergen triggers in patients who have asthma
- AR not controlled with usual medications, specific avoidance is desired in such cases, e.g., pet dander
- Food allergy
- Insect sting allergy
- Vaccine, drug, or latex allergy
- Evaluation for moderate-to-severe atopic dermatitis
- Other conditions, including allergic fungal sinusitis, allergic bronchopulmonary aspergillosis, and eosinophilic esophagitis

Medication that alters the result of skin test

- First-generation nonselective antihistamines, e.g., diphenhydramine, suppress skin reactivity for 3 days
- Second-generation antihistamines (e.g., cetirizine, loratadine) may blunt skin test for up to 7 days

- Ranitidine and famotidine may blunt the skin test for up to 7 days
- Tricyclic antidepressants and phenothiazines may block skin reactivity for 2 weeks

Medications do not interfere with allergy skin test

- Corticosteroids
- Asthma medications, e.g., albuterol and montelukast

Method of testing

- A small amount of concentrated allergen is deposited on the skin and a tiny puncture is made with a plastic device
- IgE receptors undergo cross-linking and activate mast cells, causing a release of histamine and other products leading to local vasodilatation and increased vascular permeability, resulting in wheals

In Vitro Allergy Testing

Enzyme-linked immunosorbent assay (ELISA)

- Radioallergosorbent (RAST) testing is outdated because of radiation and is rarely used today
- ELISA, which uses antibodies linked to enzymes, as well as fluorescent enzyme immunoassay (EIA) and chemiluminescent immunoassays
- The accuracy of immunoassays varies with the system being used and the quality of the allergen
- There is a good predictive value (> 90%) for pollens of grass, trees, dust mites, and cats, whereas less accurate results may be obtained from venoms, weeds, latex, dogs, and molds
- If testing is equivocal, it can be further evaluated by skin testing and, if indicated, a challenge to the allergen
- Both skin and ELISA are evidence of sensitization but not necessarily of clinical reactivity to a particular allergen. In contrast, a negative skin-prick test is strong evidence against clinically relevant allergy to the tested allergen

General Rules in the Management of Allergies

Avoidance of specific triggers

- Exposure to indoor allergens can be minimized with relatively simple measures
- Outdoor allergens are usually more difficult to avoid
- Strict avoidance of food allergens, including hidden sources and restaurant meals
- Selection of alternative medications in the case of drug allergies
- Latex-free materials during procedures for patients with latex allergies

Medications

- **First-generation** antihistamine: Diphenhydramine, chlorpheniramine, and hydroxyzine
  - Adverse effects of first-generation antihistamines:
    - Sedation
    - Interaction with acetylcholine receptors and can cause dry mouth, blurry vision
- **Second-generation** antihistamine: Cetirizine, fexofenadine, loratadine, and desloratadine
  - Does not cross the blood–brain barrier and are more specifically aimed at H1 receptor and not the other receptors
- **Steroid**
  - Intranasal corticosteroids are the most effective agents for nasal allergy and do not have the systemic effects seen with oral steroids
  - Inhaled corticosteroids are important treatment measure in the patient with persistent asthma

Immunotherapy

- Only therapy capable of changing the course of allergic disease

- The goal is to decrease the severity of reaction upon exposure
- Permanent cure (tolerance) can be achieved in some cases
  - Involves giving increasing doses of allergens via the subcutaneous, sublingual, or oral route to induce an alteration in the immune response to the allergen
  - Usually takes 1–2 years before beneficial effect occurs. Minimum length of therapy estimated around 5 years
  - Effective in the treatment of venom allergy, pollen allergies, dust mites, and animal dander allergies
  - Efficacy currently being tested for the treatment of IgE-mediated food allergies
  - Local reactions are common, but systemic (anaphylactic) reactions can occur during allergen immunotherapy

IMMUNOLOGY

Overview of the Immune System

Two main arms of vertebrate immunity

- **Innate immune system** (rapid and always available)
  - Physical barriers—skin, hair, cilia, mucous membranes, mucous and chemical secretions, digestive enzymes, stomach acid, etc.
  - Internal defenses—inflammatory responses, complement proteins, phagocytic cells, natural killer (NK) cells
  - NK cells: Do not require antigen to be presented with HLA antigen
    - Produce large quantities of interferon-gamma, IL-4, and granulocyte-macrophage colony-stimulating factor, and multiple other cytokines and chemokines (IL-2, IL-13, IL-17, IL-21, and TNF-alpha)
- **Adaptive immune system** (recognizes "self" versus "non-self," tailors immune response for specific pathogens/infected cells, possesses immunologic memory)
  - Humoral immunity (antibodies)
  - Cell-mediated immunity
  - Memory response

T-Lymphocytes

Characteristics

- **T**-cells mature in the **t**hymus
- Play a central role in cell-mediated immunity
- Cell surface marker: CD3+

Subtypes of T-lymphocytes

- Helper T-cells (CD4+ T-cells)
  - Promote maturation of B-cells and interact with B-cells to allow antibody production
  - Interact with cells that express class II major histocompatibility complex (MHC), which is loaded with extracellular proteins
- Cytotoxic T-cells (CD8+ T-cells)
  - Kill cells infected by intracellular bacteria/virus/cancer
  - Recognize their targets by binding to an antigen associated with MHC class I molecules, which are present on the surface of all nucleated cells

B-Cells

Background

- **B**-cells mature in the **b**one marrow
- B-cells are surface membrane immunoglobulin-positive. B-cell receptor composed of membrane-bound IgG, IgA, IgM, IgE, or IgD
- Cell surface marker: CD19+/CD20+

Antibodies (IgG, IgA, IgM, IgE, and IgD)

- **IgG:** In its four forms (IgG1, IgG2, IgG3, and IgG4) provides the majority of antibody-based immunity against invading pathogens. The only antibody capable of crossing the placenta to give passive immunity to the fetus
- **IgM:** Expressed on the surface of B-cells (monomer) and in a secreted form (pentamer) with very high avidity. Eliminates pathogens

in the early stages of disease before class switching to other immunoglobulin isotypes. Good at activating complement
- **IgA:** Main immunoglobulin in mucosal secretions. Found in mucosal areas such as the gut, respiratory tract, and urogenital tract and prevents colonization by pathogens. Also found in saliva, tears, and breast milk
- **IgD:** Functions mainly as an antigen receptor on B-cells that have not been exposed to antigen. Has been shown to activate basophils and mast cells to produce antimicrobial factors
- **IgE:** Binds to allergens and triggers histamine release from mast cells and basophils and is involved in allergy. Also protects against parasites

Initial Immunologic Testing of a Child with Recurrent Infections

CBC with manual differential and erythrocyte sedimentation rate (ESR)
- Normal absolute lymphocyte count rules against T-cell defect
- Normal absolute neutrophil count rules against congenital or acquired neutropenia
- Normal platelet count excludes Wiskott–Aldrich syndrome
- Absence of Howell–Jolly bodies rules against asplenia
- Normal ESR makes chronic bacterial and fungal infection unlikely

Additional testing for B-cell defects
- Quantitative immunoglobulins (IgG, IgA, and IgM)
- Antibody titers to vaccines (e.g., tetanus, diphtheria, *Haemophilus influenzae* type B, and pneumococcus)
- Isohemagglutinins

Additional testing for T-cell defects
- T-cell quantification
- T-cell functional studies: Lymphocyte proliferation assay to mitogens (phytohemagglutinin, concanavalin A, pokeweed mitogen) and/or to antigens (candida, tetanus)
- T-cell receptor excision circles (TREC); newborn screening (as of December 2018, all newborns in the United States are screened for severe combined immunodeficiency (SCID))

Additional testing for phagocyte defects
- Absolute neutrophil count
- Neutrophil oxidative burst assay (dihydrorhodamine [DHR] assay)

Additional testing for complement deficiencies
- CH50

Clinical patterns in some of the primary immunodeficiencies (Table 11.2)

Table 11.2 Clinical patterns in some of the primary immunodeficiencies

Clinical features	Diagnosis
0–6 months of age	
Unusual facial features, hypocalcemia, heart disease (conotruncal)	22q11.2 deletion syndrome (DiGeorge syndrome)
Delayed umbilical cord detachment, leukocytosis, recurrent infection	Leukocyte adhesion defect
Persistent thrush, pneumonia, failure to thrive, diarrhea, small tonsils, nonpalpable lymph nodes, profound lymphopenia, usually present in the first few months of life	Severe combined immunodeficiency
Bloody stools, draining ears, small platelets, atopic eczema	Wiskott–Aldrich syndrome
4- to 9-month-old with recurrent mild infections, but appropriately makes antibodies to diphtheria and tetanus toxoids	Transient hypogammaglobulinemia of infancy (THI)
6 months to 5 years	
Boy presents between 6 and 9 months with severe and recurrent infection, absent antibodies and absent tonsils	X-linked agammaglobulinemia

(continued)

Table 11.2 (continued)

Clinical features	Diagnosis
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 infections, silvery hair	Chediak–Higashi syndrome
Boy with liver abscesses, suppurative lymphadenopathy, antral outlet obstruction, pneumonia, osteomyelitis, nitroblue tetrazolium (NBT) or dihydrorhodamine assay reduced or no color change	Chronic granulomatous disease
Recurrent respiratory, gastrointestinal, and genitourinary tract infections, many patients are asymptomatic, risk of anaphylaxis with blood products	IgA deficiency
Older than 5 and adults	
Healthy male until acquires fulminant often fatal infectious mononucleosis or EBV infection (mean age of presentation is < 5 years)	X-linked lymphoproliferative syndrome
Sinopulmonary infections, neurologic deterioration, telangiectasia	Ataxia–telangiectasia
Recurrent *Neisseria* infections	Terminal complement defect
Sinopulmonary infections, normal B-cell counts, hypogammaglobulinemia, autoimmune cytopenias	Common variable immunodeficiency

EBV Epstein–Barr virus

DISORDERS OF PHAGOCYTE FUNCTION

Chronic Granulomatous Disease (CGD)

Background

- Defect in NADPH oxidase complex
- Neutrophils unable to generate hydrogen peroxide or hydroxyl radicals (superoxides) to kill phagocytosed organisms
- X-linked form most common; AR disease also occurs

Clinical presentation

- Pyogenic infections of the skin, lungs, bones, liver, and GI tract
- Characteristic infections with
  - *Aspergillus* spp.
  - *Staphylococcus aureus*
  - *Burkholderia (Pseudomonas) cepacia*
  - *Serratia marcescens*
  - *Nocardia* spp.
  - Outside of the United States: *Salmonella* and bacillus Calmette–Guérin (BCG)
- Most common sites of disease: Lung, skin, lymph nodes, GI, liver, urinary tract
- Autoimmune/inflammatory complications

Diagnosis

- DHR assay: Functional neutrophils take up DHR and oxidize it to a green fluorescent compound detectable by flow cytometry
- Nitroblue tetrazolium (NBT): An older method that is now less used due to operator subjectivity and higher false-negative rate
  - **Normal:** NBT oxidized to purple/blue color
  - **CGD:** Reduced or no color change

Treatment
- Prophylactic antibiotics (antibacterial and antifungal)
- Interferon (IFN)-gamma can be added
- Aggressive treatment of infections
- Definitive therapy:
  - Hematopoietic cell transplant
  - Gene therapy

Leukocyte Adhesion Defect

Background
- Defect in adhesion molecules that allow neutrophils to leave circulation in response to infection
- Keywords: *Delayed umbilical cord separation, leukocytosis*

Clinical presentation
- **Delayed umbilical** cord separation > 1 month
- **Leukocytosis** with average white blood cell (WBC) count (45×10^9/L)
- Recurrent bacterial infections, especially staphylococcal infections (recurrent skin abscess)
- Absence of pus and neutrophils at the wound site
- Poor wound healing

Diagnosis
- Delayed separation of an umbilical cord and persistent high WBC count is highly suggestive
- Flow cytometric measurements of surface glycoprotein (CD18 or CD11) expression

Treatment
- Prophylactic antibiotics
- Definitive therapy with hematopoietic cell transplant

Chediak–Higashi Syndrome

Background
- Autosomal recessive
- Mutation in *CHS1/LYST* gene on chromosome 1q42.1-2
- Disease characterized by abnormal lysosomes/granules in all cell types

Clinical presentation
- Partial oculocutaneous albinism due to improper transfer of melanosomes to epithelial cells (fair skin, light blond/gray/white hair)
- Neutrophil abnormalities (impaired chemotaxis and dysfunction)
  - Contains giant azurophilic granules that do not release contents with infection
  - Recurrent pyogenic infections (mostly skin and respiratory tract)
- Coagulation defects due to decreased platelet stores
- Progressive neurologic abnormalities
- "Accelerated phase"—massive systemic lymphohistiocytosis

Risk of malignancy
- Life-threatening lymphoma-like syndrome
- Leukemia and lymphoma
- Lymphohistiocytic infiltration of the liver, spleen, and lymph nodes
- Pancytopenia
- Fulminant Epstein–Barr virus (EBV) infections

Diagnosis
- Classic giant azurophilic granules (peroxidase positive) in neutrophils, eosinophils, and granulocytes
- Neutropenia
- Poor NK-cell cytotoxicity
- B-cell function usually normal

Treatment
- Prophylactic antibiotics/aggressive treatment of infections
- Hematopoietic cell transplantation (but does not correct neurologic decline or oculocutaneous albinism)

ANTIBODY DEFICIENCY SYNDROMES

Transient Hypogammaglobulinemia of Infancy (THI)

Background

- Maternal IgG traverses placenta to the fetus throughout gestation; most pronounced during the latter half of the third trimester
- After birth, IgG levels in the infant fall as newborn IgG contribution is still catching up, resulting in a physiologic IgG nadir
- THI results from a prolongation of the physiologic hypogammaglobulinemia that usually occurs around age 3–6 months
- Most common age of developing symptoms is 6–12 months

Clinical presentation

- Most infants are asymptomatic, but some can develop recurrent respiratory infections (otitis media and bronchial infections)
- Life-threatening infections (cellulitis, bacteremia, meningitis) are unusual but may occur
- T-cell immunity is intact
- By definition, a self-limited disorder
  - Recurrent infections usually resolve by 9–15 months of age
  - IgG normalizes by 2–4 years of age (but can take up to 10 years)

Diagnosis

- Low serum IgG levels
- Antibody titers to protein immunizations (e.g., tetanus toxoid, diphtheria toxoid, polio) are at normal or near-normal concentrations

Treatment

- Supportive
- Antibiotic prophylaxis
- IgG replacement can be considered in severe cases

X-Linked Agammaglobulinemia

Background

- Defect in Bruton tyrosine kinase (BTK) causing arrest in B-lymphocyte development
- Almost no circulating B-cells → panhypogammaglobulinemia

Clinical presentation

- Presents at 3–9 months of age when maternally transferred antibodies disappear
- Unusually severe or recurrent bacterial respiratory tract infections
  - Sequelae of infections include chronic cough, rhinitis, digital clubbing, and failure to thrive
- Absence or near absence of B-cell-rich tonsils and adenoids
- Episodes of sepsis with encapsulated bacteria
- Increased susceptibility to certain infections such as enterovirus (echovirus, coxsackie), causing meningoencephalitis or hepatitis, even with adequate IgG replacement

Diagnosis

- Absent circulating CD19+/CD20+ B-cells by flow cytometry
- Very low serum IgG, IgA, IgM
- Deficient antibody responses to immunizations
- Neutropenia in ~20% of patients
- Absent *BTK* expression by flow cytometry
- Abnormal *BTK* gene sequencing

Treatment

- IgG replacement
- Aggressive treatment of infections

Common Variable Immune Deficiency (CVID)

Background

- Markedly reduced serum IgG in combination with low IgA and/or IgM

  - Poor or absent response to immunizations
  - Absence of other defined immunodeficiencies
- Genetics: Most cases are sporadic and likely due to multiple genes, but more monogenic causes are being identified
- Usually in the second and third decades and very rare before the age of 6 years

Clinical presentation

- Recurrent infections—Permanent damage to the bronchi may occur, resulting in bronchiectasis
- As many as 20% of patients with CVID develop autoimmune complications:
  - Immune thrombocytopenia (ITP)
  - Autoimmune hemolytic anemia (AIHA)
  - Evans syndrome
  - Rheumatoid arthritis
  - Systemic lupus erythematosus (SLE)
  - Autoimmune thyroid disease
- GI diseases also commonly associated (malabsorption, chronic diarrhea, inflammatory bowel disease)

Risk of malignancy

- Increased risk of malignancy, particularly non-Hodgkin lymphomas

Diagnosis

- Quantitative immunoglobulins (IgG, IgA, IgM)
- Evaluation of antibody responses after immunization with polysaccharide and protein conjugate antigens

Treatment

- IgG replacement
- Antibiotics for bacterial infections
- Treatment of autoimmunity. (Note: autoimmunity needs to be diagnosed clinically, since patients may not have detectable autoantibody production)
- Monitoring for malignancy

Selective IgA Deficiency (sIgAD)

Background

- sIgAD is the most common immunologic defect in humans
- Deficiency of serum IgA in the setting of normal IgG and IgM in an individual > 4 years of age

Clinical presentation

- Majority are asymptomatic
- Various GI tract infections with viruses and bacteria
- *Giardia* manifests as chronic diarrhea with or without malabsorption
- Recurrent sinopulmonary infections can occur
- Increased incidence of autoimmunity and atopy

Diagnosis

- Very low or absent IgA
- Low serum IgA levels in children aged 6 months to 4 years should be confirmed to be persistently low at age 4 years before making a lifetime diagnosis of sIgAD

Treatment

- Antibiotics
- Clean drinking water due to increased risk of *Giardia*

DEFECTS OF CELLULAR IMMUNITY

22q11.2 Microdeletion Syndrome/DiGeorge Syndrome (see Table 11.2)

Background

- Microdeletion at 22q11.2 → disorder of third and fourth pharyngeal pouches
- CATCH 22
  - **C**ardiac (conotruncal: tetralogy of Fallot, truncus arteriosus, interrupted aortic arch)

  - **A**bnormal facies (short philtrum, low-set ears, hypertelorism, antimongoloid slant)
  - **T**hymic hypoplasia
  - **C**left palate (palate anomalies, speech delay, learning disability)
  - **H**ypoparathyroidism with hypocalcemia and tetany
  - Chromosome **22**
- Types
  - Partial DiGeorge syndrome (most common)
  - Complete DiGeorge syndrome (< 1% of cases); association with CHARGE (**C**oloboma [eye]; **H**eart defects of any type; Atresia [choanal]; **R**etardation [of growth and/or development]; **G**enital anomaly; **E**ar anomaly) syndrome

Clinical presentation

- Cardiac abnormalities (ranges from asymptomatic to cyanotic)
- Neonatal hypocalcemia
- Immunodeficiency: Ranges from asymptomatic to recurrent sinopulmonary infections to severe combined immunodeficiency, depending on the degree of thymic hypoplasia
- Intellectual disability

Diagnosis

- Serum calcium and phosphorus
- Lymphocyte count (SCID workup if there is evidence of complete DiGeorge syndrome)
- Chest radiograph to evaluate for thymic shadow
- Immunoglobulin levels +/− vaccine antibody titers if indicated
- Renal ultrasound to rule out genitourinary tract abnormalities
- Genetic analysis (FISH, now being replaced by microarray)

Treatment for complete DiGeorge syndrome

- Thymus transplant
- Hematopoietic cell transplant

Prognosis

- Varies significantly—depends on the nature and degree of involvement of different organs
- Many live long productive lives

Chronic Mucocutaneous Candidiasis (CMC)

Background

- The unifying feature of these heterogeneous disorders is impaired cell-mediated immunity against *Candida* species
- Classic forms are due to mutations in the autoimmune regulator gene (*AIRE*) and signal transducer and activator of transcription 1 gene (*STAT1*)

Clinical presentation

- Endocrinopathies
- Autoimmunity: AIHA, ITP, autoimmune neutropenia
- Immunodeficiency
  - Abnormal T-cell proliferation to *Candida* antigen
  - Increased bacterial and viral infections

Diagnosis

- Evaluation for immunodeficiency (CBC, quantitative immunoglobulins, vaccine antibody titers, lymphocyte subsets, lymphocyte proliferation studies)
- *STAT1* function can be evaluated by flow cytometry
- The definitive test is a genetic analysis
- Endocrine evaluation

Treatment

- Systemic antifungal therapy
- Treatment of associated endocrinopathies and autoimmunity
- IgG replacement if indicated

X-Linked Lymphoproliferative (XLP) Syndrome

Background
- Mutation in signaling lymphocyte activation molecule (SLAM)-associated protein (*SAP*) gene

Clinical presentation
- Healthy male until EBV infection
- Average of presentation is 2.5 years
- Fulminant, often fatal **infectious mononucleosis causing** multi-organ failure
  - Can result in secondary hemophagocytic lymphohistiocytosis (HLH)
- Dysgammaglobulinemia
- Lymphoproliferative disease, predominantly non-Hodgkin B-cell lymphomas
- 70% of affected boys die by age 10

Diagnosis
- EBV studies
- Peripheral blood smears will show atypical lymphocytosis, particularly CD8+ T cells
- Hypogammaglobulinemia is common
- NK-cell activity often reduced
- Chemistry profiles will show transaminitis and other findings of acute hepatitis/liver failure
- HLH labs if indicated, including bone marrow biopsy
- Mutation analysis for the *SAP* gene mutation

Treatment
- Rituximab to ablate B-cells
- IgG replacement
- Definitive therapy—hematopoietic cell transplantation

Hyper-IgE Syndrome (HIES)

Background
- Autosomal dominant (AD) (*STAT3*) is more common
- Autosomal recessive (*DOCK8*) also occurs but more rare

Clinical presentation
- AD HIES
  - Recurrent skin abscesses
  - Eczema
  - Recurrent pneumonia with pneumatoceles (staphylococcal infections)
  - Mucocutaneous candidiasis
  - Coarse facial features
  - Bone fractures, scoliosis

Diagnosis
- Elevated serum IgE levels (does not correlate with disease severity)
- Eosinophilia
- Some have decreased IgG levels and poor vaccine antibody responses

Treatment
- Skin care (hydration and control of itch)
- Prophylactic antibiotics to prevent cutaneous and respiratory infections
- Aggressive treatment of infections
- Monitor/treat skeletal abnormalities
- Hematopoietic cell transplantation addresses immunodeficiency but not somatic abnormalities

COMBINED ANTIBODY AND CELLULAR IMMUNODEFICIENCY

Severe Combined Immunodeficiency (SCID)

Background
- Caused by multiple mutations (X-linked, AR, or sporadic) that affect T- and B-cell development
- CD3 T-cell count typically < 300/μL

- CD19/CD20 B-cells and CD16/56 NK-cells may or may not be present, depending on the genetic defect
- Keywords: *Lymphopenia, chronic diarrhea, thrush, failure to thrive, absent thymus, severe recurrent infections, bone abnormalities*

Clinical presentation

- Sibling death in infancy (e.g., multiple deaths during infancy due to infection or unexplained deaths) or previous miscarriages in the mother
- Family history of SCID or other primary immunodeficiency
- Family history of consanguinity
- Most patients present before 3 months of age
- Poor feeding
- Failure to thrive
- Chronic diarrhea
- Recurrent infections, especially pneumonia
- Very small/absent thymus

Diagnosis

- Low CD3 T-cell count, usually < 300/μL. (Note that the normal lymphocyte count in a newborn is ~2500/μL)
- Flow cytometry for lymphocyte subsets to quantify CD3/4/8 T-cells, CD19 B-cells, and CD16/56 NK-cells
- Abnormal lymphocyte proliferation studies to mitogens
- Low quantitative immunoglobulins (initially normal due to maternal transfer of IgG)
- No antibody response to vaccination
- Newborn screening for T-cell receptor excision circles (TREC)

Treatment

- Initial management: Protective isolation, intravenous immunoglobulin (IVIG), *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis, fungal prophylaxis, no live vaccines, palivizumab, cytomegalovirus (CMV) negative blood products, discontinue breastfeeding if mother is CMV positive
- Adenosine deaminase (ADA) enzyme replacement for ADA-deficient SCID
- Definitive: Stem cell transplant, preferably before the onset of severe persistent opportunistic infections and with a matched sibling donor
  - Gene therapy available for some forms of SCID (ADA, X-linked, Artemis)
  - Good survival with early transplant

Complications

- Early graft-versus-host disease (GVHD) from maternal cells crossing the placenta (maternal engraftment)
- Without intervention, SCID usually results in severe infection and death in children by 2 years of age

Wiskott–Aldrich Syndrome

Background

- Genetics: X-linked recessive (Xp11.22–23)
- Results from mutations in Wiskott–Aldrich syndrome protein (WASp) (important in actin cytoskeleton remodeling and impacts interactions between T-cells and APCs, B-cells, etc.)
- Keywords: *Eczema, small platelet, bleeding, recurrent infection*

Clinical presentation

- Classic triad
  - Thrombocytopenia (small platelets)
  - Increased susceptibility to infections
  - Eczema
- Prolonged bleeding from the umbilical stump or circumcision site
- Eczema is often seen during the first year of life
- Recurrent infections (sinopulmonary infections, meningitis, and sepsis) with encapsulated bacteria including *Streptococcus pneumoniae, Neisseria meningitidis, H. influenzae*

- Hepatosplenomegaly
- Autoimmunity: Cytopenias, vasculitis
- Increased risk of lymphoma associated with EBV infection and increased risk of leukemia
- Bleeding is the main cause of death

Diagnosis

- Early onset thrombocytopenia with small platelets
- Screening for WASp by flow cytometry
- Gene sequencing
- Other lab findings:
  - T-cell lymphopenia
  - Abnormal lymphocyte proliferation
  - Abnormal immunoglobulin isotypes
  - Poor vaccine response

Treatment

- Supportive care
  - IgG replacement
  - Prophylactic antibiotics
  - Platelet transfusions
  - Skin care
  - Splenectomy to increase circulating platelets. Not routinely recommended given the increased risk of septicemia with asplenia
- Definitive care
  - Hematopoietic cell transplantation
  - Gene therapy

Ataxia-Telangiectasia

Background

- Affected gene: Ataxia–telangiectasia mutated (*ATM*) at 11q22.3
- *ATM* is expressed in all tissues in the body. Involved in DNA repair and recombination

Clinical presentation

- Progressive ataxia
  - Usual presenting symptom
  - Often appears healthy during the first year and begins to walk, but with slow progression
  - Usually reliant on a wheelchair by 10 years of age. Also, develop dysarthria around this time
- Telangiectasia
  - Conjunctiva (3–5 years of age)
  - Cutaneous (on exposed areas such as pinnae, nose, face, neck)
- Immunodeficiency
  - Humoral and cellular immunodeficiency
  - Recurrent sinopulmonary infections
  - Infections outside of the respiratory tract are not increased

Risk of malignancy

- Lymphoma and leukemia most common
- AT cells are susceptible to ionizing radiation and chemotherapeutic drugs due to defective DNA repair making treatment more difficult and late complications more common

Diagnosis

- Elevated alpha-fetoprotein level (AFP) in children > 8 months of age
  - Level does not correlate with disease severity
- Wide range of immune laboratory abnormalities
  - Immunoglobulin deficiency (often IgA and/or IgG subclasses)
  - Poor antibody response to polysaccharide vaccines
  - Lymphopenia, predominantly of T-cells
- Brain imaging: Cerebral atrophy and ventricular enlargement

Treatment

- IgG replacement
- Antibiotics
- Close monitoring of chronic lung disease
- Swallow evaluation

- Physical and occupational therapy
- Minimize tests with ionizing radiation
- Close monitoring for malignancy

X-Linked Hyper-IgM Syndrome (XHIM)

Background

- Rare primary immunodeficiency caused by mutations in CD40 ligand (CD40L)
  - CD40L (on T-cells) interacts with CD40 (on B-cells) to induce class switching of IgM to other immunoglobulin isotypes
- Considered a combined immune deficiency because dendritic cells and monocytes/macrophages also express CD40 and require CD40L stimulation

Clinical presentation

- Recurrent sinopulmonary infections (primarily encapsulated bacteria)
- Opportunistic infection (PJP pneumonia) is often the presenting symptom
- *Cryptosporidium* infection is common and causes biliary tract disease
  - Common cause of chronic diarrhea that is present in a large percentage of patients
- Increased risk of malignancy

Laboratory findings

- Normal or elevated serum IgM levels associated with low or absent IgG, IgA, and IgE serum levels
- Lack of antibody response to vaccines
- Approximately two-thirds of patients have neutropenia

Diagnosis

- Lack of CD40L expression on T-cells by flow cytometry
- Absent CD40L function as measured by binding to CD40 by flow cytometry
- Confirmatory gene sequencing

Treatment

- Immunoglobulin replacement
- Prompt treatment of infections
- Prevention of *Cryptosporidium* infection by using boiled or filtered water
- Patients with neutropenia may benefit from treatment with granulocyte colony-stimulating factor (G-CSF)
- Definitive: Hematopoietic cell transplantation

DISORDERS OF THE COMPLEMENT SYSTEM

Complement Defect

Background

- Initial defect: Associated with autoimmune diseases
- Terminal defect: Increased risk of infection

Clinical presentation

- Genetic deficiency of C1q, C1r/s, C2, C4, and C3 is associated with autoimmune inflammatory diseases (SLE) and recurrent pyogenic bacterial infections
- Genetic deficiency of C5, C6, C7, C8, and C9 is associated with increased susceptibility to *Neisseria* infections (also some association with rheumatic diseases)

Diagnosis

- Complement (CH50) test: Screen for deficiencies in complement by performing the total serum classic hemolytic complement (CH50) test
  - Note that complement hemolytic activity is unstable and temperature sensitive → CH50 can be reduced if left only a few hours at room temperature
- Direct measurement of individual serum complement proteins, such as C3 and C4, can

also be performed and is helpful in determining the diagnosis

Treatment

- Watch closely for meningococcal disease and treat early
- Vaccination (especially meningococcal and pneumococcal vaccines)
- Antibiotic prophylaxis is not routinely done, but may be needed in some
- Plasma infusions (to replace complement factors) done very rarely

PEARLS AND PITFALLS

- Environmental allergies are responsible for a large proportion of asthma exacerbations in children 5 years and older.
- A positive skin test or an elevated IgE to a particular allergen does not always translate into clinical reactivity.
- Atopic dermatitis developing the first few months of life is an important risk factor for food allergies.
- Allergen immunotherapy has been proven to be effective for treating environmental and insect venom allergy. A similar approach is now being evaluated for the treatment of food allergies.
- Mastocytosis in children is usually limited to the skin and follows a benign course.
- Functional neutrophil disorders include the inability to generate superoxides to kill phagocytosed organisms (CGD) or the inability to properly adhere to blood vessels and leave the circulation to sites of infection (LAD).
- Most of a newborn's IgG is received through the placenta from the mother during the last trimester. There is a physiologic nadir that occurs around 3–6 months of age.
- Normal T-lymphocyte counts in a newborn are usually around 2500/μL. In SCID, CD3 T-cell counts are usually < 300/μL and must be accompanied by poor T-cell function via lymphocyte proliferation assays.
- Newborn screening for SCID is now performed in every state in the United States.
- Terminal complement defects are associated with recurrent *Neisseria* infections, while early complement defects are associated with autoimmunity.
- Hematopoietic stem cell transplant has the potential to cure many immunodeficiencies by using healthy donor stem cells that are capable of producing functional blood immune cells. However, this will not address somatic features of diseases such as ataxia telangiectasia, Chediak–Higashi syndrome, etc.

Suggested Reading

Arunachalam M, Sanzo M, Lotti T, Colucci R, Berti S, Moretti S. Common variable immunodeficiency in vitiligo. G Ital Dermatol Venereol. 2010;145(6):783–8.

Bonilla FA, Khan DA, Ballas ZK, Chinen J, Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2015;136(5):1186–1205.e78. https://www.jacionline.org/article/S0091-6749(15)00883-0/pdf. Accessed 4 Feb 2019.

Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice

parameter: 2010 update. J Allergy Clin Immunol. 2010;126(3):477–80.e1-42.

Munir AK, Björkstén B, Einarsson R, Ekstrand-Tobin A, Möller C, Warner A, Kjellman NI. Mite allergens in relation to home conditions and sensitization of asthmatic children from three climatic regions. Allergy. 1995;50(1):55–64.

National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma, Full Report 2007. NIH Publication 07-4051. Bethesda: National Heart, Lung, and Blood Institute; 2007.

Scadding G. Optimal management of nasal congestion caused by allergic rhinitis in children. Pediatr Drugs. 2008;10(3):151–62.

Shprintzen RJ, Goldberg RB, Lewin ML, Sidoti EJ, Berkman MD, Argamaso RV, et al. A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: velo-cardiofacial syndrome. Cleft Palate J. 1978;15(1):56–62.

Tiller TL, Buckley RH. Transient hypogammaglobulinemia of infancy: review of the literature, clinical and immunologic features of 11 new cases, and long-term follow-up. J Pediatr. 1978;92(3):347–53.

Endocrinology

12

Amr Morsi

GROWTH DISORDERS

Normal Growth Rate

- Birth length increases by 5% at 1 year (approximately 25 cm or 10 in./year)
- At 1–2 years of age, children grow 12.5 cm or 5 in./year (approximately half the growth rate of the 1st year of life)
- By 2 years of age, children are approximately half of their final adult height
- After 2–3 years of age, height increases by approximately 6.25 cm or 2.5 in./year
- Careful attention to growth rate (not only the height) facilitates early detection of a growth-slowing disorder

What is the relationship between the linear growth rate and weight gain?

- Poor nutrition and excess caloric intake can influence linear growth
- If a weight deceleration precedes and is greater than the height deficit, the child needs a gastrointestinal consultation (Fig. 12.1)
- Excess weight gain associated with a decline in growth rate is not nutritional and requires endocrine consultation

Family history of pubertal onset, age of adult height attainment, and bone age

- Height and pubertal onset in parents can be helpful in assessing the likelihood that similar growth pattern in the child represents a normal variation

Midparental target height (MPTH)

- Calculated as an average ± 2 SD (1 SD = 2 in.)

Midparental height (MPH) for boys

- Paternal height + (maternal height + 13 cm or 5 in.)/2

MPH height for girls

- Maternal height + (paternal height −13 cm or 5 in.)/2

Short Stature

Classification

Normal variant short stature

- Constitutional delay of growth and puberty (CDGP)
- Familial short stature
- Idiopathic short stature

Pathological short stature

- Chronic disease
- Chronic undernutrition
- Endocrine disorders (e.g., growth hormone deficiency [GHD], hypothyroidism, Cushing syndrome)
- Genetic syndromes (e.g., Turner, Noonan)
- Psychosocial

A. Morsi (✉)
Division of Endocrinology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA
e-mail: amr.morsi@chp.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_12

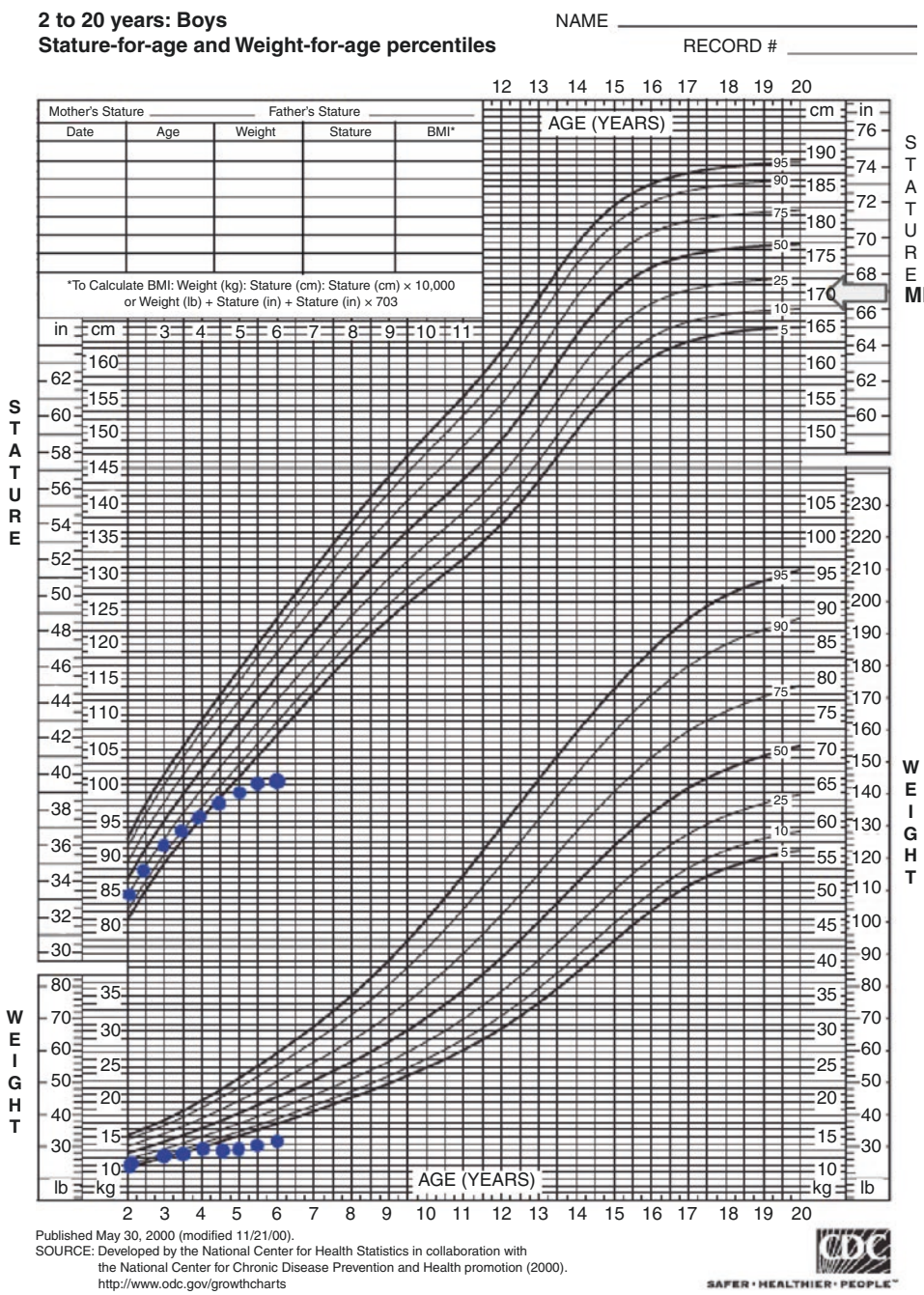


Fig. 12.1 Growth curve of a child with failure to thrive secondary to malabsorption. Weight is affected before height (http://www.cdc.gov/growthcharts)

Clinical Approach for Evaluating Short Stature and Poor Linear Growth

History

- Birth history (intrauterine growth retardation [IUGR], small for gestational age [SGA]), developmental history, and history of chronic illnesses
- Parental history of pubertal onset in males and menarche in females

Physical examination

- Anthropometric measurements to determine height and weight percentiles, as well as linear growth velocity and weight gain
- Detailed physical examination to look for signs of genetic syndromes, endocrinopathies, and signs of pubertal development
- Parental height for determining the mid-parental height (MPH) and MPTH height range

Laboratory evaluation

- Indications: Height ≤ 2 SD below the mean for age, sex, and population or poor linear growth (i.e., reduced growth velocity):
  - Complete blood count (CBC)
  - Electrolytes
  - Calcium, phosphate, and alkaline phosphatase (Ca, Phos, ALP)
  - Celiac disease screen: Total immunoglobulin A (IgA), tissue transglutaminase (tTG) IgA
  - Thyroid-stimulating hormone (TSH,) free thyroxine 4 (free T4)
  - Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
  - Insulin-like growth factor 1 (IGF-1), IGF binding protein 3 (IGFBP-3)
  - Bone age radiograph for skeletal maturation
  - Karyotype (for girls)

Imaging: Bone age radiograph to determine skeletal maturation

- Bone age will be similar to chronological age in familial short stature and genetic causes of short stature
- Bone age will be more delayed than the chronological age in CDGP and endocrinopathies
  - Bone age is usually mildly delayed in CDGP (usually > 2 SD below mean for age and sex)
  - The degree of bone age delay in endocrinopathy will depend on the duration of disease, e.g., in severe long-standing GHD, the bone age is usually > 3 SD below the mean for age and sex

Constitutional Delay of Growth and Puberty (CDGP)

Background

- The most common cause of short stature and pubertal delay
- Typically have retarded linear growth within the first 3 years of life
- Most children resume a normal growth velocity by the age of 2–3 years
- During childhood, these individuals grow along or parallel to the lower percentiles of the growth curve
- Children with CDGP are often referred to as "late bloomers" with onset of puberty also being later than peers

Diagnosis

- Family history of growth and pubertal delay is common (in 50% of cases)
- Delayed bone age
- Linear growth is 2 SD deviation below the mean for age in the first 3 years of life (Fig. 12.2)
- Pubertal growth spurt is delayed, and the growth rate continues to decline after those of their classmates have begun to accelerate
- IGF-1 tends to be low for chronological age but normal for bone age
- GH and thyroid studies are usually normal

Management

- Medical care in CDGP is aimed at obtaining several careful growth measurements at frequent intervals, often every 6 months
- These measurements are used to calculate linear height velocities and to establish a trajectory on the growth curve
- Medical treatment of this variation of normal growth is not necessary but may be initiated in adolescents experiencing psychosocial distress
- Boys with more than 2 years of pubertal delay may benefit from a short course of testosterone therapy after the age of 14 years

Familial Short Stature (FSS)

Background

- Height below the fifth percentile
- Growth velocity, i.e., parallel to but below the normal growth curve (Fig. 12.3)

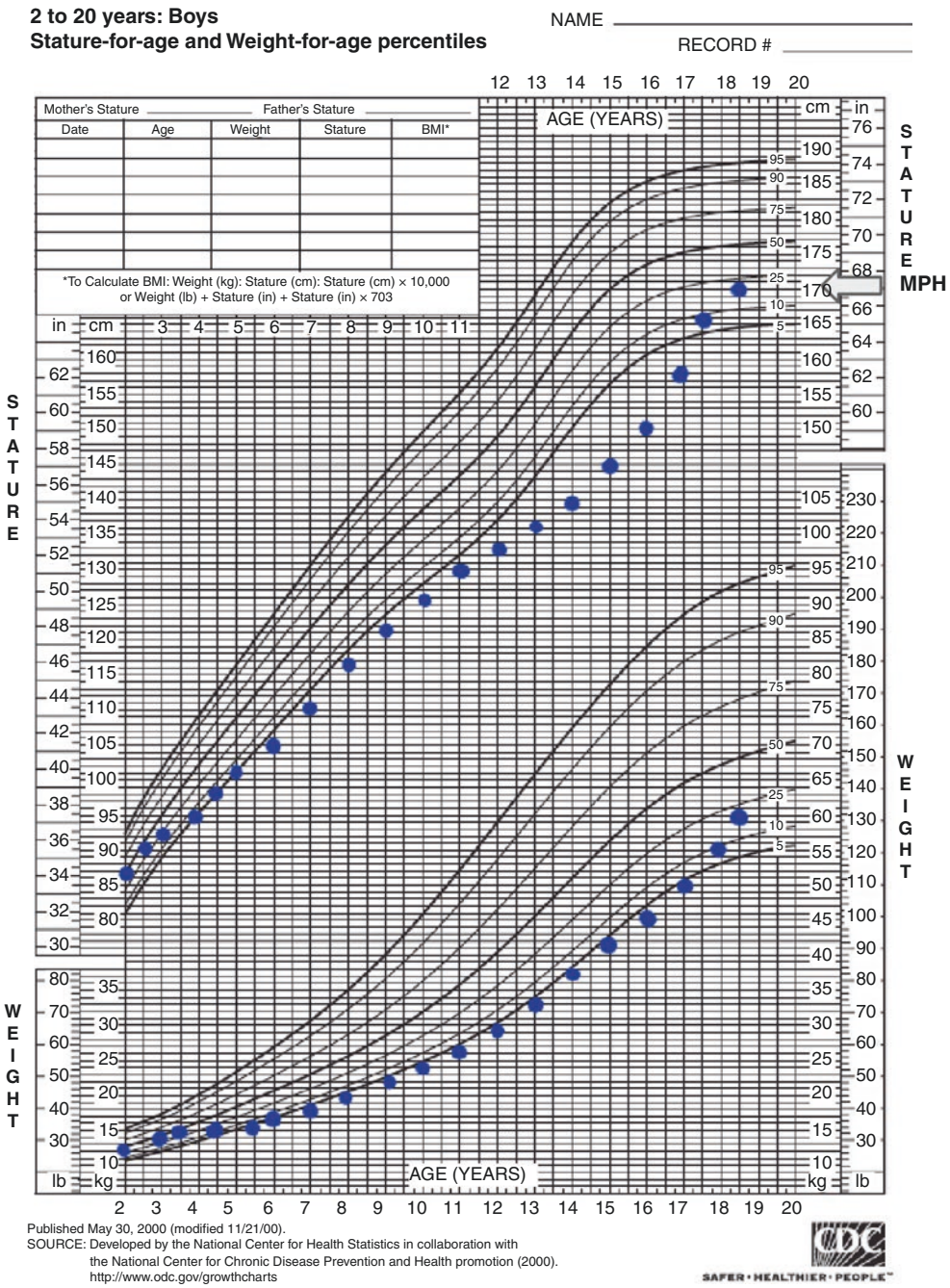


Fig. 12.2 Short stature secondary to constitutional delay. Growth is noted along or parallel to the lower percentiles of the growth curve and pubertal initiation is also delayed. Catch-up growth is noted from age of 16 to 17 years, and at 19 years of age, the boy reached his midpaternal target height ("late bloomer") (http://www.cdc.gov/growthcharts)

Diagnosis

- Bone age is congruent with child's chronological age
- The time of pubertal onset is normal
- Height percentile tracks that predicted by parental genetics

Idiopathic Short Stature (ISS)

- ISS is defined as a height ≤ 2 SD below the mean for age, sex, and population
- ISS is a diagnosis of exclusion. The diagnosis is given after a comprehensive workup fails to identify cause for the short stature
- ISS is differentiated from normal variant short stature (CDGP, FSS) by a predicted final adult height that is < –2 SD below the child's target height range
- GH therapy aiming to improve adult height is approved for ISS by the U.S. Food and Drug Administration (FDA)

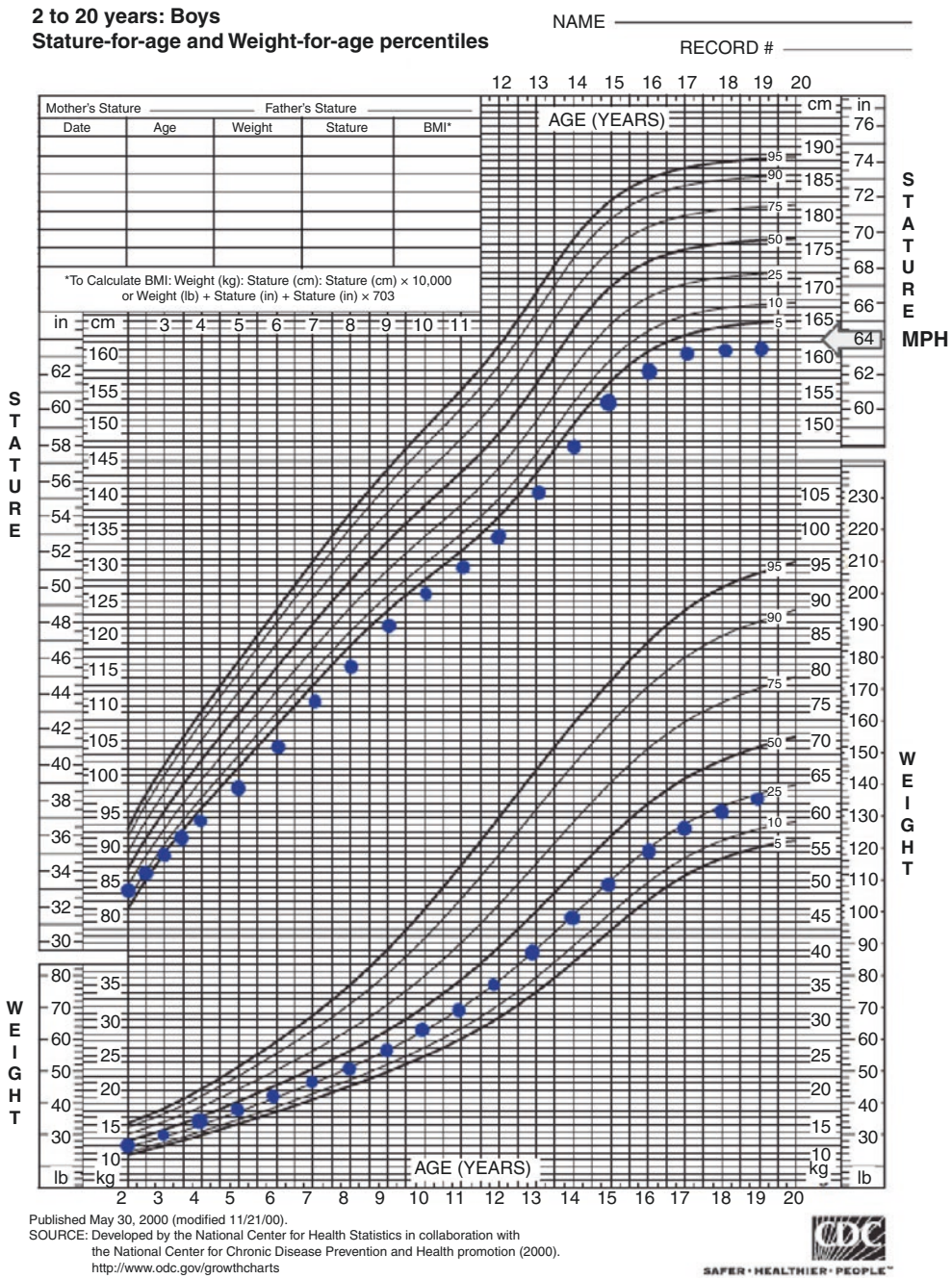


Fig. 12.3 Familial short stature. Growth rate is parallel to the lower percentiles of the growth curve and final adult height corresponds to midpaternal target height (http://www.cdc.gov/growthcharts)

Psychosocial Dwarfism

Background

- Emotional deprivation can cause short stature and growth failure
- A good history may reveal a disturbed child–family relationship

Diagnosis

- Diagnosis of exclusion

Common causes of short stature (Table 12.1)

DISORDERS OF PITUITARY GLAND

Introduction

- The pituitary gland, located at the base of the brain, is composed of anterior (i.e., adenohypophysis) and posterior (i.e., neurohypophysis) regions
- Origin of the adenohypophysis is from the Rathke pouch as an invagination of the oral ectoderm

Table 12.1 Common causes of short stature: differences between constitutional delay, familial short stature, and growth hormone deficiency

	Constitutional delay	Familial short stature	Growth hormone deficiency
Growth curve	Growth velocity along or parallel to the lower percentiles of the growth curve	Growth velocity is parallel to but below the normal growth curve	Height or length > 3 SD below the mean
Family history	Positive late bloomers	One or two parents are short	Depends on the cause
Bone age	Mildly delayed	Equal to chronological age	Delayed
Hormonal studies	Normal	Normal	Low IGF-1 and low IGFBP-3
Treatment	Reassurance Some may benefit from testosterone short course if puberty is delayed	Reassurance and monitoring	Growth hormone

IGF-1 insulin-like growth factor 1, *IGFBP-3* IGF binding protein 3

The major biologically active hormones released into systemic circulation include the following

- Growth hormone (GH)
- Adrenocorticotropic hormone (ACTH)
- TSH
- Luteinizing hormone (LH)
- Follicle-stimulating hormone (FSH)
- Prolactin (PRL)
- Antidiuretic hormone (ADH)

Growth hormone (GH)

- GH is 191-amino acid (191-AA) single-chain polypeptide. The GH gene is called *GH1* and is located on chromosome 17

Biologic effect of GH

- Linear growth
- Bone thickness growth
- Soft tissue growth
- Protein synthesis
- Fatty acid release from adipose tissue
- Insulin resistance

IGF-1

- IGF-1 *is both* synthesized in the liver and formed locally in bones and muscles of children
- Gene located on chromosome 12
- Circulating IGF-1 is directly related to GH activity and nutritional status

GH therapy (Fig. 12.4)

- In children with classic GHD, treatment should be started as soon as possible to ensure the greatest effect on final adult height
- Higher doses during puberty can be considered
- Maximal response is usually during the 1st year

Criteria for discontinuing GH treatment

- Decision by the patient/parent to discontinue
- Growth rate less than 2 cm/year
- Bone age of 14 years in girls and 16 years in boys

Adverse effects of GH

- Pseudotumor cerebri (headaches and papilledema)
- Slipped capital femoral epiphysis (limping, and hip or knee pain)
- Gynecomastia
- Worsening scoliosis (needs to be monitored)
- Insulin resistance

Other indications for GH therapy

1. Turner syndrome
2. Noonan syndrome
3. *SHOX*-gene mutation
4. Prader–Willi syndrome
5. Idiopathic short stature
6. Small for gestational age

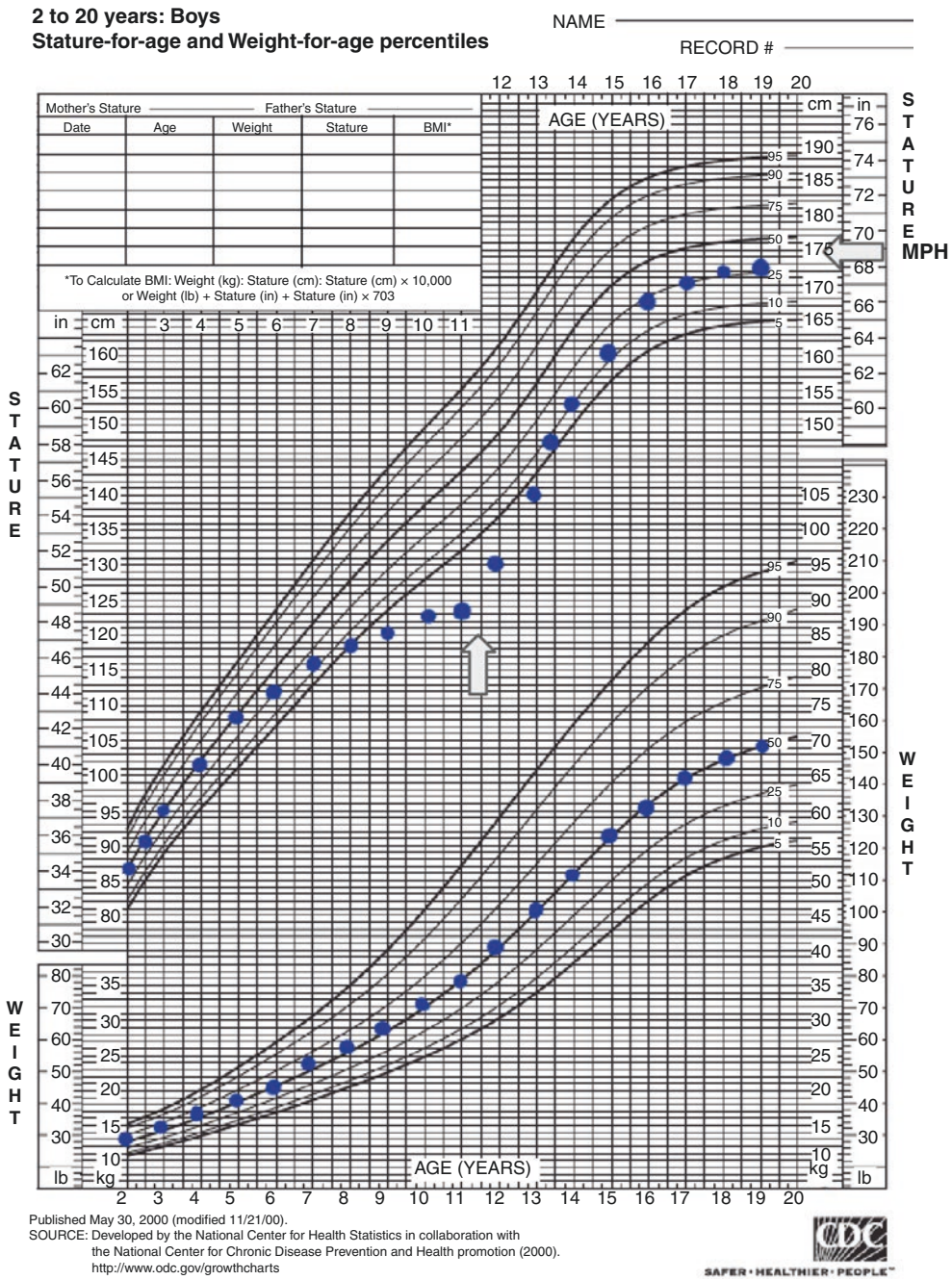


Fig. 12.4 Short stature secondary to growth hormone (GH) deficiency. Height deceleration is noted after 3 years of age and weight is not very much affected. GH therapy initiated at 11 years of age with marked improvement in auxology (http://www.cdc.gov/growthcharts)

Congenital Hypopituitarism

Background

- Involves one or more of the six hormones secreted by the pituitary gland
- Could be isolated GHD (IGHD) or combined pituitary hormone deficiency (CPHD). Some patients start as having IGHD then progress to having CPHD

Conditions associated with GHD

Hall–Pallister syndrome

- Absence of pituitary gland
- Hypothalamic hamartoblastoma
- Postaxial polydactyly
- Nail dysplasia
- Bifid epiglottis
- Imperforate anus
- Anomalies of the heart, lungs, and kidneys

Septo-optic dysplasia

- Absence of optic chiasm, optic nerve hypoplasia, or both
- Agenesis of the septum pellucidum, and schizencephaly
- Midfacial anomalies, e.g., solitary maxillary central incisors, cleft lip/palate
- Micropenis/microphallus

Clinical presentation

- Neonate
  - Hypoglycemia usually severe and persistent, with or without seizure
  - Micropenis/microphallus (diagnostic clue in boys; < 2.5 cm stretched in term infants)
  - Apnea
  - Cyanosis
  - Prolonged neonatal jaundice
  - Most neonates with hypopituitarism have normal length and weight at birth
- Older infants and children
  - Growth failure is the most common presentation
  - Delayed tooth eruption
  - Central diabetes insipidus may develop or become clinically obvious as they become older

Diagnosis

- Height or length > 3 SD below the mean, failure to thrive
- Slow growth velocity (< 5 cm/year)
- Delayed skeletal age
- Low IGF-1 and low IGFBP-3
- Provocative tests: Administration of insulin, arginine, clonidine, or glucagon rapidly increases the level of GH in normal children
  - GH < 10 ng/ml in two provocative tests with different agents is the usual diagnostic criteria
- Other pituitary hormones must be tested, e.g., TSH, ACTH, gonadotropins (age-dependent)
- Clinical history (polydipsia, cold water craving)

Treatment

- Appropriate hormone replacement

Neonatal Hypoglycemia

Background

- Hypoglycemia is the most common metabolic problem in neonates
- Plasma glucose less than 30 mg/dL in the first 24 h and less than 70 mg/dL thereafter in newborns. (Point-of-care glucose measurements not diagnostic, needs confirmation with serum level)
- Plasma glucose value of less than 50 mg/dL in children

Causes

- Transient hypoglycemia
  - Prematurity (low glycogen stores), infant of diabetic mother, SGA, perinatal stress, and sepsis
- Inborn errors of metabolism, e.g., carnitine–acylcarnitine translocase deficiency
- Glycogen storage disorders
- Gluconeogenesis disorders
- Fatty acid oxidation disorders
- Disorders of hormonal regulation of glucose metabolism:
  - GHD or hypopituitarism
  - Isolated cortisol deficiency (congenital adrenal hyperplasia [CAH)]
  - Congenital hyperinsulinism (genetic defect) is the most common permanent cause in the first 3 months of life
- Genetic diseases, e.g., Beckwith–Wiedemann syndrome

Diagnosis

- Micropenis is a red flag for possible GHD
- Critical sample should be taken during hypoglycemia (usually if the cause is unknown and in persistent cases):
  - Glucose

  - CO2 (chemistry panel)
  - Insulin, C-peptide
  - Ammonia, lactate
  - GH
  - Cortisol
  - Free fatty acids
  - Beta-hydroxybutyrate and acetoacetate (serum ketones)
  - Acylcarnitine profile, total and free carnitine
  - Save serum tube
  - Urine ketones, urine organic acids
- Hypopituitarism or adrenal failure
  - Ketonemia and ketonuria
  - Low GH or low cortisol
  - Appropriately suppressed insulin
- Glycogen storage disease
  - Ketonemia and ketonuria
  - Normal response of GH and cortisol to hypoglycemia
  - Appropriately suppressed insulin
- Fatty acid oxidation defect or carnitine deficiency
  - No ketonemia and no ketonuria
  - No acidosis
  - Appropriately suppressed insulin
- Hyperinsulinism or insulinoma in older children
  - No ketonemia, no ketonuria
  - Usually induced by fasting
  - Inappropriately elevated insulin concentration (in the presence of hypoglycemia)
  - May respond to diazoxide
  - Consider multiple endocrine neoplasia type 1 (MEN-1) syndrome
- Ketotic hypoglycemia in older children
  - The most common cause of childhood hypoglycemia and is a diagnosis of exclusion
  - Typical age is 18 months to 5 years with resolution by age 7 years
  - Normal physiologic response to hypoglycemia with elevated serum and urine ketone levels
  - Cortisol and growth hormone are counter-regulatory hormones and are normally elevated in response to hypoglycemia
  - Appropriately suppressed insulin (undetectable)
  - Acute treatment is IV dextrose
  - Long-term management consists of avoidance of fasting and ensuring adequate sugar-containing fluids when ill

Craniopharyngioma

Background

- Most common pituitary tumor: Benign histology and malignant behavior
- Persistence of remnants of the original connection between the Rathke pouch and the oral cavity
- Peak incidence in children aged 5–10 years
- More common in males

Clinical presentation

- Headache
  - Most common presentation (55–86%)
  - Hydrocephalus
- Visual disturbance (37–68%)
  - Decline of visual acuity
  - Constriction of visual fields, bitemporal hemianopsia
  - Papilledema
  - Horizontal double vision
- Endocrine dysfunction (66–90%), e.g.,
  - Hypothyroidism (e.g., weight gain, fatigue, cold intolerance, and constipation)
  - Diabetes insipidus
  - Growth failure and delayed puberty

Diagnosis

- Contrast magnetic resonance imaging (MRI)
- Magnetic resonance angiography (MRA)
- Complete endocrinologic and neuro-ophthalmologic evaluation with formal visual field documentation

- Neuropsychological assessment

Management

- Surgical removal
- Postsurgical follow-up should be planned in 1–2 weeks for all patients
- Appropriate hormone replacement

Diabetes Insipidus (DI)

Background

- DI is defined as the passage of large volumes of dilute urine (< 300 mOsm/kg)
- **Central DI,** (neurogenic, pituitary, or neurohypophyseal) characterized by decreased secretion of antidiuretic hormone (ADH; also referred to as arginine vasopressin [AVP])
- **Nephrogenic DI,** characterized by decreased ability to concentrate urine because of resistance to ADH action in the kidney

Cause of central DI

- Trauma or surgery to the region of the pituitary and hypothalamus are common causes
- Neoplasm
- Infiltration (histiocytosis X)
- Infection
- Autoimmune
- Congenital

Cause of nephrogenic DI

- Congenital X-linked or autosomal dominant
- Electrolyte disturbances (hypercalcemia, hypomagnesemia, and hypokalemia)
- Drugs (lithium, demeclocycline, cisplatin, amphotericin B, loop diuretics)
- Ureteral obstruction, chronic renal failure, polycystic kidney disease, Sjogren syndrome, and sickle cell anemia
- Psychogenic

Clinical presentation

- Polyuria
- Irritability
- Failure to thrive
- Intermittent fever

Diagnosis

- Serum osmolality > 300 mOsm/kg
- Urine osmolality < 300 mOsm/kg
- Hypernatremia
- Urine specific gravity of 1.005 or less and a urinary osmolality less than 200 mOsm/kg are the hallmarks of DI
- Polyuria and elevated plasma osmolality despite a relatively high basal level of ADH suggests nephrogenic DI
- Water deprivation test and response to desmopressin can differentiate between central and nephrogenic DI
- If serum osmolality < 270 mOsm/kg and urine osmolality > 600 mOsm/kg, this will rule out DI
- Suspect primary polydipsia when large volumes of very dilute urine occur with plasma osmolality in the low–normal range

Treatment of central DI

- Desmopressin
- Complication is water intoxication; patient should have water breakthrough every day to prevent water intoxication
- Under most circumstances, water intake should be limited to 1 L/m^2/24 h during antidiuresis
- **Important:** Water should always be made available to the child with DI and intact thirst mechanism
- **Important:** Some patients may *not* have intact thirst mechanism. They need to be put on a daily fluid (free water) goal
- *Infants can also be treated with thiazides and low solute formulas*

Treatment of nephrogenic DI

- Thiazide diuretics
- May be combined with amiloride and indomethacin

Syndrome of Inappropriate ADH Secretion (SIADH)

Background

- Hyponatremia and hypo-osmolality resulting from inappropriate, continued secretion or action of the hormone despite normal or increased plasma volume, which results in impaired water excretion

Causes

- Central nervous system (CNS) pathology
  - Infection, e.g., tumor, thrombosis, neurosurgery, hydrocephalus, meningitis, pneumonia, hypoxia, and brain abscess
  - Head trauma
- Pulmonary disease
  - Pneumonia, asthma, positive pressure ventilation, tuberculosis, cystic fibrosis
- Neoplastic, e.g., lymphoma and leukemia
- Hypothyroidism
- Excessive treatment of central DI
- Carbamazepine/oxcarbazepine, cyclophosphamide, phenothiazines, fluoxetine, vincristine, and cisplatin—important drugs that cause SIADH
- Anorexia
- Schizophrenia

Clinical presentation

- Hypervolemic state
- Depending on the magnitude and rate of development, hyponatremia may or may not cause symptoms
- Anorexia, nausea, and malaise are early symptoms when the serum Na^+ level is less than 125 mEq/L
- Headache, muscle cramps, irritability, drowsiness, confusion, weakness, seizures, and coma can occur with further decrease in the serum Na

Diagnosis

- Hyponatremia (i.e., serum $Na^+ < 135$ mmol/L) with concomitant hypo-osmolality (serum osmolality < 280 mOsm/kg) and high urine osmolality is the hallmark of SIADH

Management

- Depends on the severity of hyponatremia and chronicity of condition
- Correcting hyponatremia too rapidly may result in central pontine myelinolysis with permanent neurologic deficits
- Fluid restriction in mild cases
- Administration of 3% hypertonic saline should be used only in severe and emergent cases
- The objective is to raise serum Na^+ levels by 0.5–1 mEq/h and not more than 10–12 mEq in the first 24 h, to bring the Na^+ value to a maximum level of 125–130 mEq/L

Cerebral Salt Wasting

Background

- Hypersecretion of atrial natriuretic peptides

Causes

- Head trauma, hydrocephalus, neurosurgery, cranial irradiation, hypothalamic/pituitary neoplasms, cerebral vascular accident, and brain death

Presentation (Table 12.2)

- Excessive salt wasting
- Very high urinary Na^+
- Hyponatremia

Diagnosis

- Hypovolemic state (SIADH is euvolemic/hypervolemic)
- High urine output (SIADH is the opposite)
- Normal or high uric acid
- High atrial natriuretic peptide

Treatment

- Hydration
- Treatment of underlying cause

Table 12.2 Difference between diabetes insipidus, SIADH, and cerebral salt wasting

	Diabetes insipidus	SIADH	Cerebral salt wasting
Cause	Low or resistance to ADH	High ADH	Unclear pathophysiology; however, may be associated with increased natriuretic peptides
Na^+ level	High	Normal or low	Low
Serum osmolality	High	Low	Low
Urine osmolality	Low	High	Relatively dilute because of high urine output
Intravascular volume	Hypovolemia	Euvolemia or hypervolemia	Hypovolemia
Urine output	High	Low	High
Urine Na^+	Low	High or match Na intake	Very high, more than Na^+ intake, > 40 mEq/L
Management	Allow access to free water all the time + desmopressin or treat for nephrogenic DI	Fluids restrictions	IV fluids, NS, or even 3% NS May need salt supplement

SIADH syndrome of inappropriate ADH secretion, *ADH* antidiuretic hormone, *Na^+* sodium, *IV* intravenous, *NS* normal saline, *DI* diabetes insipidus

- If hyponatremia occurred in < 12 h, rapid correction is required if serum Na^+ < 120 mEq/L
- Serum Na^+ should be raised only enough to make patient stable, 0.5 mEq/h (12 mEq/L/24 h)

Hyperpituitarism

Gigantism and acromegaly

- Hypersecretion of GH before ossification of the epiphysis causes gigantism and after epiphyseal closure causes acromegaly

Prolactinoma

Background

- Prolactin-secreting tumor is the most common cause in adolescents
- Based on its size, a prolactinoma can be classified as a microprolactinoma (< 10 mm diameter) or a macroprolactinoma (> 10 mm diameter)

Clinical presentation

- Headache
- Amenorrhea
- Galactorrhea
- Visual disturbance if tumor affects the optic chiasm, e.g., bitemporal hemianopsia or total vision loss in severe cases

Diagnosis

- Elevated serum PRL
- TSH and pregnancy test must be performed
- MRI: A serum PRL value of 200 ng/mL or greater in the presence of a macroadenoma (> 10 mm) is virtually diagnostic of prolactinoma

Treatment

- Bromocriptine
- Cabergoline (better tolerated than bromocriptine)

THYROID DISORDERS

Introduction

Location

- The thyroid gland is found in the neck, below the thyroid cartilage (which forms the laryngeal prominence or "Adam's apple")

Function

- It produces thyroid hormones, the principal ones being triiodothyronine (T3) and thyroxine, sometimes referred to as tetraiodothyronine (T4)
- These hormones regulate the growth and rate of function of many other systems in the body
- T3 and T4 are synthesized from iodine and tyrosine. The thyroid also produces calcitonin, which plays a role in calcium homeostasis
- Hormonal output from the thyroid is regulated by TSH produced by the anterior pituitary, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus

Congenital Hypothyroidism

Background

- Thyroid dysgenesis (aplasia, hypoplasia, or an ectopic) is the most common cause of congenital hypothyroidism
- Most common form of thyroid dysgenesis is ectopic thyroid
- Occasionally associated with thyroglossal cyst

Clinical presentation

- Most infants are asymptomatic at birth because of transplacental passage of maternal T4
- Length and weight are normal at birth, but head may be larger at birth
- Prolongation of physiologic jaundice
- Poor feeding, especially sluggishness
- Somnolence and choking spells during feeding may be the first sign in the 1st month
- Respiratory difficulties due to large protruded tongue, apneic episodes, noisy breathing, nasal obstruction
- Cold, mottled, and dry skin
- Constipation that usually does not respond to treatment
- Umbilical hernia
- Large anterior fontanelle
- Associated congenital anomalies; cardiac is the most common
- Hypotonia

Laboratory

- High TSH and low T4
- Low to normal total T4 and TSH within reference range indicates thyroid-binding globulin (TBG) deficiency (normal free T4)
- If maternal antibody-mediated hypothyroidism is suspected, maternal and neonatal antithyroid antibodies may confirm the diagnosis
- Thyroid ultrasound
- Thyroid scanning (many clinicians treat without imaging studies)

Treatment

- Levothyroxine given orally is the treatment of choice
- 10 to 15 μg/kg/day initial dose
- No liquid preparations of levothyroxine should be given to neonates or infants. These preparations are very difficult to keep in suspension, and the delivery of drug is inconsistent
- **If the newborn screen is positive for hypothyroidism, order TSH and free T4 to confirm, then start the treatment immediately, before the results of the confirmatory tests are available**
- No treatment is required for TBG deficiency

Prognosis

- Early diagnosis and treatment of congenital hypothyroidism prevents severe intellectual disability and other neurologic complications

Thyroid-Binding Globulin Deficiency

- X-linked condition
- Could be partial (1 in 4000) or complete (1 in 15,000)
- Heterozygous males are more frequently detected

- Depending on X inactivation, females may have normal, partial, or complete deficiency
- T4 and T3 levels are low, TSH is normal, free T4 and free T3 are normal, high T3 uptake (T3U)
- Prognosis: Benign condition → no treatment needed

Hashimoto, Lymphocytic Thyroiditis (Autoimmune Thyroiditis)

Background

- Hashimoto thyroiditis is part of the spectrum of autoimmune thyroid diseases and is characterized by the destruction of thyroid cells by various cell- and antibody-mediated immune processes
- The most common cause of hypothyroidism in the United States in individuals older than 6 years
- Girls 2 to 3 times > boys
- Familial clusters of lymphocytic thyroiditis are common

Clinical presentation

- Goiter and growth retardation (most common)
- Fatigue
- Constipation
- Dry skin
- Cold intolerance
- Hair loss
- Weight gain
- Depression, dementia, and other psychiatric disturbances
- Decreased school performance
- Menstrual irregularities
- Galactorrhea
- Other manifestations, depending on the severity of hypothyroidism and other factors, e.g., age (myxedema)
  - Puffy face and periorbital edema typical of hypothyroid facies
  - Cold, dry skin, which may be rough and scaly
  - Peripheral edema of hands and feet, typically non-pitting
  - Thickened and brittle nails (may appear ridged)
  - Bradycardia
  - Elevated blood pressure (typically diastolic hypertension)
  - Diminished deep tendon reflexes and the classic prolonged relaxation phase
  - Macroglossia
  - Slow speech
  - Ataxia
- In most cases, the thyroid is diffusely large, firm, and nontender (Fig. 12.5)
- In 30%, the gland is lobular and may seem to be nodular

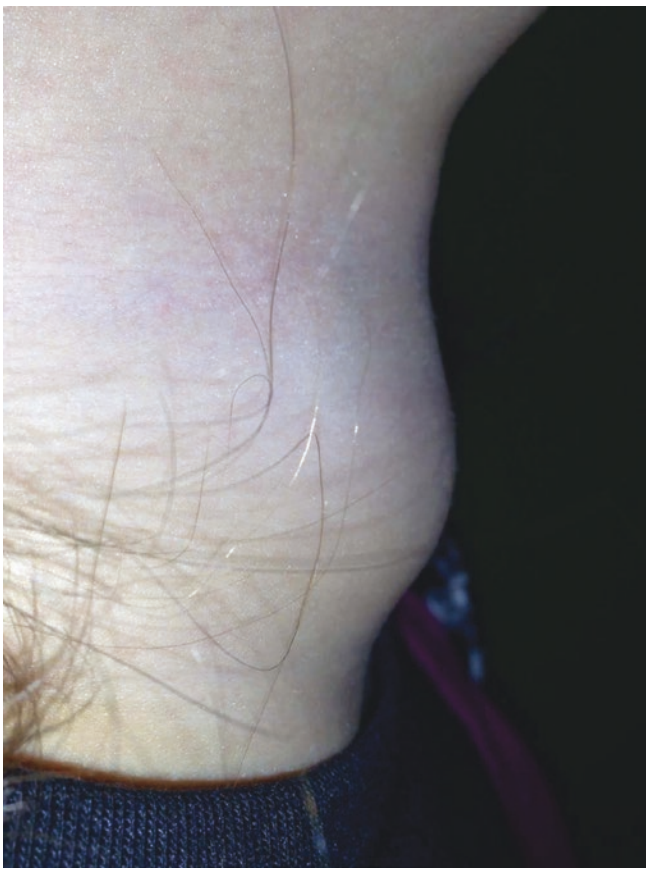


Fig. 12.5 A 4-year-old female with thyroid enlargement, fatigue, and daytime somnolence. Thyroid-stimulating hormone > 150 mIU/L and free thyroxine 4 < 0.4 ng/dL. Antithyroid peroxidase antibodies were very high

Diagnosis

- Thyroid function tests are usually normal
- Elevated TSH and presence of thyroid autoantibodies, antithyroid peroxidase (TPO) and antithyroglobulin (TG) antibodies, are the best markers of progression to overt hypothyroidism; however, degree of elevation does not predict severity of disease

Management

- If there is evidence of hypothyroidism, levothyroxine can be given
- Fine-needle aspiration/biopsy (FNAB) of any dominant or suspicious thyroid nodules to exclude malignancy or the presence of thyroid lymphoma in fast-growing goiters

Subacute (de Quervain) Thyroiditis

Background

- Subacute thyroiditis is a self-limited disease of thyroid gland
- Usually occurs after an upper respiratory tract infection

Clinical presentation

- Fever
- Thyroid gland tenderness and pain

Laboratory

- Initially hyperthyroidism (elevated T4 and T3)
- Followed by more prolonged period of hypothyroidism

Management

- Nonsteroidal anti-inflammatory drugs (NSAIDs) for pain
- Prednisone in severe cases

Prognosis

- Almost all patients recover with no thyroid problems

Stepwise approach to a child presenting with elevated TSH

- It is important to note that children have higher thyroid hormone and TSH level values than adults. Hence, it is important to use pediatric reference ranges while interpreting laboratory data
- TSH has a diurnal variation, with an 8:00 AM measurement being more sensitive in detecting primary hypothyroidism
- TSH is obtained to screen for primary hypothyroidism usually only after a thorough history and physical examination
- If TSH is elevated: Thyroid hormone levels including total T4 and free T4 levels need to be obtained
- If TSH is elevated with low free T4 level: An arbitrary cutoff of 10 uIU/ml or above is generally used to start therapy with levothyroxine. Levels between 5 and 10 uIU/ml are considered mild elevations and repeat testing is indicated
- If TSH is elevated with normal free T4 level (subclinical hypothyroidism), monitoring is warranted with repeat thyroid function every 6 months to 1 year. This scenario is common in obese children who tend to have mild elevations in TSH

Graves Disease

Background

- Graves disease is the most common cause of hyperthyroidism in pediatric patients
- An immune-mediated disorder that results from the production of thyroid-stimulating immunoglobulins by stimulated B lymphocytes
- These immunoglobulins bind to the TSH receptor to mimic the action of TSH and stimulate thyroid growth and thyroid hormone overproduction

Clinical presentation

- Weakness

- Weight loss or muscle wasting
- Diarrhea
- Heat intolerance
- Pruritus
- Palpitations
- Sleeplessness
- Behavioral changes
- Enlarged thyroid, which may cause dysphagia if very large
- Exophthalmos usually mild and more common in adults
- Upper eyelid retraction
- Infrequent blinking (Stellwag sign)

Laboratory

- Elevated free T4 and T3
- Suppressed TSH
- Sometimes free T3 is more elevated than T4
- Antithyroid antibodies (TPO) are often present
- Thyrotropin receptor-stimulating immunoglobulin (TSI) confirms the diagnosis, and its absence means remission
- To differentiate between Graves disease and exogenous thyroid hormone administration, all labs are the same, except thyroglobulin will be low in exogenous thyroid hormone and high in Graves disease

Treatment

- Methimazole is the most common antithyroid drug used in the United States
- Propylthiouracil (PTU) is the drug of choice in pregnant women with Graves disease
  - Sides effects of antithyroid hormone
    - Transient urticarial rash (the most common side effect)
    - Agranulocytosis (more common in elderly)
    - PTU associated with more cases of liver injuries
- Radioactive iodine
  - Permanent hypothyroidism almost inevitable
  - Might worsen ophthalmopathy
  - May carry a small risk of malignancy in children
  - Pregnancy must be deferred 6–12 months and mother cannot breastfeed
- Beta-blockers to blunt the toxic effect of the circulating T4 and T3

Treatment follow-up

- Monitor the patient at 6-week to 3-month intervals with thyroid function tests (TSH, total T4/free T4 levels), liver function tests, and CBC
- Assess other potential adverse effects of the agent by history

Neonatal Thyrotoxicosis

Background

- Due to transplacental transmission of TSH receptor immunoglobulin from the mother to the fetus

Clinical presentation

- Irritability
- Flushing
- Tachycardia
- Hypertension
- Thyroid enlargement
- Exophthalmos

Diagnosis

- High T4 and T3
- Low TSH
- Positive TSI

Treatment

- Mild cases: Symptomatic treatment with a beta-blocker (e.g., propranolol)
- More severe cases: Antithyroid medications are necessary
- In very severe cases: Iodides in the form of Lugol iodine solution or saturated solution of potassium iodide (SSKI) are used

Prognosis
- Usually resolve in 3–12 weeks

Solitary Thyroid Nodules

Background
- Thyroid nodules are much more likely to be malignant in children than they are in adults

Diagnosis
- Child's history, including familial history and radiation exposure
- Thyroid function is usually normal
- Ultrasonography to determine whether the nodule is cystic, solid, or mixed
- FNAB is used for definitive diagnosis (study of choice)
- FNAB is not necessary or recommended in the case of toxic nodules

Management
- All solitary nodules including cold or non-toxic nodules must be biopsied
- After initial diagnosis and investigation of the thyroid nodule, medical and/or surgical therapy is decided
- Presumed benign nodule, especially in an adolescent, may simply be observed
- Close observation and follow-up care are essential

Important to know
- Palpable thyroid nodule, more than or equal 1 cm on imaging, next step:
  - Thyroid ultrasound-guided FNAB

Thyroid Cancer

Background
- Prior radiation therapy to the neck increases the risk of thyroid cancer
- More than 95% of thyroid cancers are of thyroid-cell (well-differentiated) origin
- Papillary (subtype) carcinoma is the most common
- High rate of regional and distant metastasis
- MEN type 2 is autosomal dominant

Types of thyroid cancers
- Follicular cell origin
  - Papillary cell carcinoma
  - Follicular cell carcinoma
- Medullary thyroid cancer
  - MEN type 2
    - MEN-2A (medullary thyroid cancer, hyperparathyroidism, and pheochromocytoma)
    - MEN-2B (medullary thyroid cancer, pheochromocytoma, and mucosal neuroma)

Clinical presentation
- Most childhood thyroid nodules are asymptomatic and are detected as a neck mass by parents or by physicians during routine examination

Diagnosis
- Thyroid ultrasound to confirm the presence of a nodule
- FNAB is indicated if nodule is suspicious-looking or is 1 cm or more in diameter
- Calcitonin level is elevated in medullary thyroid cancer
- Abnormal biochemical labs, e.g., elevated calcium level (hyperparathyroidism) due to associated conditions in medullary thyroid cancers (MEN type 2)

Management
- TSH suppressive therapy in children with papillary or follicular-type thyroid cancer
- Surgery
- Radiotherapy
- Surveillance

Thyroid Storm

Background

- Thyrotoxic crisis is an acute, life-threatening, hypermetabolic state induced by excessive release of thyroid hormones in individuals with thyrotoxicosis

Clinical presentation

- Fever (may be the only presenting symptom)
- Profuse sweating
- Poor feeding and weight loss
- Respiratory distress
- Fatigue (more common in older adolescents)
- Nausea and vomiting
- Diarrhea
- Abdominal pain
- Jaundice
- Anxiety (more common in older adolescents)
- Altered behavior
- Seizures
- Coma

Diagnosis

- Elevated triiodothyronine (T3), thyroxine (T4) levels
- Suppressed TSH levels

Management

- Patients with thyroid storm should be treated in an ICU setting
- Correct electrolyte abnormalities
- Propranolol to minimize sympathomimetic symptoms
- Treat cardiac arrhythmia, if necessary
- Aggressively control hyperthermia by applying ice packs and cooling blankets and by administering acetaminophen
- Consider methimazole and consult pediatric endocrinologist
- Consider iodine compounds (Lugol iodine or potassium iodide) orally or via nasogastric tube to block the release of thyroid hormone (at least 1 h after starting antithyroid drug therapy)
- Consider glucocorticoids to decrease peripheral conversion of T4–T3

BONE AND MINERAL DISORDERS

Hypocalcemia

Background

- Hypocalcemia is defined as a total serum calcium concentration of less than 8.5 mg/dL in children, less than 8 mg/dL in term neonates, and less than 7 mg/dL in preterm neonates

Causes

- Early neonatal hypocalcemia (48–72 h of birth)
  - Prematurity
  - Birth asphyxia
  - Diabetes mellitus (DM) in the mother (magnesium depletion in mothers with DM)
  - IUGR
- Late neonatal hypocalcemia (3–7 days after birth)
  - Exogenous phosphate load; this is most commonly seen in developing countries (phosphate-rich formula or cow's milk)
  - Gentamicin use
  - Magnesium deficiency
  - Transient hypoparathyroidism of newborn
  - Hypoparathyroidism due to other causes
- Infants and children
  - Hypoparathyroidism
  - Vitamin D deficiency
  - Acquired or inherited disorders of vitamin D metabolism
  - Resistance to the action of vitamin D
  - Liver diseases
  - Renal failure

  - Malabsorption
  - Pseudohypocalcemia due to hypoalbuminemia

Clinical presentation

- Newborn period
  - Possibly no symptoms
  - Lethargy
  - Poor feeding
  - Vomiting
  - Abdominal distension
- Children, possible presentation
  - Seizures
  - Twitching
  - Cramping
  - Laryngospasm, a rare initial manifestation
  - Tetany and signs of nerve irritability, such as the Chvostek sign, carpopedal spasm, the Trousseau sign, and stridor

Diagnosis

- Total and ionized serum calcium levels
  - A decrease in total calcium can be associated with low serum albumin concentration and abnormal pH
- Serum magnesium levels
  - Serum magnesium levels may be low in patients with hypocalcemia, which may not respond to calcium therapy if hypomagnesemia is not corrected
- Severe hypomagnesemia causes hypocalcemia by impairing the secretion of and inducing resistance to parathyroid hormone
- Serum electrolyte and glucose levels
  - Low bicarbonate levels and acidosis may be associated with Fanconi syndrome and renal tubular acidosis
- Phosphorus levels
  - Phosphate levels are increased in cases of exogenous intake
  - High phosphate may indicate
    - Endogenous phosphate loading
    - Renal failure
    - Hypoparathyroidism
  - Low phosphate may indicate
    - Vitamin D abnormalities and rickets
- PTH levels
  - Hormone studies are indicated if hypocalcemia persists in the presence of normal magnesium and normal or elevated phosphate levels
  - Low PTH (or inappropriately normal) levels suggest
    - Hypoparathyroidism; serum calcium rises in response to PTH challenge
  - High PTH levels suggest
    - Vitamin D abnormalities
    - Pseudohypoparathyroidism (PHP)
    - Calcium levels do not rise in response to PTH challenge
- 25-Hydroxyvitamin D and 1,25-dihydroxyvitamin D
- Urine calcium, magnesium, phosphorus, and creatinine levels
  - These values should be assessed in patients with suspected renal tubular defects and renal failure. Urine should also be evaluated for pH, glucose, and protein
- Urine calcium-to-creatinine ratio of more than 0.3 on a spot sample in the presence of hypocalcemia suggests inappropriate excretion
- Serum alkaline phosphatase (ALP) levels (generally elevated in patients with rickets)

Management

- Treatment of the underlying cause
- Treatment of asymptomatic patients with hypocalcemia remains controversial
- Hypocalcemia should be treated promptly in any symptomatic neonate or older child because of the condition's serious implications for neuronal and cardiac function

- Intravenous (IV) infusion with calcium-containing solutions can cause severe tissue necrosis

Hypoparathyroidism

Background

- Hypoparathyroidism is a condition of PTH deficiency

Causes

- Iatrogenic (most common cause), e.g., secondary thyroidectomy with accidental removal of parathyroid glands
- Congenital causes, e.g., DiGeorge syndrome
- Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) (aka autoimmune polyendocrinopathy syndrome type 1 [APS 1])
- Metal overload, e.g., Wilson disease or hemochromatosis
- Maternal hypercalcemia in unborn infant may cause suppression of PTH in neonate

Clinical presentation

- Paresthesias (involving fingertips, toes, perioral area)
- Hyperirritability
- Fatigue
- Anxiety
- Mood swings and/or personality disturbances
- Seizures (especially in patients with epilepsy)
- Hoarseness (due to laryngospasm)
- Wheezing and dyspnea (due to bronchospasm)
- Muscle cramps, diaphoresis, and biliary colic
- Hypomagnesemia, hypokalemia, and alkalosis (e.g., hyperventilation), which worsen signs and symptoms of hypocalcemia
- Hypocalcemia may be demonstrated at the bedside by eliciting the following signs:
  - Chvostek sign: Facial twitching, especially around the mouth, is induced by gently tapping the ipsilateral facial nerve as it courses just anterior to the ear
  - Trousseau sign: Carpal spasm is induced by inflating a blood pressure cuff around the arm to a pressure 20 mmHg above obliteration of the radial pulse for 3–5 min

Diagnosis

- Primary hypoparathyroidism
  - Low (or inappropriately normal) PTH and low calcium level
- Pseudohypoparathyroidism
  - High PTH (due to resistance and PTH receptor mutation) and low calcium
- Secondary hypoparathyroidism
  - Low PTH and high calcium level
- Calcium
  - Hypoalbuminemia causes a drop in total calcium concentration, but the ionized fraction may be within the reference range
  - Alkalosis may trigger symptoms of hypocalcemia
- Serum magnesium
  - Hypomagnesemia may cause PTH deficiency and subsequent hypocalcemia
  - Exclude it in any patient with primary hypoparathyroidism
- Serum phosphorus
  - PTH is a phosphaturic hormone. In its absence, phosphorus levels in the blood rise
- 25(OH)D to exclude vitamin D deficiency as a cause of hypocalcemia

Management

- Correct the hypocalcemia by administering calcium and vitamin D (calcitriol)

Pseudohypoparathyroidism (PHP); Albright Hereditary Osteodystrophy (AHO)

Background

- PHP is a heterogeneous group of disorders characterized by hypocalcemia, hyperphos-

phatemia, increased serum concentration of PTH, and insensitivity to the biological activity of PTH

Genetic defect
- PHP IA
  - Account for majority of patients
  - It is a resistance to PTH
  - Genetic defect of the alpha subunit of stimulatory guanine nucleotide-binding protein. This factor is required for PTH bound to cell surface receptors to activate cyclic adenosine monophosphate (cAMP)
  - It is inherited as autosomal dominant trait
- PHP IB
  - Affected patients have normal level of G protein activity and a normal phenotype appearance
  - These patients have tissue-specific resistance to PTH but not to other hormones
- PHP II
  - Rare
  - Normal phenotype appearance (no AHO)

Clinical presentation
- Hypocalcemia can present in infancy
- Tetany
- Albright hereditary osteodystrophy (AHO; PHP type 1A) characterized by:
  - Short stature
  - Stocky habitus
  - Round face
  - Brachymetacarpals (particularly the fourth and fifth digits)
  - Dimpling over the knuckles of a clenched fist due to short metacarpals
  - Brachymetatarsals
  - Intellectual disability
  - Subcutaneous calcifications

Diagnosis
- High serum PTH/low serum Ca/high phosphate/skeletal defect is a classic finding in Albright hereditary osteodystrophy
- High serum PTH/low serum Ca is either PHP or secondary hyperparathyroidism
- Skeletal defect/normal PTH/normal Ca/normal phosphate is pseudopseudohypoparathyroidism

Management
- All patients with severe symptomatic hypocalcemia should be initially treated with IV calcium
- Administration of oral calcium and 1 alpha hydroxylated vitamin D metabolites, such as calcitriol, remains the mainstay of treatment

Familial Hypocalciuric Hypercalcemia (Familial Benign Hypercalcemia)

Background
- Autosomal dominant condition of benign hypercalcemia
- Asymptomatic
- Usually discovered incidentally on routine labs

Diagnosis
- Hypercalcemia with calcium level > 10.2 mg/dL
- Urine calcium to creatinine ratio < 0.01 and urine calcium < 200 mg/day
- Normal PTH and normal phosphate

Treatment
- None

Hyperparathyroidism

Background
- Hyperparathyroidism is rare in children
- Primary hyperparathyroidism is caused by a single adenoma and is the most common cause
- Familial cases can occur as part of the MEN syndromes (MEN-1 or MEN-2A)
- Secondary hyperparathyroidism can occur with chronic renal failure, cholestatic liver disease, or as an iatrogenic effect, e.g., lithium

Clinical presentation

- Commonly presents without symptoms
- Hypercalcemia
- Muscular weakness
- Bone pain
- Abdominal pain
- Acute pancreatitis
- Nephrolithiasis

Diagnosis

- Serum calcium usually > 12 mg/dL
- Low serum phosphorus < 3 mg/dL
- High PTH
- Normal calcitonin level

Management

- For primary hyperparathyroidism, subtotal or total parathyroidectomy is the most common choice for adults or children
- Calcitriol may help in cases with chronic renal failure
- Treatment of acute severe hypercalcemia: Ca > 14 mg/dL
  - IV hydration
  - Loop diuretics (e.g., furosemide) after hydration
  - Hemodialysis in severe cases

RICKETS

Vitamin D Deficiency Rickets

Background

- Disease of growing bone that is unique to children and adolescents
- Caused by a failure of osteoid to calcify in a growing person. Failure of osteoid to calcify in adults is called osteomalacia
- Vitamin D deficiency rickets occurs when the metabolites of vitamin D are deficient
- Less commonly, a dietary deficiency of calcium or phosphorus may also produce rickets

Vitamin D metabolism

- Cholecalciferol (i.e., vitamin D-3) is formed in the skin from 5-dihydrotachysterol
- First hydroxylation step occurs in the liver (position 25)
- Produces calcidiol (aka 25-hydroxycholecalciferol or 25-hydroxyvitaminD) or 25(OH)D
  - 25(OH)D is the best indicator of overall vitamin D status and commonly tested
- Second hydroxylation step occurs in the kidney (position 1)
  - Calcitriol (1,25-dihydroxycholecalciferol) is active metabolite
  - Calcitriol acts at three known sites to tightly regulate calcium metabolism:
    - Promotes absorption of calcium and phosphorus from the intestine
    - Increases reabsorption of phosphate in the kidney
    - Acts on bone to release calcium and phosphate
- Calcitriol
  - Increases calcium and phosphorus in extracellular fluid
  - Increases calcification of osteoid, primarily at the metaphyseal growing ends of bones
- Parathyroid hormone (PTH)
  - PTH facilitates the 1-hydroxylation step in vitamin D metabolism in the kidney
  - In the vitamin D deficiency state, hypocalcemia develops, which stimulates excess secretion of PTH
  - In turn, renal phosphorus loss is enhanced, further reducing deposition of calcium in the bone
  - Excess PTH also produces changes in the bone similar to those occurring in hyperparathyroidism
  - Early in the course of rickets, the calcium concentration in the serum decreases. After the parathyroid response, the calcium concentration usually returns to the reference range, though phosphorus levels remain low

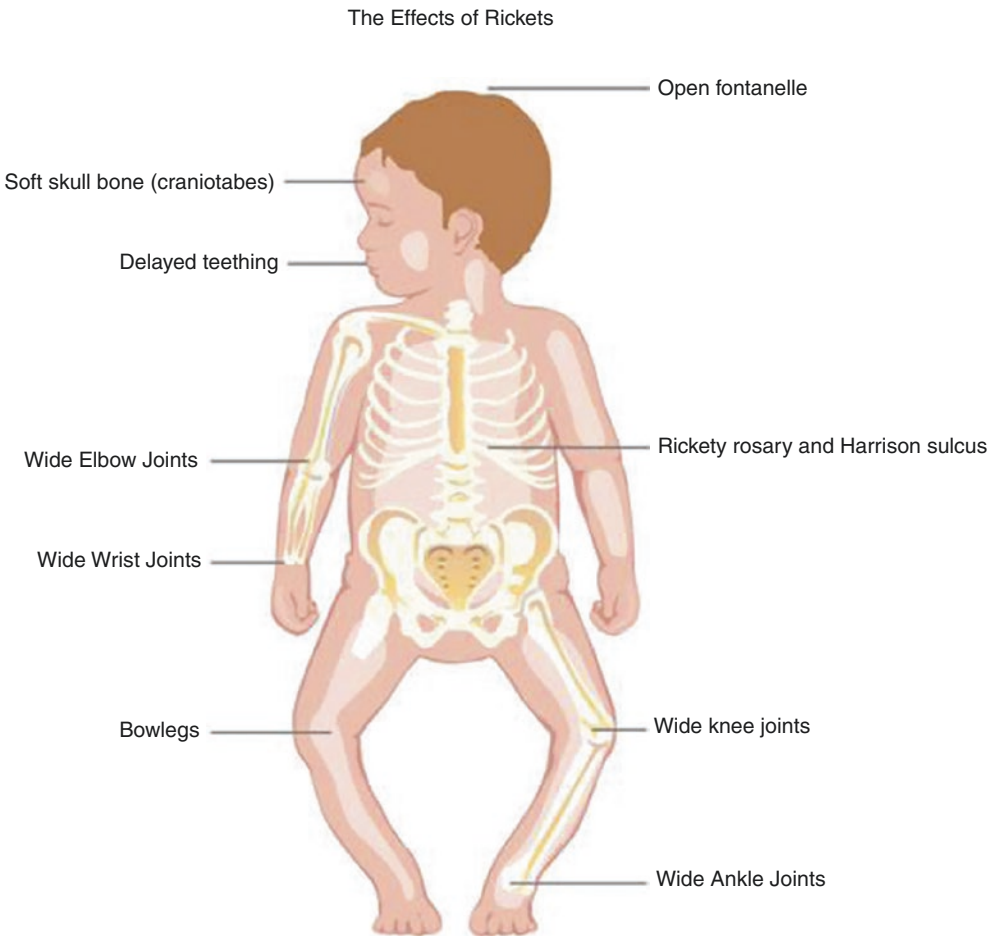


Fig. 12.6 Skeletal manifestations of rickets

- Alkaline phosphatase
  - Produced by overactive osteoblast cells
  - Usually very high levels in growing children

Causes of rickets

- Nutritional deficiency still the most common cause of rickets worldwide
- Prolonged and exclusive breastfeeding without vitamin D supplementation with minimal sunlight exposure
- Intestinal malabsorption of fat
- Liver or kidney disease
- Anticonvulsant drugs (e.g., phenobarbital, phenytoin)
- Accelerate metabolism of 25(OH)D
- Vegan diets, especially lacto-vegans
- Genetic defects

Clinical presentation (Fig. 12.6)

- At very young ages, vitamin D deficiency is more likely to present as hypocalcemia than as rickets
- Muscular hypotonia
- Craniotabes (areas of thinning and softening of the bones of the skull)
- Frontal bossing and delays the closure of the anterior fontanelle
- Bowlegs and knock knees on weight limbs
- Rachitic rosary along the costochondral junctions
- Harrison groove due to weakened ribs pulled by muscles also produces flaring over the diaphragm
- Kyphoscoliosis in older children

- Knobby deformity of long bone, which is visualized on radiography as cupping and flaring of the metaphyses
- Marfan sign; palpation of the tibial malleolus gives the impression of a double epiphysis
- Greenstick fracture

Diagnosis (Table 12.3)

- Low to normal calcium
- Low phosphorus
- High alkaline phosphatase
- High PTH
- Low 25(OH)D
- Low to high 1,25-dihydroxyvitamin D
- Normal HCO3

Radiography (Fig. 12.7)

- Anterior view of the knee is the best site to study, also the wrist and ankle
- Widening and cupping of the metaphysis
- Fraying of metaphysis
- Epiphyseal plate is widened and irregular
- Osteopenia

Management

- Indication for treatment
  - Vitamin D therapy is necessary for infants and children who manifest clinical features of hypocalcemia as a result of vitamin D deficiency or rickets and when vitamin D levels are in the deficient range
- Vitamin D and calcium replacement
  - Vitamin D given daily for a 2- to 3-month period to normalize 25(OH)-D levels and replenish stores
  - Vitamin D_3 can be given 2000 IU PO daily or 50,000 IU PO weekly for 6 weeks
  - With therapy, radiologic evidence of healing is observed in 2–4 weeks, after which the dose of vitamin D can be reduced to 400 IU/day
  - Lack of compliance is an important cause of lack of response, and an option after the 1st month of life is to administer high doses of vitamin D in a single administration as "stoss therapy," instead of smaller doses over a longer period, followed by maintenance dosing
  - High-dose vitamin D may need to be intermittently repeated (usually every 3 months) if poor compliance persists with maintenance dosing
- Calcium replacement
  - Hypocalcemia should be treated with calcium supplements
  - Parenteral calcium as calcium gluconate becomes necessary in case of tetany or convulsions
  - Calcitriol may be necessary until calcium levels normalize
- Monitoring therapy
  - It is important to obtain calcium, phosphorus, and ALP levels 1 month after initiating therapy

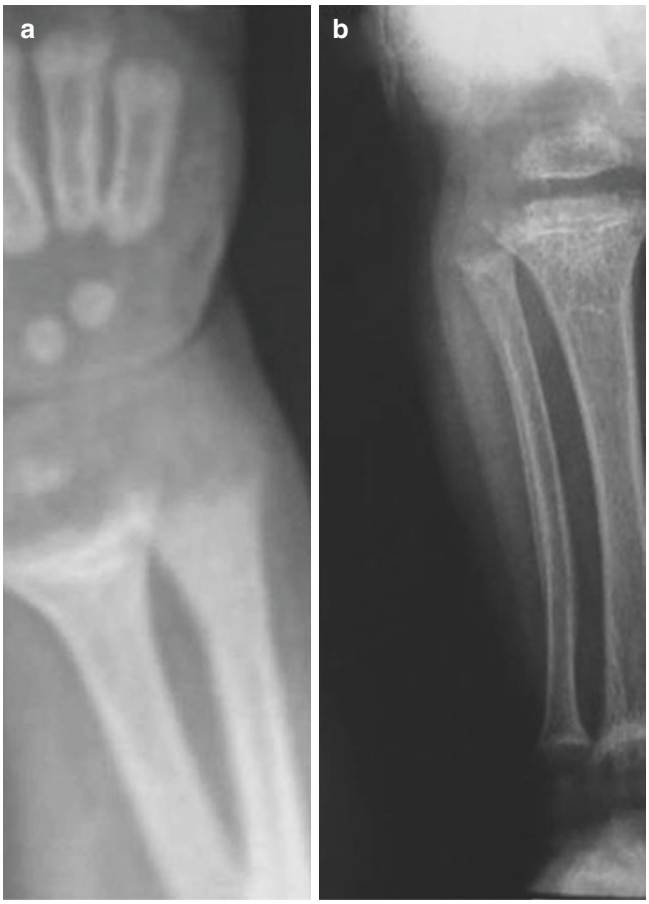


Fig. 12.7 Radiographs of rickets. Radiographs of the wrist (**a**) and leg (**b**) of a 3-year-old boy with nutritional rickets showing the cupping, fraying, and widening of the physis

  - With stoss therapy, a biochemical response occurs in 1 or 2 weeks, the first sign of which is an increase in phosphate
  - It is important to remember that ALP levels may actually increase in the short term as bone formation rates increase
  - Complete radiologic healing may take months, but changes are evident in 1 week
  - In 3 months, it is important to obtain calcium, phosphate, magnesium, ALP, 25(OH)D, and PTH levels, and one may consider obtaining a urine sample to determine the calcium/creatinine ratio
  - A radiograph should also be repeated at 3 months
  - 25(OH)D levels should be monitored yearly
- When to refer
  - If radiographic evidence of some healing is not observed with vitamin D and calcium replacement in 3 months
  - Considerations should include malabsorption, liver disease, or a lack of compliance with replacement therapy
  - Important to remember: Normal levels of ALP and 25(OH)D; very low or very high levels of 1,25-dihydroxyvitamin D; and high serum urea nitrogen and creatinine levels are red flags for considering other causes of rickets (e.g., inherited forms of hypophosphatemic rickets and vitamin D receptor mutations)
- Orthopedic referral if severe deformities have occurred

Prevention of vitamin D deficiency

- Supplementation with 400 IU of vitamin D should be initiated within days of birth for all breastfed infants
- Appropriate exposure to sunlight

Hypophosphatemic Rickets (X-Linked)

Background

- X-linked hypophosphatemic rickets is an X-linked dominant disorder
- Affects both males and females

Clinical presentation

- Failure to thrive
- Hypotonia
- Reluctance to bear weight when beginning to stand or walk
- Delayed dentition

Diagnosis

- Normal calcium level
- Low phosphorus
  - Concentration reference range for infants (5.0–7.5 mg/dL) is high compared with that for adults (2.7–4.5 mg/dL), e.g., 3 mg/dL is considered low in young children
  - Hypophosphatemia can easily be missed in an infant
- Very high ALP (significantly high)
- Normal HCO3
  - HCO3 is low in Fanconi syndrome or oculocerebrorenal dystrophy (Lowe syndrome), i.e., non-anion gap metabolic acidosis
- Radiography
  - Same as vitamin D deficiency rickets

Management (Table 12.3)

- Calcitriol and phosphorus

DISORDERS OF PUBERTY

General considerations

- Positive relation between degree of obesity and early puberty has been reported (African-American and Hispanic populations especially)
- Delayed puberty is common in gymnasts and marathon runners (lack critical adiposity)

Normal Variants of Puberty: Premature Adrenarche

Background

- Benign, self-limited
- Onset before age 6 years

Table 12.3 Types of rickets, differential diagnosis, and common laboratory findings

Disorder	Defect	Ca	Ph	PTH	25(OH) D	Calcitriol	ALP	Treatment
Vitamin D deficiency	Decreased vitamin D	N, L	L	H	L	N, L, H	H	Vitamin D
1-αhydroxylase mutation	25-(OH)D cannot be converted to calcitriol	N, L	L	H	N	Very L	H	Calcitriol
Vitamin D receptor mutation resistance	End-organ resistance to vitamin D	N, L	L	H	N	Very H	H	Ca
Chronic renal failure	Decrease activity of 1-αhydroxylase in the kidney	N, L	H	Very H	N	L	H	Ca and phosphate binders
Hypoparathyroidism	Low PTH	L	H	L	N	N	N	Ca, vitamin D, and calcitriol in some cases
X-linked hypophosphatemic rickets	Proximal tubular defect, Ph wasted in the urine	N, L	L	N, H	N	N, slightly L	H	Phosphate and calcitriol
Mostly due to *PHEX* mutation								
Pseudohypoparathyroidism (*Gsα* mutation)	PTH resistance	L	H	H	N	N	N	Ca and vitamin D
Fanconi syndrome	RTA	N	L	N	N	Slightly L or H	H	Phosphate, calcitriol, or 1α-hydroxy vitamin D3

Ca calcium, *Ph* phosphorus, *PTH* parathyroid hormone, *25(OH)D* 25-hydroxyvitamin D, *ALP* alkaline phosphatase, *N* normal, *H* high, *L* low, *RTA* renal tubular acidosis

Clinical presentation

- Early pubic hair and axillary hair development
- Increased sebaceous activity
- Adult-type body odor
- No sexual development (breast buds in girls; testicular enlargement in boys)
- Normal growth pattern

Diagnosis

- Bone age approximates chronological age or mildly advanced
- Other imaging studies are normal
- Slight increase in DHEA-S level
- Other adrenal steroid hormones are normal
- Normal sex hormones
- No CAH
- Consistent with prepubertal pattern

Management

- Reassurance

Isolated (Benign) Premature Thelarche

Background

- Premature thelarche refers to isolated breast development that occurs in the first 2 years of life
- Possible underlying cause must be investigated if it occurs after 3 years of age

Diagnosis

- Normal bone age
- No other signs of puberty
- No growth acceleration
- All labs are normal for age
- Unilateral or bilateral with waxing and waning course
- Regression usually occurs within 18 months but may persist for 3–5 years
- Regression might not happen if presenting breast development is > Tanner II

Management
- Benign condition and self-limited
- However, patients should be followed at 3- to 6-month intervals, as studies have indicated that about 18% of premature thelarche will progress to central PP
- Thelarche after the first 3 years of life must be investigated

Premature Menarche

Background
- Premature menarche by itself is very rare

Differential diagnosis
- Foreign bodies
- Vulvovaginitis
- Sexual abuse

Clinical presentation
- Most girls with isolated premature menarche have only 1 to 3 episodes of bleeding, then puberty occurs at normal time

Diagnosis
- Gonadotropin levels are normal
- Estrogen may be elevated
- Ovarian cyst may be noted

Precocious Puberty (PP)

Definitions
- Thelarche: Breast development
- Adrenarche: Maturation of adrenal androgen production leading to body odor, acne, axillary and pubic hair development
- Pubarche: Pubic hair development; usually part of adrenarche
- Menarche: First vaginal bleeding
- Gonadarche: Earliest gonadal changes in response to pituitary gonadotropins

Background
- The hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gonadotrophs to release LH and FSH, which stimulate the gonads to release sex hormones (gonadarche: estrogen from ovaries and testosterone from testes)
- First manifestation of gonadarche in boys is testicular enlargement (> 3 ml in volume) and in girls is breast budding (Tanner II)
- Normal pubertal timing (gonadarche) is between 8 and 13 years in girls and 9 and 14 years in boys
- Pubertal signs are considered precocious if they happen before the age of 8 years in girls and 9 years in boys
- PP can be classified as gonadotropin-dependent (centrally mediated) and gonadotropin-independent (peripherally mediated)

Sexual Maturity Ratings (SMRs)

Sexual development in boys (Fig. 12.8, and Table 12.4)
- Thinning of scrotum
- Increased pigmentation of scrotum
- Enlargement of testis > 3 ml or 2.5 cm
- Pubic hair
- Height acceleration occurs late at SMR 4–5 (typically age 13–14)

Sexual development in girls (Fig. 12.9, and Table 12.5)
- Breast buds
- Pubic hair
- Height acceleration peak during SMR 2–3 (typically 11–12 years)
- Menarche takes usually 2–2.5 years after breast development but can take up to 6 years

Differential Diagnosis for Precocious Puberty

A. Gonadotropin-dependent PP = centrally mediated PP
- Idiopathic = most common cause
- CNS disorders

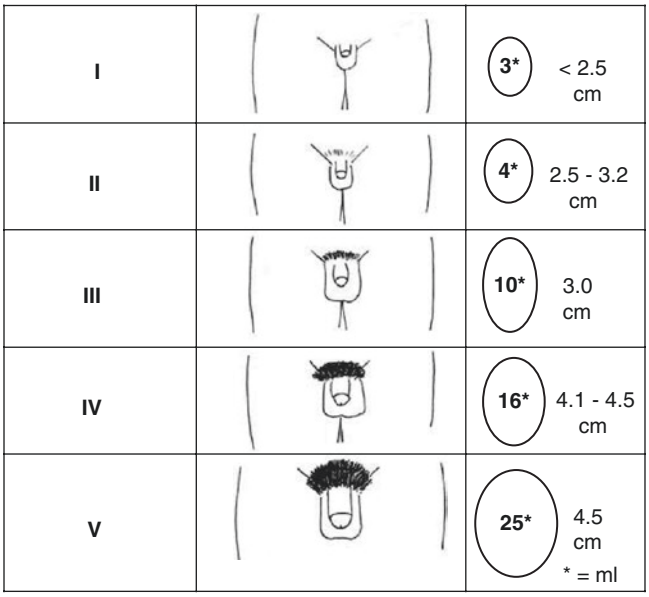


Fig. 12.8 Sexual maturity rating in boys

Table 12.4 Sexual maturity rating in boys

Stages	Pubic hair	Genitalia
1	Prepubertal	Prepubertal
2	Sparse, lightly pigmented at the base of the penis	Scrotum and penis enlarge slightly
3	Begins to curl, extend laterally	Testes and scrotum continue to grow
4	Coarse, curly, adult type but less in quantity	Large and darker scrotum, penis becomes large and increased in width, glans penis develops
5	Adult distribution and extends to medial thigh	Adult size scrotum and penis

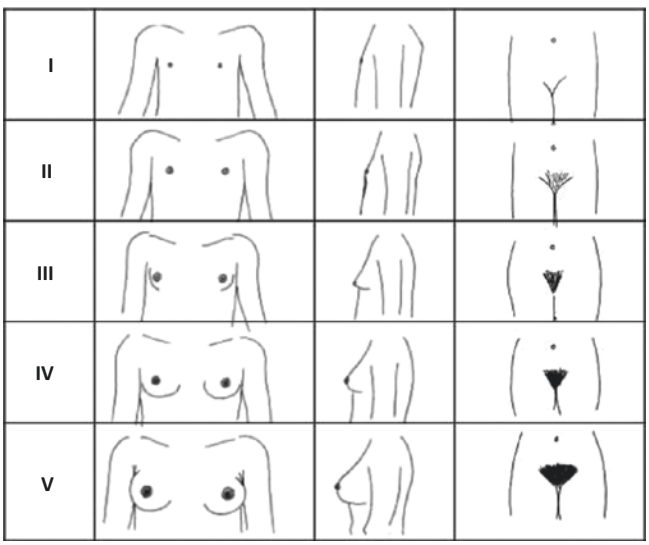


Fig. 12.9 Sexual maturity rating in girls

Table 12.5 Sexual maturity rating in girls

Stages	Pubic hair	Breasts
1	Prepubertal: no pubic hair present, fine hair may be noted	Prepubertal: Juvenile breast with small flat areola and elevated papilla
2	Sparse, lightly pigmented	Small mound and areolar diameter increases
3	Increased in amount and becomes darker, starting to curl	Breast and areola are larger, no separation of breast contour is noted
4	Abundant, coarse, curly, but less than adult	Areola and papilla form secondary mound, separation from contour is noted
5	Adult female triangle, extends to medial thigh	Mature, more projection of papilla, areola becomes part of general breast contour

  - Hypothalamic hamartomas: Most common identified CNS lesion. Benign and usually requires no intervention
  - Tumors (e.g., astrocytoma, gliomas, germ cell tumors secreting human chorionic gonadotropin [HCG])
  - Acquired CNS injury caused by inflammation, surgery, trauma, radiation therapy, or abscess
- Congenital anomalies (e.g., hydrocephalus, arachnoid cysts, suprasellar cysts)
- Genetic mutations: e.g., *MKRN-3, DLK-1, KISS1, KISSR1*
- Syndromes, e.g., neurofibromatosis type 1

B. Gonadotropin-independent PP = peripherally mediated PP

- Gonads
  - McCune Albright syndrome (see below)
  - Testotoxicosis (familial male gonadotropin-independent PP)
  - Tumors (e.g., theca cells, granulosa cells, Leydig cells, Sertoli cells)
- Adrenal gland
  - CAH (see below)
  - Tumors (adenoma or carcinoma)
- HCG-secreting tumors, e.g., hepatoblastoma (HCG acts as a gonadotropin)
- Exogenous exposure to estrogen or testosterone or endocrine disruptor chemicals
- Severe primary hypothyroidism (= Van Wyk–Grumbach syndrome)

C. Gonadotropin-dependent PP = centrally mediated

- PP increases the risk for psychological and social stress, including sexual abuse and compromise of final adult height in untreated cases

Clinical presentation

- PP in girls < 8 years
  - Breast enlargement, which may initially be unilateral
  - Pubic and axillary hair may appear first
  - Accelerated linear growth and bone age advancement
- PP in boys < 9 years
  - Testicular enlargement, a subtle finding that often goes unnoticed by patients and parents
  - Growth of the penis and scrotum
  - Accelerated linear growth and bone age advancement

Diagnosis

- Random gonadotropin and sex hormones may be elevated; however, in many occasions, random measurements are not diagnostic
- Definitive diagnosis of central PP may be confirmed by measuring LH (by ultrasensitive assay) levels 60 min after stimulation with a parenteral injection (subcutaneous or IV) with a short-acting GnRH analog
- Bone age radiograph is a quick and helpful means to estimate the likelihood of PP and its speed of progression

Management

- MRI of the brain is indicated in all boys (any age) with central PP and in girls with onset less than 6 years of age. There is no consensus on ordering MRI brain for girls between 6 and 8 years of age
- Long-acting GnRH analogs are the standard of care for central PP. They act by inhibiting the hypothalamic–pituitary–gonadal axis
- Treatment of the cause, e.g., surgical resection of tumor and irradiation

Gonadotropin-independent PP = peripherally mediated PP

- Clinical presentation and management will depend on the underlying cause
- Random and GnRH-stimulated levels of gonadotropins are suppressed with elevated sex hormone levels
- Adrenal androgens can be measured, including DHEA-S, androstenedione, and 17-hydroxyprogesterone
- Thyroid functions should be measured in all patients presenting with signs of PP to rule out severe primary hypothyroidism
- Ultrasound or imaging of gonads/adrenals may be needed

McCune–Albright Syndrome

Background

- Caused by an activating mutation of the *GNAS* gene
- Characterized by the following triad:
  - Polyostotic fibrous dysplasia
  - *Café-au-lait* skin pigmentation
  - Gonadotropin-independent PP

Clinical presentation

- PP
  - Breast development
  - Vaginal bleeding (may occur before breast development)
  - Genital maturation (with or without pubic hair growth)
  - Increased height velocity and advanced bone age
  - Macro-orchidism
- *Café-au-lait* pigmentation
  - Segmental distribution
  - Frequently predominating on one side of the body without crossing the midline
- Polyostotic fibrous dysplasia
  - Multiple pathologic fractures
  - Gait anomalies
  - Visible bony deformities (including abnormal bone growth of the skull), bone pain, and joint stiffness with pain

- Other signs of *GNAS* activation: e.g., hyperthyroidism or hypercortisolism

Diagnosis

- Elevation of sex hormones (estrogen in girls and testosterone in boys) with suppressed gonadotropins (both random and GnRH analog stimulated)
- Plain radiography can show multiple patchy areas of bony lysis

Management

- No specific treatment for this syndrome
- Treatment of PP
  - Aromatase inhibitors

Delayed Puberty

- In boys, puberty is considered delayed if testicular volume is less than 4 ml by 14 years of age or if started before 14 years of age and is taking more than 5 years to complete
- In girls, puberty is considered delayed if no breast development is happening by 13 years of age or if no menarche by age 16 years or 3 years after breast budding

Differential diagnosis of delayed puberty includes the following

- Constitutional delay of growth and puberty (normal variant of normal pubertal timing)
  - The most common cause of delayed puberty
  - Positive family history is usually present
- Functional disorders and chronic systemic illness
  - Chronic illnesses
  - Nutrition disorders, e.g., malnutrition, anorexia nervosa, etc.
  - Endocrinopathies
  - Psychological stress
  - Medications, e.g., steroids
- Central causes or hypogonadotropic hypogonadism
  - Congenital causes
    - Kallmann syndrome (delayed puberty and anosmia (loss of smell sensation)
    - Bardet–Biedl syndrome
    - Prader–Willi syndrome
    - Congenital panhypopituitarism
  - Acquired causes: Tumors, radiation, or surgery affecting the hypothalamus and/or pituitary gland
- Primary gonadal failure or hypergonadotropic hypogonadism, e.g., Turner syndrome and Klinefelter syndrome

Primary Hypogonadism

Causes

- Primary hypogonadism in males or vanishing testis syndrome
- Developmental anomalies associated with the genital system (e.g., hypospadias, micropenis, and cryptorchidism)
- Mumps orchitis, trauma, radiation exposure of the head or testes, and chemotherapy can cause testicular failure
- Spironolactone, cyproterone, marijuana, heroin, and methadone can inhibit the synthesis of testosterone
- Klinefelter syndrome

Clinical presentation

- In male infants, the testicles are abnormally small
- Failure to develop secondary sexual characteristics
- Eunuchoid body habitus

Diagnosis

- Elevated FSH and LH

Klinefelter Syndrome (See Also Chap. 4 "Genetic Disorders")

Background
- Most common major sexual differentiation abnormality
- 47,XXY karyotype
- Abnormalities of nondisjunction during meiosis

Clinical presentation
- Gynecomastia
- Male breast cancer
- Mild intellectual disability
- Small penis
- Testes are small and firm (usually < 2 cm or 2 ml)
- Azoospermia
- Decreased facial hair, but the pubic hair is abundant

Diagnosis
- Karyotype
- Elevated FSH and LH
- Low inhibin B level
- Increased estradiol to testosterone ratio

Management
- Testosterone replacement after age 11 years (intramuscular [IM], or transdermal)
  - Testosterone 25–50 mg IM every 3–4 weeks
  - Increase the dose by 50 mg every 6–9 months
  - Goal: 200–250 mg every 3–4 weeks
- Breast cancer surveillance

Gynecomastia

Background
- Gynecomastia is a benign enlargement of the male breast (usually bilateral but sometimes unilateral) resulting from a proliferation of the glandular component of the breast
- Presence of a rubbery or firm mass extending concentrically from the nipples
- Gynecomastia should be differentiated from pseudogynecomastia (lipomastia), which is characterized by fat deposition without glandular proliferation
- Common in adolescence

Causes
- Estrogen–androgen imbalance
- Pubertal (physiologic gynecomastia)
- Klinefelter syndrome
- Testicular tumor
- Ectopic production of HCG, e.g., germ cell tumor
- Chronic liver disease
- Hyperthyroidism
- Adrenal tumor
- Familial gynecomastia
- Prolactinoma

Approach and considerations
- Asymptomatic and pubertal gynecomastia does not require further tests and should be reevaluated in 6 months
- Red flags
  - Breast size greater than 5 cm (macromastia)
  - A lump that is tender, of recent onset, progressive, or of unknown duration
  - Signs of malignancy (e.g., hard or fixed lymph nodes or positive lymph node findings)
- Further investigation if abnormal underlying cause is considered

Treatment
- Generally, no treatment is required for physiologic gynecomastia
- Pubertal gynecomastia resolves spontaneously within several weeks to 3 years in approximately 90% of patients

Turner Syndrome (See also Chap. 4 "Genetic Disorders")

Background

- More than 95% of adult women with Turner syndrome are short and infertile
- 45,X chromosome

Clinical presentation

- Short stature
- Ovarian failure
- Heart murmur
  - Bicuspid aortic valve (most common heart defect)
  - Coarctation of the aorta
- Hypertension
- Lymphedema at birth
- Webbed neck
- Madelung deformity
- Hypothyroidism

Diagnosis

- Karyotype: Diagnosis is confirmed by the presence of a 45,X cell line or a cell line with deletion of the short arm of the X chromosome (Xp deletion), also mosaic forms
- The buccal smear for Barr bodies is obsolete
- Y-chromosomal material should be investigated for possibility of mixed 45,X/46,XY mosaicism may have mixed gonadal dysgenesis and are at a high risk for gonadoblastoma
- LH and FSH rise to menopausal level after age of 10 years
- TSH and thyroid study must be followed due to high risk of hypothyroidism

Management

- GH to improve final height
- Estrogen replacement therapy is usually required
- Estrogen is usually started at age 12–15 years after height optimized
- Treatment can be started with continuous low-dose estrogens at 12 years
- These can be cycled in a 3-weeks on, 1-week off regimen and after 6–18 months; progestin can be added later

ADRENAL DISORDERS

For the purpose of this review, the following disorders will be discussed:

- Disorders of the adrenal cortex: Cushing syndrome, Addison disease, and hyperaldosteronism. CAH syndrome will be discussed under disorders of sexual differentiation
- Disorders of the adrenal medulla: Pheochromocytoma

Cushing Syndrome

Background

- Caused by prolonged exposure to elevated levels of either endogenous glucocorticoids or exogenous glucocorticoids
- Exogenous glucocorticoid exposure is the most common overall cause. ACTH therapy is another cause of hypercortisolism but is much less common
- Endogenous causes
  - ACTH-secreting pituitary adenoma
    - Most common endogenous cause (75%)
    - More common above 7 years of age
  - Adrenal causes of Cushing (adenoma, carcinoma, and bilateral hyperplasia)
    - More common below 7 years of age
  - Ectopic ACTH-secreting tumors represent less than 1% of cases and is very rare in children
- Cushing syndrome causes can be classified as ACTH-dependent (Cushing disease and ectopic secretion) and ACTH-independent (exogenous exposure or adrenal causes)

Clinical presentation

- Excessive weight gain, especially in the face (moon facies), supraclavicular region, upper back (buffalo hump), and torso
- Failure to grow or short stature
- Hypertension
- Purple stretch marks, easy bruising, and other signs of skin thinning
- Proximal muscle weakness
- Depression, cognitive dysfunction, and emotional lability may develop
- Hypertension
- DM or glucose intolerance
- Decreased bone density and fractures

Diagnosis

- Evidence of hypercortisolism
  - Elevated 24-h urinary free cortisol
  - Low-dose dexamethasone suppression test showing no suppression of 8:00 AM cortisol
  - Loss of normal circadian rhythm, i.e., elevated cortisol at midnight
- If there is evidence of hypercortisolism → ACTH levels will be elevated in Cushing disease and ectopic secretion and will be low in adrenal causes
- Imaging is recommended: e.g., brain MRI to look for Cushing disease (pituitary) and abdominal CT for adrenal causes
- Nonspecific laboratory evidence: Elevated white blood cell count greater than 11,000/mm^3, hyperglycemia, and hypokalemic metabolic alkalosis

Management

- Depends on lesion and location
- Unilateral adrenalectomy for benign adrenal tumor
- Treatment of choice for pituitary adenoma: Transsphenoidal pituitary microsurgery

Remember

- Children with obesity are usually tall
- Children with Cushing syndrome (and other endocrine causes of short stature) are obese and short

Hyperaldosteronism

Background

- Rare in children
- Primary hyperaldosteronism usually due to adrenal tumor
- Secondary hyperaldosteronism, e.g., nephrotic syndrome, congestive heart failure, and liver cirrhosis

Clinical presentation

- Hypertension
- Headache
- Hypokalemia-related symptoms, e.g., constipation and weakness

Diagnosis

- Primary hyperaldosteronism
  - Elevated aldosterone level
  - Low renin level
  - Hypertension
  - Hypokalemia
- Secondary hyperaldosteronism
  - Elevated plasma renin activity (PRA)

Management

- Surgical removal of adenoma
- Prednisone for glucocorticoid-suppressible hyperaldosteronism

Adrenal Insufficiency

- Can be classified into **primary adrenal insufficiency** and **secondary or central adrenal insufficiency**
- The most common cause of **primary adrenal insufficiency** is autoimmune adrenal insufficiency, also known as Addison disease

- The most common cause of **secondary/central adrenal insufficiency** is chronic use of exogenous supraphysiological doses of corticosteroids (iatrogenic adrenal insufficiency)
- It is important to note that chronic use of corticosteroids will inhibit ACTH secretion with resulting adrenal gland atrophy
- Sudden cessation or withdrawal of corticosteroids in these patients will lead to acute adrenal insufficiency or crisis
- A similar scenario will happen if the patient is on physiological doses of steroids but is exposed to stress (e.g., surgery, illness) with no additional replacement

Addison Disease

Background

- Addison disease is adrenocortical insufficiency due to the destruction or dysfunction of the entire adrenal cortex
- Idiopathic autoimmune Addison disease tends to be more common in females and children

Associated autoimmune diseases

- Diabetes mellitus (DM) type 1
- Celiac disease, Hashimoto thyroiditis
- Graves disease
- Vitiligo
- Alopecia areata, totalis, and universalis
- Premature ovarian or testicular failure
- Pernicious anemia
- Autoimmune polyglandular syndrome (APS) type 2

Other causes

- Tuberculosis, sarcoidosis, histoplasmosis, blastomycosis, and cryptococcosis could involve the adrenal glands

Acute Addison Disease

Causes

- Bilateral adrenal hemorrhage, e.g., meningococcemia
- Failure to increase steroids in patients with adrenal insufficiency in time of stress, e.g., surgery

Clinical presentation

- Hyperpigmentation
  - Caused by the stimulant effect of excess adrenocorticotropic hormone (ACTH) on the melanocytes to produce melanin
- Vitiligo
- Hypotension
- Myalgias and flaccid muscle paralysis may occur due to hyperkalemia
- Acute adrenal crisis
  - Nausea, vomiting, and vascular collapse
  - Shock; may appear cyanotic and confused
  - Acute abdomen
  - Hyperpyrexia, with temperatures reaching 105 °F or higher
  - In acute adrenal hemorrhage, the patient is usually in an acute care setting, deteriorates with sudden collapse, abdominal or flank pain, and nausea with or without hyperpyrexia

Diagnosis

- High-dose ACTH stimulation test (Cortrosyn, cosyntropin, or Synacthen)
- Low cortisol with elevated ACTH suggestive
- Hyponatremia
- Hyperkalemia
- Mild non-anion-gap metabolic acidosis due to the loss of the sodium-retaining and potassium and hydrogen ion-secreting action of aldosterone

Management of adrenal crisis

- In stress situations, the normal adrenal gland output of cortisol is approximately 100 mg/m^2 of bovine serum albumin (BSA) in 24 h
- IV access should be established urgently
- Infusion of isotonic NaCl to restore volume deficit and correct hypotension
- IV bolus of hydrocortisone and then 100 mg/m^2/day divided into three or four times a day until resolution of crisis, then consult endocrinology to discontinue or taper

Pheochromocytoma

Background

- Rare catecholamine-secreting tumor that arises from chromaffin cells of the sympathetic nervous system (adrenal medulla and sympathetic chain)

Clinical presentation

- Headache is the most frequent symptom in children (75%)
- Sweating in two-thirds of patients
- Nausea and vomiting in half of patients
- Hypertension
- Palpitation with or without tachycardia
- Weakness or exhaustion
- Chest pain
- Dyspnea
- Epigastric pain
- Tremor
- Nervousness or anxiety
- Numbness or paresthesia
- Blurred vision

Diagnosis

- High blood pressure or recurrent hot flushes that are indicative of blood pressure peaks
- An adrenal mass
- Family history of MEN type 2 (MEN-2) or von Hippel–Lindau disease
- Measurement of urinary catecholamines and their metabolites in a 24-h specimen
  - Homovanillic acid (HVA)
  - Vanillylmandelic acid (VMA)
  - Epinephrine
  - Norepinephrine
- Abdominal ultrasound may detect large adrenal tumor
- CT scan of adrenal gland

Management

- Treat with surgical removal and pretreat with alpha-blockade
- During a hypertensive crisis, immediately institute alpha-blockade with phenoxybenzamine
- Nitroprusside should also be used for uncontrolled hypertension

Polycystic Ovarian Syndrome (PCOS)

Background

- Women with PCOS have abnormalities in the metabolism of androgens and estrogen and in the control of androgen production
- PCOS can result from abnormal function of the hypothalamic–pituitary–ovarian (HPO) axis

Clinical presentation

- Menstrual dysfunction due to anovulation
- Hirsutism
- Infertility
- Obesity
- Metabolic syndrome
- DM
- Obstructive sleep apnea
- Virilizing signs
- Acanthosis nigricans
- Hypertension

Diagnosis

- FSH levels are within the reference range or low
- LH levels are elevated for Tanner stage, sex, and age
- The LH to FSH ratio is usually greater than 2–3
- Elevated testosterone (or free testosterone) level
- Recommended tests:
  - TSH and free thyroxine
  - Serum prolactin level
  - Total and free testosterone
  - Serum hCG level
  - Glucose level
  - Insulin level
  - Lipid panel
  - 17-hydroxyprogesterone level (to exclude late onset CAH)
  - Karyotype usually excludes mosaic Turner as a cause of primary amenorrhea

- Ovarian ultrasonography
  - Enlarged ovaries and cysts may or may not be present

Management

- Diet and exercise are considered first-line treatment
- Oral contraceptive to induce regular menses
- Metformin for insulin resistance

DISORDERS OF SEXUAL DEVELOPMENT (DSD)

Background

- Congenital conditions in which the genetics (chromosomes), gonads, or genitals (anatomic sex) are atypical
- Current classification is based on genetics and does not use the phenotype, as in the past. Terms such as "hermaphrodite," "pseudohermaphrodite," or "sex errors of body" are no longer acceptable
- The embryonic mesoderm develops the genital ridge and primitive kidney. The genital ridge then develops into the bipotential gonad
- The most common cause of atypical genitalia is CAH due to 21-hydroxylase deficiency leading to a virilized female phenotype
- The screening laboratory level for 21-hydroxylase deficiency is 17-hydroxyprogesterone, which will be markedly elevated and is screened for on the newborn screen

In 46 XY males

- The presence of *SRY* (sex-determining region on the Y chromosome) in addition to other autosomal genes will lead the bipotential gonad to differentiate in testis
- The Leydig cells in the testes produce testosterone, which will lead to the development of the Wolffian structures, including epididymis, vas deferens, seminal vesicles, and ejaculatory ducts
- Testosterone is further converted into dihydrotestosterone (DHT) by the action of 5-alpha-reductase enzyme
- DHT is essential for complete masculinization of the external genitalia
- Both testosterone and DHT bind to the androgen receptors to exert their effects; however, DHT has a higher affinity to the androgen receptor
- The Sertoli cells produce anti-Müllerian hormone (AMH), which leads to regression of the Müllerian structures
- The result is normal testicular development with normal male-appearing external genitalia

In 46 XX females

- In the absence of *SRY,* the bipotential gonad develops into an ovary. This also requires interaction of multiple autosomal genes, and the notion that ovarian development is passive is no longer accepted
- In the absence of AMH, the Müllerian structures also under control of autosomal genes will develop into the uterus, fallopian tubes, and upper third of the vagina
- In the absence of androgens, the external genitalia will develop into the normal female phenotype

Classification of DSD is quite complex and the following is a suggested classification

46 XY DSD

- Disorders of testicular development
  - Complete gonadal dysgenesis (Swyer syndrome)
  - Partial gonadal dysgenesis
- Disorders of androgen synthesis or action
  - LH receptor defects → Leydig cell hypoplasia/aplasia
  - Steroidogenic pathway defects: e.g., 17-hydroxysteroid dehydrogenase deficiency, steroidogenic acute regulatory

protein (StAR) deficiency, and 5-alpha-reductase deficiency
  - Androgen receptor defects: Complete and partial androgen insensitivity syndromes
- Disorders of AMH and its receptor, e.g., persistent Müllerian duct syndrome

46 XX DSD
- Disorders of ovarian development
- Disorders of androgen excess
  - 21-hydroxylase deficiency, 11-hydroxylase deficiency, aromatase deficiency, maternal exogenous exposure to androgens
- Others, e.g., vaginal atresia

Sex chromosome DSD
- 45 XO (Turner syndrome)
- 47 XXY (Klinefelter syndrome)
- Mixed gonadal dysgenesis syndrome (45 X/46 XY)
- Ovotesticular DSD (46 XX/46 XY)

Clinical approach to a child with ambiguous genitalia
1. Refer to newborn as "infant" without assigning a gender
2. Consult endocrinology, psychology, urology, genetics, and social services
3. History and physical exam with careful description of genitalia
   (a) Is the newborn a genetic 46 XX female exposed to excess androgens (virilized female)?
   (b) Is the newborn a genetic 46 XY male with underproduction of androgens or decreased action (undervirilized male)?
   (c) Is a gonad palpable? In almost all cases, palpable gonads are testes
4. Laboratory evaluation
   (a) Karyotype
   (b) First 24 h of life: Testosterone, DHT, LH, FSH, AMH
   (c) After 48 h of life: Electrolytes, 17-hydroxyprogesterone, PRA (plasma renin activity)
5. Imaging: Abdominal/pelvic ultrasound to look for uterus, ovaries/testes (gonads)

Congenital Adrenal Hyperplasia (CAH)

Background
- The term encompasses a group of autosomal recessive disorders, each of which involves the deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both

Causes
- The most common form of CAH is due to mutations or deletions of *CYP21A,* resulting in 21-hydroxylase deficiency
- 17-hydroxylase deficiency
- 11-beta-hydroxylase deficiency
- 3-beta-hydroxysteroid deficiency

Clinical presentation in females
- Severe form of CAH
  - Ambiguous genitalia at birth due to excess adrenal androgen production in utero
- Mild forms of 21-hydroxylase deficiency (simple virilizing adrenal hyperplasia)
  - Usually females are identified later in childhood
  - Precocious pubic hair
  - Clitoromegaly
  - Accelerated growth and skeletal maturation due to excess postnatal exposure to adrenal androgens may occur
- Milder deficiencies of 21-hydroxylase or 3-beta-hydroxysteroid dehydrogenase activity (nonclassic adrenal hyperplasia)
  - May present in adolescence or adulthood
  - Oligomenorrhea
  - Hirsutism and/or infertility
  - This is termed nonclassic adrenal hyperplasia
- Females with 17-hydroxylase deficiency
  - Phenotypically female

  - Do not develop breasts or menstruate in adolescence because of inadequate estradiol
  - May present with hypertension

Clinical presentation in males

- 21-hydroxylase deficiency
  - Generally, not identified in the neonatal period because the genitalia are normal
- Severe form of 21-hydroxylase deficiency in males (classic salt-wasting congenital adrenal hyperplasia)
  - Usually results in salt wasting at age 1–4 weeks
  - Failure to thrive
  - Recurrent vomiting
  - Dehydration
  - Hypotension
  - Hyponatremia
  - Hyperkalemia
  - Shock
- Mild form of 21-hydroxylase deficiency (simple virilizing adrenal hyperplasia)
  - May present later in childhood
  - Early development of pubic hair
  - Phallic enlargement
  - Accelerated linear growth and advancement of skeletal maturation
- In male infants, CAH may be misdiagnosed as pyloric stenosis
- Hypertension: Associated with two forms
  - 11-hydroxylase deficiency
  - 17-hydroxylase deficiency

Diagnosis

- High serum concentration of 17-hydroxyprogesterone (usually > 1000 ng/dL)
- Salt-wasting forms
  - Low serum aldosterone concentrations
  - Hyponatremia
  - Hyperkalemia
  - Elevated PRA
- Hypertensive forms of adrenal hyperplasia (i.e., 11-beta-hydroxylase deficiency and 17-alpha-hydroxylase deficiency)
  - Suppressed PRA
  - Hypokalemia
- Karyotype
  - It is essential in the evaluation of an infant with ambiguous genitalia to establish the patient's chromosomal sex

Management

- Stabilization of patient with IV fluids if presenting in shock or dehydration
- IV dextrose if hypoglycemic
- IV hydrocortisone (50–100 mg/m^2 or 1–2 mg/kg initial dose if signs of adrenal insufficiency, e.g., hypotension)
- Followed by 50–100 mg/m^2/day IV divided every 6 h
- Long-term treatment
  - Hydrocortisone oral
  - Fludrocortisone (0.05–0.2 mg/day PO) to patients with mineralocorticoid deficiency
  - Oral NaCl (2–5 g/day) to infants with salt-wasting form

Remember

- 11-Hydroxylase deficiency
  - Non-salt wasting; hypertension is the most presenting symptom, virilization can cause very large clitoris mistaken for penis
- 17-Hydroxylase deficiency
  - Same as 11-hydroxylase deficiency with hypertension but no sex hormone or virilization in females, very rare
- 3β-Hydroxysteroid dehydrogenase deficiency
  - Can be confused with 21-hydroxylase and 11-B with late-onset and salt-wasting forms

Denys–Drash Syndrome

Background

- Occurs in 46, XY individual
- Complete Müllerian ducts usually found in these patients

Clinical presentation

- Nephropathy

- Renal failure usually by 3 years of age
- Ambiguous genitalia
- Wilms tumor

Swyer Syndrome (XY Pure Gonadal Dysgenesis)

Background
- Most patients have mutation in *SRY* gene
- Y chromosome is cytogenetically normal
- The gonads are undifferentiated streaks

Clinical presentation
- Complete female phenotype at birth
- Presence of vagina and fallopian tubes
- At puberty, no breast development and no menstruation

Prognosis
- Development of gonadoblastoma is the highest risk

Management
- Gonads must be removed as soon as the diagnosis is made

5-Alpha-Reductase Deficiency

Background
- Autosomal recessive
- Due to defect in androgen action on external genitalia
- This causes ambiguity of external genitalia
- Peripheral action of testosterone is normal

Clinical presentation
- Newborn with small penis, bifid scrotum, urogenital sinus, and a blind vaginal pouch
- Testes are in inguinal canal
- Most infants are raised as female and changed to male at the time of puberty
- At puberty
  - Virilization occurs
  - Male hair distribution
  - Enlargement of penis and scrotum
  - Sperm formation
- Normal adult height

Androgen Insensitivity Syndrome (AIS)

Background
- X-linked disorder
- Due to defect in androgen receptor gene
- All infants are 46, XY
- All infants have testes and normal testosterone levels

Clinical presentation
- Infant is phenotypically female at birth
- Most infants raised as female and identify with female gender
- External genitalia are female and the vagina ends in a blind pouch
- No uterus
- Fallopian tubes may or may not be present
- Testes are usually intra-abdominal
- At puberty, breasts develop normally
- No menses
- Sexual hair does not appear
- Normal male adult height
- Testosterone may be normal or high

Summary of DSD (Table 12.6)

DIABETES MELLITUS

Type 1 Diabetes Mellitus

Background
- Type 1 DM is a chronic illness characterized by the body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas
- Most pediatric patients with DM have type 1 and a lifetime dependence on exogenous insulin

Table 12.6 Keywords of common causes of disorders of sexual development

Description of DSD	Diagnosis
XX newborn	Congenital adrenal hyperplasia (CAH)
Virilization of external genitalia	
Ultrasound: normal Müllerian structures	
17 hydroxyprogesterone is very high	
XY female phenotype (raised female)	Androgen insensitivity syndrome (AIS)
Breast, no menses, no sexual hair	
Blind vaginal pouch (MIS is normal)	
Undescended testes	
Elevated testosterone level → estradiol → breast	
XY female phenotype (raised female)	Swyer syndrome (XY pure gonadal dysgenesis)
No breast, no menses, no sexual hair	
Has vagina, uterus, and fallopian tube	
Streak gonads	
Low testosterone	
XY female phenotype at birth	5-Alpha-reductase deficiency (no dihydrotestosterone)
No breast, no menses	
Develop sexual hair, enlarging penis	
No internal Müllerian structures	
Testes are inguinal canal	
XY normal male phenotype	Persistent Müllerian duct syndrome
Inguinal hernia, undescended testes	
Mullerian structure found incidentally	

Clinical presentation

- Hyperglycemia
- Glycosuria
- Polydipsia
- Unexplained weight loss
- Nonspecific malaise
- Symptoms of ketoacidosis

Diagnosis

- Diagnostic criteria by the American Diabetes Association (ADA) include the following:
  - Fasting plasma glucose (FPG) level ≥ 126 mg/dL (7.0 mmol/L), *or*
  - 2-hour plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT), *or*
  - Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
  - HbA1C≥ 6.5%
- Glycated hemoglobin
  - Measurement of HbA1c levels is the best method for medium- to long-term diabetic control monitoring
  - New target for HbA1C in children is < 7.5%
  - Benefits of tight glycemic control include not only continued reductions in the rates of microvascular complications but also significant differences in cardiovascular events and overall mortality
- Positive autoimmune markers (glutamic acid decarboxylase [GAD], insulin islet cell, and Zn transporter antibodies)
- Blood glucose tests
  - Capillary blood samples, reagent sticks, and blood glucose meters are the usual methods for monitoring day-to-day diabetes control

Management

- Insulin therapy
  - All children with type 1 DM require insulin therapy
  - Most require two or more injections of insulin daily, with doses adjusted on the basis of self-monitoring of blood glucose levels
  - Insulin replacement is accomplished by giving basal insulin and a preprandial (premeal) insulin
  - The basal insulin is either long-acting (glargine or detemir) or intermediate-acting (neutral pH protamine [NPH]). The preprandial insulin is either rapid-acting (lispro, aspart, or glulisine) or short-acting (regular)

- Diet and activity
  - The aim of dietary management is to balance the child's food intake with insulin dose and activity and to keep blood glucose concentrations as close as possible to reference ranges, avoiding extremes of hyperglycemia and hypoglycemia
  - Carbohydrates should provide 50–55% of daily energy intake; no more than 10% of carbohydrates should be from sucrose or other refined carbohydrates
  - Fat should provide 30–35% of daily energy intake
  - Protein should provide 10–15% of daily energy intake
- Exercise
  - An important aspect of diabetes management
  - Has real benefits for a child with diabetes
  - Patients should be encouraged to exercise regularly

Screening for associated autoimmune conditions:

Thyroid screening

- Autoimmune thyroiditis is the most common autoimmune disease associated with type 1 DM
- Screening start and frequency: At diagnosis and then annually

Celiac screening

- Celiac disease is the second most common autoimmune disease associated with type 1 DM
- Clinical picture: Classic symptoms include abdominal pain, diarrhea, or constipation. Some patients present with growth failure, reduced insulin requirement, or hypoglycemia due to erratic absorption of nutrients. Many children especially at a younger age are completely asymptomatic
- Screening start and frequency: At diagnosis and then annually
- How to screen: tTG IgA (in addition to a total IgA level)
- Positive screening: High tTG IgA titer
- Positive screening management: Refer to gastroenterologist to confirm diagnosis before starting a gluten-free diet

Addison disease

- Rare association with type 1 DM, so no universal screening warranted
- Suspect if patient is having unexplained hypoglycemia or decreased insulin requirements, losing weight, increased pigmentation of the skin and gingival mucosa, salt craving, weakness, and postural hypotension

Important to know: Consider the diagnosis of **autoimmune polyglandular syndrome type II** in patients with type 1 DM, autoimmune thyroiditis, and autoimmune adrenal insufficiency

Screening for associated comorbidities/ complications

Dyslipidemia

- Screening starts and frequency: 10 years of age or when puberty starts, whichever comes first, and then annually
- Risk factors: Family history of early cardiovascular disease (< 55 years of age)
- How to screen: Non-fasting lipid panel
- Positive screening management
  - Positive screening: Low-density lipoprotein (LDL) 100 mg/dl or above
  - Start by lifestyle change and Step II American Heart Association (AHA) diet
  - If lifestyle not effective, a statin is warranted if the child is 10 years or older

Retinopathy screening (dilated eye exam)

- Screening starts: 10 years of age or above and DM duration of 3–5 years
- How frequent: Annually if normal

Nephropathy screening

- Screening starts: At puberty or age ≥ 10 years, whichever is earlier, once the child has had DM for 5 years

- How to screen: Spot urine albumin to creatinine ratio. (12–24 h urine collections did not improve detection of albuminuria and are more burdensome)
- Positive screening management
  - Positive if ratio 30 mg/gm creatinine or above
  - If persistently positive (2 out of 3 samples): Treatment with an ACE inhibitor is warranted

Type 2 Diabetes Mellitus

Background

- Characterized by
  - Hyperglycemia
- Insulin resistance
  - Family history of type 2 DM in first- or second-degree relative
- Obesity strongly associated with type 2 in children and adolescents

Clinical presentation

- Slow and insidious onset
- Signs of insulin resistance, e.g., acanthosis nigricans
- Strong family history of type 2 DM: Familial lifestyle risk factors leading to obesity may be present; family history of cardiovascular disease or metabolic syndrome
- PCOS
- Hypertension
- Retinopathy

Screening and diagnosis

- Screening for type 2 DM should be considered when a patient is overweight or obese and has one or more of the following:
  - Family history of type 2 DM in first- or second-degree relative
  - Signs of insulin resistance or conditions associated with insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, PCOS and SGA birth weight)
  - Race/ethnicity: Native American, African-American, Latino, Asian American, or Pacific Islander
  - Maternal history of DM or gestational DM during the child's gestation
- Screening should start at 10 years of age or at the start of puberty if it occurs at a younger age
- Screening should be repeated every 3 years
- Diagnosis is established in the presence of one of the following criteria:
  - A random plasma glucose concentration of 200 mg/dL or greater in association with classic symptoms of hyperglycemia (polyuria, polydipsia, or nocturia) or a hyperglycemic crisis
  - FPG value of 126 mg/dL or greater
  - 2-hour plasma glucose value of 200 mg/dL or greater during an OGTT
  - HbA1c levels equal or greater than 6.5%
- Other laboratory results that are suggestive of type 2 DM but not needed for diagnosis are as follows:
  - Elevated fasting C-peptide level
  - Elevated fasting insulin level
  - Absence of autoimmune markers (see Type 1 DM)

Management

- Diabetes education and lifestyle changes (diet, exercise, and weight control)
- The only pharmacologic therapy that is FDA-approved in children is metformin and insulin
- Metformin is the initial drug of choice for treatment of type 2 DM in metabolically stable patients (A1C < 8.5% and asymptomatic) if renal functions are normal
- Children with marked hyperglycemia (blood glucose ≥ 250 mg/dL, A1C ≥ 8.5%) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin while metformin is initiated and titrated

- In patients with ketosis/ketoacidosis, treatment with subcutaneous or IV insulin should be initiated to rapidly correct the hyperglycemia and metabolic derangement.
- Once ketosis/ketoacidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued

Management of Comorbidities/ Complications

Nephropathy screening

- Screening starts: At diagnosis and then annually if normal
- How to screen: Spot urine albumin to creatinine ratio. (12–24 h urine collections did not improve detection of albuminuria and are more burdensome)
- Positive screening management
  - Positive if ratio is 30 mg/gm creatinine or above
  - If persistently positive (2 out of 3 samples): Treatment with an ACE inhibitor is warranted

Hypertension

- Increases risk for cardiovascular and renal disease
- Blood pressure should be measured accurately and reviewed at each visit
- Both systolic and diastolic blood pressures should be below the 90th percentile for age, gender, and height
- Pharmacological therapy with an ACE inhibitor is indicated if hypertension persists after 6 months of lifestyle modifications

Dyslipidemia

- Screening starts and frequency: At diagnosis and then annually
- How to screen: Non-fasting lipid panel
- Positive screening management
  - Positive screening: LDL 100 mg/dl or above, or high-density lipoprotein (HDL) 35 mg/dL or lower, triglycerides 150 mg/dL or above
  - Start by lifestyle change and Step 2 AHA diet
  - If lifestyle is not effective after 6 months, a statin is warranted with a goal of LDL below 100 mg/dl

Retinopathy screening (dilated eye exam)

- Screening starts and frequency: At diagnosis and then annually

Neuropathy screening:

- Screening starts and frequency: At diagnosis and then annually
- How to screen: Examination should include inspection, assessment of foot pulses, pinprick, and 10-g monofilament sensation tests; testing of vibration sensation using a 128-Hz tuning fork, and ankle reflexes

Nonalcoholic fatty liver disease

- Screening starts and frequency: At diagnosis and then annually
- How to screen: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels
- Positive screening management: Lifestyle modifications and referral to gastroenterologist

PCOS

- Screening is indicated if showing signs/symptoms of PCOS
- Metformin may be beneficial in the treatment of girls with type 2 DM and PCOS. Oral contraceptives can also be used

Obstructive sleep apnea

- Start screening at diagnosis and at each visit
- Refer to a pediatric sleep specialist for evaluation and a sleep study if showing positive symptoms (snoring, insufficient or disrupted sleep, circadian rhythm dysregulation)

Depression

- The prevalence of clinically significant symptoms of depression were reported to be at 14.8% in the TODAY cohort of youth with type 2 DM
- Screen using age-appropriate tools and refer to specialty care when indicated

Summary

- Treatment goals include improvement of glycemia (HbA1c) levels (< 7%), dyslipidemia (LDL level < 100 mg/dL, triglyceride < 150 mg/dL, HDL level > 35 mg/Dl), and hypertension (blood pressure < 90th percentile for age, sex, and height)

Diabetes Ketoacidosis (See Chap. 7 also "Emergency Medicine")

Precipitating factors that could lead to the onset of DKA

- Infection
- Insulin omission
- Insulin pump failure
- Failure to match insulin dosing to metabolic requirements during illness or stress

Diagnosis

- Blood glucose level greater than 200 mg/dL
- Presence of serum/urine ketones
- Venous pH < 7.30 or a bicarbonate level less than 15 mmol/L

Severity of DKA can be classified according to the severity of the acidosis

- Mild
  - Venous pH 7.21–7.30
  - Bicarbonate (mmol/L) 11–15
- Moderate
  - Venous pH 7.11–7.20
  - Bicarbonate (mmol/L) 6–10
- Severe
  - Venous pH < 7.10
  - Bicarbonate (mmol/L) < 5

Management

- Hydration is the most important first step
  - IV fluid replacement is begun as soon as the diagnosis of DKA is established
  - Initial fluid resuscitation begins with 10 mL/kg of isotonic fluid, 0.9% saline administered over 1 h
  - After the initial fluid resuscitation, the remainder of the fluid deficit is replaced evenly over 48 h (most patients are 6% dehydrated)
  - Maintenance fluid requirements are added to this deficit replacement to provide the total fluid requirements, which rarely exceed 1.5 times the usual daily fluid requirement
  - The 0.9 saline with added 30–40 mEq/L of potassium is continued as the hydration fluid until the blood glucose value declines to less than 300 mg/dL
  - Replacement fluid should be changed to D5 0.45% with added potassium when glucose value declines to less than 300 mg/dL
  - If the blood glucose concentration declines below 150 mg/dL (8.3 mmol/L), dextrose content may need to be increased to 10% or even 12.5%

Insulin

- Time of insulin initiation is controversial
- Insulin is administered as a continuous IV infusion of regular insulin at a rate of 0.05–0.1 units/kg/h
- Bolus of insulin should not be given at the start of therapy
- If IV administration of insulin is not possible, short- or rapid-acting insulin injected subcutaneously every 2 h can be effective

Resolution of the acidosis in DKA

- Acidosis (pH > 7.3)
- Bicarbonate > 15 mEq/L
- IV insulin therapy should continue as long as the patient is still acidotic

- Decrease IV insulin rate if there is persistent hypoglycemia despite maximum dextrose administration
- Subcutaneous insulin must be started before discontinuation of IV insulin when acidosis is resolved

Monitoring
- Vital signs
- Mental status and neurologic evaluation
- Serum glucose, electrolytes including serum phosphorus (including blood urea nitrogen and creatinine), and pH and urine ketones should be measured at presentation
- Serum glucose and pH should be measured hourly
- Serum electrolytes and urine ketones assessed every 2–3 h
- If phosphate is administered, serum calcium concentrations must be monitored

Outpatient Management of Sick Days in Patient with Diabetes Mellitus

Management steps
- Check blood glucose level every 2–3 h until feeling well. Urine ketones should be checked frequently
- It is important to teach families that adjustments in the insulin doses are necessary during intercurrent illness, but a complete cessation of all insulin replacement will quickly lead to diabetic ketoacidosis
- Encourage fluid intake. Ideally, give 1 oz (30 mL) per year of age per hour in small, frequent sips
  - If glucose level is ≥ 200 mg/dL, sugar-free fluids should be given
  - If glucose level is < 200 mg/dL, sugar-containing fluids should be included

Factors warranting medical evaluation
- Persistent vomiting (e.g., vomiting more than twice after starting sick day rules) with moderate to large urine ketone levels (or blood ketone levels greater than 1.5 mmol/L)
- Inappropriately rapid breathing
- Altered mental status
- Inability to perform sick day rules

Maturity-Onset Diabetes of Youth (MODY)

Background
- MODY is the most common form of monogenic diabetes
- The genes involved control the pancreatic beta cell development, function, and regulation, hence leading to defects in glucose sensing and insulin secretion
- Onset is usually before 25 years of age
- Inherited in an autosomal dominant pattern

Types
- MODY 1–MODY 6 are the most common identified gene mutations, with MODY 3 (hepatocyte nuclear factor-1 alpha = *HNF1A*) being the most common, representing about 50% of monogenic diabetes cases

Diagnosis
- Suspect in individuals with the following characteristics:
  - Diabetes diagnosis before 25 years of age
  - Autosomal dominant pattern of inheritance of diabetes (> 2 generations affected)
  - Nonobese (usually)
  - Negative islet antibodies (markers of type 1 DM)
- Genetic testing is readily available

Treatment
- MODY 4–6 are treated with insulin
- MODY 1 and MODY 3 are treated with sulfonylureas
- MODY 2 is treated with diet and exercise but may require insulin during illness or pregnancy

Obesity

Background

- The most commonly used measure is body mass index (BMI)
- BMI is defined as kilograms (kg) of body weight per height in square meters (m^2)
- Overweight: BMI between 85th and 94th percentile
- Obesity: BMI at or above 95th percentile

Causes

- Idiopathic or familial obesity
  - Poorly understood
  - Most common cause of childhood obesity
- Hormonal, e.g.,
  - Hypothyroidism
  - GHD
  - Hypogonadism
  - Cushing syndrome
  - PCOS
- Syndromic, e.g.,
  - Down syndrome
    - Hypotonia
  - Prader–Willi syndrome
    - Hypotonia, hypogonadism, hyperphagia, small hands and feet
  - Albright hereditary osteodystrophy
    - Short stature and skeletal defect
  - Bardet–Biedl syndrome
    - Retinal dystrophy, renal abnormalities, mental retardation
  - Fragile X syndrome
    - Macro-orchidism and large ears
- Genetic, e.g.,
  - Melanocortin 4 receptor deficiency (*MC4R*)
  - Congenital leptin deficiency
  - Leptin receptor defect

Definition of *Pediatric Metabolic Syndrome* (International Diabetes Federation Criteria)

- Central obesity (required feature) > 90th percentile for age, gender, and ethnicity with waist circumference ≥ 94 cm in men or ≥ 80 cm in women
- Plus at least two of the following four clinical risk factors:
  - BP ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or drug treatment for hypertension
  - HDL < 40 mg/dL in men or < 50 mg/dL in women or treatment for lipid abnormalities
  - Triglyceride level ≥ 150 mg/dL
  - FPG level ≥ 100 mg/dL or previously diagnosed type 2 DM

Obesity-related conditions

- Depression and isolation are the most common complications of obesity in children and adolescents
- Liver
  - Fatty liver infiltration (nonalcoholic steatohepatitis [NASH]) 25–83%
  - Cholelithiasis (50% are obese)
- Pulmonary
  - Obstructive sleep apnea
  - Metabolic alkalosis and respiratory acidosis
  - Hypoventilation
  - Pulmonary hypertension
  - Right-sided heart failure
  - Obesity hypoventilation syndrome
  - Asthma
  - Renal
- Nocturnal enuresis
  - Related to obstructive sleep apnea and excess secretion of atrial natriuretic peptide (ANP)
- Cardiovascular
  - Hypertension (60% are obese)
  - Systolic blood pressure > 95% for age, sex, and height
  - Dyslipidemia
  - HDL < 40 mg/dL
  - LDL > 130 mg/dL
  - Triglyceride > 150 mg/dL
  - Total cholesterol > 200 mg/dL
- Musculoskeletal complications
  - Slipped capital femoral epiphysis (30–50% are obese)

  - Blount disease or tibia vara (70% are obese)
  - Severe leg bowing of tibia, knee pain, and limp
  - Osteoporosis
  - Back pain
  - Joint pain
- Acanthosis nigricans and insulin resistance (Fig. 12.10)
  - Not a criteria of metabolic syndrome diagnosis
  - High concentration of insulin in obese patients may exert potent proliferative effects via high-affinity binding to IGF-1, which stimulate epidermal keratinocyte and dermal fibroblast proliferation

Management

- Multidisciplinary approach
- Weight reduction
- Diet and exercise
- Management of obesity-related conditions
- Treatment of the cause if applicable

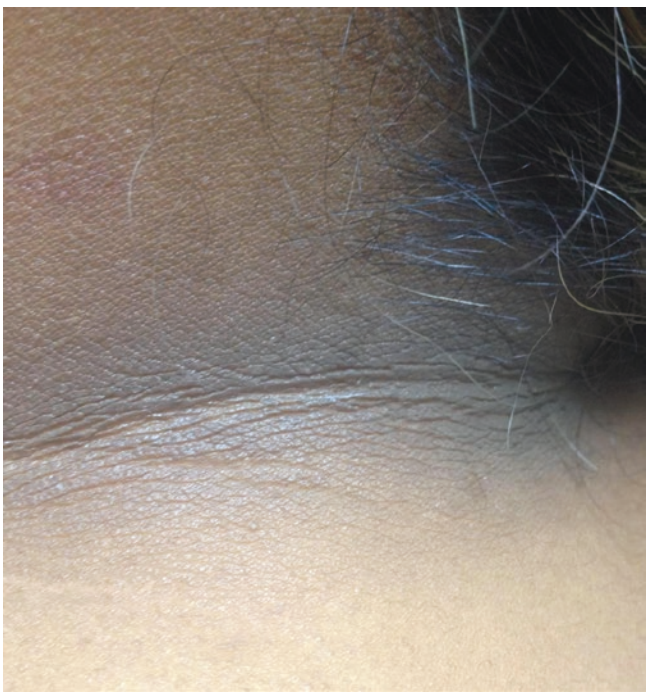


Fig. 12.10 **A** 17-year-old female with obesity and metabolic syndrome. Weight 180 lbs, height 60 in., BMI 35th percentile, blood pressure 140/90 mmHg. She has poorly defined, velvety hyperpigmentation of the skin around the neck

PEARLS AND PITFALLS

- Assessing growth velocity (linear growth) is as important as assessing height percentiles when assessing short stature in children.
- Bone age radiograph is a useful tool that can be used to differentiate between different causes of short stature or poor linear growth.
- Growth hormone is not the major determinant of growth in the first 4–6 months of life.
- Signs of congenital hypopituitarism include hypoglycemia and micropenis (in boys).
- Congenital hypothyroidism is the most common cause of preventable intellectual disability. Treatment with thyroid hormone replacement should not be delayed.
- Children presenting with normal variants of puberty (premature thelarche, premature adrenarche) need to be followed more closely than regular well-child visits, as they may be presentations for true precocious puberty in 18–20% of cases.
- Klinefelter syndrome is the most common cause of hypergonadotropic hypogonadism with a prevalence of 1 in 700 males.
- Always consider the diagnosis of Turner syndrome when evaluating a girl with short stature, as it may be the only presenting sign.
- Be aware of the different potencies of oral steroids commonly used. Hydrocortisone is equivalent to our endogenous cortisol (×1), prednisone (4 × hydrocortisone equivalent), dexamethasone (40 × hydrocortisone equivalent).
- Inhaled corticosteroids are associated with endocrine effects, including hyperglycemia, iatrogenic adrenal insufficiency, and linear growth effects.
- When interpreting an endocrine laboratory result, it is important to use pediatric reference ranges. Also, a normal value might not always be considered normal in certain scenarios. For example, a low normal TSH level with a low normal thyroid hormone level is suspicious of central hypothyroidism despite both values being in the normal range.

Acknowledgment The author gratefully acknowledges the contributions of Kuk-Wha Lee, MD, PhD, Division of Endocrinology, Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, California, USA, to the 1st edition of this chapter, many of which have been incorporated into this edition as well.

Suggested Reading

American Diabetes Association. 13. Children and adolescents: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S148–64. Review.

Anderson BJ, Edelstein S, Abramson NW, Katz LE, Yasuda PM, Lavietes SJ, et al. Depressive symptoms and quality of life in adolescents with type 2 diabetes: baseline data from the TODAY study. Diabetes Care. 2011;34(10):2205–7.

Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, ESPE-LWPES GnRH Analogs Consensus Conference Group, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009;123(4):e752–62. Review.

Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr. 2016;86(6):361–97.

Lee PA, Houk CP, Ahmed SF, Hughes IA, International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006;118(2):e488–500.

Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(11):4043–88.

Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, Pediatric Endocrine Society, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. J Pediatr. 2015;167(2):238–45.

Orthopedics

13

Amr Abdelgawad and Marwa Abdou

GENERAL CONDITIONS

Limping Child

Background

- Limping is a common complaint in pediatrics, a condition that may be due to pain, weakness, or musculoskeletal deformities
- Growing pains usually do not cause limping

Causes

- Antalgic gait (limping because of pain)
  - Osteomyelitis, diskitis, transient synovitis, septic arthritis, toddler fractures, juvenile idiopathic arthritis, pedal puncture wound
  - Slipped capital femoral epiphysis (SCFE)
  - Tumors: Ewing sarcoma, osteoid osteoma, acute leukemia, neuroblastoma
  - Legg–Calve–Perthes disease
  - Overuse syndrome (patella–femoral overload), stress fractures of the foot
  - Osteochondritis (Osgood–Schlatter disease, Sever disease)
  - Osteochondritis dissecans (of the distal femur or the talus)
- Trendelenburg gait (weak hip abductors cause shift of body weight to the weak side)
  - Developmental dysplasia of the hip (waddling gait when bilateral)
  - Chronic SCFE
  - Chronic Legg–Calve–Perthes disease
  - Muscular dystrophy (high creatine kinase [CK]), and bilateral affection)
- Circumduction (swing around and to the side)
  - Leg-length discrepancy (also toe walking or steppage gait)
  - Cerebral palsy with stiff gait
- Toe walking
  - Idiopathic toe walking
  - Leg-length discrepancy
  - Cerebral palsy (hypertonia of the gastrocnemius)
  - Muscular dystrophy (high CK) (the ankle dorsiflexors affected more than the gastrocnemius muscle)

Diagnosis

- Based on detailed history and thorough physical examination
- Narrow the differential diagnosis by classifying the limp according to:
  - Gait pattern
  - Chronicity of limping
  - Presence or absence of pain
  - Age of the child
  - Anatomic region involved

A. Abdelgawad (✉)
Department of Orthopaedic Surgery and Rehabilitation, Texas Tech University Health Sciences Center, El Paso, TX, USA

M. Abdou
Department of Pediatrics, Texas Tech University Health Sciences Center, El Paso, TX, USA

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_13

- Choice of imaging modalities and laboratories is dependent on the differential diagnosis and the most likely cause of limp; this may include:
  - Radiograph, bone scan, ultrasound, computerized tomography (CT) scan, magnetic resonance imaging (MRI)
  - Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), CK

Leg-Length Discrepancy

Background

- Up to 35% of adults have discrepancies between 0.5 and 1.5 cm
- Clinically significant leg-length discrepancies usually have an identifiable cause

Causes

- Idiopathic leg-length discrepancy
- Affection of the growth plate by trauma, infection, or tumors
- Congenital conditions, e.g., fibular hemimelia, hemihypertrophy
- Unilateral hip dislocation

Clinical presentation

- Abnormal gait
- Toe walking
- Compensatory scoliosis
- Back or hip pain

Diagnosis

- History and physical exam
  - Measure the leg length using a tape measure from the midline (umbilicus to the tip of the medial malleolus)
- Radiograph: A weight-bearing anteroposterior (AP) radiograph of both lower extremities

Management

- Observation, e.g., if the discrepancy is less than 2 cm, nonprogressive with no symptoms
- Progressively worsening leg-length discrepancies that occur after trauma and infections or from undetermined source should be referred to a pediatric orthopedics as soon as they are recognized
- Shoe lifts
- Limb shortening (for discrepancies between 2 and 5 cm)
- In skeletally immature children: Stopping the growth of the contralateral side
- Limb lengthening (usually for discrepancies > 5 cm)

Arthrogryposis

Background

- A group of syndromes associated with decreased fetal movement that results in multiple joint contracture. The most common syndrome is amyoplasia (characterized by the four limbs being involved and by replacement of skeletal muscle by dense fibrous tissue).
- The incidence is 1 in 3000.

Clinical Presentation

- History of decreased fetal movement during pregnancy
- Loss of skin creases across joints
- Severe muscle atrophy and a decrease in subcutaneous fat
- Restricted range of motion (ROM)
- Shoulders are internally rotated, elbows are extended, and fingers are thin and tapered
- Scoliosis
- Knee contractures
- Clubfoot is the most common foot deformity

Diagnosis

- Diagnosis is based on history and physical examination
- Prenatal ultrasound may suggest the diagnosis due to decreased fetal movement, micrognathia, joint contractures, and oligohydramnios

Management

- Multidisciplinary team approach: Pediatric orthopedic surgeon, geneticist, occupational and physical therapists
- Patient-specific equipment to help the patient perform his/her daily activities (e.g., specific utensils, patient-specific walker)
- Surgical treatment for joint contracture

Polydactyly of the Hand

Background

- Definition: Presence of an extra digit (or duplication)
- The most common congenital digital anomaly of the hand and foot
- A common form is an extra thumb (radial polydactyly or preaxial polydactyly), more common among Caucasians (Fig. 13.1)
- Ulnar (postaxial) polydactyly is usually a small, poorly formed, extra digit attached by a thin stalk of soft tissue (Fig. 13.2). More common among African Americans
- It may appear in isolation or in association with other birth defects. Isolated polydactyly is often autosomal dominant or occasionally random, while syndromic polydactyly is commonly autosomal recessive

Diagnosis

- About 15–20% of children born with polydactyly have other congenital anomalies, usually as a part of a defined syndrome (more common among preaxial polydactyly). Hand postaxial polydactyly is less often associated with other congenital anomalies.

Treatment

- Unless there is a clear family history of isolated polydactyly, any newborn with polydactyly should be investigated for the presence of associated anomalies.
  - Thorough medical examination and genetic workup in these patients are recommended
- Postaxial polydactyly in black children does not need further workup
- Surgical removal: For small rudimentary ulnar polydactyly attached by a thin stalk, the

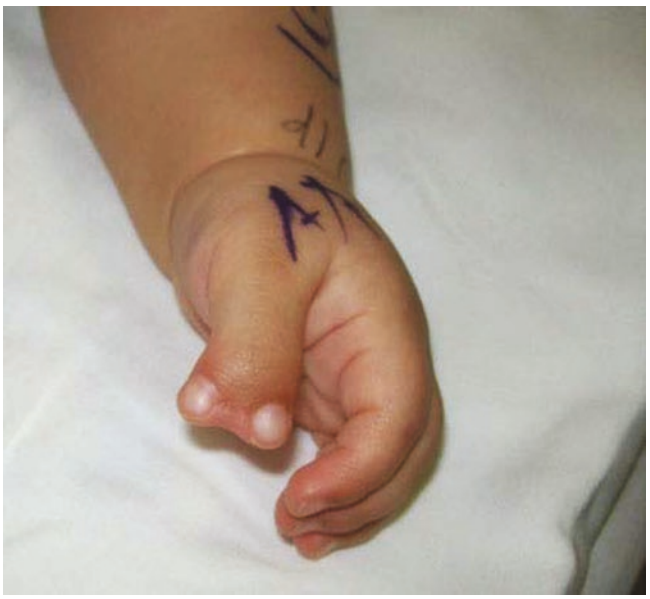


Fig. 13.1 Thumb polydactyly. A 1-year-old boy with radial polydactyly

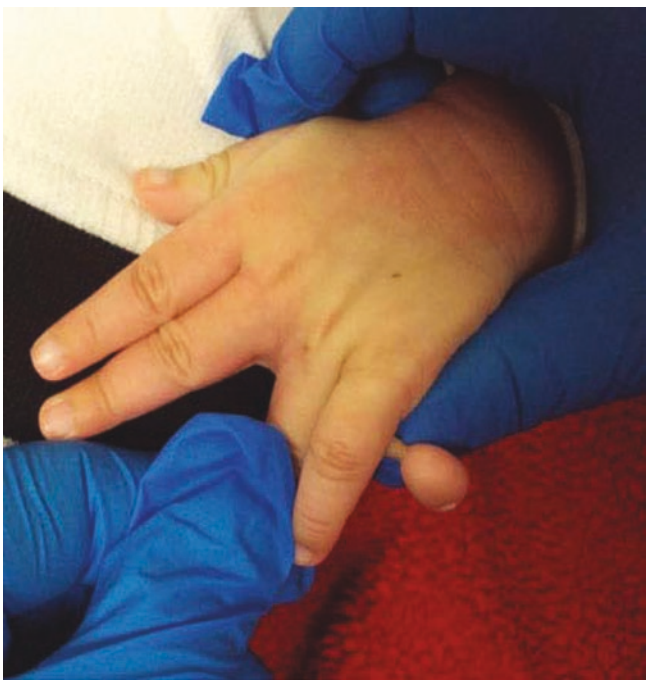


Fig. 13.2 Ulnar polydactyly. An extra small digit on the ulnar side of the hand attached to the hand with a stalk

base can be tied with a suture in the newborn period, and it will fall off spontaneously.
- For more developed extra digits, radial polydactyly, or polydactyly in older children: Orthopedic referral for surgical excision

Viral Myositis

Causes
- Viral infections, e.g., influenza virus infection

Clinical presentation
- Muscle weakness and tenderness

Diagnosis
- Elevated creatinine kinase

Treatment
- Supportive

BONE AND JOINT INFECTION/ INFLAMMATION

Transient Synovitis

Background
- Nonspecific inflammation of the joint (may be related to viral infection or trauma)

Diagnosis (transient synovitis of the hip joint)
- Variable clinical pictures; hip pain, limping, inability to bear weight on the affected side, or complete rigidity
- Markers of infection: Normal to mildly elevated
- Low-grade fever can be seen in some cases

Treatment
- NSAIDs, rest

Septic Arthritis

Background
- Bacterial inflammation of the synovium of the joint
- The most common route by which the bacteria enter a joint is by hematogenous spread to the synovium
- Most common organism in general is *Staphylococcus aureus*
- In newborns, group B streptococcus is more common
- In sexually active adolescents, *gonococcus* is the most common organism
- *Kingella kingae* bacteria is a common cause of musculoskeletal infections in young children less than 5 years old
- Most commonly affected joints: Hip, shoulder, and knee

Diagnosis
- General signs of infection (fever, chills)
- Swelling (effusion), rigidity of the joint (very limited ROM), tenderness, inability to bear weight with lower extremity joints
- Elevated markers of infection (white blood cell count [WBC], ESR, CRP)
- Joint aspiration (arthrocentesis/ultrasound-guided aspiration of the joint fluid) for Gram stain, culture, and cell count (cell count > 50,000/mL is indication for septic arthritis)

Treatment
- Septic arthritis is an urgent surgical condition. Urgent orthopedic consult is needed for urgent irrigation and debridement of the joint

Antimicrobial management of pyogenic arthritis
- If methicillin-resistant *S. aureus* (MRSA) is suspected, e.g., history of hospitalization, contact with MRSA cases, and recurrent tissue abscesses or positive nasal MRSA testing: Best initial IV empiric antimicrobials are
  - Clindamycin
  - Vancomycin
- Methicillin-sensitive *S. aureus* cases:
  - IV cefazolin
- Cases of *K. kingae*:
  - Third-generation cephalosporins (e.g., ceftriaxone) are effective

Table 13.1 Differentiation between septic arthritis of the hip and transient synovitis

	Septic arthritis	Transient synovitis
Fever	Usually present	Normal or mild elevation
ESR, CRP, WBC	Usually elevated	Normal or mild elevation
Inability to walk	Common	Rare
Aspiration	Positive for Gram stain +/− culture	Negative for Gram stain and culture
	Cell count > 50,000/ml	Cell count < 50,000/ml
Blood culture	May be positive	Negative

From Abdelgawad and Naga [3], with permission
ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *WBC* white blood cell count

- Neonates with septic arthritis must be covered for group B streptococcal disease and enteric Gram-negative rods in addition to *S. aureus*
  - For example, nafcillin with either gentamicin or cefotaxime

How to differentiate between transient synovitis and septic arthritis of the hip joint (Table 13.1) [1]
Modified Kocher Criteria

- History of fever > 38.5C
- Inability to bear weight on the affected limb
- ESR > 40 mm/h
- WBC > 12,000 cells/mL
- CRP level of more than 20 mg/L
- The more criteria the child has, the more likely the diagnosis of septic arthritis

Arthritis associated with rheumatic fever (Table 13.2)

- Arthritis due to acute rheumatic fever is very painful and has a migratory nature (joint will stay swollen for about 12 h, and then another joint will become symptomatic while the symptoms of the first joint subsides)
- Patient must meet the criteria for the diagnosis of acute rheumatic fever (see Chap. 19 "Cardiology").

Table 13.2 Difference between septic arthritis, arthritis due to rheumatic fever, and juvenile rheumatoid arthritis

Septic arthritis	Arthritis due to rheumatic fever	Juvenile rheumatoid arthritis
Acute onset	Acute onset	Chronic > 6 weeks
Staphylococcus aureus most common cause	Post-streptococcal infection	Autoimmune disease
Painful, limited range of motion	Very painful and migratory	Joint swelling and limping
Usually one joint ([a])	More than one joint	Usually more than one joint
Urgent surgical drainage/irrigation and antibiotics	Treatment of acute rheumatic fever	Anti-inflammatory (see Chap. 15, "Rheumatology")

[a]Multiple joint involvement is uncommon but occurs in up to 50% of *Neisseria gonorrhoeae* infections

Acute Hematogenous Osteomyelitis

Background

- Acute bacterial infections of the bone (mainly metaphysis of long bones)
- *S. aureus* is the most common organism
- Group B streptococcus and *Escherichia coli* are common in neonates. *Pseudomonas* is common in osteomyelitis after puncture wound through tennis shoes
- *K. kingae* is becoming an increasingly identified cause in children less than 5 years old

Diagnosis

- General signs of infection (fever, chills)
- Swelling, tenderness, and redness over the affected bone
- Nearby joint is mildly swollen; however, movement of the joint is largely preserved
- Elevated markers of infection (WBC, ESR, CRP)
- Radiographs are normal in the first 10–14 days and then show periosteal reaction
- MRI: Very sensitive, positive early in the disease; can show development of subperiosteal abscess

- Bone scan: Positive early in the disease process; the affected area will appear "hot" in the scan
- Blood culture: Positive in 50% of cases
- Bone aspiration for Gram stain, culture, and pathology

Treatment

- Osteomyelitis is a medical condition
  - Antibiotics should be given according to sensitivity studies (either blood culture or bone biopsy cultures) and according to organism sensitivity prevalence in the community
  - Appropriate antimicrobial therapy (see treatment of septic arthritis)
- Indication for surgical debridement (orthopedic consultation):
  - No improvement after 36 h of antibiotic administration
  - Development of subperiosteal abscess
  - Extension to nearby joint

Diskitis and Vertebral Body Osteomyelitis

Background

- Diskitis is an inflammation of the intervertebral disk usually seen in toddlers. It occurs most commonly in the lumbar vertebrae
- Vertebral body osteomyelitis is an inflammation of the vertebral body; usually starts at the vertebral end plates
- The distinction between diskitis and vertebral osteomyelitis is difficult, and most cases will have some affection of both the intervertebral disk and the vertebral body
- Etiology: Hematogenous spread. *S. aureus* is the most common organism isolated

Diagnosis

- Back pain
- Limping and refusal to walk (especially in toddlers who may not be able to communicate the fact of having back pain)
- Mild or no fever
- Paraspinal muscle spasm
- Flexion of the spine compresses the anterior element and causes discomfort (child will refuse to pick up an object from the ground; instead, he/she will flex hips and knees, not the back)
- Older children might have fever and abdominal pain
- Laboratory: CBC may remain normal. ESR and CRP are usually elevated
- Image-guided biopsy from the affected area for culture
- Radiographs: PA and lateral radiographs of the thoracolumbar spine is the first image to be ordered when the condition is suspected. Characteristic finding often takes 2–3 weeks to show these changes: narrowing of the disk space
- MRI: Most sensitive imaging study. Becomes positive early in the disease process
- Technetium bone scan: Hot spot in the affected disk

Treatment

- Start antibiotics covering *for S. aureus*, then according to culture results. Length of therapy is 4–6 weeks.
- Rest, analgesic, and immobilization in spinal orthosis
- Surgical treatment is rarely required.

NECK DISORDERS

Torticollis

Background

- Clinical finding of tilting the head to one side in combination with rotation of face to the opposite side (Fig. 13.3)
- May be associated with tight intrauterine space and other conditions that are related to the same pathology of tight uterine cavity (e.g., congenital dysplasia of the hip or metatarsus adductus)

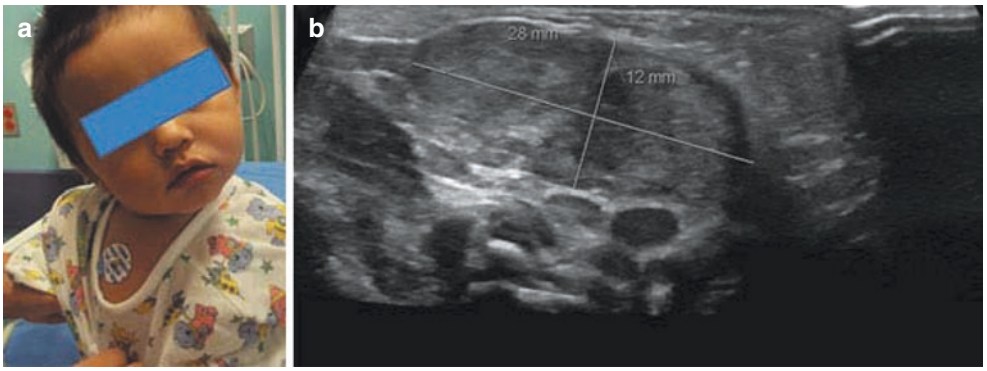


Fig. 13.3 Torticollis. A 1-year-old boy with congenital muscular torticollis. (**a**) Note the child's head is tilted to the right (the right ear is close to the right shoulder) with the face and chin directed to the left side. Patient has tight sternomastoid on the right side. (**b**) Ultrasound showed fibrotic mass in the sternomastoid (2.8 × 9 × 1.2 cm)

- Orthopedic causes of torticollis include:
  - Congenital muscular torticollis, C1–C2 subluxation, and upper cervical spine anomalies
  - Congenital muscular torticollis is the most common cause of torticollis due to fibrosis of the sternomastoid muscle.
  - May be related to birth injury or malformation within the muscle (see Fig. 13.3)
- Non-orthopedic causes of torticollis include:
  - Sandifer syndrome (gastroesophageal reflux, hiatal hernia)
  - Neoplasm (posterior fossa tumor and soft tissue tumor)
  - Infection (retropharyngeal abscess)
  - Ocular
  - Neurological (syringomyelia and Arnold–Chiari malformation)
  - Dystonic drug reaction (metoclopramide)
- Imaging: Radiography and CT of the cervical spine. MRI: If neurological cause is suspected
- Ultrasound helps to differentiate congenital muscular torticollis from other pathologies
- Ophthalmology and neurology consult may be needed if no identifiable cause can be found

Congenital Muscular Torticollis

- Child will have head turned to one side in combination with rotation of face to the opposite side (see Fig. 13.3). Decreased neck ROM to the opposite side
- In older children with long-standing torticollis, may also present with plagiocephaly, facial asymmetry, and a unilateral epicanthal fold
- A palpable, firm mass can be present at the distal third of sternocleidomastoid muscle
- Diagnosis is based on history, physical examination, and normal radiographs
- AP and lateral cervical spine radiographs to rule out any bony malformation or C1–C2 subluxation and are necessary to confirm diagnosis before starting physical therapy

Treatment

- Congenital muscular torticollis: Aggressive physical therapy for stretching sternocleidomastoid muscle
- Referral to orthopedic surgeon:
  - If no improvement (release of muscle is indicated if no improvement after 6 months of physical therapy)
  - For those who present after 1 year of age

Klippel–Feil Syndrome

Background

- Congenital fusion of cervical vertebrae (failure of segmentation)

Diagnosis

- Clinical triad: Short-webbed neck, low hairline, restriction of neck motion (this may expose the child to increased risk of neck injuries due to decreased flexibility)
- In adulthood, patients may develop neck pain or neurological disorders as a result of disk degeneration and spinal stenosis
- Associated anomalies: Sprengel deformity (high scapula); cervical scoliosis; thoracolumbar anomalies; genitourinary system anomalies (unilateral renal agenesis, duplicating renal collecting system, horseshoe kidney); auditory system anomalies; heart and neural axis anomalies
- Imaging: Radiographs of the cervical spine (will show the vertebral fusion)
- MRI can detect neural compression or intrathecal anomalies (e.g., syringohydromyelia, diastematomyelia)
- Screening for associated anomalies, e.g., thoracolumbar radiograph, renal ultrasound

Treatment

- Most cases have near normal function and need no treatment
- If neurological or musculoskeletal problems, orthopedic referral

Sprengel Deformity

Pathology

- Congenital elevation of scapula
- Occurs more frequently in female

Clinical presentation

- Shoulder asymmetry and limited shoulder abduction
- Patients may complain of neck or shoulder pains

Associated conditions

- Presents in 35% of children with Klippel–Feil syndrome
- Anomalies in clavicles, ribs, and shoulder musculature
- Patients may present with renal anomalies or pulmonary disorders

Atlantoaxial Subluxation

Background

- Fixed rotation of C1 on C2
- Causes: Retropharyngeal irritation (Grisel syndrome), trauma, or Down syndrome

Diagnosis

- Imaging: Dynamic CT (CT with head straightforward and then rotated to right and left) will show fixed rotation of C1 on C2 that does not change with head position

Treatment:

- If subluxation is less than 1 week: NSAIDs, soft collar, and stretching exercise program. Most cases will improve
- If subluxation is more than 1 week: Orthopedic/neurosurgical referral for possible need for traction (if subluxation is 1-week to 1-month duration) or fusion of the upper cervical spine (for subluxation more than 1 month)

BACK DISORDERS

Back Pain

Background

- Common in adolescents and uncommon in young children
- Most cases of back pain in children have no identifiable cause
- The etiology can range from simple benign causes, e.g., mechanical back strain, to very serious causes, e.g., malignancies

Causes

- Infections: Diskitis, osteomyelitis
- Tumors: Osteoid osteoma or malignant tumors

- Bone cyst: Unicameral or aneurysmal
- Spine: Herniated intervertebral disc, spondylolysis, spondylolisthesis, Scheuermann kyphosis
- Mechanical: Heavy backpack, musical instrument, or poor mechanics
- Postural hump back; activity related or prolonged sitting

Clinical approach and diagnosis

- History: Fever, chills, weight loss, loss of appetite, loss of bladder or bowel control, and unrelenting pain are all red flags of serious causes
- Physical examination: Inspect the spine for any deformities, sacral dimple, or swelling; assess for leg-length discrepancies; gait observation and neurological examination

Investigations

- Depending on history and physical examination
- Best initial study is radiograph prior to any advance imaging
  - Thoracic and lumbar AP and lateral views
- Bone scan and MRI are helpful if the diagnosis cannot be made by history, physical examination, and radiographs
- Laboratory studies: CBC, ESR, and CRP if concern about infection or malignancies, urinalysis if urinary tract infection is suspected, and human leukocyte antigen (HLA)-B27 if concern about ankylosing spondylitis or Reiter syndrome

Management

- Treatment of underlying cause
- Limit backpack weight to no more than 15% of body weight or use rolling bag instead of a backpack

Spondylolysis

Background

- Spondylolysis is a bone defect in pars interarticularis of the vertebra (Fig. 13.4)

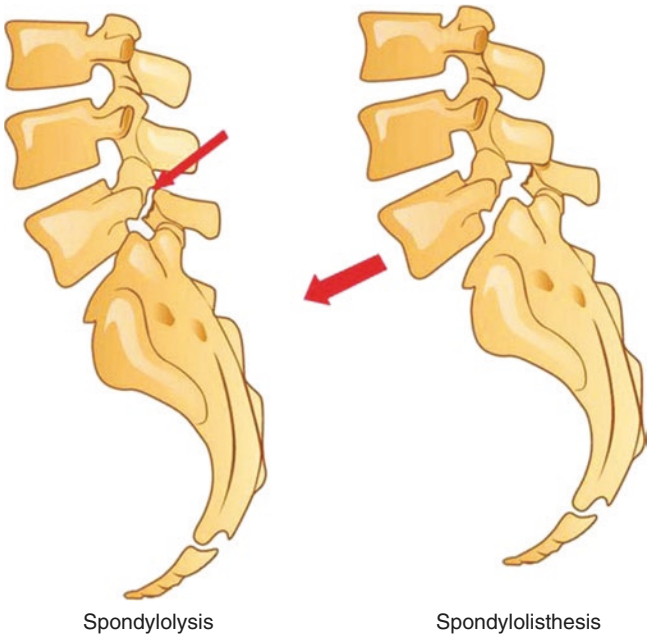


Fig. 13.4 Spondylolysis is the presence of defect in the pars of the vertebra. Spondylolisthesis is the "slippage" of the vertebra above in relation to the vertebra below

- The condition is present in about 7% of adolescents and in up to 20% of participants in sports that involve repeated extension of the back (football, gymnastics, and diving).
- Most commonly affected vertebra is L5, less common is L4

Diagnosis

- The condition is asymptomatic in the majority of cases
- The most common cause of non-muscular back pain in adolescents, low back pain that increases with extension of the spine
- Straight leg raising test: Pain in the posterior thigh but usually does not extend distal to the knee (hamstring tightness)
- Imaging:
  - Spondylolysis can be found in the radiograph as an accidental finding
  - The defect can be seen in the lateral view of the lumbar spine, but it is more obvious in the oblique view (Scottie dog with a collar appearance) (Fig. 13.5)
  - CT scan will show the defect in the pars interarticularis

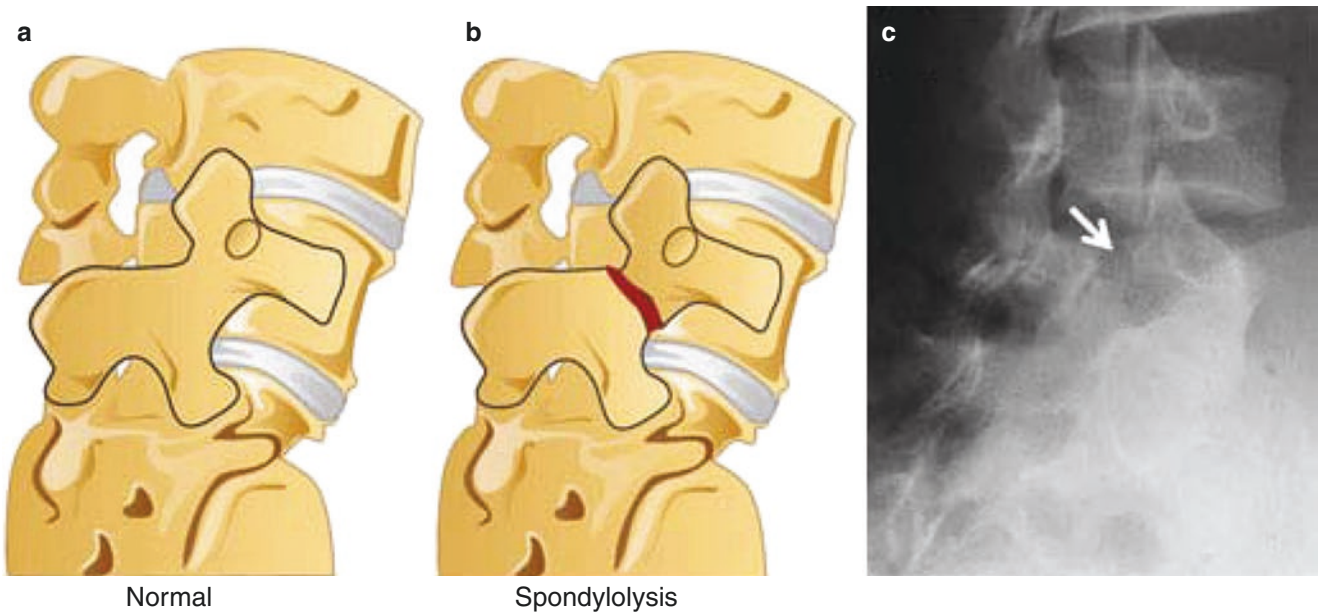


Fig. 13.5 Scottie dog collar sign. (**a**) Oblique view of the lumbar vertebrae has the shade of Scottie dog. (**b**) With spondylolysis, the defect in the pars interarticularis gives the appearance of collar in the neck. (**c**) Oblique radiograph showing the defect in the pars interarticularis and Scottie dog collar sign (*arrow*)

  - Bone scan with single-photon emission CT (SPECT) can help to differentiate acute cases from chronic ones

Treatment

- NSAIDs and rest from the sport until the pain decreases
- Adolescent can resume sport activity when they are pain-free
- Brace (lumbar corset) if the pain does not improve with rest. Acute lesion can be treated with more aggressive immobilization (thoracolumbar–sacral orthosis (TLSO)
- Orthopedic referral if no improvement (surgery is rarely indicated in spondylolysis)

Spondylolisthesis

Background

- Forward slippage of upper vertebra in relation to the vertebra below (see Fig. 13.4)
- There are two types of spondylolisthesis in children and adolescents:
  - *Dysplastic:* Due to dysplastic lumbosacral articulation, about 15% of cases
  - *Ischemic*: Due to pars defect (spondylolysis), most common type (about 85%)

Diagnosis

- Low back pain with extension activities
- Hamstring tightness
- Radiographs: Forward slippage of L5 over S1
- The degree of slippage is expressed as a percentage of the vertebral width

Treatment

- Orthopedic referral: Surgical treatment is usually needed for high slip (> 50%)
- No contact sports if the slippage is more than 50% of the vertebral width

Scoliosis

Background

- Lateral curvature of the spine associated with a rotational element
- Types of scoliosis:
  - *Congenital*: Due to bony deformity (vertebral column or chest wall)
  - *Neuromuscular:* Due to neuromuscular causes (e.g., cerebral palsy, high-level spina bifida, traumatic spinal cord injury, muscular dystrophies)
  - *Syndromic:* Almost all syndromes can be associated with scoliosis (e.g., dysplasias,

connective tissue disorders, e.g., Marfan syndrome, osteogenesis imperfecta, Prader–Willi syndrome, neurofibromatosis)
– *Idiopathic:* Most common cause. No underlying cause can be identified. Idiopathic scoliosis is further classified according to the age of onset into:
  - Infantile (scoliosis starts in the first 2 years of life)
  - Juvenile (starts between 3 and 9 years old)
  - Adolescent (starts at or after the age of 10 years), which is the most common type (adolescent idiopathic scoliosis)

Adolescent Idiopathic Scoliosis (AIS)

Background

- The condition runs in families (genetic predisposition). More common in girls
- The curve continues to progress as long as the child is growing. At the end of skeletal growth, most curves will stop progression except for large curves
- The curve of the AIS progresses maximally in the period of "peak height velocity" or "rapid growth phase." This period is 1 year before menarche age in girls

Diagnosis

- The condition is usually asymptomatic
- In advanced condition, the deformity can become more obvious:
  – Unequal shoulder level, unequal breast sizes, and leaning toward one side
- Pain is not a symptom of AIS. If there is pain, MRI is recommended
- Physical exam: The ADAM forward-bending test will show thoracic hump
- Motor, sensory, and reflexes of the lower extremities are normal
- Scoliometer (a leveling assessment device used to objectively assess if one side of the body is higher than the other side with forward-bending) will show 7° or more of rotation (an indication for referral to orthopedic surgeon) (Fig. 13.6)

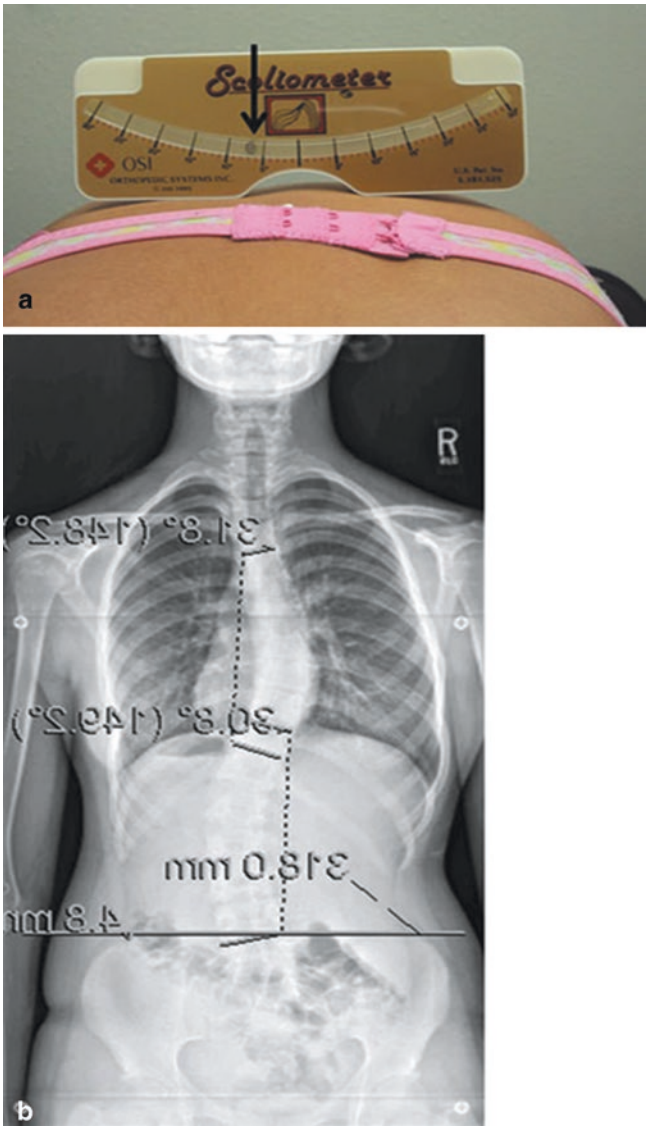


Fig. 13.6 Scoliometer. A 14-year-old girl with adolescent idiopathic scoliosis. **(a)** Scoliometer shows 7° of asymmetry (*arrow*). **(b)** Radiograph shows 31° at mid thoracic level

- Radiographs: The curve of the scoliosis is measured with Cobb angle (see Fig. 13.6). The typical curve is right thoracic (convexity is toward the right)
- Risser stage indicates the stage of skeletal maturity (Fig. 13.7). It depends on the ossification of the iliac apophysis, which proceeds from lateral to medial

Treatment

- Indication for referral to orthopedic surgeon:
  – Curves more than 20°
  – Curves more than 7° rotation by scoliometer

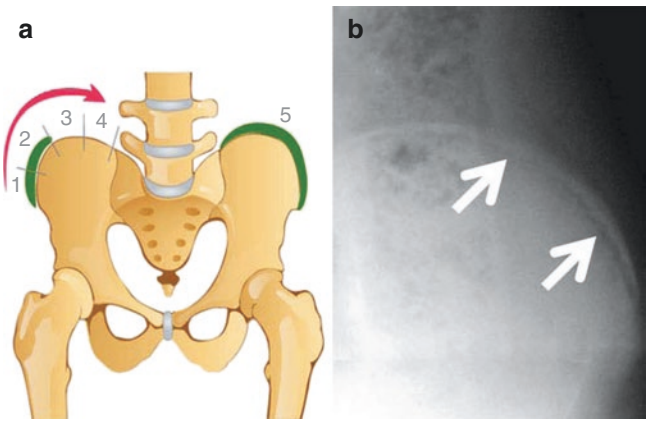


Fig. 13.7 Risser sign. Fusion of the iliac apophysis proceeds from lateral to medial. Complete fusion indicates Risser stage 5. Radiograph shows Risser stage 4 (the apophysis is ossified from medial to lateral but still not fused with the iliac bone; *arrows* point to the open growth plate)

- Indications for obtaining MRI for patient with AIS:
  - Pain
  - Left thoracic curves
  - Abnormal neurological exam
  - Infantile and juvenile scoliosis (curves that develop before the age of 10 years; due to high incidence of intrathecal anomalies, e.g., syringomyelia)
- Indications for bracing:
  - Patients with significant skeletal growth remaining and more than 5° of curve progression
  - Curves more than 25°
- Indications for surgery
  - Thoracic curves of more than 50° in skeletally mature children
  - Thoracic curves of more than 45° in skeletally immature children

Scheuermann Kyphosis

Background

- Juvenile developmental disease with increased thoracic or thoracolumbar kyphosis due to structural deformity of the spine with increased anterior wedging of the vertebrae
- Pathology: Osteochondritis of the growth plate of the vertebra. This will cause abnormal growth of the vertebra with anterior wedging
- More common in adolescent boys

Diagnosis

- Deformity (bent back deformity). The deformity is fixed and cannot be corrected by straightening the back (in contrast to postural kyphosis)
- Mid-back pain
- Neurological exam of the lower extremity: Usually normal (rarely, with advancing disease, neurological deficits can occur in lower extremities)
- Lateral radiograph of the spine shows increased thoracic kyphosis with minimum of three consecutive vertebrae of more than 5° anterior wedging (Fig. 13.8)

Treatment

- Physical therapy: Thoracic extensor strengthening and hamstring stretching exercises
- Refer to orthopedics: Bracing for curves less than 70° if the child still has more than 2 years of skeletal growth. For curves more than 70°, possible surgical treatment to correct the deformity
- Most important surgical indication is esthetic—unacceptable appearance
- Persistence of back pain and neurological manifestation are other indications for surgery but less common

HIP DISORDERS

Developmental Dysplasia of the Hip (DDH)

Background

- Ranges from complete dislocation of the hip joint (the femoral head is outside the acetabulum) to dysplasia of the acetabulum (shallow acetabulum)
- More in: Female, firstborn, family history, breech presentation

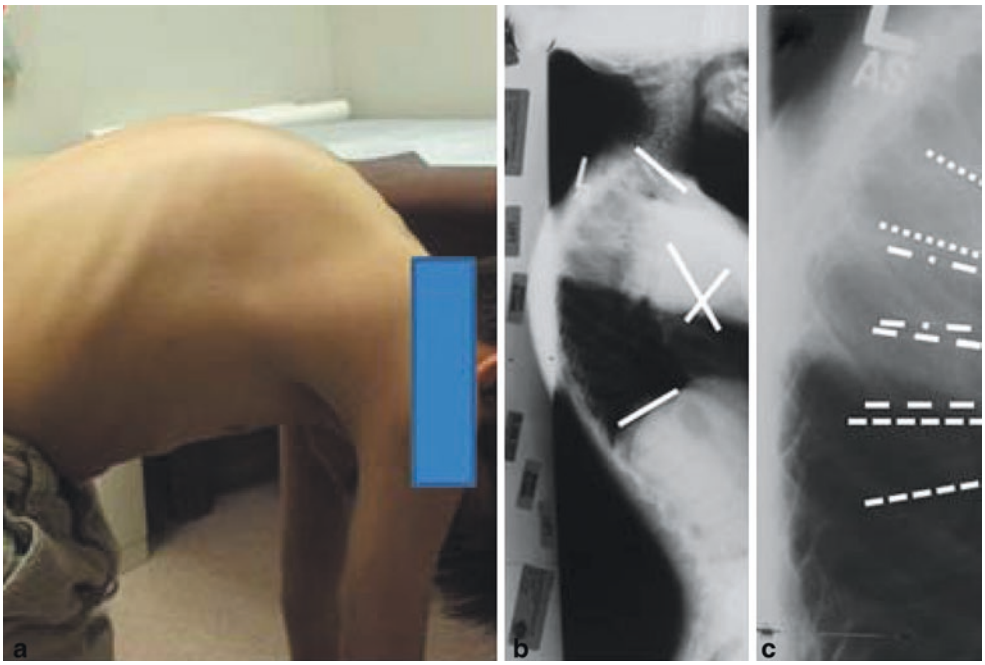


Fig. 13.8 Scheuermann kyphosis. (**a**) A 14-year-old boy with increased thoracic kyphosis. (**b**) Lateral thoracic radiograph shows thoracic kyphosis between T1 and T12 of 67 degrees. (**c**) Close view of the vertebrae shows anterior wedging of the vertebra (anterior part of the vertebra narrower than the posterior part)

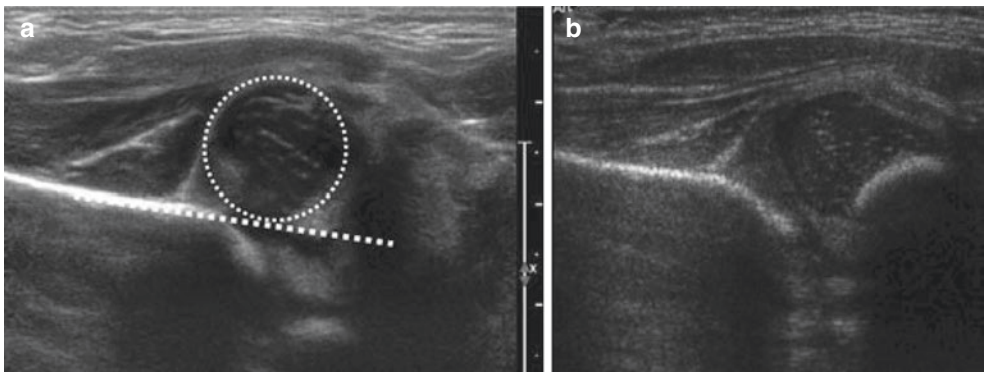


Fig. 13.9 Dynamic ultrasound. Assessment of the hip position by ultrasound during various positions. (**a**) To the left with hip adduction, the femoral head (*dotted circle*) lies outside a line along the pelvic bone (*dotted line*). (**b**) With hip abduction, partial reduction occurs

- Can be associated with other conditions related to tight intrauterine position (e.g., torticollis and metatarsus adductus)

Diagnosis

- In neonatal period: Screening all newborns by Barlow or Ortolani test
- Hip ultrasound (before 4 months of age) or plain radiographs (after 4–6 months) will show the dislocation and/or dysplasia (Figs. 13.9 and 13.10)
- Females with breech presentation or positive family history should be screened using imaging study in addition to the physical exam
- Whether by risk factors or by suspicious physical examination, it is best to defer diagnostic hip ultrasound until age 6 weeks
- Toddlers and children: Limping (unilateral cases) or waddling gait (bilateral cases); limb length discrepancy (dislocated side is shorter); limited abduction of the affected side
- The limb length discrepancy can be detected by Galeazzi sign (flexing the hip and knee and comparing the knee height) (Fig. 13.11) [1]

Risk factors for which the pediatrician *may* consider an imaging study in the child with a normal screening with physical examination are [2, 3]:

- Breech position in the third trimester—both males and females
- Family history of DDH

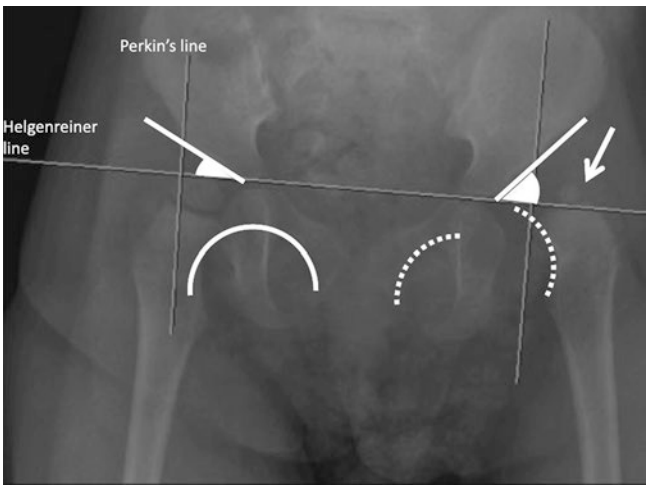


Fig. 13.10 Anteroposterior pelvis radiographs of a 14-month-old girl with developmental dysplasia of the left hip. The radiograph shows the ossific center on the left side (*arrow*) smaller than the right side and lying in the *upper lateral quadrant* of the crossing two lines (Hilgenreiner and Perkins; the normal right side lies in the *lower medial quadrant*). The Shenton line (*curved line* across the obturator foramen and lower border of the neck) is intact on the right side (*continuous curved line*) and broken on the left side (*curved dotted line*). The dislocated side shows increased acetabular index (the angle between the Hilgenreiner line and line from the triradiate to the lateral part of the acetabulum)

- History of abnormal hip physical examination in the neonatal period, which subsequently normalizes
- History of improper swaddling:
  - If parents choose to swaddle their infants, encourage hip-healthy swaddling that allows freedom of hip motion and avoids forced position of hip extension and adduction

Treatment

- Orthopedic referral (Pavlik harness for children less than 6 months; closed reduction and casting for children 6–18 months; open reduction for children > 18 months)

Legg–Calve–Perthes Disease

Background

- Avascular necrosis of the head of the femur in a growing child (skeletally immature)
- Self-limiting disease; the pathological process usually takes about 24–36 months

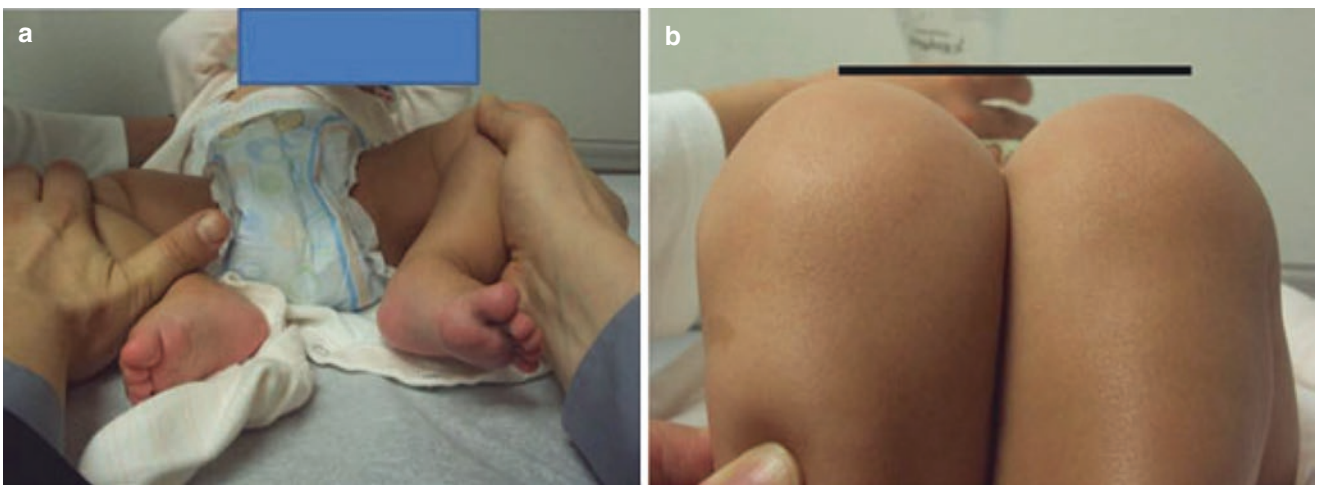


Fig. 13.11 A 10-month-old infant with developmental dysplasia of the left hip. (**a**) Notice the limited abduction of the left hip. (**b**) Galeazzi sign: While flexing both legs and putting the feet together, the knee on the short (left, dislocated) side will be at a lower level compared to the right; this indicates limb length discrepancy, with the dislocated side shorter than the normal side

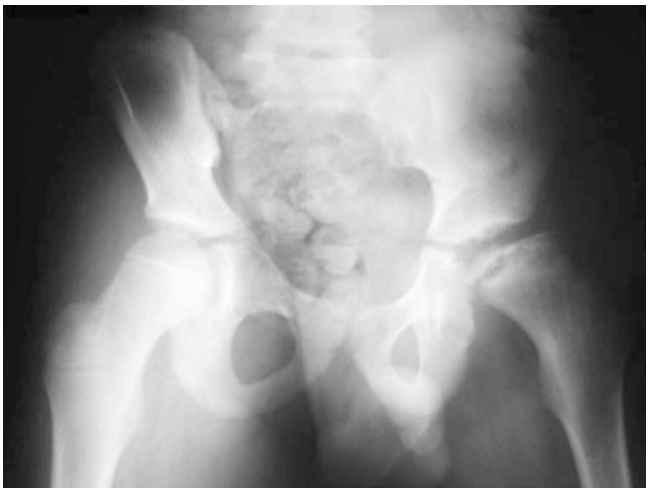


Fig. 13.12 An 8-year-old boy with 1-year history of Perthes disease in the left hip

Diagnosis

- More in boys between the ages of 4 and 8 years
- Limping
- Hip pain or knee pain (*always consider hip etiology in any child presenting with limping and knee pain)*
- Hip radiographs will show the collapse and increased density of the femoral head (Fig. 13.12)

Treatment

- Orthopedic referral
- Symptomatic treatment (mostly in children less than 6 years), through avoiding sports and the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) for pain, or surgery (pelvic or femoral osteotomy)

Slipped Capital Femoral Epiphysis (SCFE)

Background

- Displacement of the proximal femoral metaphysis in relation to the capital (proximal) femoral epiphysis (Fig. 13.13)
- Most cases are idiopathic; some cases are related to endocrinopathies (hypothyroidism or hypopituitarism) or renal osteodystrophy

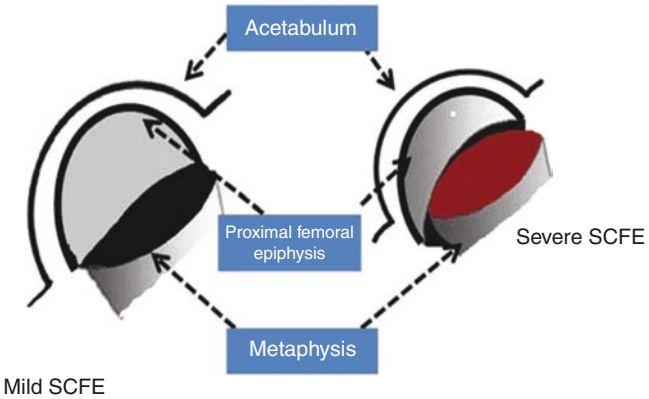


Fig. 13.13 The pathology of slipped capital femoral epiphysis (SCFE) . The proximal femoral epiphysis is contained in the acetabulum and does not move, while the slippage occurs when the metaphysis starts to move in relation to the epiphysis

- Can be stable (patient is able to bear weight on the affected side) or unstable (patient is not able to bear weight on the affected side with or without crutches)
- Can lead to avascular necrosis of the femoral head due to stretching of the vessels supplying the femoral head by the displacement of the proximal metaphysis

Diagnosis (Table 13.3)

- More in obese African American boys between 12 and 14 years
- Clinical presentation: Hip or knee pain (referred pain); limping, external rotation of the affected extremity
- Hip radiographs will show the displacement (Fig. 13.14)

Treatment

- Admission to the hospital and urgent orthopedic consult

KNEE PAIN AND INJURIES

Meniscal Injury of the Knee

Background

- Anatomy of the menisci: Two cartilaginous crescent-shaped structures that act like a cushion inside the knee (Fig. 13.15)

Table 13.3 Difference between developmental dysplasia of the hip (DDH), Legg–Calve–Perthes disease (LCPD), and slipped capital femoral epiphysis (SCFE)

DDH	LCPD	SCFE
Toddler < 3 years	3–10 years	> 10 years
Painless limp (infants and toddlers)	Painful limp	Painful limp
Older children: vague activity-related discomfort due to leg-length discrepancy	Hip pain or knee pain	Hip pain or knee pain
Positive Ortolani and Barlow signs	Limited hip motion	Limited hip motion
Galeazzi positive (unilateral)	Decreased internal rotation and abduction	Decreased internal rotation
Waddling gait (bilateral)		
Hip ultrasound < 6 months	Pelvis radiograph: Anteroposterior (AP) and frog-lateral views	Pelvis radiograph: AP, and frog-lateral views
Pelvis radiograph > 6 months		
Referral to orthopedic	Referral to orthopedic	Urgent referral to orthopedic

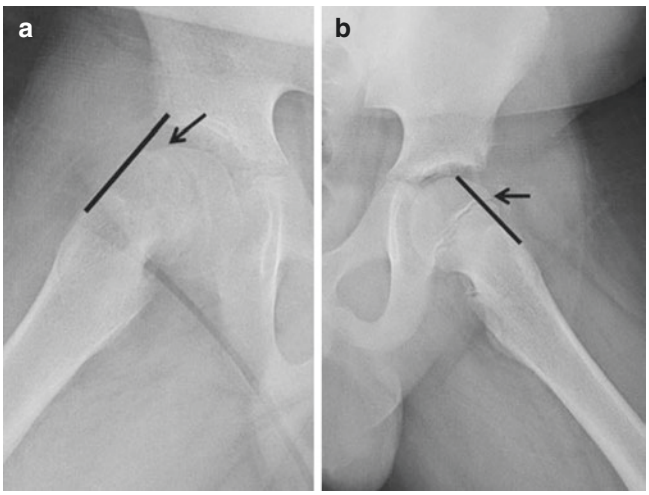


Fig. 13.14 A 13-year-old boy with right hip and knee pain of 2 weeks duration. Lateral radiographs of both hips are presented in this figure. The Klein line (the *black line*) is drawn along the anterior femoral neck. Normally (*left*), the Klein line should intersect part of the epiphysis of the proximal femur (an *arrow* is pointing to the anterior edge of the epiphysis). *Right* (slipped capital femoral epiphysis; SCFE), the Klein line does not intersect any part of the epiphysis

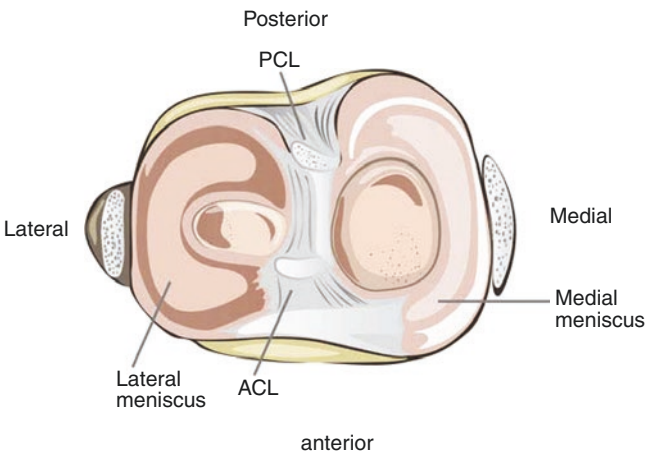


Fig. 13.15 Medial and lateral meniscus

- The medial meniscus is more prone to injury because it is more fixed to the joint capsule and more likely to be caught in between femur and tibia in case of injury
- More common in adolescents as a result of twisting injury to the knee
- Can be associated with other ligament injuries like anterior cruciate ligament (ACL) injury
- The tears are classified according to the shape and the site
  - According to the shape: Longitudinal (most common), radial, flap, or bucket handle tear (Fig. 13.16)
  - According to the site: Peripheral tear (has the highest healing potential as it has the best blood supply); middle; central (has the least healing potential due to poor blood supply)

Diagnosis

- Injury to the knee followed by pain and swelling. The swelling usually develops a few hours after the injury (in contrast to ACL injury in which the swelling develops immediately after injury)
- Locking, "catching" of the knee
- Positive McMurray sign (extension of the knee with internal and external rotation by the examiner); apply grinding (downward push on the foot with the patient lying prone and the knee flexed 90°) tests and deep squats (Fig. 13.17)

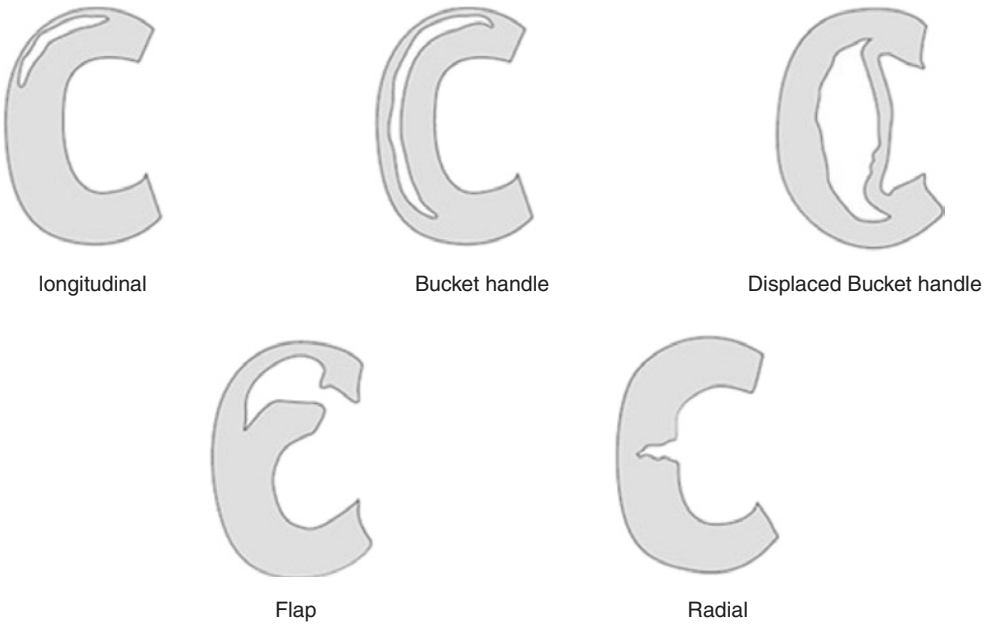


Fig. 13.16 Types of meniscal tears

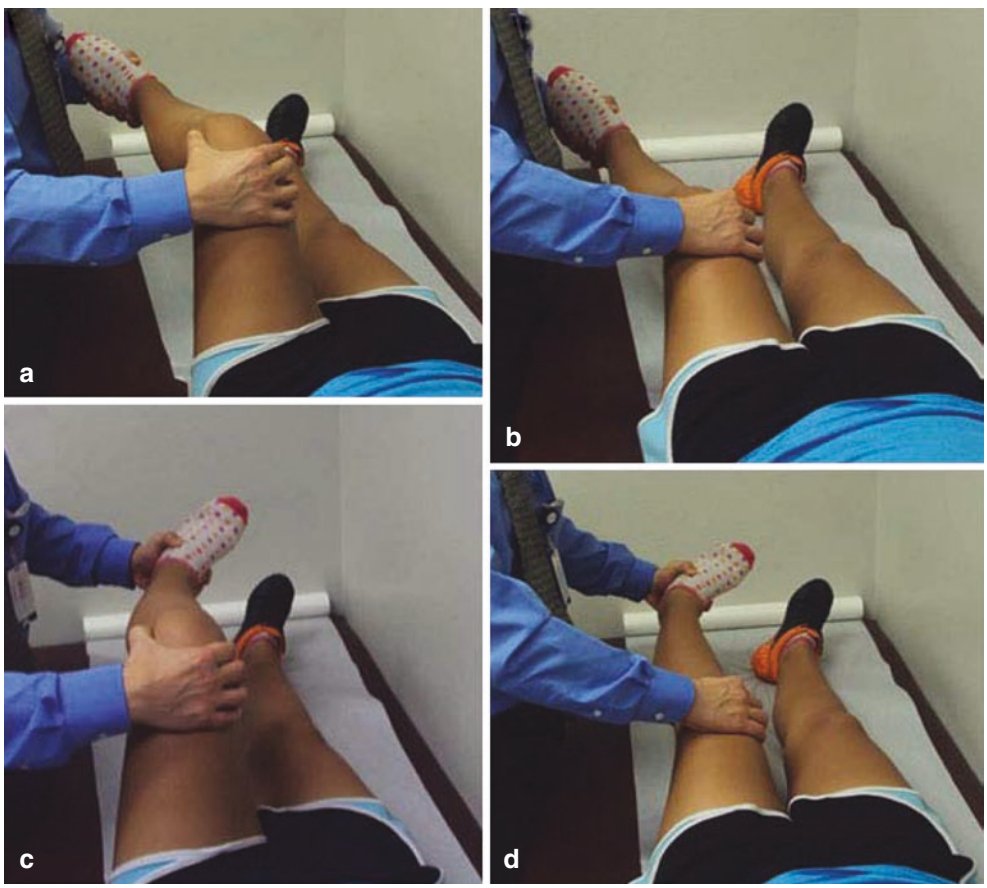


Fig. 13.17 McMurray test: (**a**) The knee is flexed with one hand holding the knee at the joint line and the other knee holding the foot. (**b**) The knee is flexed, and the leg is put in external rotation and valgus while extending the knee. (**c, d**) This is repeated with leg in varus and internal rotation. Pain or a "click" constitutes a positive McMurray test

- Plain radiographs (AP, lateral, and sunrise) to exclude fractures or other bone pathology
- MRI can detect the meniscal tear and can also show associated injuries (e.g., ACL injury)

Treatment

- Most meniscal tears in adolescents are longitudinal peripheral tear that have good healing potential (in contrary to adults in which most tears have minimal healing potentials)

- Acute management: RICE (rest, ice, compression, and elevation)
- Physical therapy for ROM exercises and strengthening
- Return to sports: Full ROM (compared to the other knee) with no pain
- Indication for orthopedic referral:
  - Failure of conservative therapy
  - Bucket handle and flap tears
  - Associated ACL injuries

Medial Collateral Ligament Injury (MCL)

Background

- Anatomy: Extends from the medial femoral epicondyle to the medial aspect of the tibia. It consists of two parts: superficial and deep
- MCL: Primary restrain of the knee joint against drifting into valgus (the tibia points laterally)

Diagnosis

- Pain in the medial aspect of the knee following valgus injury
- Instability of the knee on valgus stress
- Radiograph: AP, lateral, and sunrise view to exclude fractures
- MRI will show the injury to the medial collateral

Treatment

- Most MCL injuries can be treated conservatively: RICE, physical therapy for ROM exercises, and strengthening
- Return to sports: When the patient has full ROM with no pain

Anterior Cruciate Ligament (ACL) Injury

Background

- Anatomy: Extends from the anterior part of the tibia to posterior femoral notch. It prevents anterior displacement of the tibia on the femur
- Most common ligamentous knee injury with increasing incidence in adolescent population due to increased sports participation at younger age
- More common in adolescent females playing sports with cutting movements (e.g., soccer)
- The injury occurs secondary to direct trauma to the knee or noncontact twisting or hyperextension injury to the knee
- May be associated with injuries to medial and lateral collateral ligaments and menisci

Diagnosis

- Child will describe injury followed by "popping" of the knee and immediate swelling with inability to bear weight
- Marked swelling (hemarthrosis)
- Stressing the knee joint: Positive Lachman and anterior drawer tests; cannot be performed in the acute setting because of pain
- Imaging: AP, lateral, 20° tunnel, and sunrise radiographs to rule out fracture
- MRI is diagnostic for ACL disruption. Also assess the integrity of menisci, collateral ligaments, and chondral surfaces

Management

- Initial conservative management: Rest, ice, activity modification, bracing, and physical therapy
- Early orthopedic referral for surgical consideration: Surgical reconstruction (by graft whether autograft (from the patient him/herself) or from donor (allograft) is the standard of treatment if the patient wants to continue sport activity
- Reconstruction by graft requires drilling and passing tissues across the growth plate of the distal femur and proximal tibia, which may affect these growth plates. This is of more concern in younger children

Osteochondritis Dissecans

Background

- Affection of a piece of bone close to the articular cartilage that becomes avascular and ultimately separates from the surrounding bone
- Etiology unknown but may be related to repetitive trauma

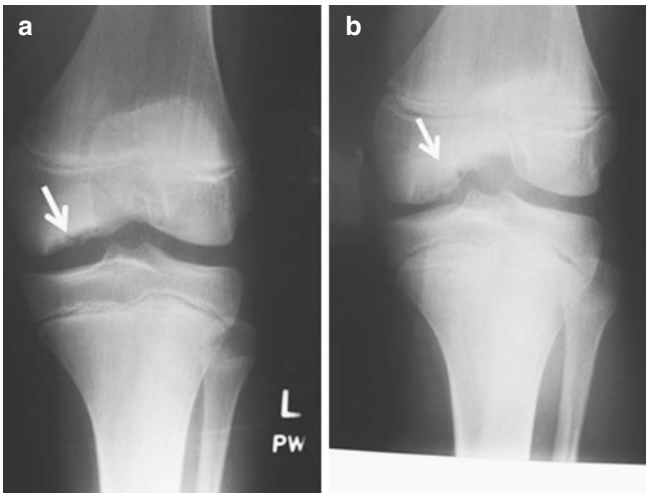


Fig. 13.18 Osteochondritis dissecans. Radiographs of left knee (**a**) anteroposterior, (**b**) notch view, showing osteochondral defect on the medial femoral condyle

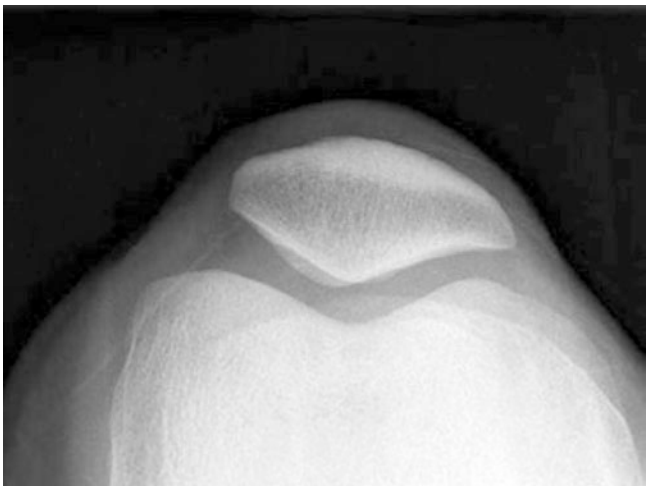


Fig. 13.19 Sunrise view can show the position of the patella in the trochlear groove. Computed tomography (CT) and magnetic resonance imaging (MRI) can better delineate the tilt of the patella and trochlear hypoplasia

- Most common site is the knee but can also occur in the ankle and elbow
- More common in adolescents

Diagnosis (Osteochondritis Dissecans of the Knee)

- Vague knee pain, more with activity
- Mild recurrent effusion
- Loss of extension or flexion if the lesion is detached and loose in the knee, blocking movement
- Radiographs: A radiolucent area may be seen surrounding the lesion. In advanced cases, the affected lesion may be fragmented and detached (Fig. 13.18)

Treatment

- Orthopedic referral. Most cases (especially in young children) will heal spontaneously without surgery

Recurrent Patellar Dislocation/ Subluxation

Background

- Patients will complain of history of repeated dislocation events (the patella will lie on the lateral side of the knee and has to be reduced back by the patient herself or someone else) or subluxation events (the patient feels that the patella is unstable and tilting toward the side, but no full dislocation)
- Common in adolescent females
- Usually associated with knee pain
- Predisposing factors for recurrent dislocation and subluxation:
  - Dysplastic trochlear groove
  - Patella alta (high-riding patella)
  - Increase Q angle (angle between pull of quadriceps muscle and patellar tendon)
  - Genu valgum
  - Increased femoral anteversion
  - External tibial torsion

Diagnosis

- General examination for signs of increased laxity (e.g., elbow hyperextension)
- Parapatellar tenderness
- Mild effusion
- Specific test for patellar stability:
  - Positive J sign: Patella will deviate laterally at the end of knee extension
  - Apprehension sign: Extension of the knee with laterally directed pressure on the patella will give positive result (apprehensive facial expression)
- Radiographs: Sunrise view will show the lateral tilt of the patella (Fig. 13.19)

Treatment

- After first dislocation: Knee immobilizer for 1–2 weeks followed by physical therapy
- Recurrent dislocation/subluxation: Therapy referral for isometric quadriceps-strengthening exercise and vastus medialis obliquus (VMO) strengthening
- Orthopedic referral: Surgery is indicated if conservative treatment fails

ANGULAR DEFORMITIES

Genu Varum (Bowleg)

Background

- Lower limb deformity in which the lower legs are pointing toward the midline (Bowleg) (Fig. 13.20)
- Common causes of genu varum in children include:
  - Physiological development up to the age of 2 years:
    - The normal alignment of children is genu varum until the age of 2 years, and then alignment changes to valgus which reaches maximum around the age of 3 years
    - The normal adult alignment (7° of valgus) is usually reached by the age 8 years
  - Blount disease (see below)
  - Rickets
  - Achondroplasia

Diagnosis

- Increase intercondylar distance (distance between the two medial femoral condyles; see Fig. 13.20)
- Radiographs will identify the underlying pathology

Treatment

- Physiological cases: No treatment needed, should improve by the age of 3 years

Indication for plain radiographs in cases of genu varum (possible need for orthopedic referral):

- Persistence of genu varum after 24 months or worsens after age 1 year
- Unilateral genu varum
- Severe genu varum (clinical angle between thigh and leg of more than 20° or intercondylar distance of more than 6 cm)
- If suspecting general medical condition (e.g., rickets)

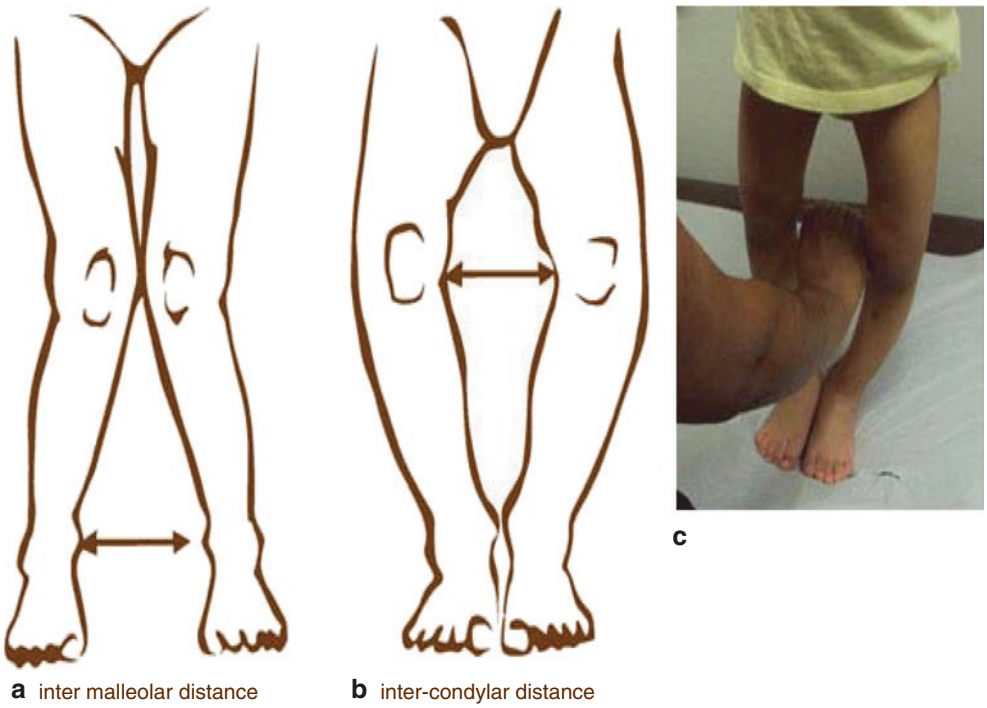


Fig. 13.20 **(a)** Intermalleolar distance. This distance increases in cases of genu valgum. **(b)** Intercondylar distance: This distance increases in cases of genu varum. **(c)** **A** 3-year-old boy with genu varum and intercondylar distance of more than handbreadth

Genu Valgum (Knock-Knee)

Background

- Lower limb deformity in which the lower legs are pointing away from the midline (knock-knee) (Fig.13.21)
- Common causes of genu valgum in children include:
  - Physiologic genu valgum (around the age of 3 years)
  - Metabolic: Rickets and renal osteodystrophy
  - Post-traumatic physeal arrest
  - Proximal tibial fractures

Diagnosis

- Increased intermalleolar distance (distance between the two medial malleoli; see Fig. 13.21)

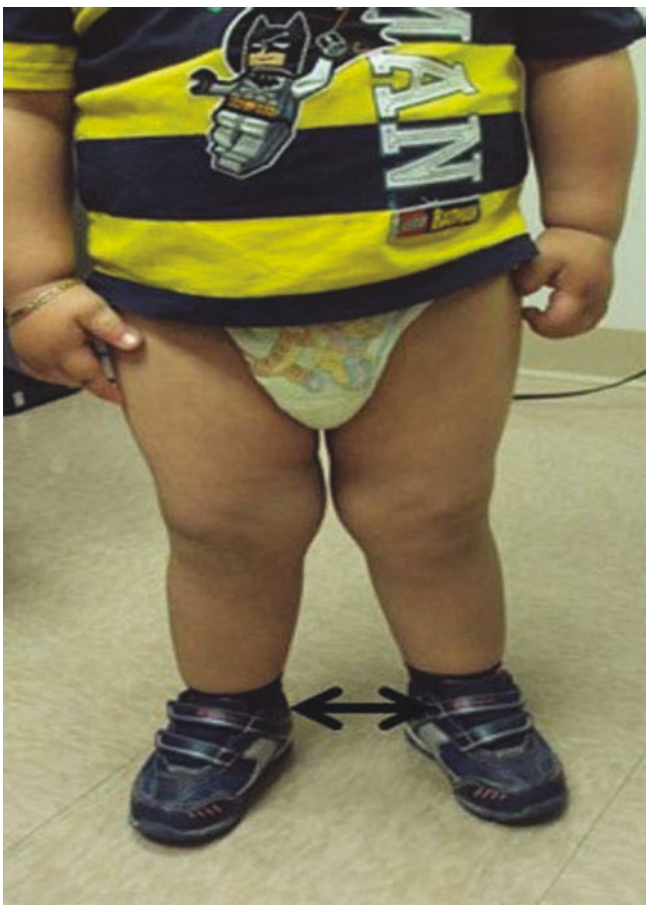


Fig. 13.21 Physiological genu valgum. A 30-month-old boy with physiological genu valgum. Notice the increased angle between the leg and the thigh and the increased intermalleolar distance (*double-headed arrow*)

- Radiographs will identify the underlying pathology

Treatment

- Physiological cases: No treatment needed, should improve by age of 8 years. Other causes of genu valgum will require orthopedic consultation

Blount Disease (Tibia Vara)

- Developmental deformity resulting from abnormal endochondral ossification of the medial aspect of the proximal tibial physis leading to varus deformity and internal rotation of tibia
- More common in obese African American children
- Types:
  - ***Infantile type***
    - Starts around 3 years of age
    - More progressive than adolescent type due to greater growth potential
    - Radiographs will show the varus deformity with medial proximal tibial growth plate abnormalities (Fig. 13.22)

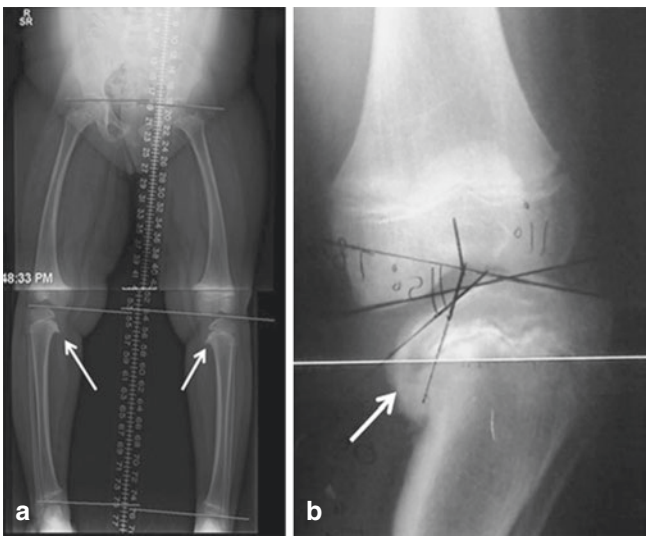


Fig. 13.22 Radiological changes in Blount disease. (**a**) Long radiographs (scanogram) of a 3-year-old girl showing the proximal tibial metaphyseal beaking (*arrow*). (**b**) A 4-year-old boy with depression of the medial tibial plateau and fusion of the growth plate on the medial side (*arrow*). Note the difference between the medial and lateral sides of the tibial growth plate

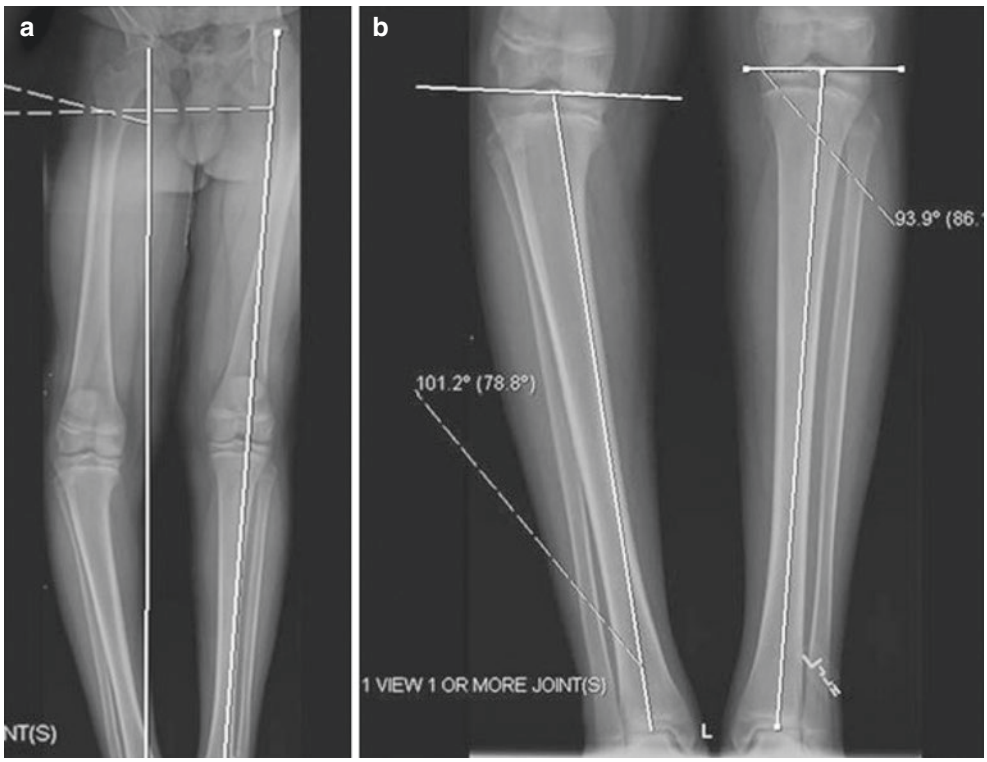


Fig. 13.23 Radiographic changes of adolescent tibia vara. A 15-year-old black male presented with unilateral adolescent tibia vara on the right side. (**a**) Scanogram shows varus alignment on the right side with the mechanical axis of the lower extremity medial to the joint. (**b**) Radiographs of the leg show varus deformity of the proximal tibia

- Treatment: Knee brace to correct varus before the age of 3 years. If no improvement or if the patient is older than 3 years, orthopedic referral for surgical treatment
- Surgical intervention is contraindicated in children younger than 2 years

– ***Adolescent type***

- Occurs in adolescents (especially obese boys) (Fig. 13.23)
- Treatment is by referral for orthopedic intervention

INTOEING

Three Main Causes

- Excess femoral anteversion
- Internal tibial torsion
- Metatarsus adductus

Femoral Anteversion

Background

- Femoral anteversion is the angle between the neck of the femur and the shaft in the sagittal plane (Fig. 13.24)
- This angle is about 40° at birth and decreases as the child starts walking. It reaches the adult normal value (about 17°) by the age of 8 years
- Diseases that affect the child's ability to walk (e.g., cerebral palsy) will result in the child continuing to have increased angle of femoral anteversion
- Excess femoral anteversion is the most common cause of intoeing between the ages of 3 and 8 years

Diagnosis

- Hip internal rotation exceeds hip external rotation (Fig. 13.25)

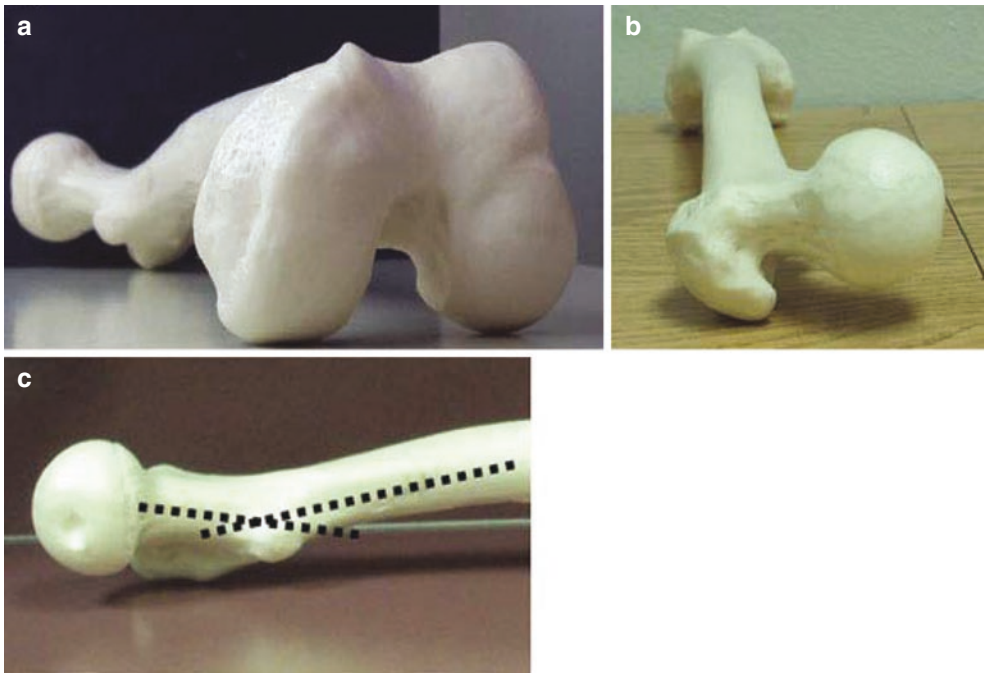


Fig. 13.24 Femoral anteversion. (**a**) The angle between the femoral shaft and the femoral neck in the sagittal planes. (**b**, **c**) Notice when the femur rests on the flat surface, the femoral head is elevated on that surface by the anteversion of the neck

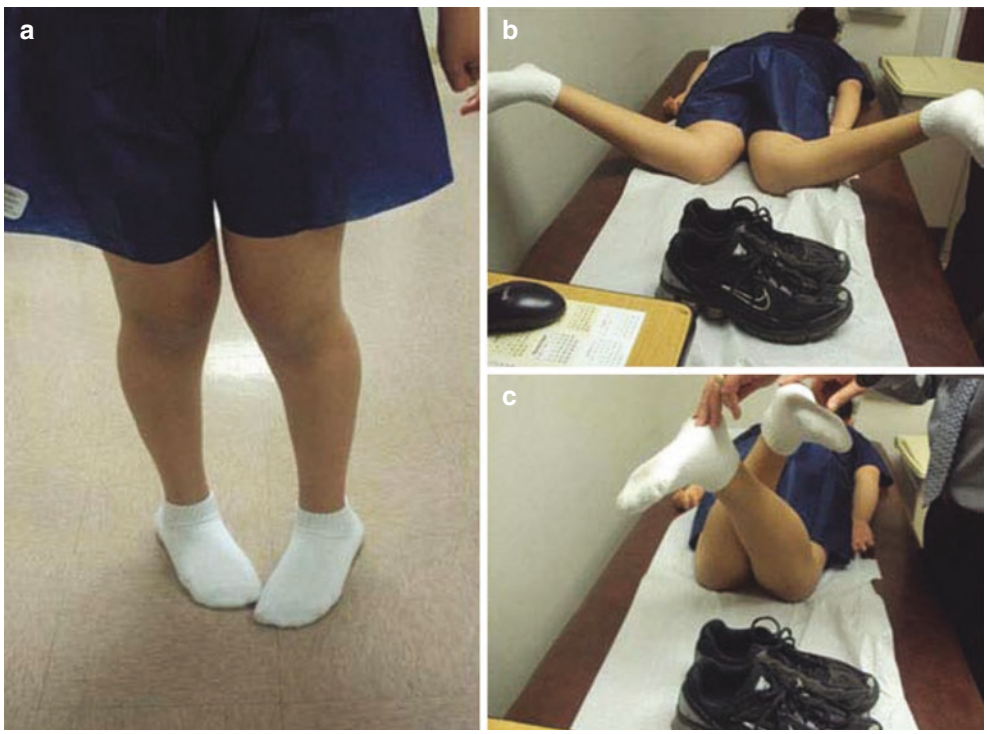


Fig. 13.25 A 12-year-old girl with severe intoeing (notice the inward position of both patellae) (**a**). Examination shows increased hip internal rotation (**b**) compared to external rotation (**c**)

Treatment

- No treatment is required, as the condition usually resolves spontaneously around the age of 8 years
- Bracing and orthotics do not change the natural history of the condition

Internal Tibial Torsion

Background

- Inward rotation of the shaft of the tibia. It is considered normal finding in newborn/ infants due to intrauterine position

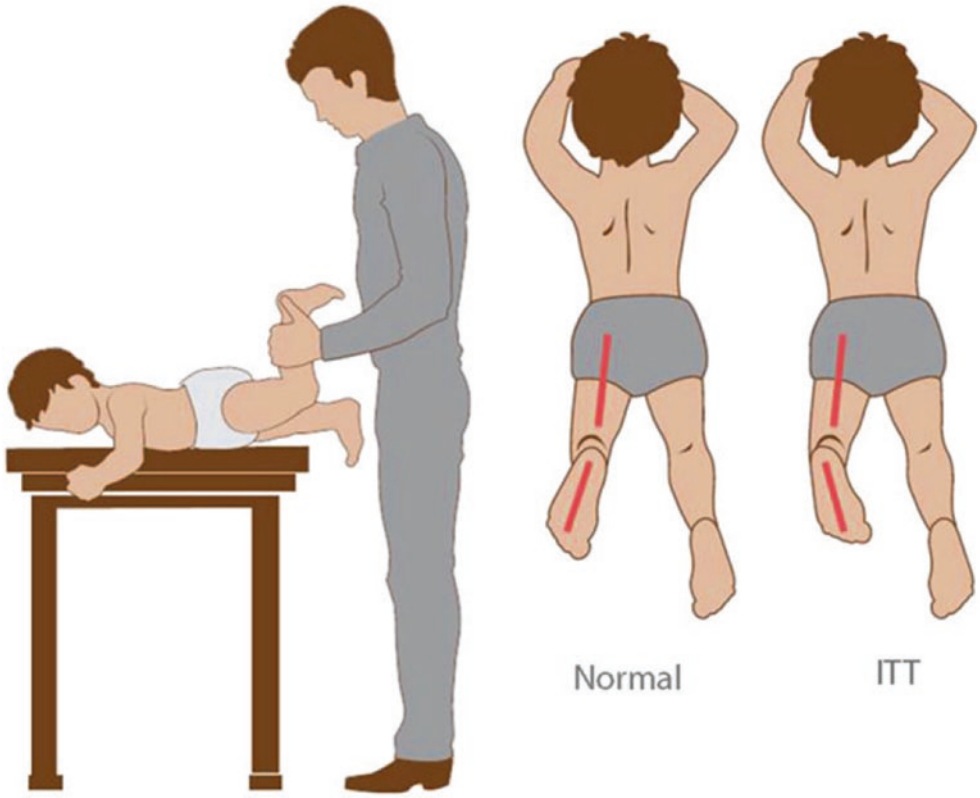


Fig. 13.26 Assessment of the tibial torsion (thigh foot angle). The child lies prone on the table, and the physician assesses the angle between the thigh and foot with the knee flexed

- Internal tibial torsion is the most common cause of intoeing in infants around the age of 2–3 years

Diagnosis

- With the child lying prone flexing the knee, the foot will be pointing inward in relation to the thigh (thigh foot angle) (Fig. 13.26) [1]

Treatment

- No treatment is required. The condition usually resolves spontaneously over the first few years of life

Metatarsus Adductus

Background

- Adduction and inward position of the forefoot compared to the heel (Fig. 13.27)
- May be related to intrauterine position and may be associated with other conditions related to uterine malposition (e.g., hip dysplasia, torticollis)

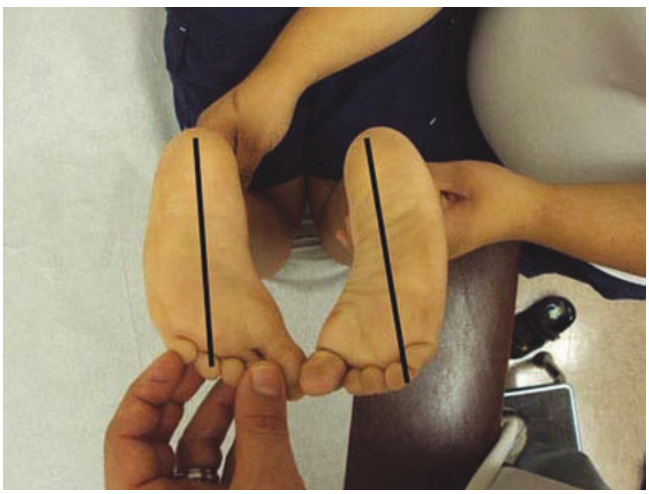


Fig. 13.27 Metatarsus adductus. A 4-year-old with moderate metatarsus adductus on the *left* side and severe on the *right* side (patient is prone with flexed knee). Notice the curved lateral border of the foot

Diagnosis

- The foot has a curved lateral border (instead of straight border)
- Differentiated from clubfoot by absence of ankle equinus (plantar flexion) and hindfoot varus (inward deviation of the heel)

Treatment

- Most infants will improve without interference
- If the condition persists beyond 6 months of age and the deformity is rigid, orthopedic referral for either serial casting or bracing. Surgery is rarely indicated

FOOT DISORDERS

Clubfoot (Talipes Equinovarus)

Background

- Complex rigid deformity of the ankle and the foot
- Unknown etiology: May be related to muscular, neurogenic, genetic, and/or connective tissue etiologies
- Affects about 1 in 1000 live births. More common in boys (2:1). 50% of cases are bilateral
- Types:
  - ***Idiopathic:*** No other congenital condition can be found. Most common type
  - ***Postural:*** Due to posture of the newborn in the uterus. The deformity can be corrected easily by the examiner. Not considered real clubfoot
  - ***Syndromic:*** Some congenital conditions are associated with clubfoot, such as arthrogryposis and diastrophic dwarfism
  - ***Neuromuscular conditions:*** Myelomeningocele and cerebral palsy

Diagnosis

- Rigid deformity (cannot be corrected by the examiner)
- Clubfoot has three main deformities (Fig. 13.28)
  - Ankle and foot equinus (plantar flexion of the ankle and the foot)
  - Hindfoot varus (inward deviation of the heel)
  - Forefoot adduction (inward position of the forefoot in relation to the hindfoot)
- Other components: High-arched foot (cavus) and internal tibial torsion of the leg
- Clubfoot is a clinical diagnosis; no radiographs are needed

Treatment

- Orthopedic referral: Two treatment options are currently utilized:
  - Serial casting: weekly change of cast
  - Physical therapy and stretching
- Early orthopedic referral is needed to ensure early start of treatment
- After correction of the foot deformity, a brace (corrective shoes with a bar in between the shoes to turn the feet outward) should be used for 2–3 years to prevent the recurrence

Calcaneovalgus Foot

Background

- A condition in the newborn in which the foot is in excessive dorsiflexion and valgus (Fig. 13.29). It is related to intrauterine position

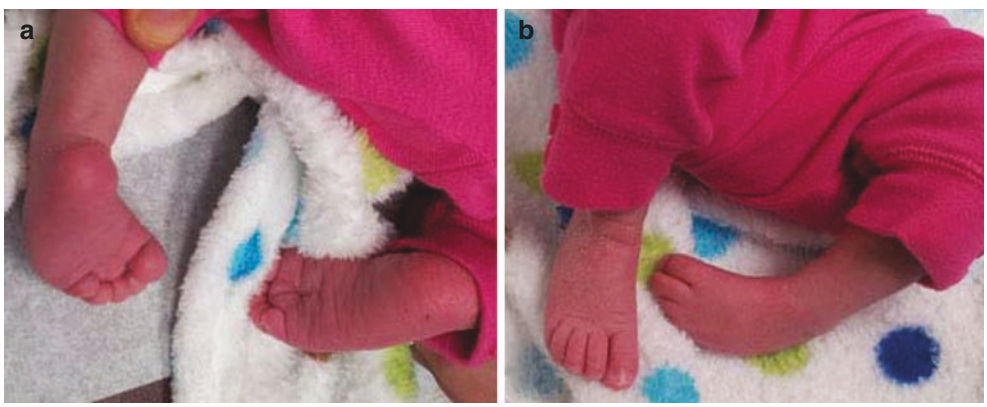


Fig. 13.28 Clubfoot. A 2-week-old girl with left clubfoot. Notice the deformity of the left foot (equinus, varus, forefoot adduction, and cavus). On the *left* (**a**), notice the hindfoot varus. On the *right* (**b**), notice the forefoot adduction and equinus

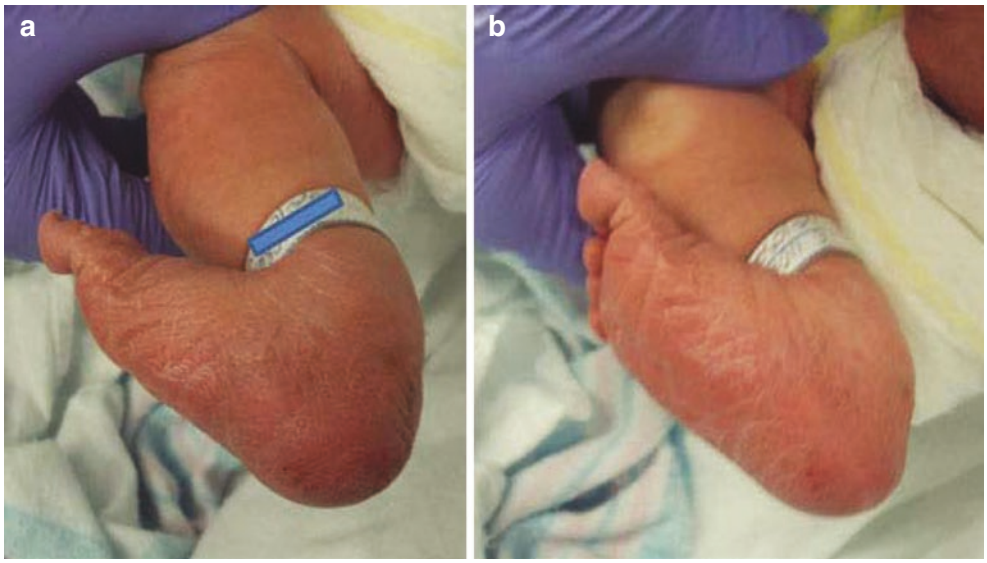


Fig. 13.29 Calcaneovalgus foot. (**a**, **b**) Newborn baby with right foot deformity. The foot is in valgus and dorsiflexion (calcaneus position). No treatment required, as the condition is self-limiting

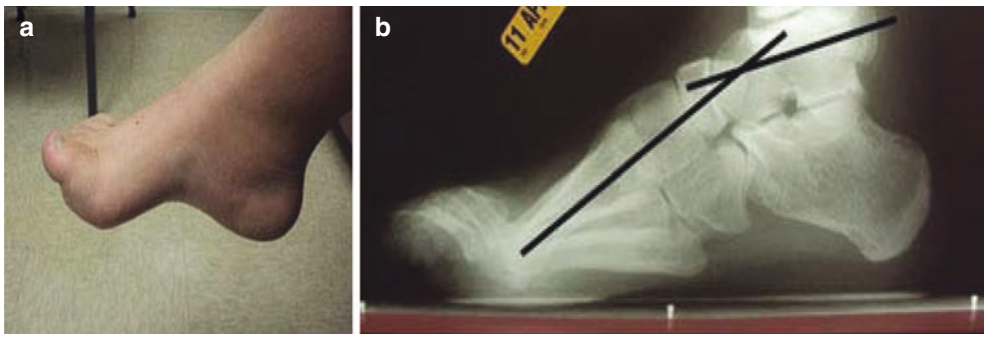


Fig. 13.30 Cavus foot. A 15-year-old boy with Charcot–Marie–Tooth disease. Patient has right foot high-arch deformity (cavus). Lateral radiograph of the foot (standing) shows increased lateral talar–first metatarsal (Meary's) angle

Diagnosis

- The foot is in excess dorsiflexion (calcaneus position of the foot) and valgus to the degree that the dorsum of the foot is touching the front of the tibia.
- The ankle and hindfoot are flexible enough to easily correct the deformity

Treatment

- Most cases do not require treatment, as they will improve with growth within a few weeks

Cavus Foot

Background

- High-arched foot (Fig. 13.30)
- Cavus foot is usually an indication of neurological pathology (e.g., Charcot–Marie–Tooth disease), spina bifida (sacral-level affected), lipoma of the cord, or other intrathecal pathology

Diagnosis

- The foot will have high-arched appearance
- Thorough neurological exam must be done to identify possible underlying cause
- Radiographs: The lateral talar–first metatarsal (Meary's) angle is more than 5° convex dorsally (normally, it should be 0°)

Treatment

- Identification and treatment of the underlying cause
- Neurology/neurosurgery and orthopedic surgery referral

Flatfoot (Pes Planus)

Background

- The medial arch of the foot does not develop until the age of 4 years and reaches close to the adult value by the age of 8 years

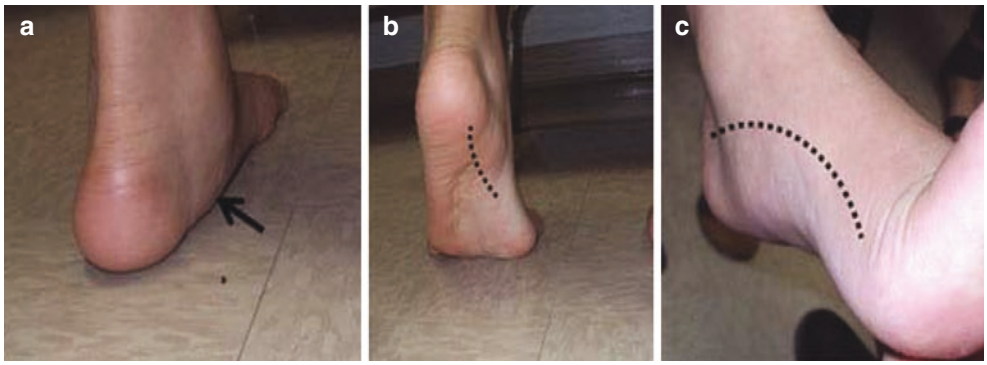


Fig. 13.31 Flexible flatfeet. A 9-year-old girl with bilateral flexible flatfeet. When patient stands, there is loss of arch (*arrow*; **a**). When she tiptoes (**b**) or with dorsiflexion of the big toe (**c**), there is restoration of the arch (*dotted arch*)

- *Flexible flatfoot:*
  - Loss of the medial arch support when the child stands. This is a normal finding in about 10% of the population
  - It is a universal finding in neonates and toddlers and is associated with physiological ligamentous laxity and excess fat at the sole of the foot.
- *Rigid flatfoot:*
  - Due to foot pathology such as tarsal coalition or congenital vertical talus

Diagnosis

- Loss of the arch of the foot (the heel will be in valgus) when the patient stands
- *Flexible flatfoot:*
  - With tiptoeing or with dorsiflexion of the big toe (tightening of the plantar fascia), restoration of the arch (Fig. 13.31)
  - Normal subtalar joint movement (supination/pronation of the foot)
  - The condition in most cases is asymptomatic. Rarely, the condition can cause pain at the medial aspect of the foot over the tarsal head
  - Some cases are associated with tight Achilles tendon. Other cases may be associated with generalized laxity of the joints
- *Rigid flatfoot:*
  - Rigid deformity that is not corrected by tiptoeing or dorsiflexion of the big toe
  - Decreased or absent subtalar motion

Treatment

- *Flexible flatfoot:*
  - Reassurance (the condition is a variation of normal development)
  - Achilles tendon stretching for children with tight Achilles tendon
- *Rigid flatfoot:*
  - Orthopedic referral

Tarsal Coalition

Background

- Abnormal connection (bridging) between two of the tarsal bones
- The condition usually starts as fibrous or cartilaginous connection and then matures to bony bridge between two bones by the adolescence
- The condition is usually asymptomatic and bilateral. About 5% of the population has tarsal coalition
- Most common coalition is calcaneonavicular and subtalar (talocalcaneal) fusion

Diagnosis

- Usually presents around 10–14 years old
- Stiff flatfoot with foot pain
- History of recurrent ankle sprains with persistence of the pain after the injury
- Decreased subtalar movement (supination and pronation of the hindfoot)
- Radiographs can show the bony fusion especially calcaneonavicular type (anteater sign). Subtalar (talocalcaneal) coalition is harder to detect in plain radiographs. If radiograph is normal and the condition is suspected clinically, CT of the foot is indicated (Fig. 13.32)

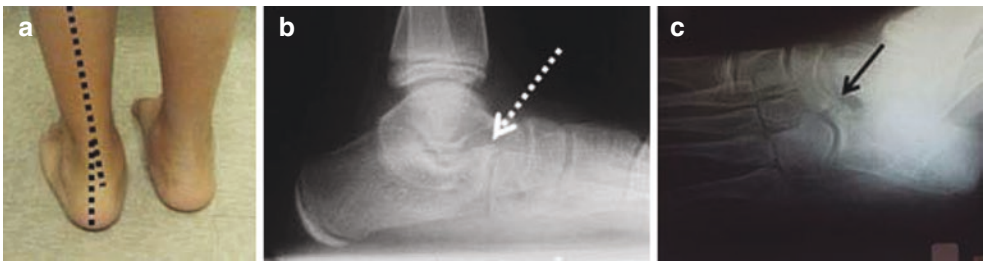


Fig. 13.32 Calcaneonavicular coalition. An 11-year-old boy with left flatfoot and valgus heel (**a**; *dotted line)* and foot pain for 6 months. Lateral standing radiograph (**b**) shows flatfoot with no arch and bony prominence of the calcaneus (*white arrow*; anteater sign). Oblique radiograph (**c**) shows the calcaneonavicular coalition (*black arrow*)

Treatment

- If discovered accidentally during foot radiographs taken for other reasons: No treatment is needed. Orthopedic referral for symptomatic cases only

Tiptoe Walking

Background

- Pattern of walking in which the child walks on his/her toes with ankle plantar flexion. If no underlying neurological cause is identified, it is referred to as "habitual toe walking or idiopathic toe walking"
- It is common in toddlers and young children when they are starting to learn how to walk. Sometimes associated with autism or speech delay
- Other causes of tiptoeing (differential diagnosis of idiopathic toe walking):
  - Cerebral palsy: Mild cerebral palsy is very hard to differentiate from idiopathic toe walking. Upper extremities movement during gait is normal in idiopathic toe walking and restricted in mild cerebral palsy
  - Duchenne muscular dystrophy: Positive Gower sign, pseudohypertrophy of the calf, elevated creatine phosphokinase (CPK)
  - Tether cord syndrome: Other neurological manifestations (e.g., bladder dysfunction)
  - Limb length discrepancy will cause unilateral toe walking (on the short side)

Diagnosis

- The child walks on his/her toes with no pain
- Tight Achilles tendon especially with the knee extended

Treatment

- Toe walking is a normal variant in children younger than 3 years, and no treatment is warranted in this age range.
- Unilateral toe walking should always be evaluated further, because it may indicate the presence of hemiplegia, developmental dysplasia of the hip, or leg-length discrepancy
- Full neurological exam to exclude underlying neurological disease
- If the child had just learned how to walk, is less than 3 years old, or the toe walking is occasional:
  - Observation and reassessment after 6 months
- If the child is older than 3 years and the toe walking is constant:
  - Physical therapy for Achilles tendon stretching
  - If no improvement after 6 months of therapy: Orthopedic referral for botulinum toxin injection of the calf muscle, Achilles tendon lengthening, or serial casting

Ingrowing Toenail

Background

- The penetration of the border of the nail plate into the nail fold causing pain and inflammation in the surrounding tissue (Fig. 13.33)

- Etiology: Unknown; may be related to tight-fitting shoes, trauma to the toe, incorrect trimming of toenails, and/or genetic susceptibility

Diagnosis

- Significant pain in the toe with inflammation of tissue surrounding the nail bed

Treatment

- Proper care of the nail (comfortable wide toe box or open-toed shoes; the nail should be cut straight across and avoid cutting back the lateral margins; the nail edge should extend past the nail fold)
- Frequent soaking of the foot in warm water
- Local antibiotic application (oral antibiotic can be prescribed if the infection is advanced)
- Elevating the offending edge of the nail from the soft tissue and placing a small piece of gauze between the nail and the skin
- If no improvement with the above measures: Orthopedic or podiatry referral

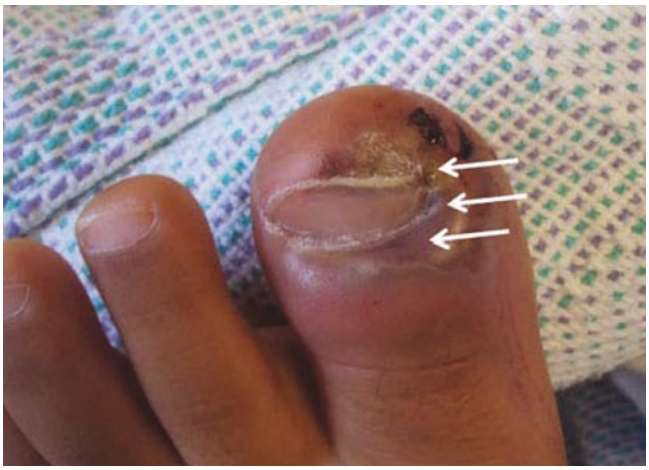


Fig. 13.33 A 6-year-old with an ingrown toenail. Notice the pocket of pus (*arrows*)

FRACTURES

Salter–Harris Injuries

Background

- Injuries of the bone that go through the growth plate (physis)
- Classification: Type I through type V (Fig. 13.34)
- Complication of Salter–Harris injuries: These fractures can cause injury to the growth plate and possible growth disturbance
  - If the growth disturbance is through the whole growth plate (complete), it will

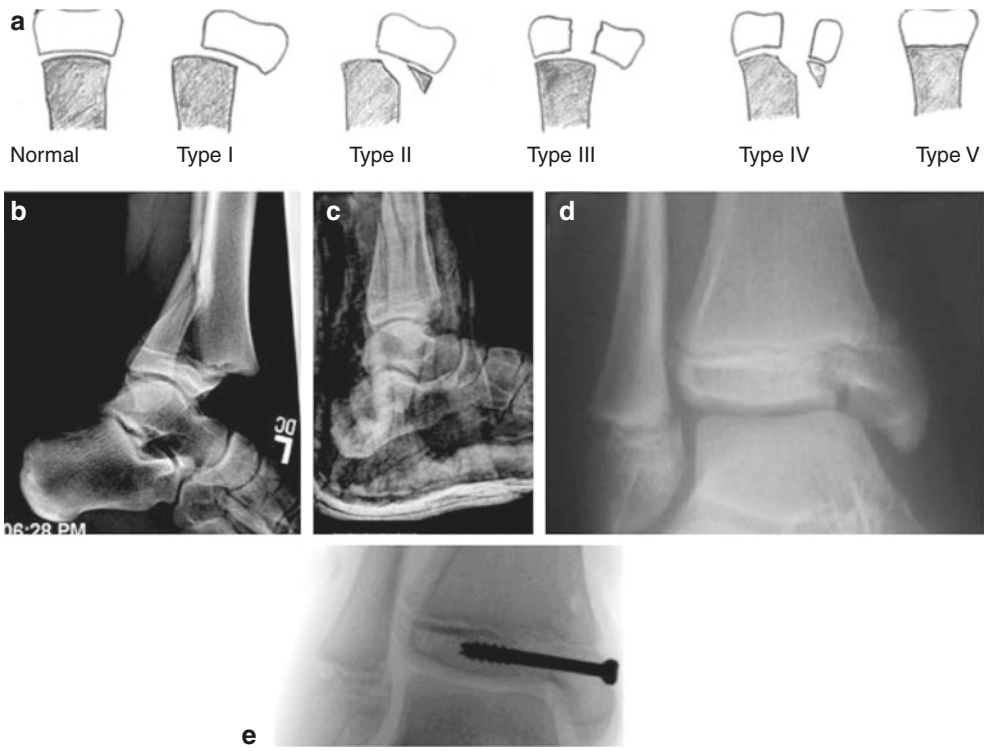


Fig. 13.34 Physeal (Salter–Harris) injuries classification. (**a**, **b**, **c**) Type II distal tibial fracture before and after closed reduction. (**d**, **e**) Type IV distal tibial fracture before and after open reduction and internal fixation

result in a short bone (and possible limb length discrepancy)
  - If the growth disturbance is partial (only part of the growth plate is affected), the bone will grow in deformed position

Diagnosis

- Radiographs will show the fracture line passing through the growth plate (see Fig. 13.34)
- The growth disturbance is more common in certain fracture patterns (types III and IV injuries) and in certain growth plates (distal femur and proximal tibia growth plates)

Treatment

- Urgent orthopedic referral. Physeal injuries heal faster than other fractures because they occur through rapidly dividing cells; they have to be reduced as soon as possible

Clavicular Fracture

Background

- A common fracture in pediatric patients due to the superficial location of the clavicle

Diagnosis

- Pain, deformity, and swelling over the clavicle after falling on an outstretched hand
- Radiographs will show fracture of the clavicle with possible deformity (angulation and/or displacement) (Fig. 13.35)

Treatment

- Arm sling for comfort. The child can take it off when he/she feels more comfortable. No need for the figure-of-8 sling. Fractured clavicle will heal with obvious bump (bony callus)
- Indication for referral: Open fracture, fractures associated with neurovascular injuries, markedly displaced or shortened fractures

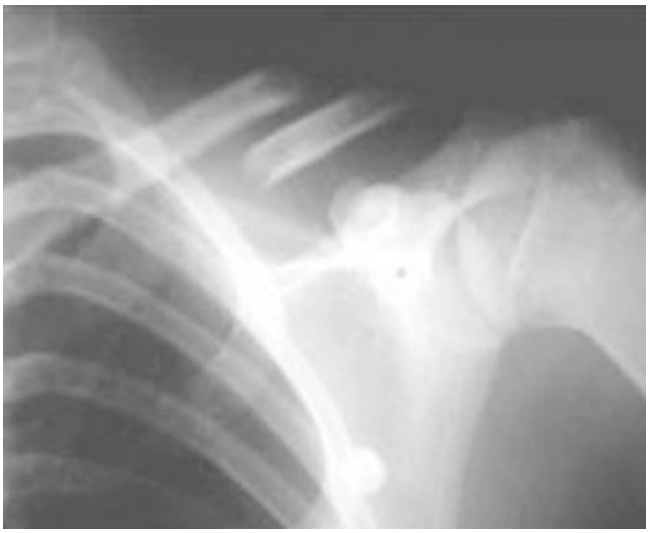


Fig. 13.35 Radiograph of a 12-year-old boy who fell down and had pain over the clavicle. The radiograph shows a midshaft clavicle fracture

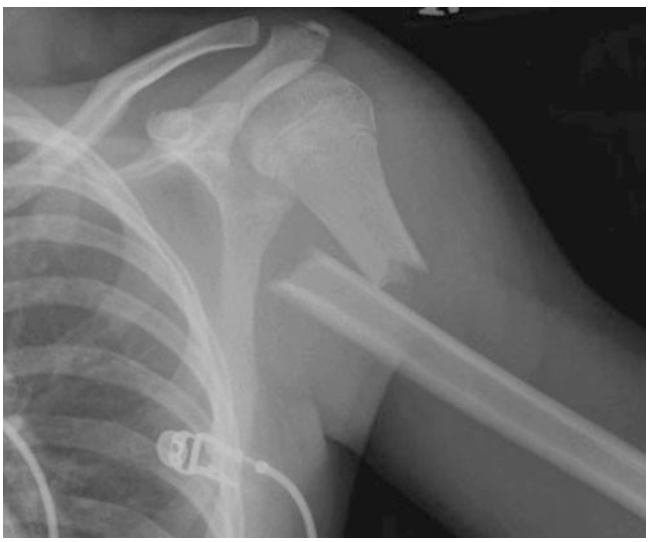


Fig. 13.36 Complete fracture of the proximal humerus. Note the displacement of the fracture ends

Proximal Humeral Fracture

Diagnosis

- Pain and swelling of the proximal arm
- Radiographs will show the fracture (Fig. 13.36)

Treatment

- Most of the fractures of the proximal humerus can be managed nonoperatively, especially in young children. Immobilization of the arm in a sling

Humerus Fracture

Diagnosis

- Pain, swelling, and deformity of the arm
- Can be associated with wrist drop due to radial nerve palsy. The vast majority of these palsies will improve spontaneously with no treatment needed
- Radiographs will show the fracture (Fig. 13.37)

Treatment

- Orthopedic referral is needed to this condition
- Most humeral shaft fractures can be managed nonoperatively in braces

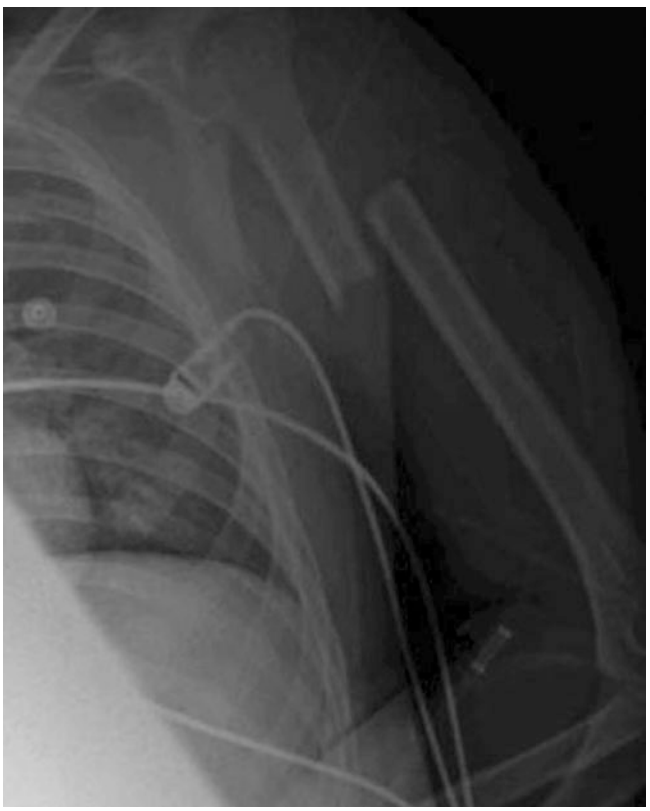


Fig. 13.37 Transverse fracture of the shaft of the humerus in an 11-year-old boy involved in an all-terrain vehicle (ATV) accident

Supracondylar Fracture of Humerus

Background

- Transverse fracture of the distal part of the humerus proximal to the articular surface
- Incidence: 60–70% of elbow fractures, more common in boys, between 4 and 7 years old
- Can be associated with many complications (compartment syndrome, malunion, nerve injury)

Diagnosis

- Pain, swelling, and deformity of the affected elbow
- With marked displacement of the fracture ends, bruises of the anterior elbow will occur (the proximal fragment button through the brachialis muscle)
- Radiograph will show the fracture line, which passes across the supracondylar area (Figs. 13.38 and 13.39)
- According to the displacement, the fracture is classified into:
  - Nondisplaced (type I), angulated (type II; see Fig. 13.39), displaced (type III; see Fig. 13.38)

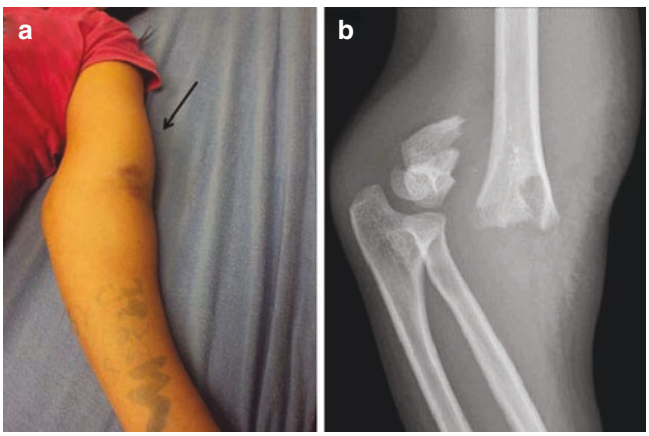


Fig. 13.38 Bruising of the anterior elbow with displacement of the fracture in a 7-year-old girl who fell and has obvious deformity of the left elbow. Cubital fossa shows bruising (**a**) (*arrow*). Radiograph (**b**) shows type III supracondylar fracture of the humerus with marked displacement of the fracture ends. The proximal fragment had "buttoned through" the brachialis muscle, causing this bruising

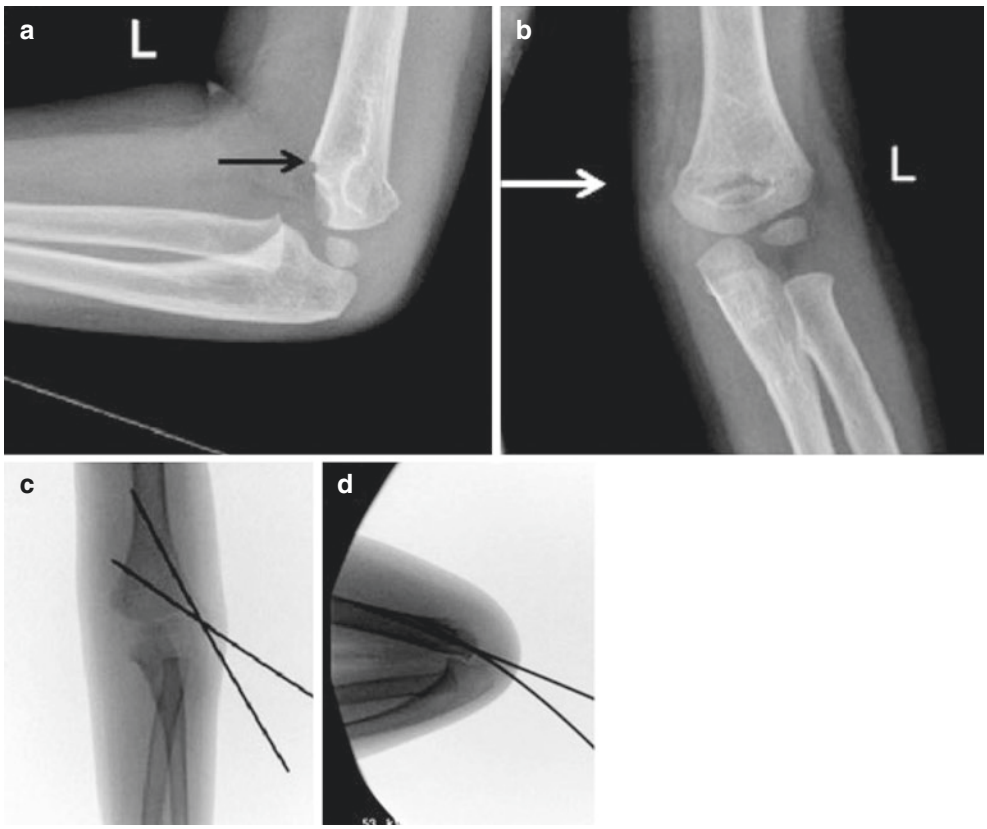


Fig. 13.39 Type II supracondylar fracture of the humerus. A 4-year-old boy with left supracondylar fracture of the humerus type II (notice the angulation of the fracture ends in the lateral view) (**a**), with no displacement of the fracture in the anteroposterior view (**b**). The treatment was closed reduction and percutaneous fixation of the humerus by K wires (**c**, **d**)

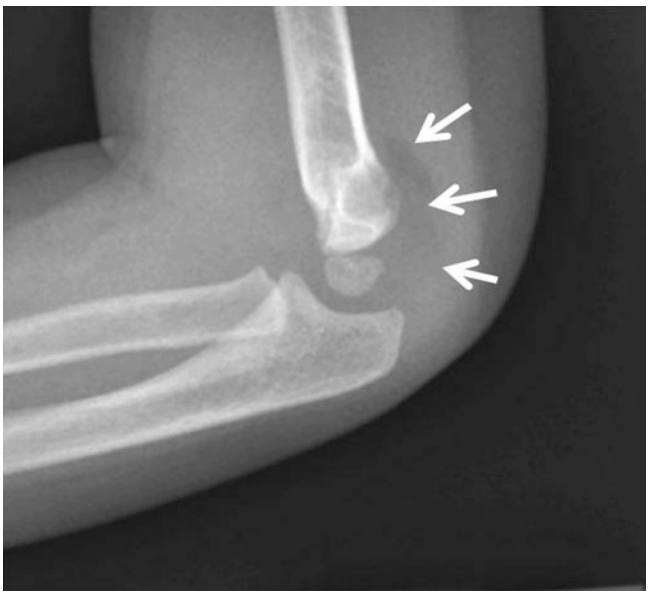


Fig. 13.40 Type I supracondylar fracture of the elbow with posterior fat pad sign (*arrows*)

  - For nondisplaced fracture, posterior fat pad sign will be seen in the lateral radiographs, indicating blood in the joint from the fracture (Fig. 13.40)

Treatment

- Assess radial and ulnar pulses. If there is an absent distal pulse or possible compartment syndrome, urgent orthopedic consultation
- Assess nerve function
- Orthopedic referral for possible surgical intervention:
  - Angulated/displaced supracondylar humerus fracture (stages 2 and 3): Treatment is closed reduction and percutaneous pinning (see Fig. 13.39)

Lateral Condyle Fracture

Background

- Fracture of the lateral condyle of the humerus (which includes the capitellum)
- Incidence is about 10% of the fractures of the elbow
- Can be complicated by nonunion

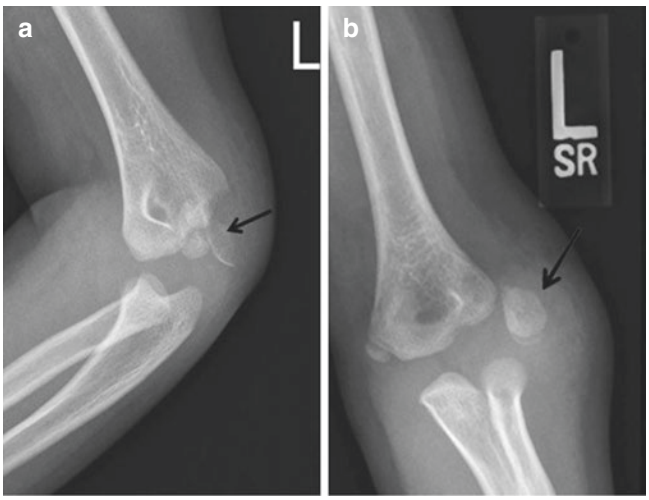


Fig. 13.41 Lateral condyle fracture. A 4-year-old boy fell on an outstretched hand and had elbow pain and swelling. Radiographs (**a**, **b**) show a lateral condyle fracture (*arrow*)

Diagnosis

- Pain, swelling, and deformity of the affected elbow
- Radiographs: The fracture line will pass through the lateral condyle and the capitulum (Fig. 13.41)

Treatment

- Orthopedic referral. These fractures are prone to develop nonunion
- If nondisplaced: Casting with close follow-up to detect possible displacement. If displaced, the fracture will require surgery. Displaced fracture requires open reduction and internal fixation

Medial Epicondyle Fracture

Background

- Can occur as a stress fracture (repeated stress to the medial epicondyle during throwing activities, which will result in the fracture with low-energy injury) or can also occur as an acute fracture due to acute injury to the elbow

Diagnosis

- Pain, swelling, and deformity of the affected elbow

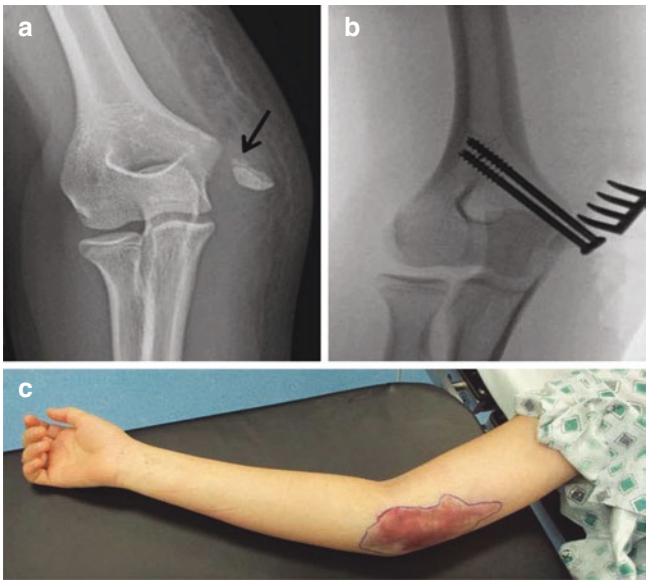


Fig. 13.42 Acute medial epicondyle fracture. A 13-year-old boy who fell while playing basketball. Radiograph shows the fracture displacement (**a**). The clinical picture shows the large bruising on the medial aspect of the elbow (**b**). Due to the amount of fracture displacement, surgery was done for open reduction and internal fixation (**c**)

- Radiographs will show the fracture and displacement of the medial epicondyle (Fig. 13.42)

Management

- Orthopedic referral. In most cases, the fracture can be managed conservatively with no need for surgery
- Surgery is indicated in cases of fracture–dislocation in which the fractured piece is incarcerated in the joint (Fig. 13.43) or if there is more than 20 mm displacement of the fracture ends (see Fig. 13.42)

Scaphoid Fracture

Background

- Most common carpal fracture in pediatric patients
- Peak incidence at 15 years of age and rare before the age of 8
- Can be complicated by nonunion due to pattern of blood supply. Fractures can result in disruption of the blood supply to the bone, resulting in avascular necrosis and collapse of the bone

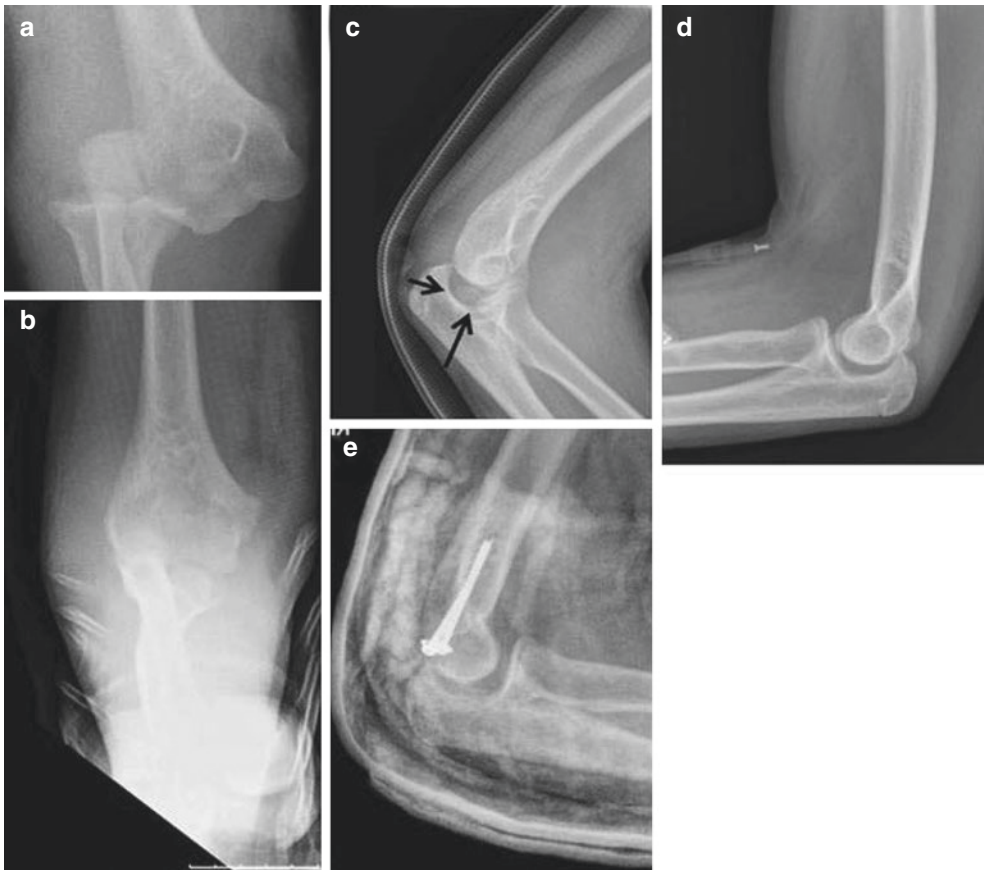


Fig. 13.43 Fracture dislocation of the medial epicondyle. A 12-year-old boy fell on his hand while skating. He dislocated his right elbow (**a**). Closed reduction of the elbow was done. Post reduction radiographs (**b**, **c**) showed incongruence lateral view of the elbow; compare with the normal side (**d**). The medial epicondyle can be seen in the joint (*arrows*). Surgery was done for removal of the piece from the joint and internal fixation by screws (**e**)

Diagnosis

- Pain and swelling on the radial aspect of the wrist
- Tenderness over the anatomical snuff box
- Radiograph with PA, lateral, oblique, and scaphoid views (Fig. 13.44) can show the fracture. High index of suspicion is required for early diagnosis, as the radiographs may be negative in the first 2 weeks
- MRI can be used in cases with negative radiographs if the clinical suspicion of fracture is high

Treatment

- Initial suspicion of fracture with negative radiographs: Treat as if a scaphoid fracture is present. Place the child in short thumb spica splint for 1–2 weeks and then radiographs repeated after 2 weeks
- If repeat radiographs are negative and child's exam is unchanged, then immobilization should continue with thumb spica cast, and MRI should be obtained

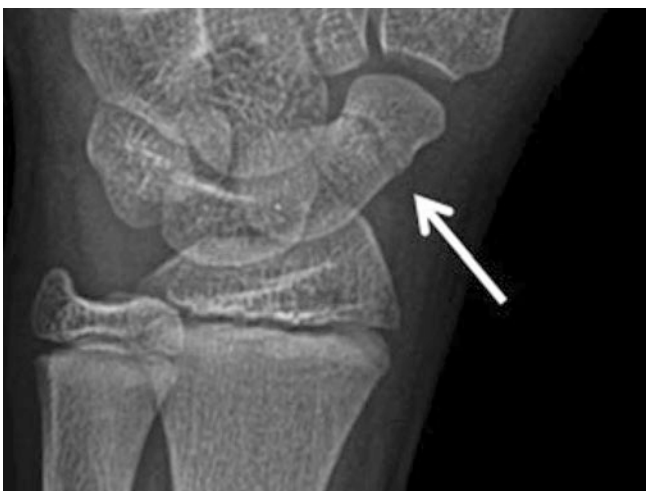


Fig. 13.44 Scaphoid fracture. A 13-year-old child fell down while playing football. The patient had pain at the wrist centered over the anatomical snuff box. Oblique radiograph shows fracture of the scaphoid

- If repeat radiographs are negative and child is pain-free, then likelihood of fracture is low, and immobilization can be discontinued

- If radiographs are positive for fracture (either from start or after repeat film), orthopedic referral for:
  - Nondisplaced fracture: Thumb spica cast
  - Displaced fracture: Surgical intervention

Tibial Shaft Fracture

Diagnosis

- Pain, swelling, and deformity of the affected extremity
- Can be complicated by compartment syndrome (pain increases after application of cast)
- Radiograph will show the fracture (Fig. 13.45).

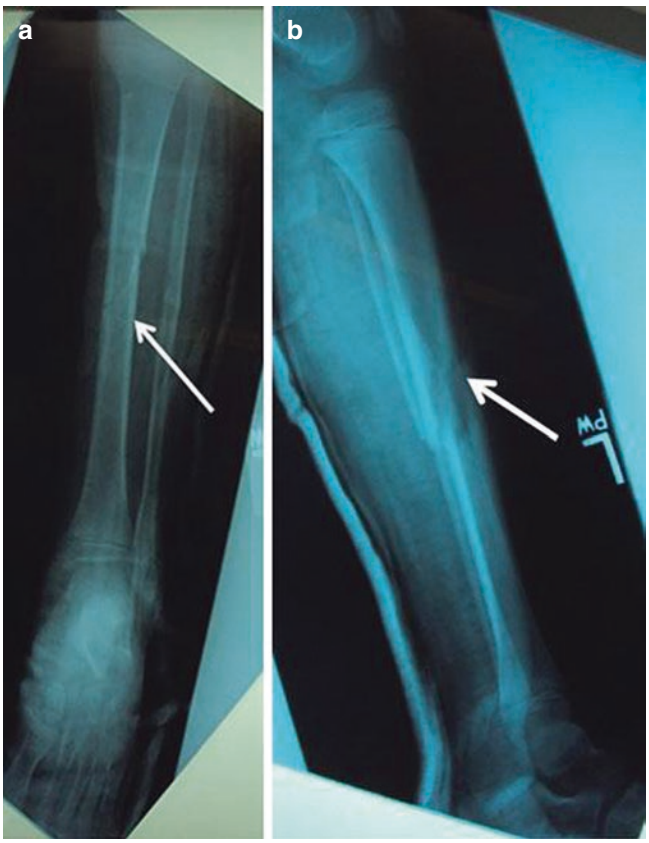


Fig. 13.45 Tibial shaft fracture. A 14-year-old boy fell down while running down the stairs and had left leg pain and swelling. Radiographs (**a**, **b**) show mid-shaft tibia fracture, which was managed nonsurgically with casting

Treatment

- Orthopedic referral. Treatment is according to age and displacement. Most cases can be treated by closed reduction and casting; some cases will require internal fixation

Toddler Fracture

Background

- A spiral tibial shaft fracture that occurs in toddlers due to twisting trauma
- It is a relatively common injury in children less than 4 years old

Diagnosis

- The parents recall no or minimal trauma in most cases
- Limping or inability to bear weight on the affected side. Minimal swelling and no deformity
- External rotation of foot will cause pain and discomfort to the child
- Radiographs will show spiral nondisplaced fracture of the distal tibia (Fig. 13.46)
- Sometimes, primary radiograph is negative, but the follow-up radiograph will show the evidence of healing (periosteal new bone formation and callus at the fracture site)

Management

- Orthopedic referral (treatment is above-knee cast for 2–3 weeks with repeat radiographs after cast removal)

Ankle Fractures

Background

- The mechanism of the fracture is twisting injury to the ankles
- Can lead to disruption of the syndesmotic ligaments between the tibia and fibula (syndesmotic injury) (Fig. 13.47)

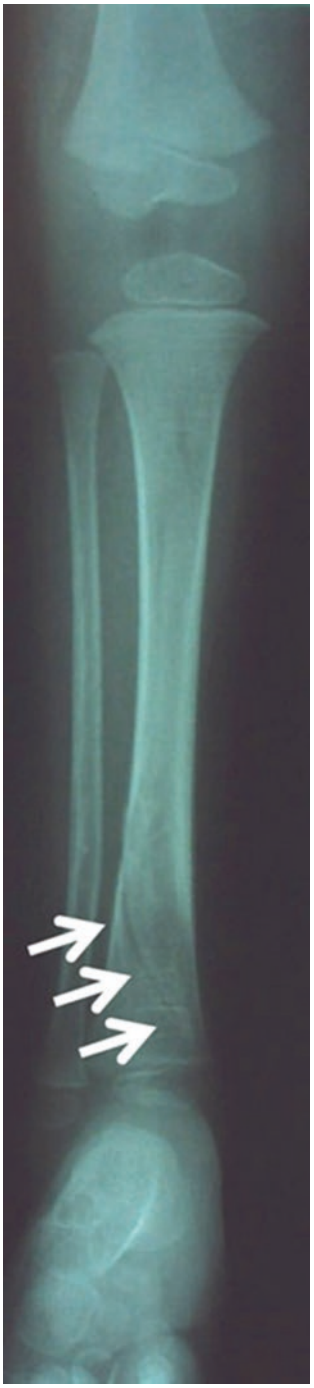


Fig. 13.46 Toddler fracture. A 3-year-old boy presented with his parents because of 2 days' refusal to walk. On exam, there was tenderness of the lower leg with pain on external rotation of the tibia. Radiograph shows spiral nondisplaced fracture of the lower end of the tibia

- Nondisplaced distal fibular physeal injury (Salter–Harris type I): Common injury in children due to twisting injury of the ankle, equivalent to ankle sprain

Diagnosis (Table 13.4)

- Pain, swelling, and deformity of the affected ankle
- Inability to bear weight on the affected side

Treatment

- Orthopedic referral. Displaced fracture or fracture with widening of the distance between fibula and tibia will require surgical fixation (see Fig. 13.47)
- Nondisplaced distal fibular physeal injury can be treated by immediate weight bearing in a controlled ankle motion (CAM) walking boot, boot, or cast

Compartment Syndrome

Background

- Elevation of the interstitial pressure in a closed osteofascial compartment that results in microvascular compromise
- Compartment syndrome should be suspected in children involved in accidents with high-energy trauma to the extremities
- More common with fractures of the lower leg and forearm

Diagnosis

- *Tense non-compressible swelling* of the affected compartment
- Increase in the narcotic requirements to keep the child comfortable is an early sign of increased compartment pressure

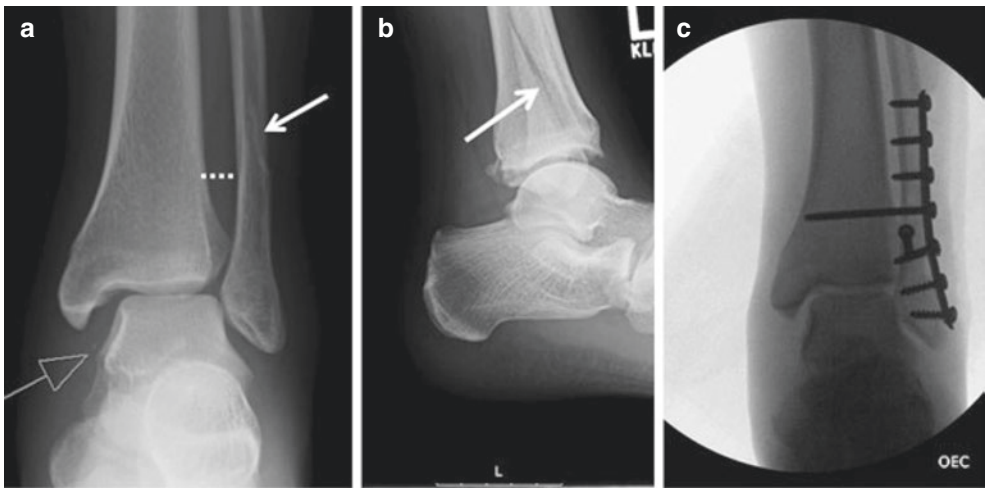


Fig. 13.47 Ankle fracture. A 16-year-old had left ankle injury while playing soccer. (**a**, **b**) Radiographs showed fracture distal fibula (*arrows*) with widening of the distance between tibia and fibula (*dotted line*) and widening of the medial joint space (*open arrow*). (**c**) Surgery was done for fixation of the fracture with plates and screws (notice reduction of the distance between tibia and fibula and narrowing of the medial joint space)

Table 13.4 Clinical differentiation between ankle sprain and ankle fracture

Ankle sprain	Ankle fracture
Depending on the degree of injury, most cases can bear slight weight	Cannot bear weight immediately after injury
No bony tenderness	Bony tenderness/ crepitation
	Palpate medial and lateral malleolus, base of the fifth metatarsal, mid-foot bone
Maximal point of tenderness in anterior talofibular ligament and/or calcaneofibular ligament areas	Maximal point of tenderness in the affected bone
Painful and swollen	Painful and swollen

- Severe excruciating pain with passive stretch of the distal joints (toes or fingers)
- Paresthesias, pulselessness, and paralysis are late findings, and the absence of these signs does not rule out this diagnosis
- Compartment pressure can be measured using pressure needle. Pressure more than 30 mmHg suggests that patient may have compartment syndrome

Treatment

- Once compartment syndrome is suspected, cast and splints should be removed or split immediately
- The affected extremity should be elevated to the level of the heart (elevating the extremity above the level of the heart will decrease tissue perfusion)
- Urgent orthopedic consult: Definitive treatment of compartment syndrome consists of wide prompt release of the affected compartments (fasciotomy)

RADIAL HEAD SUBLUXATION

Nursemaid Elbow (Pulled Elbow)

Background

- Subluxation of the radial head from the annular ligament
- Common condition in young children aged 1–4 years

Diagnosis

- A child with no obvious history of trauma will suddenly refuse to use his/her arm.
- Common scenarios include the following: A toddler held by his or her hand, then the child and adult move in opposite directions
- Radiograph will be negative

Treatment

- Reduction maneuvers: One hand supports the elbow and the other hand applies axial compression at the wrist while fully supinating the forearm and then flexing the elbow
- A click or snap can usually be felt at the radial head with successful reduction.
- Most children will show immediate return of function 15–30 min after the reduction

BONE TUMORS/TUMORLIKE CONDITIONS

Unicameral Cyst

Background

- The unicameral bone cyst is not a true neoplasm; unknown pathogenesis
- Age usually ranges between 5 and 15 years. More in males
- Most commonly found in the proximal humerus and upper femur

Diagnosis

- Most cases are asymptomatic
- Pathological fracture: Pain after minor trauma due to pathological fracture of the affected bone
- Occasionally, accidentally discovered in radiograph done for another reason
- Radiographs: A well-defined lytic lesion situated in the intramedullary metaphyseal region immediately adjacent to the physis. A cortical piece of bone can be seen in the middle of the lesion (fallen leaf sign) and is pathognomonic of a simple bone cyst (Fig. 13.48)

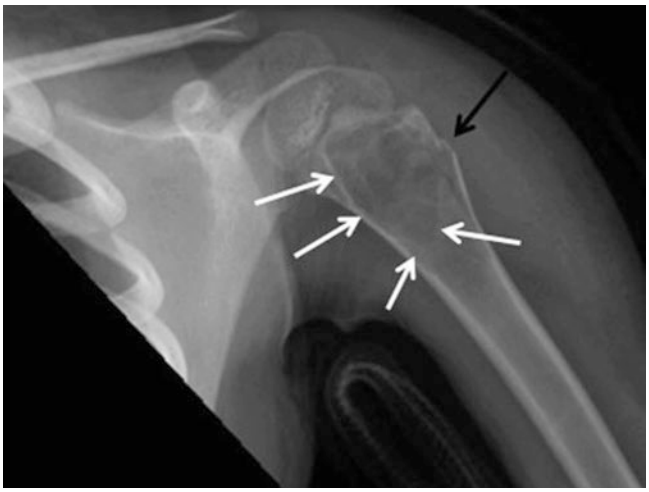


Fig. 13.48 Radiograph of a 6-year-old boy who had sudden left shoulder pain while playing shows proximal humeral fracture (*black arrow*). Notice the simple bone cyst that affected the proximal humerus (*white arrows*)

Treatment

- Orthopedic referral for symptomatic lesion. Treatment can be by surgical debridement or steroid injection. Nonsymptomatic lesions discovered accidentally do not need intervention. For lesions with associated pathological fractures, management of the fracture should be done first, as the lesion may heal during the healing process of the secondary fracture

Aneurysmal Bone Cyst (ABC)

Background

- The ABC is an expansile cystic lesion
- The true etiology is unknown; however, most experts believe that ABCs are the result of a vascular malformation within the bone
- The gross appearance of the ABC is that of a blood-soaked sponge. A thin subperiosteal shell of new bone surrounds the structure and contains cystic blood-filled cavities

Diagnosis

- Pain and swelling over the affected bone
- Pathologic fracture

- Radiographs: Soap-bubble appearance with an eggshell-appearing bony rim surrounding the lesion

Treatment

- Orthopedic referral: The lesion can be treated with intralesional curettage and bone grafting or wide excision of the lesion

Osteoid Osteoma

Background

- Osteoid osteoma is a benign tumor consisting of a well-demarcated bone-forming lesion called a nidus, surrounded by a radio-dense, reactive zone of host bone
- More common in males, in second and third decades
- Usually affects the diaphysis of long bones

Diagnosis

- Pain that increases at night and is relieved by aspirin and other NSAID, not relieved by rest
- Radiographs: Small defect less than 1.5 cm in diameter and is associated with a variable degree of cortical and endosteal sclerosis. In most cases, the defect cannot be seen, and surrounding sclerosis is the only finding in the radiograph. CT will more clearly show the lesion and the nidus

Treatment

- Orthopedic referral for excision of the lesion. CT-guided percutaneous radiofrequency ablation of the nidus can also lead to complete resolution of symptoms

Osteochondroma

Background

- The most common benign bone tumor
- Osteochondromas can be solitary or multiple. Hereditary multiple exostoses (HME) is an autosomal dominant syndrome characterized by multiple osteochondromas affecting different bone
- Pathology: The medullary canal of the osteochondroma and the host bone are in continuity. It is most commonly found around the knee and the proximal humerus in the metaphyseal areas (Fig. 13.49)

Diagnosis

- Osteochondromas are commonly diagnosed incidentally, based on a radiograph obtained for another reason
- The second most common presenting symptom is a mass

Treatment

- Asymptomatic lesions can be safely observed. No orthopedic referral is needed for asymptomatic lesions
- If painful or multiple: Orthopedic referral

Osteosarcoma

Background

- Osteosarcoma is a primary malignant tumor of bone with malignant osteoid formation arising from bone-forming mesenchymal cells

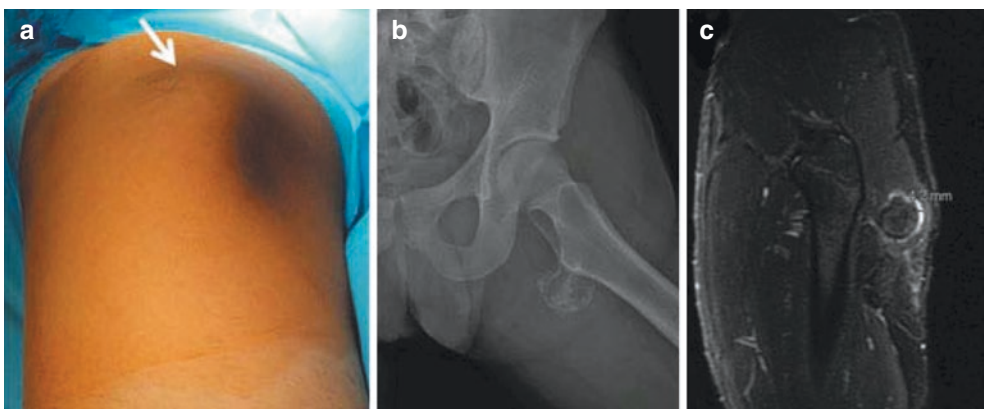


Fig. 13.49 A 15-year-old boy presented with mass in the posterolateral part of the left gluteal area (*arrow*). Radiograph showed osteochondroma (pedunculated). Magnetic resonance imaging (MRI) assessed the thickness of the cartilaginous cap (4 mm)

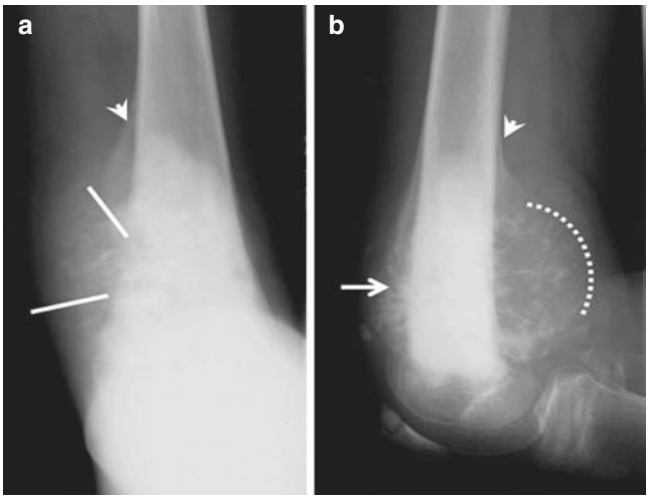


Fig. 13.50 Osteosarcoma. Anteroposterior (**a**) and lateral (**b**) views of right knee showing signs of osteosarcoma: Sunray appearance (*arrow*), Codman's triangle (*arrow head*), cortical erosion (*line*), and soft tissue shadow *(dotted line*)

- The strongest genetic predisposition to osteosarcoma is found in patients with hereditary retinoblastoma. In hereditary retinoblastoma, mutations of the *RB1* gene are common
- Osteosarcoma is the most common primary malignant bone tumor under the age 20 years
- Occurs in the metaphysis of long bones, commonly found around the knee

Diagnosis

- Pain is the first and most common symptom; it is usually constant and severe
- Swelling (usually pain precedes swelling)
- Pathological fracture
- Radiographs: Skeletally immature patient with an osteolytic lesion that is metaphyseal, eccentric, and having ill-defined edges with new bone formation and erosion of the cortex (Fig. 13.50)
- CT: Better assessment of bone destruction
- MRI: Better assessment of soft tissue mass, invasion of nearby neurovascular bundle, and satellite lesions (skip lesions in the same bone)

Treatment

- Requires cooperation between the orthopedic surgeon and the oncologist
- Treatment and prognosis depend on the subtype and grade of the tumor
- Treatment is usually by wide resection with reconstruction and adjuvant chemotherapy. Osteosarcomas do not respond to radiation therapy

Ewing Sarcoma

Background

- A primary malignant bone tumor (round cell sarcoma) that arises from the medullary tissue, mostly from the lining cells of the medullary blood or lymphatic channels
- The most common primary malignant tumor in patients less than 10 years old
- More common in male
- Occurs in diaphysis of the long bones

Diagnosis

- Pain and tenderness over the involved area
- Swelling (slowly growing, warm, tender, ill-defined, hard, diaphyseal)
- Fever, anorexia, headache, and malaise may be the presenting symptoms (clinical presentation may be similar to osteomyelitis)
- Radiographs: Medullary destruction, soft tissue mass with reactive new bone formation. Multiple layers of elevated periosteum (onion-peel appearance) (Fig. 13.51)

Treatment

- Orthopedic referral: Chemotherapy, radiotherapy, and surgical excision of the tumor

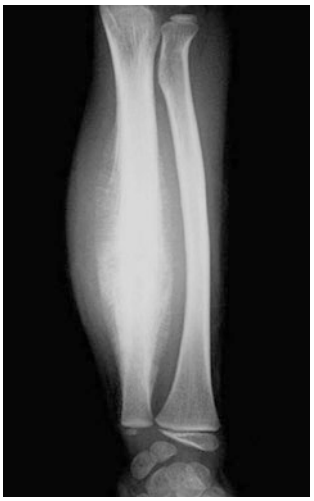


Fig. 13.51 Ewing sarcoma. An 8-year-old boy with left forearm pain and swelling. Radiograph showed Ewing sarcoma of the ulnar diaphysis. Notice the location of the lesion (diaphysis) and the periosteal new bone formation

PEARLS AND PITFALLS

- Polyhydramnios, short umbilical cord, and fetal akinesia are associated with arthrogryposis.
- DDH risk increases in firstborn, female, breech presentation, and positive family history for DDH.
- Hip ultrasound screening for DDH before 6 weeks of age may be overly sensitive and result in overtreatment.
- Physical examination is the most important diagnostic tool in diagnosing DDH in neonates.
- In any child with unexplained knee pain, e.g., no history of knee trauma and normal knee examination, the hip joint must be considered as a possible source of pain or limp.
- Septic arthritis is a surgical emergency and should be immediately referred to a pediatric orthopedic surgeon. A rapid and progressive joint destruction may occur if urgent surgical drainage and irrigation are not performed.
- Congenital muscular torticollis can be associated with congenital dysplasia of the hip and/or metatarsus adductus.
- Most cases of intoeing represent normal development and do not need orthopedic referral.
- Tibial torsion usually improves by the age of 3 years, and femoral anteversion usually improves by the age of 8 years.
- If the foot deformity in cases of metatarsus adductus is flexible (the forefoot can be abducted), stretching exercises are sufficient.
- Flexible flatfoot is a normal finding and does not require treatment or referral.
- The longitudinal foot arch does not develop until the age of 4 years.

References

1. Abdelgawad A, Naga O. Pediatric orthopedics: a handbook for primary care physicians. New York: Springer Science+Business Media; 2014.
2. Pediatric Orthopaedic Society of North America, International Hip Dysplasia Institute, American Academy of Orthopaedic Surgeons, United States Bone and Joint Initiative, Shriners Hospitals for Children. Position statement: swaddling and developmental hip dysplasia. Rosemont: Pediatric Orthopaedic Society of North America; 2015. www.aaos.org/uploadedFiles/PreProduction/About/Opinion_Statements/position/1186%20Swaddling%20and%20Developmental%20Hip%20Dysplasia%281%29.pdf. Accessed 5 Oct 2018.

3. Pacana MJ, Hennrikus WL, Slough J, Curtin W. Ultrasound examination for infants born breech by elective cesarean section with a normal hip exam for instability. J Pediatr Orthop. 2017;37(1):e15–8.

Suggested Reading

Abdelgawad A, Kanlic E. Orthopedic trauma. In: Abdelgawad A, Naga O, editors. Pediatric orthopedics. A handbook for primary care physicians. New York: Springer; 2014. p. 409–83.

Abdelgawad A, Naga O. Pediatric spine. In: Abdelgawad A, Naga O, editors. Pediatric orthopedics. A handbook for primary care physicians. New York: Springer; 2014. p. 503–43.

Sarwark JF., LaBella CR. Back pain; general approach and differential diagnosis. In: Pediatric orthopedics and sports injuries: a quick reference guide. 2nd ed. Elk Grove Village: American Academy of Pediatrics; 2014a. p. 151–60.

Sarwark JF., LaBella CR. Congenital anomalies of the upper extremities. In: Pediatric orthopedics and sports injuries: a quick reference guide. 2nd ed. Elk Grove Village: American Academy of Pediatrics; 2014b p. 247–59.

Sarwark JF., LaBella CR. Leg-length discrepancy. In: Pediatric orthopedics and sports injuries: a quick reference guide. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics. 2014c. p. 561–7.

Sarwark JF., LaBella CR. Torticollis. In: Pediatric orthopedics and sports injuries: a quick reference guide. 2nd ed. Elk Grove Village: American Academy of Pediatrics. 2014d p. 169–77.

Sponseller PD. Bone, joint, and muscle problems. In: McMillan JA, Feigin RD, DeAngelis C, Jones MD, editors. Oski's pediatrics: principles and practice. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2006. p. 2470–504.

Sports Medicine

14

Daniel Murphy

PRE-PARTICIPATION EVALUATION

Background

- Preventative tool to ensure the safety of the athlete
- Screen for illness and past injuries, to identify athletes who may be at risk or may develop complications based on lifestyle choices and goals
- Promote the health and wellness of the athlete

Screening tests

- No routine tests are required for pre-participation clearance
- Routine electrocardiogram (ECG) screening remains controversial and has not been implemented as a standard protocol
- The history and physical will dictate if further diagnostic testing is required

Objective

- Identify life-threatening conditions and/or illnesses that would increase the risk for injury in an athlete
- Expose and educate the athlete to health and wellness and promote self-awareness
- Discuss issues that may be concerning to the athlete

Evaluation

- Evaluation must be completed at a minimum of 6 weeks prior to starting preseason practice
- Injuries sustained during the previous year should be discussed with the examiner to ensure proper recovery
- At the collegiate level, pre-participation physical exam should occur yearly
- At the secondary school level, each state has their own required timeline; therefore, parents should inquire the school about necessary requirements
- Completing a medical history in high school and collegiate athletes will identify 65–77% of all medical conditions
- All positive responses should be further investigated and questioned by the screening physician
- The physical examination plays an integral part in identifying musculoskeletal, visual, or cardiovascular disorders

Clearance

- The pre-participation physical is not designed to prevent student athletes from competing, but acts as a safeguard to identify conditions that may need further evaluation
- The individual sport needs to be taken into consideration when completing the examination
- Cardiovascular demands are extremely important when providing final clearance

The original version of this chapter was revised. The correction to this chapter can be found at https://doi.org/10.1007/978-3-030-21267-4_34

D. Murphy (✉)
Department of Family and Community Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Center, El Paso, TX, USA
e-mail: Daniel.murphy@ttuhsc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_14

- Static versus dynamic exercises must be taken into consideration, with static exercises increasing pressure load and dynamic increasing volume load
- If full and unrestricted participation is not granted to the student athlete, it is imperative that the athlete and guardian/parents are aware of the restrictions and how they affect the level of participation
- The level of participation may change based on new or changing medical conditions

Medical Conditions Affecting Sports Participation (Table 14.1)

Fever

- No participation in sports during febrile illness
- Athletes with systemic symptoms including fever and myalgias should refrain from physical activity for at least 7–14 days
- Individuals with infectious mononucleosis are restricted from physical activity for a minimum period of 3 weeks

Syncope and chest pain

- A personal history of syncope, near-syncope, chest pain, palpitations, or excessive shortness of breath or fatigue with exertion should prompt a more thorough evaluation, either by the primary clinician or a cardiologist

Table 14.1 Medical conditions affecting sports participations

Medical condition	Participation	Comments
Fever	No	Increased risk of heat illness
Diarrhea, infectious	No	Increased risk of dehydration
Seizure	Yes	Excludes swimming, diving, archery, or other sports that impose risk to others
Atlantoaxial instability	Yes	Needs evaluation to assess risk of spinal cord injury during sport
History of heat illness	Yes	Conditioning, sufficient acclimatization, hydration, salt intake to prevent recurrence
Enlarged spleen	Yes	Not in acute cases because of risk of rupture; if chronically enlarged, individual assessment is required
Heart murmur	Yes	If innocent murmur, otherwise needs cardiology evaluation
Hypertrophic cardiomyopathy	No	Cardiology consultation is recommended
Functionally one-eyed athlete	Yes	Best corrected eye is 20/40 or worse, needs individual assessment and eye protection
Pregnancy	Yes	Scuba diving and sports with high risk of falling or risk of altitude sickness should be avoided
One ovary	Yes	Risk of ovary injury is minimal
One testicle	Yes	Protective cup for certain sports
One kidney	Yes	Protective equipment for most sports especially contact or collision sports
Cerebral palsy	Yes	Individual assessment according to functional capacity and type of activity
Asthma	Yes	Albuterol before sports in cases of exercise-induced asthma, *not* during acute asthma
Upper respiratory infection	Yes	Mild cases only; not if having fever
Bleeding disorder	Yes	Needs individual assessment
Sickle cell trait	Yes	Cases of sickle cell disease will need individual assessment
Diabetes mellitus	Yes	Check blood glucose every 30 min during continuous exercise, 15 min after completion of exercise, and at bedtime
HIV	Yes	All skin lesions should be covered; if viral load is high, certain sports such as boxing and wrestling should be avoided
Skin infection	Yes	Not during contagious period especially in gymnastics, sports using mats, contact sports

Heart murmur

- If the murmur is innocent (does not indicate heart disease), full participation is permitted. Otherwise, athlete needs evaluation

Cardiac conditions that disqualify an athlete from sports

- Pulmonary vascular disease with cyanosis or a hemodynamically significant right-to-left shunt
- Severe pulmonary stenosis (untreated)
- Severe aortic stenosis or regurgitation (untreated)
- Severe mitral stenosis or regurgitation (untreated)
- Any cardiomyopathy
- Vascular Ehlers–Danlos syndrome
- Coronary anomalies (especially anomalous coronary origins)
- Catecholaminergic polymorphic ventricular tachycardia
- Acute pericarditis
- Acute myocarditis
- Acute Kawasaki disease (less than 8 weeks)

Cardiac conditions for which athletes require cardiologist consultation

- Marfan syndrome
- Mitral valve prolapse
- Dysrhythmia (irregular heart rhythm)
- Long-QT syndrome
- Wolff–Parkinson–White syndrome
- Advanced heart block
- Kawasaki disease (coronary artery vasculitis) of 8 weeks or more
- Pulmonary hypertension
- Anthracycline use

Exercise-induced bronchoconstriction

- Non-pharmacologic treatment includes:
  - Warm-up exercise
  - Using a face mask/scarf during exercise
- Pharmacologic treatment includes:
  - Short-acting beta-agonists (SABA) to treat symptoms
  - To prevent symptoms, may use SABA 5–20 min before exercise
  - If requiring medication daily or several times daily, consider adding a controller medication such as an inhaled corticosteroid with or without a long-acting beta-agonist or a leukotriene receptor agonist

Diabetes mellitus

- Athletes who have type 1 diabetes mellitus (DM1) are permitted to participate in any sport without restriction
- At a minimum, athletes who have DM1 should measure their blood glucose every 30 min during continuous exercise, 15 min after completion of exercise, and at bedtime
- Insulin pumps and rapid-acting insulins have allowed athletes to fine-tune their glycemic control much more effectively than in the past

HIV infection

- Because of the apparent minimal risk to others, all sports may be played as athlete's state of health allows
- For all athletes, skin lesions should be covered properly
- If viral load is detectable, then athletes should be advised to avoid high-contact sports such as wrestling and boxing

Seizure disorder, well-controlled

- Risk of seizure during participation is minimal
- Participation in water activities must be conducted under direct supervision at all times

Seizure disorder, poorly controlled

- Athlete needs individual assessment for collision, contact, or limited-contact sports
- The following noncontact sports should be avoided:
  - Archery, riflery, swimming, weight lifting, powerlifting, strength training, and sports involving heights; in such sports, occurrence of a seizure during activity may pose a risk to self or others
  - Physical activity should be promoted as long as there is not a significant risk to the individual

Cerebral palsy

- Athlete needs evaluation to assess functional capacity to perform sports-specific activity
- Functional aerobic and strength training that increases muscle size and strength
- Addition of anaerobic training to progressive resistance strengthening leads to improved functional capacity

Down syndrome (DS)

- Instability of the cervical spine (primarily atlantoaxial instability, but also occipitoatlantal instability) has been reported in up to 30% of patients with DS
- Check for gait disturbance, neck movements, tendon reflexes, and plantar responses.
- Sport pre-participation screening for AAI symptoms. Routine neck x-ray for asymptomatic patients is no longer recommended
- DS patients should be prohibited from participating in collision sports regardless of the radiographic appearance of their spines. However, no other limitations need be imposed for patients who have normal cervical spine radiographs
- Special Olympics considers diving, gymnastics, butterfly stroke, high jumping, soccer, and pentathlon to be "neck-stressing." Athletes with DS and cervical instability may use a cervical collar, but this practice does not change their sport restriction
- DS is associated with other abnormalities that may influence sports participation, such as cardiac abnormalities (septum defects, in particular), cataracts, diabetes, thyroid disease, hip and patellar instability, and foot abnormalities

Skin diseases

- Open wounds should be cleaned and covered for practice and play to reduce the risk of blood-borne pathogen transmission

Tinea corporis

- Tinea corporis requires a minimum of 72 h of topical treatment with antifungal cream
- Lesions must be covered with a gas-permeable dressing
- Tinea capitis requires a minimum of 2 weeks of treatment

Herpes simplex

- Free of systemic symptoms
- No new lesions for at least 72 h
- No moist lesions
- All lesions must be covered with a firm, adherent crust
- Minimum of 120 h of systemic treatment
- Active lesions cannot be covered to allow for participation

Molluscum contagiosum

- Lesions must be removed or treated with curettage
- Localized lesions may be covered with a dressing followed by underwrap and stretch tape

Furuncle/carbuncles/folliculitis/impetigo/cellulitis

- No new lesions for minimum of 48 h
- Minimum of 72 h of treatment
- No moist, exudative, or draining lesions
- Active lesions cannot be covered to allow for participation
- Prevention
  - Wash hands with soap and water
  - Avoid whirlpools or common tubs
  - Avoid sharing towels and razors
  - Clean facilities daily
  - Treat and cover skin lesions

Eyes

- Protective eyewear is recommended in all sports involving risk for eye injury
- Lenses made of polycarbonate or CR-39 are recommended for protection
- Strap is necessary to secure the protective eyewear in place
- Visual acuity of 20/40 or better is considered to provide good vision
- Visual acuity of less than 20/40 in one eye is considered functionally one-eyed
- Protective eyewear is required in all athletes considered functionally one-eyed
- Visual acuity must be checked at each well-child visit

Eating disorders
- Restriction from practice and competition until medically stable and has recovered from the eating disorder

Sickle cell disease and trait
- Regular, non-stressful exercise
- Gradual increase in physical activity over weeks
- Plenty of fluids before, during, and after exercise
- Avoid collision, endurance, and high-intensity sports
- Rest when tired
- Adequate hydration
- Focus on sports that requires focus and skill, not endurance
- Adequate oxygenation
- Counseling to prevent sickle cell crisis

Obesity
- Discourage sedentary lifestyle
- Promote physical activity
- Nutritional education
- Restrict high-sugar foods
- Restrict time spent watching TV and playing video games

Solitary kidney
- A qualified yes for participation in adolescents with only one kidney
- Individual player assessment must be conducted to determine if additional protective equipment is needed
- Protective equipment may reduce the risk of injury sufficiently to allow participation in most sports

Heat Illness

Background
- Exertional heatstroke is a potentially life-threatening condition that accounts for ~2% of all sports-related deaths
- Patients under the age of 20 account for a majority of exertional heat illnesses presenting to the emergency room
- 48% of those patients presenting to the emergency room are youth and adolescent individuals playing football

Risk factors
- Hot weather
- Humidity
- Poor fitness
- Elevated body mass index (BMI)
- Elderly
- Medications

Clinical presentation
- Cramps
- Dehydration
- Fatigue
- Elevated body temperature
- Diaphoresis
- Nausea
- Weakness
- Altered mental status
- Dizziness
- Delirium

Diagnosis
- Heat Exhaustion
  - Rectal temperature less than 104 °F
- Heatstroke
  - Core rectal temperature ≥ 104 °F
  - Multi-organ system failure

Treatment
- Heat Exhaustion
  - Lay patient in supine position in a shaded area
  - Cooling
  - Oral fluid replacement
  - Rapid cooling
  - Ice packs in neck, axilla, and groin
  - Submersion in ice water bath
- Heatstroke
  - Early recognition with rapid and immediate cooling in ice water bath
  - Oral rehydration if possible
  - Maintain airway, breathing, and circulation
  - Transport to nearest emergency facility

INJURY PREVENTION

Conditioning (Role of Conditioning in Preventing Injuries in Athletes)

Background

- Interventions based on exercise are effective in treating and preventing injuries
- Most interventions used to prevent injuries include stretching, core stability, and plyometrics
- Injuries are reduced by 40% in those who implement prevention programs

Treatment

- Physical activity-based conditioning, compared to just stretching, reduces injuries by 35–50%
- Strength-training exercise should incorporate concentric and eccentric exercises

Role of Rehabilitation of Current Injuries to Prevent Further Injuries

Background

- Loss of motion typically occurs following a sports injury or surgery
- Rehabilitation is key to successful results following injury or surgery
- A team approach with a treatment plan is essential for appropriate recovery

Treatment

- Early motion and mobility following injury
- Rehabilitation should begin immediately following the injury or surgery
- Establish milestones and goals for rehabilitation
- Create a treatment plan that is effective

Head Injuries

- Sports in which a head injury most commonly occurs:
  - Cycling, football, baseball and softball, basketball, skateboards/scooters, water sports, soccer, trampolines
- Prevention
  - Helmets can significantly reduce the risk of severe brain injuries

Mouth

- Use of a mouthguard during sports activities decreases oral injuries, including tooth avulsions, tooth fractures, and lacerations
- Custom mouthguards made for an individual by a dental health professional may fit better and be more comfortable than less expensive "boil and bite" or off-the-shelf mouthguards.
- Professionally fitted mouthguards have not consistently been shown to decrease oral injury rates compared with "boil and bite" or off-the-shelf mouthguards.
- Although mouthguards decrease the risk of dental injury, they do not provide protection against sports concussions

Neck Injury

- Over half of catastrophic injuries in sports are cervical spine injuries.
- Cervical spine injuries have been reported in most contact sports, including football, hockey, rugby, and wrestling, as well as in several noncontact sports, such as skiing, track and field, diving, surfing, powerlifting, and equestrian events
- Cervical spine injuries are estimated to occur in 10–15% of all football players, most commonly in linemen and defensive players.
- Full immobilization on a backboard is required to stabilize the neck
- When immobilizing the neck, avoid movement and maintain proper alignment of the cervical vertebrae. This usually can be done with the helmet and other protective gear

(e.g., shoulder pads) in place, and such equipment should not be removed
- In the football setting, the athlete should be immobilized with the pads and helmet both on or both off
- When direct access to the face is required, the face mask may be removed from the helmet with a screwdriver or cutting tool

SPORTS-RELATED INJURIES

Mild Traumatic Brain Injury (Concussion)

Background
- Annually, there are 300,000 sports-related concussions among high school and collegiate athletes
- Sports is the second leading cause of concussions in individuals aged 15–24
- Biomechanical forces directly or indirectly applied to the brain
- Inappropriately treated concussion may lead to second-impact syndrome, causing uncontrolled cerebral edema

Clinical presentation
- Headache
- Dizziness
- Blurred vision
- Retrograde or anterograde amnesia
- Emotional lability
- Nausea and/or vomiting
- Confusion
- Memory loss
- Poor concentration

Diagnosis
- History and physical
- The diagnosis of a concussion is a clinical decision based on presentation and an inciting event that may have led to forces transmitted to the brain
- Neuropsychological testing is utilized to identify and monitor the progression of a concussion, but currently there is no evidence to support this
- Currently, there is no imaging modality available that identifies any structural abnormalities within the central nervous system

Treatment
- The Concussion in Sports Group has identified 11 steps necessary for concussion management. These include:
  - **Recognize**
    - It is important to determine if the symptoms present are not the result of drugs, alcohol, medication, cervical injuries, or vestibular dysfunction
  - **Remove**
    - Athlete should be removed and evaluated by a health professional when a concussion is suspected
    - Athletes may not return to play during the same game
  - **Reevaluate**
    - Individual should be reevaluated for sleep/wake disturbance, ocular function, and vestibular function
    - Neuropsychiatric testing contributes clinical value, but no evidence exists suggesting that outcomes are different when neuropsychiatric testing is completed
    - Neuropsychiatric assessment is not needed for all athletes following a sports-related concussion
  - **Rest**
    - Complete rest is recommended during the first 24–48 h following the concussion
    - Following this brief period, individuals may be encouraged to increase their level of activity gradually
    - The level and intensity must not induce or worsen symptoms
    - Prolonged rest may delay recovery
    - The overall goal is to increase physical activity without inducing symptoms after a brief period of rest

- **Rehabilitation**
  - Symptoms lasting longer than 10–14 days should incorporate psychological, cervical, and vestibular therapy
  - Gradual increase in physical activity below the level of symptom induction
- **Refer**
  - Symptoms lasting longer than 4 weeks in children should have a multidisciplinary approach with specialists trained in concussion management
  - Targeted aerobic exercise program should be implemented in individuals with autonomic instability or deconditioning
  - Physical therapy should initially be directed toward vestibular- and cervical-related symptoms
  - Currently, there are no medications recommended for the treatment of sports-related concussion
- **Recover**
  - Currently, there is no evidence outlining the length of time for recovery
  - Current research is investigating various forms of imaging and blood markers to determine the presence and length of time for recovery
  - It is difficult to determine how long the symptoms will last in an individual with a sports-related concussion
- **Return to sport**
  - The first step of the return-to-play protocol has been modified and recommends that an initial 24–48 h of physical and cognitive rest be completed before the return-to-sport protocol may begin
  - Step one of the protocol recommends symptom-limited activity that does not provoke symptoms
  - Most repeat concussions occur during the first 10 days following the initial concussion
  - Athletes should wait a minimum of 10 days before returning to contact sports
- **Reconsider**
  - Prior to returning the athlete to sports, they must return to full academics
  - Prior to returning to academics, a complete rest period of 24–48 h must be implemented
  - Before returning to academics, the athlete must perform daily activities at home that do not give the individual symptoms
  - Thereafter, the athlete may return to academics part-time and, if tolerated, transition to full time
- **Residual effects and sequelae**
  - Various studies have shown that repeated concussions may lead to depression and cognitive impairment along with chronic traumatic encephalopathy
  - Further research is needed examining the cause and effect relationship
- **Risk reduction**
  - Mixed results are evident with the use of a mouthguard
  - Vision training may reduce the prevalence of concussions
  - Revisioning policies and rules of competition have had an effect in reducing the number of concussions

- The Concussion in Sports Group has recently outlined six-step recommendations for return to sport following a concussion:
  - Limited activity that does not provoke symptoms
  - Light aerobic activity
  - Sport-specific exercise
  - Noncontact drills
  - Full-contact practice
  - Return to full play
- Before the return-to-play protocol can be initiated, the athlete must return to full academics without limitations/restrictions.

Anterior Shoulder (Glenohumeral) Dislocation

Background

- The shoulder joint is one of the most mobile joints in the body, but this flexibility comes at the expense of stability, making it the most common major joint to become dislocated
- More than 90% of all dislocations are anterior glenohumeral dislocation (the humeral head is anterior to the glenoid)
- Posterior glenohumeral dislocation is less than 10% of all traumatic shoulder dislocations and commonly occurs as a result of seizures

Diagnosis

- Anterior shoulder dislocation most commonly occurs after a fall on outstretched hand with arm abducted and externally rotated
- Examination will show obvious deformity—prominent acromion; humeral head may be seen anteriorly with palpable defect inferior to acromion
- The patient holds affected arm in abducted and externally rotated position
- Radiographs (anteroposterior [AP], axillary, and trans-scapular Y view) will show empty glenoid and abnormal position of the humeral head
- Posterior shoulder dislocation may not be obvious on AP view. Axillary and trans-scapular views are necessary to show the deformity

Treatment

- Closed reduction should be accomplished as soon as possible before significant muscle spasm and pain development
- Arm should be immobilized for about 2 weeks in a sling, then gradual range of motion (ROM) exercises, and strengthening exercises as tolerated
- Return to play: Athlete must regain full ROM and strength before return to play
- Indications for surgical intervention: Recurrent shoulder dislocations or associated large bony lesion

Acromioclavicular (AC) Dislocation

Background

- Separation of the joint between the lateral end of the clavicle and acromion. Occurs after direct fall onto the point of the shoulder

Diagnosis

- Swelling and tenderness over the affected AC joint
- Deformity at the AC joint (see Fig. 14.1b)

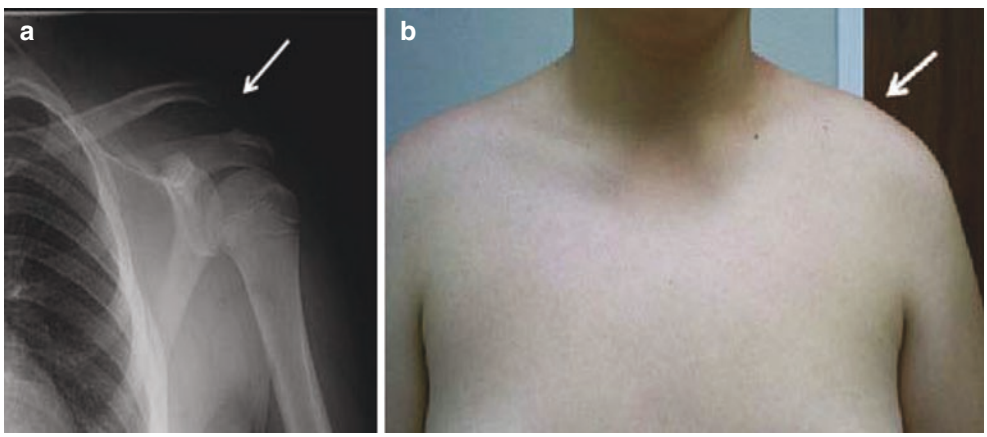


Fig. 14.1 **A** 13-year-old boy who fell in football practice on his left shoulder. (**a**) Radiograph taken at the time of injury shows separation between the clavicle and acromion (*arrow*). (**b**) Obvious deformity on the left shoulder (*arrow*)

- Limited ROM of the shoulder due to pain
- Passive adduction of the arm across the body produces pain at the AC joint
- Radiographs with AP, axillary, and Zanca views (AP with 10° cephalic tilt focused on AC joint) will demonstrate widening and/or displacement of AC joint (see Fig. 14.1a)

Treatment
- Mild displacement: Sling immobilization with early ROM
- Marked displacement: Orthopedic referral for possible surgical intervention

Little Leaguer's Shoulder and Elbow

Background
- 25% to 28% of young pitchers aged 9–12 were found to complain of elbow pain and 32–35% complained of shoulder pain
- Youth pitchers between the ages of 9–14 have a 5% risk of severe injury
- During the cocking and acceleration phase of pitching, the ulnar collateral ligament provides 55% of valgus stability
- Little Leaguer's shoulder is the result of repetitive stress to the proximal humeral growth plate
- Little Leaguer's elbow is the result of repetitive stress to the medial epicondylar plate

Little Leaguer's Shoulder
Clinical Presentation
- Typically occurs in males between the age of 13–16 during periods of rapid growth
- Pain
- Tenderness
- Widened physis of proximal humerus

Diagnosis
- History and physical
- X-ray of shoulder in both anterior and posterior views with internal and external rotation

Treatment
- Nonoperative management due to high remodeling potential
- Cessation from throwing
- Strengthening of the rotator cuff, scapulothoracic, and core musculature
- An average rest period of 3 months is needed to return to play without deficits

Little Leaguer's Elbow
Clinical presentation
- Pain and swelling over medial elbow
- Decreased ROM with extension

Diagnosis
- History and physical
- 85% of x-rays will appear normal

Treatment
- Abstinence from throwing
- Initial immobilization in an elbow brace
- Open reduction and internal fixation for more severe cases involving a fracture
- Return to play: 12 weeks of rest required if nonoperative treatment is needed; 7–8 months of rest required if operative treatment is needed

Deep Hematoma of Thigh

Background
- Result of blunt trauma to the thigh during athletic competition
- Thigh contusions are common injuries in athletes
- Rarely causes thigh compartment syndrome

Risk Factors
- Blunt trauma
- Athletic competition
- Use of anticoagulants

Clinical presentation
- Anterior thigh pain
- Swelling
- Decreased knee flexion

Diagnosis
- Clinical suspicion is best diagnostic tool to identify thigh compartment syndrome
- Chest x-ray
- CT
- Thigh compartment pressure

Treatment
- Rest
- Ice
- Elevation
- If thigh compartment syndrome is suspected, immediate surgical decompression is required

Ankle Sprain

Background
- 40% of all traumatic ankle injuries occur during sports
- Only 50% of individuals who suffer a lateral ankle sprain seek medical attention
- Chronic ankle instability may result from a lateral ankle sprain

Risk factors
- Previous history of ankle sprain
- Inversion deformity of foot
- Female
- Limited dorsiflexion
- Reduced proprioception
- BMI

Clinical presentation
- Lateral ankle pain
- Swelling
- Difficulty with ambulation
- Ecchymosis

Diagnosis
- History and physical
- X-ray if patient meets Ottawa Ankle Rules criteria
- MRI if ligamentous, osteochondral, syndesmotic, or occult fracture is suspected

Treatment
- RICE
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Functional support and exercise therapy
- Neuromuscular and proprioceptive exercise
- Surgery for chronic instability not responsive to conservative treatment
- Acupuncture and vibration therapy

OVERUSE INJURIES

Osgood–Schlatter Syndrome

Background
- Approximately 30 million children participate in sporting activities
- Limb length increases by a factor of 1.4 between the ages of 6 and 14 years, with limb mass increasing by a factor of 3, leading to musculoskeletal imbalance
- Osgood–Schlatter syndrome is the most common cause of anterior knee pain in adolescents
- During growth, the quadriceps become tighter, increasing strain on the tibial tubercle

Risk factors
- Affects males more than females
- Highly active individuals
- Mainly seen in running, jumping, kneeling, and stair-climbing activities

Clinical presentation
- Anterior knee pain
- Swelling (Fig. 14.2a)
- Localized tenderness over the tibial tubercle

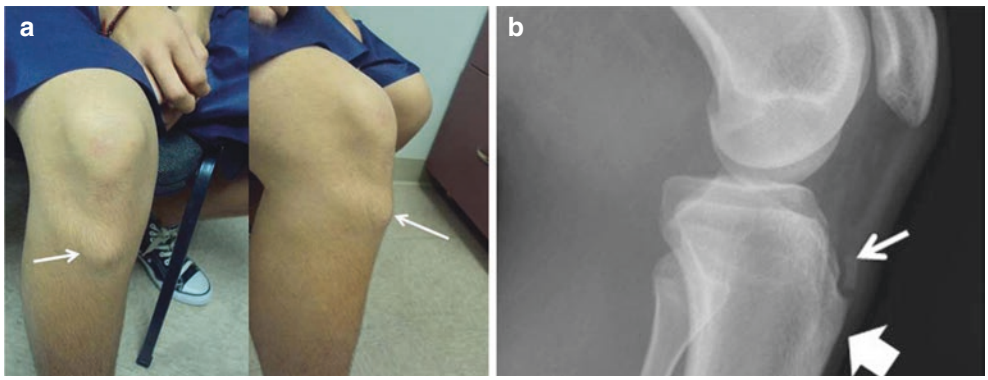


Fig. 14.2 Osgood–Schlatter disease. A14-year-old boy soccer player with right knee pain. (**a**) Examination shows anterior knee swelling over the tibial tubercle (*arrow*). (**b**) Radiographs of a patient with Osgood–Schlatter disease. *Wide arrow* points to the enlarged tibial tubercle. *Small arrow* points to the small fragment of calcification and fragmentation within the patellar ligament

Diagnosis

- History and physical
- Radiological signs of Osgood–Schlatter: Enlargement with possible fragmentation of the tibial tubercle (not required for diagnosis) (tibial apophysis; see Fig. 14.2b)

Treatment

- Conservative treatment
- Decreased activity, rest
- Ice packs for swelling and pain
- Anti-inflammatories as needed
- Symptoms may last up to 2 years before complete resolution
- Stretching and strengthening hamstring and quadriceps

Sinding–Larsen–Johansson Disease

Background

- Apophysitis of the inferior pole of the patella
- Benign condition
- Typically seen in children between the ages of 10–13 years
- Overuse injury affecting the inferior pole of the patella and the patellar tendon
- Result of repetitive traction

Clinical presentation

- Anterior knee pain localized to the distal pole of patella and proximal patella tendon
- Worsening of pain during running and jumping

Diagnosis

- History and physical exam
- Calcification identified on x-ray at the patella–patella tendon junction

Treatment

- Related to level of activity
- Conservative treatment including reduction in level of activity
- Anti-inflammatories as needed
- Icing to reduce swelling
- Stretching and strengthening of hamstrings and quadriceps
- Typically resolves within 8–12 weeks
- More severe cases with osteochondral fragmentation, knee immobilization may be required
- If fragmentation is present, referral to an orthopedic surgeon for further evaluation

Patellofemoral Pain

Background

- Accounts for 11–17% of patients presenting with anterior knee pain
- Typically affects running and jumping athletes who put excessive loads on the knee
- Females more commonly affected than males
- May be associated with recurrent patellar subluxation (see Chap. 13 Orthopedics)

Risk Factors

- Sex
- Load-bearing exercises
- Weakness
- Overtraining
- Excessive pronation

Clinical Presentation

- Anterior knee pain

Diagnosis

- Miserable malalignment syndrome consists of the following three elements:
  - Increased femoral anteversion (Fig. 14.3)
  - External tibial torsion
  - Pes planus (flatfoot)
- Physical examination demonstrating a lateral "J" sign

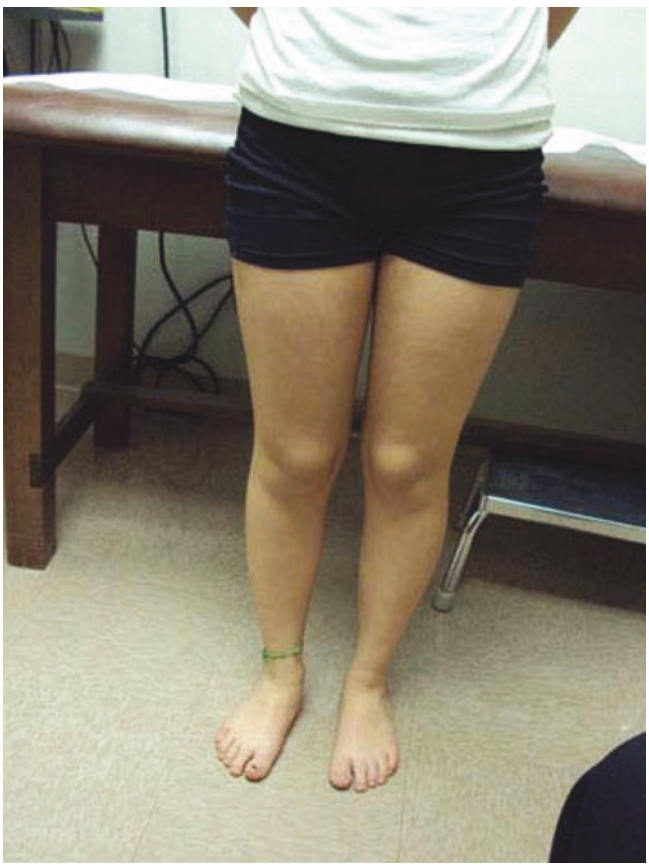


Fig. 14.3 Miserable malalignment syndrome. A 15-year-old girl with 2-year history of knee pain. Patient had excess femoral anteversion as manifested by her patellae pointing inward. Despite the inward position of the patella, her foot is still pointing forward due to her external tibial torsion

- Positive patellofemoral grind test
- Imaging does not identify any structural abnormalities

Treatment

- Rest, ice, compression, and elevation (RICE)
- Activity modification
- Muscle strengthening and stretching
- Correction of biomechanical deficits
- Bracing
- Orthotics if overpronation is present

Prepatellar Bursitis

Background

- May be caused by an infectious or noninfectious process
- Noninfectious process: Recurrent minor injuries associated with overuse (e.g., repeated kneeling)
- Infectious etiology most commonly caused by *Staphylococcus aureus*, which gains access to bone by direct inoculation (e.g., a contaminated compound fracture)

Clinical Presentation

- Pain
- Tenderness of the patella to palpation
- Warmth
- Erythema
- Swelling

Diagnosis

- Must differentiate between infectious and noninfectious
- If infection is suspected, aspiration followed by Gram stain and culture must be completed

Treatment

- If noninfectious, may be treated conservatively with RICE. May also consider intrabursal corticosteroid injection
- Antibiotics in cases of septic bursitis
- May require surgical irrigation if not improving with antibiotic administration
- Bursectomy may be necessary for chronic causes

Sever's Disease

Background

- Painful inflammation of the calcaneal apophysis due to repetitive microtrauma from the Achilles tendon
- Typically occurs during peak growth spurts and after starting a new sport or season
- Most commonly seen in boys

Risk Factors

- Increase risk in males and those physically active

Clinical presentation

- Pain in the heel with activity

Diagnosis

- History and physical
- X-ray to rule out other more serious pathology

Treatment

- Self-limited disease and typically resolves once fusion of the apophysis occurs
- Child may continue to participate in activities if pain is not severe
- Heel lifts
- NSAIDs
- Ice
- Stretching

MISCELLANEOUS

Hydration and Rehydration

- Encouraging sufficient fluid intake and optimizing hydration status can play an important role in maintaining performance and reducing the risk of exertional heat illness
- Generally, 100–250 mL (3–8 oz) every 20 min for 9- to 12-year-olds and up to 1.0–1.5 L (34–50 oz) per hour for adolescent boys and girls is enough to minimize sweating-induced body water deficits sufficiently during exercise and other physical activity, as long as pre-activity hydration status is good
- For sports activities lasting 1 h or less, water is sufficient for hydration
- Sports drinks generally contain both electrolytes and sugar and may be more palatable to children, encouraging hydration with longer activity
- Energy drinks generally contain high amounts of caffeine and are not recommended for young children or adolescents
- Healthy snacks can be offered, along with water, as an alternative to sports drinks

Female Athlete Triad

Background

- The number of adolescent girls participating in sports has increased in the last few decades
- Female athlete triad is reported to be prevalent in 1–4% of female athletes but is believed to be much higher than this
- Defined as low energy availability with or without disordered eating, menstrual dysfunction, and low bone mineral density

Risk factors

- History of depression
- Eating disorder
- Overtraining
- Pressure regarding weight from coaches, friends, and/or family
- History of stress fractures
- Nonhealing injuries
- Osteopenia/osteoporosis

Diagnosis

- *All three* components must be present to make the diagnosis:
  - Low energy availability. BMI < 17.5 kg/m^2, or < 85% expected weight in adolescents
  - Amenorrhea
  - Bone density consistent with osteopenia or osteoporosis

Treatment
- Education
- Increase energy availability
- Reduce energy expenditure
- Weight-bearing exercise
- Resistance training
- Psychotherapy if eating disorder is present
- May need a selective serotonin reuptake inhibitor (SSRI) for comorbid conditions

Performance-Enhancing Drugs

Background
- 11% of teens have admitted to using growth hormone
- Steroid use in teens has increased from 5% to 7%
- Anabolic steroids, growth hormones, stimulants, and erythropoiesis-stimulating agents are all considered performance-enhancing drugs

Clinical presentation
Anabolic steroids
- Increased muscle size
- Increased strength
- May cause acne, hepatic dysfunction, suppression of hypothalamus–pituitary–gonadal axis, aggression, and premature closure of the epiphyseal growth plate

Growth hormones
- Increase in strength, power, aerobic performance, and respiratory muscle strength
- Adverse effects include hyperglycemia, insulin resistance, edema, myalgia, gynecomastia, cardiovascular disease, and intracranial hypertension

Stimulants
- Increase alertness, improved endurance, anaerobic performance, and reaction time
- Adverse effects include hypertension, tachycardia, heart attack, headaches, tremors, insomnia, anxiety, aggression, and psychosis

Erythropoiesis-stimulating agents
- Enhance oxygen delivery to active muscles
- Enhance aerobic power and physical exercise tolerance
- Adverse effects include increased blood viscosity, heart attacks, strokes, deep vein thrombosis, and pulmonary embolism.

Diagnosis
- Urine drug screen
- Blood analysis for doping

Treatment
- Education
- Counseling
- Motivational interviewing
- Disqualification from competition

Physical Fitness

Background
- Current guidelines recommend 60 min of moderate- to high-intensity physical activity daily for individuals aged 5–18
- Increased daily screen time is related to negative effects on the cardiovascular system
- High levels of physical activity, cardiorespiratory fitness, and muscle fitness are associated with a reduced risk of cardiovascular disease

Risk factors
- Family history of cardiovascular disease and obesity
- Increased access to electronics, including TV, video games, computers, and cell phones
- Sedentary guardians

Treatment
- Increasing moderate to vigorous physical activity, muscle fitness, and cardiorespiratory fitness to reduce the risk of cardiovascular disease

PEARLS AND PITFALLS

- An increasing systolic murmur with Valsalva during the pre-participation physical should undergo further evaluation prior to clearance.
- New onset of tinea, herpes, or molluscum should restrict athlete from play until minimum duration of treatment is completed.
- Visual acuity of less than 20/40 is considered functionally one-eyed and requires protective eyewear.
- Individuals with eating disorders or reduced caloric intake should be restricted from further practice/competition until caloric intake matches energy expenditure.
- Rectal temperature of greater than 104 °F requires immediate cooling in an ice water bath followed by further evaluation in the emergency room.
- Individuals with a suspected concussion should be removed from competition/practice and not allowed to return until cleared by a physician to begin return-to-play protocol.
- Little Leaguer's shoulder and elbow should undergo physical therapy to correct throwing mechanics.
- Female athletes with energy deprivation, amenorrhea/oligomenorrhea, and decreased bone density should be evaluated for female athlete triad.

Suggested Reading

Aaron DL, Patel A, Kayiaros S, Calfee R. Four common types of bursitis: diagnosis and management. J Am Acad Orthop Surg. 2011;19(6):359–67.

Al-Rimawi H, Jallad S. Sport participation in adolescents with sickle cell disease. Pediatr Endocrinol Rev. 2008;6(Suppl 1):214–6.

Barker AR, Gracia-Marco L, Ruiz JR, Castillo MJ, Aparicio-Ugarriza R, González-Gross M, et al. Physical activity, sedentary time, TV viewing, physical fitness and cardiovascular disease risk in adolescents: the HELENA study. Int J Cardiol. 2018;254:303–9.

Bergeron MF, Waller JL, Marinik EL. Voluntary fluid intake and core temperature responses in adolescent tennis players: sports beverage versus water. Br J Sports Med. 2006;40(5):406–10.

Bernhardt DT, Roberts WO. PPE: preparticipation physical evaluation. 4th ed. Elk Grove Village: American Academy of Pediatrics; 2010.

Bratland-Sanda S, Sundgot-Borgen J. Eating disorders in athletes: overview of prevalence, risk factors and recommendations for prevention and treatment. Eur J Sport Sci. 2013;13(5):499–508.

Brennan FH, Alent J, Ross MJ. Evaluating the athlete with suspected exercise-induced asthma or bronchospasm. Curr Sports Med Rep. 2018;17(3):85–9.

Brown KA, Dewoolkar AV, Baker N, Dodich C. The female athlete triad: special considerations for adolescent female athletes. Transl Pediatr. 2017;6(3):144–9.

Caggiano S, Cutrera R, Di Marco A, Turchetta A. Exercise-induced bronchospasm and allergy. Front Pediatr. 2017;5:131. https://doi.org/10.3389/fped.2017.00131.

Capovilla G, Kaufman KR, Perucca E, Moshé SL, Arida RM. Epilepsy, seizures, physical exercise, and sports: a report from the ILAE task force on sports and epilepsy. Epilepsia. 2016;57(1):6–12.

Centers for Disease Control and Prevention. National Center for Health Statistics. Prevalence of overweight and obesity among children and adolescents: United States, 1963–1965 through 2011–2012. (n.d.). Last reviewed 6 Nov 2015; last updated 9 Sep 2014. https://www.cdc.gov/nchs/data/hestat/obesity_child_11_12/obesity_child_11_12.htm. Accessed 22 Nov 2018.

Colosimo AJ, Ireland ML. Thigh compartment syndrome in a football athlete: a case report and review of the literature. Med Sci Sports Exerc. 1992;24(9):958–63.

Dick NA, Diehl JJ. Febrile illness in the athlete. Sports Health. 2014;6(3):225–31.

Dobbe AM, Gibbons PJ. Common pediatric conditions of the lower limb. J Paediatr Child Health. 2017;53(11):1077–85.

Gessel LM, Fields SK, Collins CL, Dick RW, Comstock RD. Concussions among United States high school and collegiate athletes. J Athl Train. 2007;42(4):495–503.

Gillett JG, Lichtwark GA, Boyd RN, Barber LA. Functional anaerobic and strength training in young adults with cerebral palsy. Med Sci Sports Exerc. 2018;50(8):1549–57.

Hendrix CL. Calcaneal apophysitis (sever disease). Clin Podiatr Med Surg. 2005;22(1):55–62, vi.

Ip P, Ho FK, Louie LH, Chung TW, Cheung YF, Lee SL, et al. Childhood obesity and physical activity-friendly school environments. J Pediatr. 2017;191:110–6.

Neurologic disorders. MSD manual professional version. Kenilworth: Merck & Co; 2018. https://www.merckmanuals.com/professional/neurologic-disorders. Accessed 11 Nov 2018

Patel DR, Villalobos A. Evaluation and management of knee pain in young athletes: overuse injuries of the knee. Transl Pediatr. 2017;6(3):190–8.

Petersen W, Rembitzki I, Liebau C. Patellofemoral pain in athletes. Open Access J Sports Med. 2017;8:143–54.

Pusateri ME, Hockenberry BJ, McGrew CA. Zurich to Berlin—"where" are we now with the concussion in sport group? Curr Sports Med Rep. 2018;17(1):26–30.

Silva PV, Kamper SJ, da Cunha Menezes Costa L. Exercise-based intervention for prevention of sports injuries (PEDro synthesis). Br J Sports Med. 2018;52(6):408–9.

Styn NR, Wan J. Urologic sports injuries in children. Curr Urol Rep. 2010;11(2):114–21.

Tisano BK, Estes AR. Overuse injuries of the pediatric and adolescent throwing athlete. Med Sci Sports Exerc. 2016;48(10):1898–905.

Tsai CH, Hsu CJ, Hung CH, Hsu HC. Primary traumatic patellar dislocation. J Orthop Surg Res. 2012;7:21.

Vuurberg G, Hoorntje A, Wink LM, van der Doelen BFW, van den Bekerom MP, Dekker R, et al. Diagnosis, treatment and prevention of ankle sprains: update of an evidence-based clinical guideline. Br J Sports Med. 2018;52(15):956.

White ND, Noeun J. Performance-enhancing drug use in adolescence. Am J Lifestyle Med. 2017;11(2):122–4.

Wilk KE, Arrigo CA. Rehabilitation: common problems and solutions. Clin Sports Med. 2018;37(2):363–74.

Yard EE, Gilchrist J, Haileyesus T, Murphy M, Collins C, McIlvain N, et al. Heat illness among high school athletes – United States, 2005-2009. J Saf Res. 2010;41(6):471–4.

Zinder SM, Basler RS, Foley J, Scarlata C, Vasily DB. National athletic trainers' association position statement: skin diseases. J Athl Train. 2010;45(4):411–28.

Rheumatology

15

Amanda G. Brown, William Blaine Lapin,
Andrea A. Ramirez, and Jennifer L. Rammel

ARTHRITIS

Juvenile Idiopathic Arthritis (JIA)

Background and Definitions

- Previous classification criteria include juvenile rheumatoid arthritis and juvenile chronic arthritis.
- **Arthritis** (Fig. 15.1):
  - Joint stiffness is the most common symptom.
  - Stiffness worsens with inactivity and improves with activity.
  - Joint swelling.
  - Pain (may be absent).
  - Physical exam findings: joint effusion (swelling), joint warmth, decreased range of motion, tenderness, and pain with range of motion.
- **Enthesitis**:
  - Inflammation of the entheses (sites of tendon or ligament insertion onto bone)
  - Common sites: Achilles tendons, patellar tendons (2, 6, and 10 o'clock positions), greater trochanter, metatarsal heads, and plantar fascia
- JIA is broadly defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age.

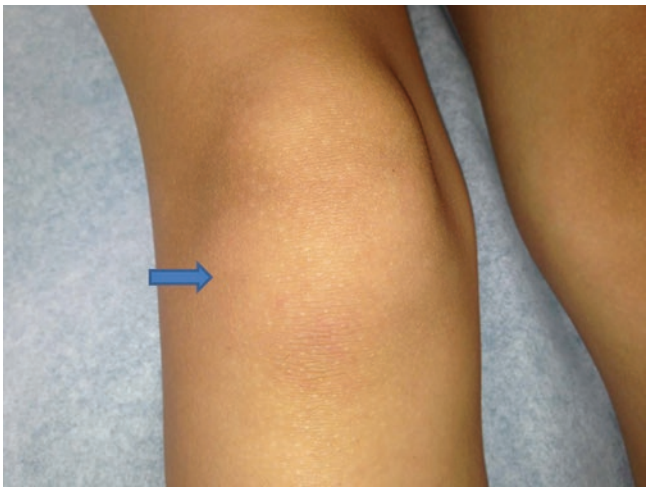


Fig. 15.1 9-year-old female with 3-year history of recurrent arthritis and morning stiffness, presenting with joint pain, swelling, and limping. Note the effusion and swelling of the right knee

- The exact etiology is unknown, but genetic and environmental factors are involved.
- Exact incidence and prevalence is unknown and varies with subtypes.
- Oligoarticular and polyarticular subtypes are more common among females.
- JIA is a clinical diagnosis; there is no laboratory test that makes the diagnosis.
- Other causes of arthritis (i.e., trauma, infection, malignancy) must be ruled out before a diagnosis of JIA is made (Table 15.1).

Classification (Table 15.2) [1]

A. G. Brown (✉) · W. B. Lapin · A. A. Ramirez · J. L. Rammel
Division of Rheumatology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
e-mail: Amanda.Brown2@bcm.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_15

Table 15.1 Differential diagnosis for child with arthritis

Autoimmune
Juvenile idiopathic arthritis
Inflammatory bowel disease
Systemic lupus erythematosus
Sjögren syndrome
Vasculitis (e.g., Henoch-Schönlein purpura, Kawasaki disease)
Neoplastic
Leukemia
Sarcoma
Pigmented villonodular synovitis (PVNS)
Trauma
Infection
Septic joint (most common pathogens: *Staphylococcus* spp., *Streptococcus* spp., *Kingella* spp.)
Tuberculosis
Osteomyelitis
Lyme disease
Neisseria gonorrhoeae
Infection-associated
Acute rheumatic fever
Post-streptococcal reactive arthritis
Reactive arthritis
Hematologic diseases
Sickle cell disease
Hemophilia
Autoinflammatory diseases
Familial Mediterranean fever
Sarcoidosis/Blau syndrome
Cryopyrin-associated periodic syndrome (CAPS)

Oligoarticular JIA

- Most common subtype of JIA.
- Most commonly affects females between 2 and 4 years of age.
- Joint involvement:
  - Most common joint affected is the knee. Other joints (wrists, ankles) can be affected. Joint involvement is asymmetric.
  - Arthritis in < 4 joints during the first 6 months of disease:
    - Persistent oligoarticular JIA: < 4 joints throughout disease course
    - Extended oligoarticular JIA: > 4 joints affected beyond 6 months
- Classic clinical vignette:
  - 2-year-old Caucasian female with persistently swollen knee whose parents note she walks with a limp in the morning or after naps. She is otherwise well, and infections and malignancies have been ruled out.
- Exclusion criteria:
  - Psoriasis in a child or first-degree relative
  - HLA-B27+ male older than age 6 years, ankylosing spondylitis/enthesitis-related arthritis/sacroiliitis with inflammatory bowel disease (IBD)/reactive arthritis or acute anterior uveitis in a first-degree relative
  - Rheumatoid factor (RF) positive in two assessments 3 months apart
  - Systemic-onset JIA in a child

Table 15.2 International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA) [1]

Category	Definition
Systemic onset JIA	Arthritis and fever (> 2 weeks, documented quotidian × 3 + days), plus one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatosplenomegaly, serositis
Oligoarthritis	Arthritis in < 4 joints in the first 6 months of disease
Polyarticular rheumatoid factor (RF)-negative	Arthritis in > 5 joints during the first 6 months of disease and RF-negative
Polyarticular rheumatoid factor (RF)-positive	Arthritis in > 5 joints during the first 6 months of disease and RF-positive × 2 at least 3 months apart
Psoriatic arthritis	Arthritis and psoriasis or arthritis plus two of the following: dactylitis, nail pitting or onycholysis; psoriasis in a first-degree relative
Enthesitis-related arthritis (ERA)	Arthritis and enthesitis, ***or*** arthritis, ***or*** enthesitis, plus two or more of the following: sacroiliac joint tenderness or inflammatory lumbosacral pain, HLA-B27 +; onset of arthritis in a male older than age 6 years; acute anterior uveitis; history of ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis in a first-degree relative
Undifferentiated arthritis	Arthritis that fulfills criteria for no category or two or more categories

- Antinuclear antibody (ANA) is positive in approximately 50% of children with JIA and confers an increased risk of uveitis.

Polyarticular JIA

- Bimodal incidence in children 1–3 years of age and again in adolescence.
- Children are either RF positive or negative, based on positive testing found on two occasions 3 months apart.
- RF-negative disease more common in Caucasians, while RF-positive disease more common in non-whites.
- RF-positive polyarthritis is a more aggressive disease and closely approximates adult rheumatoid arthritis.
- Fatigue and weight loss may be present with severe disease (unlike oligoarthritis).
- Joint involvement:
  - Children have more than 4 joints involved within the first 6 months of disease.
  - Large and small joints are affected. Joint involvement pattern is symmetric.
  - Temporomandibular and cervical spine joints may be involved and are more commonly affected in RF-negative children.
- Classic clinical vignette:
  - 15-year-old female with swelling of bilateral ankles, wrists, and proximal interphalangeal joints. She complains of morning stiffness lasting 2 h per day and difficulty with daily activities such as writing, typing, and fastening buttons.
- Exclusion criteria:
  - Psoriasis in a child or first-degree relative, HLA-B27+ male older than age 6 years
  - Ankylosing spondylitis/enthesitis-related arthritis/sacroiliitis with IBD/reactive arthritis or acute anterior uveitis in a first-degree relative
  - Rheumatoid factor (RF) positive in two assessments 3 months apart
  - Systemic-onset JIA in a child

Enthesitis-Related Arthritis (ERA)

- Background
  - More commonly affects males.
  - Prevalence: approximately 10% of children with JIA.
  - Mean age of onset: 12 years of age.
  - Commonly involves axial skeleton (spine, sacroiliac joints), although spine involvement is less common than in adult-onset disease.
- Classic findings:
  - Joint involvement pattern: Arthritis is usually pauciarticular (< 5 joints involved).
  - Ankylosing spondylitis; axial involvement does not typically occur early in disease course.
  - Axial involvement found in roughly one-third of children.
  - May develop acute-onset, symptomatic uveitis. Other subtypes of JIA present with asymptomatic uveitis. Uveitis may occur before arthritis.
  - HLA-B27 may be present or absent and is not required for diagnosis.
  - Associated with IBD (may screen with fecal calprotectin, a marker for intestinal inflammation).
- Exclusion criteria:
  - Psoriasis in a child or first-degree relative
  - RF positive in two assessments 3 months apart
  - Systemic-onset JIA in a child
- Axial disease requires anti-tumor necrosis factor (TNF) therapy.
- Complications:
  - Acute-onset, symptomatic uveitis, cardiovascular disease (aortic regurgitation)

Psoriatic JIA

- Bimodal peak onset: at 2–4 years of age and mid- to late childhood.
- Mean age of onset is roughly 9 years of age.

- May present with arthritis with psoriasis.
- Prevalence is approximately 6–10% of children with JIA.
- Classic findings:
  - Psoriasis, nail pitting, nail ridging, or onycholysis.
  - Psoriasis does not have to be present if there is a family history in at least one first-degree relative.
  - Joint involvement pattern:
    - Arthritis is usually pauciarticular (< 5 joints involved).
    - Distal interphalangeal joints (DIP) are commonly affected.
    - Dactylitis, "sausage digit."
    - Arthritis may precede the psoriasis by many years.
- Exclusion criteria:
  - HLA-B27+ male older than age 6 years, ankylosing spondylitis/ERA/sacroiliitis with IBD/reactive arthritis or acute anterior uveitis in a first-degree relative
  - RF positive in two assessments 3 months apart
  - Systemic-onset JIA in a child

Systemic-Onset JIA

- Disease characterized by fevers, arthritis, and one of the following: generalized lymphadenopathy, hepato- or splenomegaly, and/or serositis.
- Accounts for 10–20% of children with JIA.
- Peak age of onset is 1–5 years of age, although the disease may present at anytime during childhood.
- Infections and malignancy must be ruled out first as cause of fevers. Bone marrow biopsy is recommended to rule out malignancy.
- Classic findings:
  - Classic fever pattern is a quotidian fever. Children are often well appearing between fever spikes.
  - Rash described as salmon-colored macular or papular that appears during fever spikes and usually involves the trunk, neck, and proximal extremities. Rash is typically non-pruritic, and stroking of the skin elicits Koebner phenomenon.
  - In addition to arthritis, arthralgias, myalgias, and tenosynovitis may be present. Arthritis may not be present at diagnosis, but most children will develop arthritis within 3 months of disease onset.
  - Joint involvement may be oligoarticular or polyarticular and if left untreated often leads to bony erosions and joint destruction.
  - Lymphadenopathy is present in over one-quarter of patients.
  - Serositis may manifest as pericarditis, pericardial effusion, pleuritis, or pleural effusions.
- Rare manifestations:
  - Septic meningitis and interstitial lung disease
- Approximately 10% of children will present with macrophage activation syndrome (MAS). Mortality rate for MAS is approximately 8%.
- Exclusion criteria:
  - Psoriasis in a child or first-degree relative, HLA-B27+ male older than age 6 years
  - Ankylosing spondylitis/ERA/sacroiliitis with IBD/reactive arthritis or acute anterior uveitis in a first-degree relative, RF positive in two assessments 3 months apart

Macrophage Activation Syndrome (MAS)

Background

- Most commonly a complication of systemic-onset JIA.
- May be seen with other rheumatic diseases.

- Related to hemophagocytic lymphohistiocytosis (HLH).
- May be seen in up to 10% of patients with systemic-onset JIA.
- Pathogenic mechanism related to overwhelming inflammatory process.
- Patients with MAS generally appear unwell and can quickly deteriorate to shock and fulminant organ failure.

Laboratory

- Pancytopenia (platelet count the first cell line to decrease)
- Elevated serum ferritin
- Prolongation of the prothrombin time and partial thromboplastin time, elevated D-dimer
- Low or decreasing fibrinogen
- Elevated transaminases early in MAS as high as 1000s
- Falling erythrocyte sedimentation rate (ESR) with rising or persistently elevated CRP
- Elevated triglycerides
- Hemophagocytosis (bone marrow, lymph nodes, liver, or spleen)

Treatment

- Prompt treatment is critical.
- Prognosis: fatality in 5–10% of cases.
- Corticosteroids and cyclosporine can prevent life-threatening complications.

Uveitis

- Screening based on ANA status, age at diagnosis, and JIA subtype.
- **Screening recommendations for children with JIA without known uveitis:** [2]
  - ANA positive (oligoarticular JIA, polyarticular JIA) depending on the age of onset:
    - Onset age < 7 years of age
      - Uveitis screening every 3–4 months
    - Onset age > 7 years of age
      - Uveitis screening every 6 months
  - ANA negative (oligoarticular JIA, polyarticular JIA):
    - Uveitis screening every 6 months
  - Systemic-onset JIA, ERA:
    - Uveitis screening every 12 months
- The severity and disease course may not correspond to the arthritis course.
- Uveitis may develop before or after JIA diagnosis.
- Most types of uveitis associated with JIA are insidious and often asymptomatic.
- Complications of uveitis include synechiae, band keratopathy, glaucoma, cataracts, and blindness.
- Treatment: topical glucocorticoid eye drops, topical mydriatic eye drops, second-line agents same as for arthritis to achieve remission and avoid long-term steroid drops.

Laboratory Abnormalities in JIA

- JIA is a clinical diagnosis. It cannot be diagnosed by a blood test.
- Laboratory data help to exclude other causes of arthritis.
- Synovial fluid analysis can be helpful to rule out septic arthritis.
- Nighttime pain, pain out of proportion to exam, or abnormalities in complete blood count (CBC) should prompt workup for leukemia or lymphoma. Consider screening with uric acid and lactate dehydrogenase level.
- CBC may be normal. May show normocytic anemia (if chronic inflammation has been present) or mildly elevated platelet value (indicative of inflammatory state).
- Inflammatory markers C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) may be normal or elevated.
- Expect to see elevated CRP, ESR, and ferritin in untreated systemic-onset JIA.

- ANA is present in ~50% of children with JIA but is not helpful for making diagnosis. ANA status is helpful for outlining risk of uveitis (see below). Positive ANA may be detected in 10–30% of healthy pediatric population or after infection. Immunofluorescence method is the gold standard test method.
- Only 10% of children with JIA are RF positive.

Imaging

- Conventional radiographic imaging may be normal, especially in acute setting.
- Ultrasound may be useful to detect joint effusions.
- Magnetic resonance imaging (MRI) without contrast can detect synovitis and joint damage (joint space narrowing, bony erosions).
- Synovial enhancement (indicating active disease) may be better seen with addition of contrast to MRI protocol.

Complications of JIA

- Osteopenia/osteoporosis may occur.
- Untreated arthritis can lead to muscle atrophy, limb length discrepancy, or permanent joint damage.
- Untreated arthritis can lead to permanent skeletal deformity.
- Psychosocial factors such as anxiety and school absenteeism.
- Macrophage activation syndrome.
- Uveitis.

Treatment of JIA

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- The most commonly used NSAIDs in children include ibuprofen, naproxen, meloxicam, celecoxib, and indomethacin. All come in liquid form except celecoxib, which can be sprinkled.
- NSAIDs usually insufficient to control most forms of arthritis.
- Adverse effects:
  - Abdominal pain.
  - Hematologic, renal, hepatic, and neurologic adverse effects may occur.
  - Naproxen can cause pseudoporphyria, a bullous rash in fair-skinned children that occurs after sun exposure.

Steroids

- Intra-articular corticosteroid injections.
  - May be very effective in cases of oligoarthritis
- Systemic therapy: required if above therapies fail to achieve inactive oligoarticular disease, if frequent (> 3 per year) joint injections are required, or if disease extends to involve additional joints.
- Oral or intravenous (IV) corticosteroids may be used initially in severe polyarthritis or systemic disease, but prolonged use is avoided due to their adverse effects.
- The following adverse effects are high yield:
  - Immunosuppression
  - Adrenal suppression
  - Increased appetite/weight gain/Cushingoid features
  - Acne
  - Mood changes
  - Osteoporosis/avascular necrosis
  - Cataracts
  - Hypertension
  - Increased intraocular pressures
  - Steroid-induced diabetes

Disease-Modifying Antirheumatic Drugs (DMARDs)

- Methotrexate:
  - Mechanism of action: Folate analogue competitively inhibits dihydrofolate reduc-

tase leading to inhibition of DNA synthesis and purine metabolism.
  - May be administered orally or subcutaneously.
  - May take 6–12 weeks to achieve full effectiveness.
  - Folic acid is routinely given to decrease adverse (gastrointestinal) effects (nausea, vomiting, oral ulcers).
  - Other adverse effects: elevated liver enzymes (usually transient), leukopenia/immunosuppression, and teratogenicity.
    - Blood counts and liver enzymes are monitored after 4 weeks of therapy and then every 3 months while a child is taking methotrexate.
  - Long-term methotrexate appears to be safe and highly effective.

Biologics

- Anti-TNF-alpha agents:
  - Etanercept: weekly or twice-weekly subcutaneous injection
  - Adalimumab: biweekly subcutaneous injection
  - Infliximab: monthly IV infusion
- Anti-IL-6 agent:
  - Tocilizumab: IV infusion or subcutaneous injection
  - Can be used for polyarticular JIA or systemic-onset JIA
- Anti-IL-1 agents:
  - Anakinra, canakinumab
  - Daily or monthly subcutaneous injectable agents
  - Used for systemic-onset JIA
- Abatacept (T-cell co-stimulator inhibitor) and rituximab (anti-CD20) are less commonly used agents.
- Common adverse effects of biologics:
  - Immunosuppression/increased risk of infections
  - Opportunistic infections
  - Tuberculosis reactivation (must screen for before initiation)
  - Elevated liver enzymes
  - Local injection site reactions, infusion reactions/anaphylaxis
  - Cytopenias (neutropenia), hypogammaglobulinemia
  - Increased risk of malignancy ("black box" warning)
  - Live virus vaccines contraindicated

Prognosis

- Prognosis varies based on subtype.
- Approximately 50% of children who have JIA continue to have active disease into adulthood.
- Poor prognostic factors include arthritis of the hip, cervical spine, ankles, or wrists, prolonged systemic inflammation, radiologic evidence of joint deformity, and RF or anti-cyclic citrullinated peptide (CCP) antibodies.

Other Arthritides of Childhood

Post-streptococcal Reactive Arthritis

- Distinct from arthritis of acute rheumatic fever (ARF). Patients do not meet criteria for ARF (see Chap. 19 Cardiology).
- Post-streptococcal reactive arthritis (PSRA) joint involvement pattern is additive and persistent and can involve small joints, entheses, or axial skeleton.
- PSRA usually involves joints of lower extremities.
- Incidence is bimodal with peak between 8 and 14 years of age and again in early adulthood.
- PSRA has less dramatic response to NSAID therapy as compared to arthritis of ARF.
- If arthritis is unresponsive to NSAIDs, a brief oral steroid course is very effective.
- Secondary antibiotic prophylaxis against group A β-hemolytic streptococcus (GAS) recommended for 1 year if there's no evidence of carditis

Arthritis Associated with Inflammatory Bowel Disease (IBD)

- Incidence is equal in boys and girls.
- Arthritis may be associated with IBD flares; peripheral joints are commonly affected.
- Extra-articular skin disease may include oral ulcers, erythema nodosum, and pyoderma gangrenosum.

Reactive Arthritis

- Formally known as Reiter syndrome.
- Reactive arthritis is a type of arthritis associated with an infection at a distant site, distinct from that of the affected joints.
- Common infectious triggers: *Yersinia* spp., *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., and *Chlamydia* spp.
- 3:1 male predominance.
- Common mucocutaneous findings: oral ulcers, urethritis, cervicitis, circinate balanitis, and keratoderma blennorrhagicum.
- Male children and those who are HLA-B27 positive tend to have more severe disease.
- Bilateral mucopurulent conjunctivitis and symptomatic uveitis may occur.
- Other associated symptoms: arthralgia, fever, weight loss, and malaise.
- Symptoms begin a few days to 6 weeks after infection and may last weeks to months.

Diagnosis

- Synovial fluid tests can be helpful in excluding other disease processes. HLA-B27 positivity is supportive of the diagnosis. Imaging studies can be normal but should be obtained, particularly if other disorders such as pyogenic arthritis or osteomyelitis are considered.

Treatment

- NSAIDs (first-line), pathogen-specific antibiotics, sexually transmitted infections (STI) treatment for individual and sexual partners, intra-articular corticosteroid injections in select cases

Juvenile Systemic Lupus Erythematosus (jSLE)

Background

- jSLE is a chronic, multisystem, autoimmune disease with antibody to nuclear antigen. Immune complex formation causes damage to affected tissues. Any organ can be affected. jSLE has an unpredictable presentation and disease course. Pediatric patients have more severe disease.
- Average age of onset is 12 years. Mean age of diagnosis is 13 years.
- Before puberty, the male/female ratio is 3:4, but after puberty it increases to 1:9.
- Incidence 2.22 per 100,000 people in the United States. Prevalence 9.73 per 100,000 people.
- Incidence of jSLE is higher in Hispanic, Native American, Pacific Islander, and Asian individuals than in white individuals.
- Pediatric patients may not meet the adult classification criteria in Table 15.3 [3, 4].

Clinical Presentation (see Table 15.3)

General Manifestations

- Fatigue
- Fever
- Weight loss
- Lymphadenopathy
- Hepatosplenomegaly

Cutaneous Manifestations

- Hallmark: malar or "butterfly" rash:
  - Develops on the malar eminences and crosses the nasal bridge while sparing the nasolabial folds.
  - The forehead and chin also may be affected.
  - Rash can appear as a blush or a maculopapular eruption with an associated scale and usually is non-pruritic.

Table 15.3 Classification criteria for juvenile systemic lupus erythematosus [3, 4]

Malar rash
Discoid rash
Photosensitivity
Oral or nasal ulcers
Arthritis Nonerosive arthritis involving ≥ 2 peripheral joints
Serositis Pleuritis: Convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion, ***or*** Pericarditis: Documented by EKG, or rub, or evidence of pericardial effusion
Renal manifestation Persistent proteinuria > 0.5 g/day, ***or*** > 3+ if quantification not performed, ***or*** cellular casts: May be red cells, hemoglobin, granular, tubular, or mixed
Neurological manifestations Seizure or psychosis in absence of any other causes
Hematologic manifestations Hemolytic anemia with reticulocytosis, ***or*** Leukopenia: < 4,000/mm^3 total on two or more occasions, ***or*** Lymphopenia: < 1,500/mm^3 on two or more occasions, ***or*** Thrombocytopenia: < 100,000/mm^3 in absence of offending drugs
Antinuclear antibodies An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time in the absence of the drugs known to be associated with 'drug-induced lupus' syndrome

EKG electrocardiogram, *ANA* antinuclear antibody

- Discoid lupus:
  - Coin-shaped erythematous rash.
  - May affect the face, ears, and scalp, although the upper extremities and trunk can be affected.
  - The central area may be hypopigmented.
  - Active border may appear hyperpigmented.
  - The lesions may heal with a scar or atrophy.
  - Discoid patches on the scalp may result in scarring alopecia if the hair follicle is damaged.
- Mucosal ulcerations
- Periungual erythema
- Alopecia

Musculoskeletal Manifestations

- Arthralgia and nonerosive arthritis:
  - Very common in SLE
  - Symmetric involvement of both the large and small joints
  - Primarily the knees, wrists, ankles, and fingers
  - Jaccoud arthropathy (ulnar deviation of the second to fifth fingers and subluxation of the metacarpophalangeal joints)
- Morning stiffness
- Tenosynovitis
- Myalgia and myositis

Renal Manifestations

- Lupus nephritis (LN) is a glomerulonephritis that is the greatest contributor to morbidity and mortality in the jSLE population. 18% to 50% develop end-stage renal disease.
- LN may manifest as proteinuria, microscopic hematuria, hypertension, or elevated blood urea nitrogen and creatinine levels.
- Among patients, 20–75% may develop nephrotic syndrome.
- A renal biopsy with histologic, immunofluorescent, and electron micrographic analysis is necessary to classify the histologic type of renal disease.
- 80% of LN develops in the first year of diagnosis.
- Treatment is induction with cyclophosphamide or mycophenolate mofetil (MMF) and then maintenance with MMF or azathioprine.

Neuropsychiatric Manifestations

- Headaches: most common
- Decreased concentration
- Cognitive dysfunction
- Mood disorders
- Psychosis
- Seizures
- Peripheral nervous system involvement
- Central nervous system (CNS) vasculitis
- Stroke
- Movement disorders such as chorea
- Pseudotumor cerebri

Hematologic Involvement
- Leukopenia
- Lymphopenia
- Anemia (usually hemolytic)
- Thrombocytopenia
- Coagulation abnormalities

Antiphospholipid Antibody Syndrome (APS)
- Positive lupus anticoagulant, anticardiolipin antibody, or anti-β2 glycoprotein 1 antibody in the setting of vascular thrombosis or pregnancy morbidity
- Can present as follows:
  - Stroke
  - Transient ischemic attack
  - Chorea
  - Recurrent fetal loss
  - Avascular necrosis
  - Myocardial infarction
  - Organ infarction
  - Livedo reticularis
  - Pulmonary embolism
  - Deep vein thrombosis
- Laboratory abnormalities:
  - Elevated anticardiolipin, anti-β2 glycoprotein 1 antibodies, and/or positive lupus anticoagulant
  - Prolonged partial thromboplastin time

Pulmonary Manifestations
- Restrictive lung disease
- Pleuritis
- Pleural effusion
- Pneumonitis
- Infection
- Pulmonary hypertension
- Pulmonary hemorrhage: presents with shortness of breath and a sudden drop in hemoglobin concentration

Cardiac Manifestations
- Pericarditis
- Pericardial effusion
- Myocarditis
- Bacterial endocarditis
- Lupus valvulitis (Libman-Sacks endocarditis): may predispose patients undergoing dental procedures to bacterial endocarditis
- Premature atherosclerosis

Gastrointestinal Manifestations
- Abdominal pain, diarrhea, vomiting (most common)
- Acute lupus peritonitis
- Acute pancreatitis caused by active jSLE, infection, or corticosteroid use
- Enteritis or mesenteric vasculitis, patients at risk of bowel perforation
- Protein-losing enteropathy
- Intestinal pseudo-obstruction
- Liver transaminitis
- Lupus hepatitis

Endocrine Manifestations
- Hypothyroidism is most common.
- Hyperthyroidism is rare.
- Diabetes mellitus type II may develop as a result of corticosteroid use and obesity.
- Adrenal gland failure may result due to prolonged corticosteroid use.
- Delayed puberty is common.
- Irregular menses or amenorrhea is common during periods of active disease.

Laboratory Evaluation
- CBC is needed to evaluate potential cytopenias.
- A comprehensive metabolic panel may reveal transaminitis, hypoalbuminemia, or an elevated creatinine level.
- Elevated ESR is very common.
- CRP levels can remain normal.
- A urinalysis may show proteinuria, hematuria, and other components of active urinary sediment.
- The ANA is positive in 99% of patients with SLE, but also may be positive in other rheumatic diseases such as mixed connective tissue disease and dermatomyositis.

- The ANA also may be positive in up to one-third of the healthy population and in family members of patients with SLE.
- A negative ANA makes the diagnosis of SLE extremely unlikely, and ANA is not useful to monitor disease activity.
- The anti-double-strand DNA (dsDNA) is very specific for SLE and may be found in > 75% of patients.
- The anti-dsDNA level is usually checked at the time of diagnosis and throughout the disease course to monitor disease activity.
- The anti-Smith antibody is highly specific for SLE and may be found in up to 50% of patients.
- The anti-ribonucleoprotein (RNP) antibody may be found in patients who have classic SLE but often indicates that the patient's diagnosis is a mixed connective tissue disease (SLE with features of systemic sclerosis or dermatomyositis).
- SS-A (anti-Ro) and SS-B (anti-La) antibodies are common.
- Complement levels (C3 and C4) are low in SLE during periods of active disease.

Management

- Hydroxychloroquine:
  - One of the mainstays of treatment for any patient with SLE
  - Prevents disease flares
  - Adverse effects:
    - Some patients may suffer abdominal discomfort.
    - Potential retinal toxicity of treatment for any patient with SLE
  - Improves rash:
    - Requires baseline ophthalmology visit with follow-up every 6–12 months
- Methotrexate for arthritis
- Prednisone for disease control and disease flares
  - Cyclophosphamide for lupus treatment for any patient with SLE
  - Improves rash
  - Nephritis or severe organ involvement
- MMF for disease control and lupus nephritis

Neonatal Lupus Erythematosus (NLE)

Background

- NLE occurs in 1% of infants who experience transplacental passage of maternal SS-A or SS-B antibodies.

Clinical Presentation

- Congenital heart block (CHB) from antibody-mediated damage to the conducting system is the most serious complication and may be seen in up to 30% of infants born with NLE.
- Fetal bradycardia is the first sign of NLE and must be evaluated at 16 weeks gestation and at continuing intervals throughout pregnancy.
- Cytopenias and hepatitis can occur.
- Cutaneous neonatal lupus (without heart involvement) is the most common form of NLE:
  - The rash is erythematous with a raised border, particularly prominent on sun-exposed areas and around the eyes; the skin may have a fine scale.

Treatment

- In CHB, treatment is controversial and consists of dexamethasone or intravenous immunoglobulin (IVIG).
- Cutaneous NLE does not require treatment.

Prognosis

- 30% to 50% of infants who develop CHB will require pacemaker implantation within the first 24 months.
- Noncardiac manifestations will resolve without intervention, usually within 6 months when maternal antibodies are no longer present.

Drug-Induced Lupus (DIL)

Background

- The prevalence of DIL is equal in males and females, although minocycline-induced lupus is usually seen in adolescent girls using the medication for treatment of acne.
- Chronic use of the medication is required to develop DIL.
- Medications that more commonly induce DIL include minocycline, procainamide, hydralazine, penicillamine, isoniazid, quinidine, phenytoin, carbamazepine, infliximab, adalimumab, and etanercept.

Clinical Presentation

- Patients often present with constitutional symptoms, photosensitive rash, arthralgia, myalgia, and serositis.
- Subacute cutaneous lupus also may be present.

Diagnosis

- Positive antihistone antibodies are present in 95% of patients with DIL.

Treatment of DIL

- Discontinue the offending agent.
- A trial of NSAIDs, hydroxychloroquine, and possibly corticosteroids may be needed.
- Symptoms usually abate within weeks to months of stopping the medication; however, in some patients, DIL will evolve into true SLE.

Systemic Scleroderma

Background

- Scleroderma is characterized by skin induration and thickening accompanied by various degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs, prominent fibroproliferative vasculopathy, and humoral and cellular immune alterations.

Clinical Presentation

- **C**alcinosis, **R**aynaud phenomenon (swollen hands or fingers), **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia (CREST) syndrome and positive centromere antibodies
- Diffuse systemic scleroderma is more frequent with lung and renal involvement, positive SCL-70 (topoisomerase)

Management

- Angiotensin-converting enzyme (ACE) inhibitor.
- Calcium (Ca) channel blocker, e.g., nifedipine.
- Alpha blocker, e.g., doxazosin.
- Dipyridamole (e.g., Persantine, Boehringer Ingelheim, Ridgefield, CT).
- Corticosteroid can exacerbate renal crisis!

Localized Scleroderma

Background

- Most common form in children, also called linear scleroderma, morphea, deep morphea, or generalized morphea

Clinical Presentation

- Lesions can involve the face (*en coup de sabre*, dueling stroke from a sword); lesions can become more indurated, extending deeper into muscle and bone (melorheostosis). Facial lesions can be associated with seizure, uveitis, dental defects, and facial abnormalities.

Diagnosis

- All lab tests are usually normal, including SCL-70, centromere antibodies, RNP, Smith, and SS-A.
- Anti-single-strand DNA antibodies may be found positive.

Treatment

- Methotrexate and steroids can improve and resolve active lesions. Older sclerosed lesions the care is mainly supportive. Complications such as seizure or uveitis are treated appropriately
- Physical therapy if joints are involved

Prognosis
- With treatment lesions can resolve or become stable, and joint function can be preserved. Lesions can spontaneously become inactive within 3–4 years without treatment, however there can be disability and damage.

Mixed Connective Tissue Disease (MCTD)

Background
- Adult classification criteria include Raynaud phenomenon and high-titer RNP antibody and at least one sign from at least two of the following diseases: SLE, systemic sclerosis, or polymyositis.
- More common in girls.

Clinical Presentation
- Raynaud phenomenon
- Arthritis and joint abnormalities
- Fever and fatigue
- Dorsal hand edema
- Rash
- Myositis
- Acute pericarditis
- Pericardial effusion
- Mitral valve prolapse
- Dysphagia
- Restrictive lung disease
- Renal disease

Diagnosis
- Positive anti-RNP antibodies, ANA, RF, and hypergammaglobulinemia

Treatment
- Similar to SLE

Sjögren Syndrome

Background
- A slowly progressive inflammatory disorder that involves the exocrine glands: rare in pediatric patients

Clinical Presentation
- Recurrent parotitis (68%)
- Keratoconjunctivitis sicca (8%, can cause recurrent dental caries)
- Lymphadenopathy
- Fatigue
- Arthralgia
- Renal disease
- Neurologic symptoms
- Rash

Diagnosis
- Antibodies: anti-Ro (SS-A) and/or anti-La (SS-B)

Associated Diseases
- SLE
- Rheumatoid arthritis
- Scleroderma
- Biliary cirrhosis

Management
- Artificial tears
- Pilocarpine tablets
- Hydroxychloroquine for skin rash
- Methotrexate or NSAIDs for arthritis

Prognosis
- These children do very well but are at risk of developing lymphomas in adulthood.

INFLAMMATORY MYOPATHIES

Juvenile Dermatomyositis (JDM)

Background
- A systemic autoimmune disorder involving cutaneous findings, myositis, and vasculopathy affecting children younger than 18
- Peaks between 5 and 14 years
- 2:1 female predominance
- Rare disease—approximately 1 in a million

Clinical Presentation
- **Systemic features:**
  – Fever

  - Malaise
  - Fatigue
  - Anorexia
  - Weight loss
- **Musculoskeletal manifestations:**
  - Muscle weakness is symmetric and proximal and can be associated with muscle pain or stiffness.
  - Arthritis.
- **Cutaneous findings**:
  - Gottron papules
  - Heliotrope rash
  - Periungual erythema
  - Malar rash
  - "Shawl sign" rash
  - Photosensitivity
  - Skin ulceration
  - Calcinosis
  - Lipodystrophy
  - Generalized, pruritic, scaly rash
- **Vasculopathy:**
  - Gastrointestinal disease
  - Gingivitis
  - Raynaud phenomenon
- **Pulmonary/airway:**
  - Interstitial lung disease
  - Dysphonia due to muscle weakness

Diagnosis

- Diagnosis is based on the 1975 Bohan and Peter classification criteria [5]:
  - Symmetric proximal muscle weakness
  - Elevation of skeletal muscle enzymes
  - Abnormal electromyography (EMG) results
  - Abnormal muscle biopsy
  - Typical skin rash of JDM (must have for diagnosis)
- 3/5, probable JDM diagnosis; 4/5, definite JDM diagnosis
- Many modern experts accept abnormal MRI findings in place of muscle biopsy.
- Consider age-appropriate malignancy screening in atypical cases, as this rarely can be linked with JDM (up to 40% in adults).

Treatment

- Depends on the organ involved and severity of disease.
- Most begin with steroids, hydroxychloroquine, IVIG, and methotrexate.

Prognosis

- Most patients fall into one of three categories:
  - Monocyclic disease 25%
  - Polycyclic disease 25%
  - Chronic continuous 50%
- 65% to 80% will end up with a normal to good functional outcome.

Polymyositis

Background

- Uncommon in pediatrics
- 2:1 female to male
- Median age of onset: 12.1 years

Clinical Presentation

- Does not have any cutaneous features
- Often has a more severe illness onset
- Tends to have higher creatine kinase (CK) levels than in JDM patients
- Can have both proximal and distal weakness and more associated falls

Diagnosis

- Diagnosis is also based on the 1975 Bohan and Peter classification criteria [5] as listed before, with no requirement for skin findings.
- Need to confirm with muscle biopsy.

Treatment

- Depends on the organ involved and severity of disease.
- Most begin with steroids, hydroxychloroquine, IVIG, and methotrexate.

Prognosis

- 50% have a chronic disease course.
- 30% end up using a wheelchair.

AUTOINFLAMMATORY DISEASES

General Background

- Autoinflammatory diseases refer to disorders of the innate immune system.
- These include various syndromes associated with recurrent fever, rash, poor growth, and elevated inflammatory markers.

Periodic Fever Syndromes: Periodic Fever, Aphthous Stomatitis, Pharyngitis, Cervical Adenitis Syndrome (PFAPA)

Background

- Most common periodic fever syndrome of childhood
- Mean age of onset, 3 years; range, 6 months to 7 years

Clinical Presentation

- Fever episodes generally last 2–3 days.
- Episodes occur approximately every 4 weeks.
- Presents with fever and any combination of the following:
  - Aphthous ulcers
  - Cervical adenitis
  - Pharyngitis
  - Abdominal pain
  - Poor appetite
  - Fussiness
  - Arthralgias
  - Arthritis
  - Headache
- Children are in a good health between episodes.

Diagnosis

- Clinical diagnosis
- No known gene association
- Obtaining CBC, ESR, and CRP at baseline and during a flare recommended:
  - Expect to see significantly elevated CRP and possible leukocytosis during flare.

Treatment

- Depends on whether the symptoms are interfering with routine or affecting growth.
- Prednisone can be given but should be used with caution, as it can increase the frequency of fever cycles.
- Children with persistent cases can be started on colchicine therapy.
- In refractory cases, there has been some evidence that tonsillectomy is curative in 80%.

Prognosis

- Most children grow out of the illness by late childhood into adolescence.

Familial Mediterranean Fever (FMF)

Background

- Most common monogenic autoinflammatory syndrome
- Results from autosomal recessive mutations in the *MEFV* gene
- Most common in families from the Middle East and Mediterranean areas

Clinical Presentation

- 90% of cases begin before the age of 20 years.
- Fever episodes last 1–3 days and recur every few weeks to months.
- Inflammation affects a variety of organ systems and can manifest as the following:
  - Pleuritis
  - Peritonitis
  - Arthritis
  - Myalgia
  - Rash
  - Irritability
  - Poor appetite
  - Poor growth

Diagnosis

- Genetic testing is available and is diagnostic.
- ESR, CRP, fibrinogen, and white blood cell (WBC) counts may be elevated during the episodes of fever and then normalize in between flares.

Treatment

- Children with persistent cases should be started on colchicine therapy.
- Treatment is generally life-long, as there is a risk of amyloidosis from untreated inflammation.

Prognosis

- Good overall, if renal amyloidosis can be avoided, as FMF patients with end-stage renal disease have a lower survival rate with hemodialysis

Chronic Recurrent Multifocal Osteomyelitis (CRMO)

Background

- A rare autoinflammatory bone disorder
- Two to four times more likely in females
- Peak onset between 7 and 12 years old

Clinical Presentation

- Localized bone pain with or without fever.
- Can also have adjacent soft tissue swelling above lesions.
- Despite the name, it can be multifocal or unifocal and is not always recurrent.
- Can affect any bone in the body, but most commonly the following:
  - Metaphyseal region of long bones
  - Clavicles
  - Vertebral bodies
  - Pelvis
- 25% of patients will have extra-skeletal features such as a palmar-plantar rash.

Diagnosis

- Radiographic imaging may show early osteopenia or more chronic erosive changes.
- Imaging of choice: MRI, which can show early osteitis, bone marrow edema, and the classic mixed osteolytic and sclerotic lesions with or without periosteal reaction that are classic for CRMO.
- Bone biopsy should be sterile on culture and may show a predominance of inflammatory cells.

Treatment

- NSAIDs are first-line therapy.
- Refractory disease or areas that are more axial or prone to instability may require anti-TNF therapy.

Prognosis

- Most patients have periods of flares and remissions.
- CRMO resolves in most after several years, generally with no long-term sequelae.

Sarcoidosis

Background

- A multisystem autoinflammatory granulomatous disease.
- There are two primary forms of pediatric sarcoidosis:
  - Childhood-onset sarcoidosis, also known as Blau syndrome
  - Pediatric-onset adult sarcoidosis
- This is a rare diagnosis in childhood.
- Blau syndrome is associated with a mutation in *NOD2/CARD15*.

Clinical Presentation

- **Blau syndrome:**
  - Presents in early childhood with a triad of granulomatous polyarthritis, uveitis, and dermatitis.
  - Mean age of onset is 26 months.
- **Pediatric-onset adult sarcoidosis:**
  - Presents in the adolescent years with various systemic features:
    - Fever
    - Pulmonary involvement

- Lymphadenopathy (hilar and peripheral)
- Malaise
- Weight loss
- Arthritis
- Hepatosplenomegaly
- Erythema nodosum and other rashes
- Uveitis
- CNS involvement
  - Seizures
  - Encephalopathy
  - Cranial nerve palsy
- Renal involvement
  - Hypercalciuria
  - Renal granulomas
  - Proteinuria

Diagnosis

- Tissue biopsy is needed to confirm the diagnosis.
  - Hallmark is noncaseating epithelioid granulomas.
- Genetic testing is indicated in younger children with concern for possible *NOD2/CARD15* mutations.
- There is no lab test that diagnoses sarcoidosis:
  - CBC can show pancytopenia.
  - Liver enzymes can be elevated.
  - Elevated ACE is produced by the granulomas but is not diagnostic due to false positives (elevated in > 75% of cases).
  - Lysozyme level can be elevated due to metabolically active granulomas, not specific to sarcoidosis.
  - Hypercalcemia and hypercalciuria are due to overproduction or precursors by the granulomas.

Treatment

- Treatment varies on the severity of illness and organs involved.
- Usually involves steroids, anti-TNF agents, methotrexate, or cyclophosphamide.

Prognosis

- Ocular disease is the most devastating feature, and up to 30% will lose their vision despite therapy.

PAIN SYNDROMES OF CHILDHOOD

Growing Pains

Background

- Growing pains are intermittent nonarticular pains occurring in childhood and are diagnosed by exclusion based on a typical history and normal physical examination findings.
- Growing pains may occur in any growing child but usually present between the ages of 3 and 10 years.

Clinical Presentation

- The pain typically occurs at night and frequently is limited to the calf, thigh, or shin.
- Unlike inflammatory joint pain, the discomfort is short-lived and relieved with heat, massage, or mild analgesics.
- The child is otherwise healthy and asymptomatic during the day, having no functional limitations.
- There may be a history of growing pains in the family.
- Importantly, the physical examination is never associated with physical findings such as swelling, redness, warmth, or fever.

Diagnosis

- Clinical diagnosis: There are no specific laboratory or imaging findings associated with growing pains.
- Further workup is indicated if the case is atypical or has other concerning features.

Management

- Reassurance

- Supportive measures, typically does not require any further investigations
- Heat, massage, or mild analgesics, e.g., acetaminophen or ibuprofen

Prognosis
- The condition is generally regarded as benign.
- Most of these cases will self-resolve.

Benign Joint Hypermobility Syndrome (BJHS)

Background
- Refers to patients who exhibit significant joint hypermobility and often develop associated musculoskeletal pain but can be asymptomatic
- More common in females and often runs in families

Clinical Presentation
- Joint, foot, or muscle pain
- Transient joint effusions (should not last more than 3 days)
- Hyperextension of joints, flat feet with collapsible arches
- No signs of Marfan or Ehlers-Danlos syndrome

Red Flags for Possible Inherited Condition
- High arched palate
- Ocular or cardiac lesions
- Skin hyperelasticity
- Arachnodactyly
- Velvety skin texture

Diagnosis
- Clinical diagnosis: Many will use the Beighton scale.
- May consider referral to genetics for further testing if there's any of the above red flags.

Management
- NSAID therapy
- Physical therapy
- Use of supportive footwear, insoles, and neoprene sleeves

Prognosis
- Good prognosis overall; hypermobility generally decreases with age.
- Some patients have a higher risk of condition evolving into a chronic pain syndrome.

Amplified Musculoskeletal Pain Syndrome (AMPS)

Background
- AMPS is a term that encompasses the various pain syndromes of childhood and also includes fibromyalgia and complex regional pain syndrome (CRPS).
- The pain is thought to be due to inappropriate amplification of peripheral pain signals and is felt as intense pain.
- More commonly seen in females, "high achievers," and youngest siblings.

Clinical Presentation
- The pain can affect only one site of the body or can be widespread, sometimes with associated allodynia.
- It is often preceded by a prior physical or psychological trauma.
- The pain can be disabling for the patient; many times, they may be using crutches or a wheelchair or avoiding school.

Diagnosis
- Based on history and physical exam.
- Fibromyalgia does have some additional diagnostic criteria, including having pain in 11 out of 18 standardized tender points.
- Generally, normal labs and imaging.

Treatment
- Multimodal: involves coordinating care with psychology, psychiatry, and intense physical therapy.

- Also need to discuss distraction techniques, desensitization, stress management, and coping strategies for chronic pain.
- Need to insist that the child participates in school and therapies and maintains a routine.
- Need to set expectation that the pain cannot be made to completely disappear but can be made manageable.
- Narcotics are not indicated in this condition.
- NSAIDs can be tried but often do not work, as this is a more neuropathic pain.

Prognosis

- With adherence to the treatments above, the majority of these patients will become symptom-free, but there is a 15% relapse rate.

VASCULITIS

Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV)

- Are rare primary systemic vasculitides causing a necrotizing arteritis involving medium- and small-sized arteries
- Include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) and renal limited ANCA vasculitis
- Rare in children
- Target organs commonly affected: the lungs and kidneys

Granulomatosis with Polyangiitis (GPA)

Background

- GPA (formerly known as Wegener granulomatosis) is rare but is the most common AAV occurring in children.
- More common in adolescent girls.

Clinical Presentation

- Constitutional symptoms include fevers, night sweats, fatigue, lethargy, loss of appetite, and weight loss.
- Affects the upper respiratory tract, lungs, and kidneys.
- Ophthalmic manifestations: conjunctivitis, episcleritis, uveitis, optic nerve vasculitis, and orbital pseudotumor with proptosis.
- Otic involvement: recurrent ear infections and hearing loss.
- Myalgias, arthralgias, and arthritis, typically affecting large joints.
- Skin: palpable purpura, skin ulcers, and mucocutaneous involvement with strawberry gingivitis and oral ulcers
- CNS and peripheral nervous system involvement with headache, pachymeningitis, and peripheral nerve involvement.
- European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) childhood GPA criteria [6] require three of the six:
  - Granulomatous inflammation on biopsy within the wall of the artery or perivascular or extravascular area.
  - Upper airway involvement with chronic purulent discharge or bloody nasal discharge, epistaxis, or granulomata, saddle bridge nose or perforated nasal septum, also chronic or recurrent sinus involvement.
  - Laryngo-tracheo-bronchial stenosis.
  - Pulmonary involvement with imaging demonstrating nodules, cavitary lesions, or infiltrates. Pulmonary hemorrhage may present as hemoptysis.
  - ANCA positivity.
  - Renal involvement with proteinuria > 0.3 g/24 h or > 30 mmol/mg of urine

albumin/creatinine ratio on a spot morning sample, hematuria (five red blood cells/high power field) or red blood cell casts in the urinary sediment or ≥ 2+ on dipstick, presence of necrotizing pauci-immune glomerulonephritis on kidney biopsy.

Diagnosis

- Acute-phase reactants (ESR, CRP) are often elevated.
- Abnormal renal function and urinalysis.
- Cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) is most specific for GPA.
- Chest imaging with radiography or chest CT (more sensitive).
- Biopsy of the lung or kidney showing necrotizing granulomatous inflammation and pauci-immune vasculitis in small- and medium-sized blood vessels.

Treatment

- Cyclophosphamide with high-dose glucocorticoids (induction of remission).
- Maintenance medication often needed.

Microscopic Polyangiitis (MPA)

Background

- MPA is the second most common AAV in pediatrics.
- Kidneys and lungs are the most commonly affected organs.
- Involves small arteries, veins, and capillaries.

Clinical Presentation

- Lower respiratory tract involvement is common.
- Presents with hemoptysis or anemia secondary to chronic, low-grade pulmonary hemorrhage with pulmonary hemosiderosis or as catastrophic pulmonary hemorrhage.
- No pediatric-specific MPA criteria.

Diagnosis

- Nonspecific elevated ESR and CRP levels.
- Elevated WBC and platelet counts and a normochromic, normocytic anemia.
- Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) is most specific for MPA.

Treatment

- Corticosteroids plus cyclophosphamide is commonly used.
- For severe organ involvement, plasmapheresis is an essential therapy.
- Maintenance therapies described include mycophenolate mofetil, azathioprine, and methotrexate.

Takayasu Arteritis (TA)

Background

- Rare, relapsing, chronic granulomatous, large-vessel arteritis that involves the aorta and its major branches.
- Called "pulseless disease" due to the absence of peripheral pulses in the late phase of disease.
- Females > males with the majority of children being diagnosed in adolescence.
- The aorta and renal, subclavian, and carotid arteries are most commonly affected arteries.
- One of the most common causes of renovascular hypertension in children.

Clinical Presentation

- Variable symptoms of disease activity include fever, weight loss, myalgia, arthralgias, claudication, dizziness, headaches, visual disturbance, and abdominal pain.
- Carotidynia (pain and tenderness on palpation over carotid bifurcation) is one of the most distinctive symptoms during the acute phase.
- The clinical manifestations depend on the phase of disease:
  - Early phase has inflammation with nonspecific systemic symptoms lasting for weeks or months. Diagnosis is challenging.

  - Recurrent disease often occurs in new arterial territories, with the coexistence of active and inactive lesions.
  - The late, chronic phase (the "pulseless" stage) is characterized by ischemia and symptoms secondary to arterial occlusion.
- Coexistence of IBD, pyoderma gangrenosum, ankylosing spondylitis, and JIA has been reported.

Diagnosis
- No specific laboratory tests or biomarkers.
- WBC, platelet, ESR, and CRP levels are often elevated at presentation or during disease flare.
- Fibrinogen may be elevated.
- Normocytic, normochromic anemia may be present.
- Imaging helps confirm the diagnosis:
  - Conventional angiography, CT, MR angiograms, and Doppler ultrasound.
  - Positron emission tomography (PET) scans are helpful for early assessment of inflammation.

Treatment
- Corticosteroids.
- Induction and maintenance therapy, including methotrexate, azathioprine, and mycophenolate mofetil.
- Cyclophosphamide has been utilized for life-threatening or organ-threatening disease.
- Biologic therapies have been used: etanercept, adalimumab, infliximab, tocilizumab, and rituximab.
- Blood pressure control is often necessary.
- Vascular surgery is needed for severe vessel damage.
- Aortic valve replacement is necessary with severe aortic regurgitation.

Prognosis
- Early diagnosis and treatment improve morbidity and mortality.
- Biologic use has greatly improved outcomes in comparison to nonbiologic therapies.
- Mortality related to complications, including arterial dissection, aortic rupture, uncontrollable hypertension, cardiomyopathy, myocardial infarction, renal failure, and infection.
- High rate of relapse is common.

Henoch-Schönlein Purpura (HSP)

Background
- The most common systemic vasculitis of childhood.
- Characterized by palpable purpura, abdominal pain, arthritis, and occasional kidney involvement.
- HSP is a small-vessel leukocytoclastic vasculitis, also known as immunoglobulin A (IgA) vasculitis.
- IgA deposition is found in the vascular walls in histologic studies.
- Annual incidence of approximately 20 per 100,000 children.
- Peak age of onset is between 4 and 6 years of age.
- More common in boys than girls and more severe in adults than children.
- Seasonal variation has been noted in winter and spring.
- Possible infectious triggers have been implicated including group A β-hemolytic streptococcus, *Staphylococcus aureus*, influenza, parainfluenza, Epstein-Barr virus, adenovirus, parvovirus, and mycoplasma.

Clinical Presentation
- **Purpura** (Fig. 15.2):
  - Palpable non-thrombocytopenic, purpuric rash is observed in 100% of cases and is generally the presenting symptom.
  - Rash involves gravity and pressure-dependent areas such as the buttocks and lower extremities. Less commonly, the face, ears, and arms may also be involved.

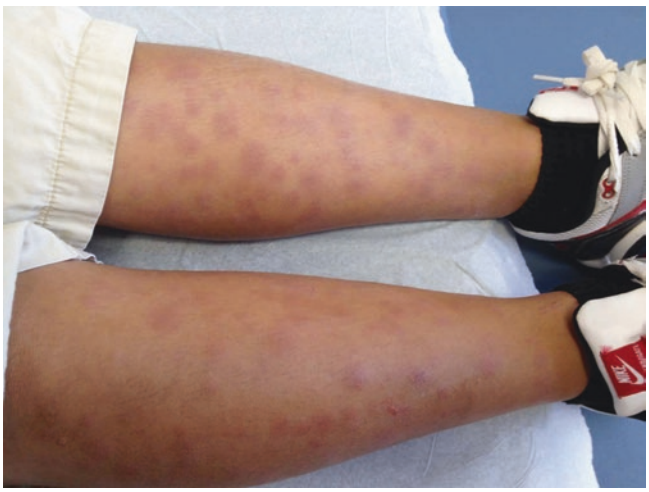


Fig. 15.2 15-year-old male with Henoch-Schönlein purpura. Note the dusky deep-red macules of varying diameters

  - Rash may present as deep-red macules and progress to palpable purpura and, less commonly, hemorrhagic bullae or necrotic lesions.
  - Comes in crops; as one crop fades, another occurs.
  - Subcutaneous edema involving the scalp, periorbital area, dorsa of hands and feet, and scrotum may occur early on, especially in the young.
- **Arthritis:**
  - Affects 50–80% of patients and associated with joint pain, swelling, and possibly difficulty with ambulation.
  - The joint swelling is periarticular and nondestructive.
  - Knees and ankles are most commonly involved joints.
- **GI involvement:**
  - GI involvement is noted in approximately 75% of children.
  - In 20% of cases, GI symptoms precede the rash by 2 weeks and may be confused with appendicitis.
  - GI manifestations may include colicky abdominal pain, vomiting, diarrhea, GI bleeding, and intussusception. Pancreatitis is rare.
  - Intussusception is usually ileo-ileal, occurring in up to 5% of patients.
  - Bowel ischemia, infarction, fistula formation, and intestinal perforation may occur due to vasculitis.
- **Nephritis:**
  - Renal involvement is the main cause of late morbidity and mortality in children with HSP.
  - Renal involvement usually occurs by week 6 but may occur 6 months from onset of diagnosis.
  - 20% to 60% of children have kidney involvement with microscopic hematuria and/or proteinuria, but nephrotic-range proteinuria and renal failure are possible.
  - Hypertension.

Other, Less Common Features

- Seizures
- Stroke
- Guillain-Barré syndrome
- Parotitis
- Pulmonary hemorrhage

Treatment

- Supportive care is recommended.
- Pain medications for abdominal and joint discomfort are helpful, but NSAIDs may exacerbate GI symptoms and renal issues if present.
- Antihypertensive therapy for persistent hypertension may be indicated.
- The role of glucocorticoid treatment is controversial but appears to shorten duration of GI and joint involvement.
- Corticosteroids, when started early, increase the odds of the abdominal pain resolving within 24 h and may reduce the risk of intussusception.

Prognosis

- Follow-up with frequent urinalysis and blood pressure evaluations is recommended for 6 months.
- The overall prognosis is good: 67% of children who have HSP run the course of the disease within 4 weeks of onset.
- Recurrence affects about 25% of patients.

- Studies confirm that chronic renal insufficiency and hypertension may develop up to 10 years after the initial onset of symptoms.
- Typically, renal failure occurs in patients who present with acute glomerulonephritis and have persistent nephrotic syndrome.
- Overall, progression to end-stage renal failure is seen in a very small number of children (1–5%) who have HSP.

Behçet Disease

Background

- A mixed vessel vasculitis that can affect any size or type of vessel, predominantly the venous system
- Characterized by painful recurrent orogenital ulcers, inflammatory eye disease, and joint and GI involvement
- Occurs equally in males and females
- Mean age of 30 years; rare in childhood, but does occur
- Highest prevalence in Turkey and Japan

Clinical Presentation

- **Aphthous ulcers:**
  - Present in 97–100% of patients.
  - Initial manifestation in 25–75%.
  - Most come in crops (three-plus lesions), < 1 cm, heal without scarring within 1–3 weeks, and are recurrent.
  - Ulcers preferentially appear on mucous membranes of the lips, gingiva, buccal mucosa, and tongue and rarely on the palate, tonsils, or posterior pharynx.
- **Genital ulcers:**
  - Present in 80–90% of patients.
  - They are similar to those in the mouth and tend to be deeper, and 66% will leave scars after healing.
  - Commonly appear on the scrotum or vulva.
  - Less common on the penis and perianal and vaginal mucosa.
  - Vulvar ulcers often develop during the premenstrual stage of the cycle.
- **Ocular involvement:**
  - Ocular lesions seen in 70–90%
  - Usually at presentation or within the first 2–3 years, rare after 5 years
  - Panuveitis (non-granulomatous)
  - Conjunctivitis
  - Corneal ulceration
  - Papillitis
  - Retinal vasculitis
  - Hypopyon (up to 20%)
- **Arthritis**
  - Seen in 40–50%.
  - Usually migratory, mono- or oligoarticular, and asymmetric.
  - Most commonly affects the knees, ankles, elbows, and wrists.
  - Enthesopathy is common also, especially in patients with acneiform lesions
  - Rare to have involvement of axial spine or small joints.
  - Erosive changes are rare.
  - Arthralgias are more common.
- **CNS involvement:**
  - Frequency of 4–10%.
  - CNS involvement has two distinct forms, which rarely co-exist:
    - Parenchymal disease (80%, poor prognosis)
    - Dural sinus thrombosis (20%, favorable prognosis)
- **Cutaneous lesions:**
  - Papulopustular (acne) lesions (85%):
    - Indistinguishable from acne vulgaris
    - May occur in atypical locations
  - Nodular lesions (60%):
    - Erythema nodosum-like lesions (more common in women), 50%
    - Superficial thrombophlebitis (associated with major vessel involvement), 50%
  - Pseudofolliculitis
  - Erythema multiforme
  - Pyoderma gangrenosum
  - Nailfold capillary changes

- **GI involvement:**
  - Can be as high as 25–30%, especially in the Japanese population
  - Involves mucosal ulcerations in the ileum and right side of the colon
  - Risk of ileocecal perforation, which is the third highest cause of mortality from Behçet disease
- **Vascular:**
  - Major vessel occlusion/thrombosis
  - Aneurysm
  - Pulmonary artery aneurysms:
    - Unique complication of Behçet disease
    - The most frequent arterial complication
    - Strongly associated with venous thrombosis

Diagnosis

- BD is a clinical diagnosis.
- International Clinical Criteria for Behçet Disease classification (1990) [7] states patients must present with the following:
  - Recurrent oral ulcerations at least three times in 1 year. Additionally, patients must present any two of the following:
    - Recurrent genital ulcerations
    - Eye lesions (uveitis or retinal vasculitis) observed by an ophthalmologist
    - Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules) found in adult patients not being treated with corticosteroids
    - Positive pathergy test read by a physician within 24–48 h of testing
- ESR and CRP may be normal except during active serositis, cerebral involvement, or vasculitis.
- *HLA-B51*:
  - Three to six times more positivity in Eastern Mediterranean and Japanese populations.
  - Positive test is associated with a more severe clinical course.
- Pathergy test:
  - Pathergy is the hyperreactivity of the skin to an intracutaneous injection or needle stick (frequently seen with blood draws).
  - Rate of a positive reaction varies, but is more common in Turkish and Japanese populations (50%) and less common in British/US populations.

Treatment

- Depends on organ involvement and severity
- Topical therapies:
  - Sucralfate, lidocaine, or steroids
- Systemic therapies:
  - Steroids, colchicine, anti-TNF agents, thalidomide, dapsone.
  - Azathioprine, methotrexate, or cyclosporine has been useful in ocular Behçet disease.
  - No controlled studies on use of anticoagulants.

Prognosis

- Behçet disease is recurrent and unpredictable.
- Male gender, early development of the disease, and *HLA-B51* gene positivity are markers of poor prognosis.
- Eye disease, the most frequent cause of serious morbidity, may lead to blindness in 20% of those affected.
- The disease may occasionally be fatal, with a mortality rate of up to 6% due to vasculitis leading to arterial occlusion, ruptured arterial aneurysms, pulmonary vasculitis, or involvement of the CNS.
- Death is associated with younger age, male sex, arterial involvement, and a high number of flares.

PEARLS AND PITFALLS

- JIA is a clinical diagnosis; there is no laboratory test that makes the diagnosis.

- JIA diagnosis is based on the chronicity of arthritis (≥ 6 weeks duration).
- JIA can be associated with normal labs including normal inflammatory markers, negative ANA, and negative RF; laboratory data help to exclude other causes; laboratory test results are only supportive.
- Any child diagnosed with JIA must be referred to a pediatric ophthalmologist for evaluation of uveitis periodically.
- JIA onset before 7 years of age with positive ANA is at the highest risk of developing uveitis and will require more frequent screening by a pediatric ophthalmologist (every 3–4 months).
- HLA-B27 may be present or absent and is not required for diagnosis of enthesitis-related arthritis.
- An ANA may be positive in up to one-third of the healthy population and in family members of patients with SLE.
- A negative ANA makes the diagnosis of SLE less likely.
- Post-streptococcal reactive arthritis (PSRA) is distinct from arthritis of acute rheumatic fever (ARF); these patients do not meet criteria for ARF.
- In cases of PSRA, secondary antibiotic prophylaxis against group A β-hemolytic streptococcus (GAS) is recommended for 1 year if there's no evidence of carditis.
- You must have the classic skin findings to have a diagnosis of JDM.
- JDM can occasionally present with a normal CK and aldolase in patients who already have severe muscle atrophy.
- Polymyositis is exceptionally rare in pediatrics, affecting an older age group than in JDM.
- Overlap myositis can be seen in lupus or mixed connective tissue disease.
- Don't forget about other causes of myositis, including:
  - Virus associated
  - Strep-associated myositis
  - Rhabdomyolysis
  - Mitochondrial myopathies
  - Muscular dystrophies
- Growing pains are a diagnosis of exclusion based on a typical history and normal physical examination findings.
- Joint pain associated with joint swelling is not a growing pain.
- Persistent joint or bone pain in a specific location must be investigated.
- The most common systemic vasculitis of childhood is Henoch-Schönlein purpura (HSP); the classic presentations are palpable purpura, abdominal pain, arthritis, and occasional kidney involvement (labs are usually normal).
- A 6-month follow-up with frequent urinalysis and blood pressure evaluations is recommended in all cases of HSP.

References

1. Wu E, Mater H, Radinovich CE, Juvenile idiopathic arthritis In: Kliegman RM, Stanton BF, Schor NF, St. Geme III JW, Behrman RE, Nelson textbook of pediatrics, 19th Philadelphia: Elsevier Saunders; 2011. 830.
2. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nationwide study in Germany: suggested modification of the current screening guidelines. Rheumatology. 2007;46:1015–9.
3. Ardoin SP, Schanberg LE. Systemic lupus Erythematosus. In: Kliegman RM, Stanton BF, Schor NF, St. Geme III JW, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier Saunders; 2011. p. 841.
4. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum. 1997;40:1725.

5. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344–7. Review.
6. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, Paediatric Rheumatology International Trials Organisation (PRINTO), 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. 2010;69(5):798–806.
7. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet. 1990;335(8697):1078–80.

Suggested Reading

Amplified musculoskeletal pain syndrome. Center for Amplified Musculoskeletal Pain Syndrome. Children's Hospital of Philadelphia. https://www.chop.edu/conditions-diseases/amplified-musculoskeletal-pain-syndrome-amps. Accessed 14 Mar 2019.

Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975;292(8):403–7. Review.

Crayne CB, Beukelman T. Juvenile idiopathic arthritis oligoarthritis and polyarthritis. Pediatr Clin North Am. 2018;65(4):657–74.

Hashkes PJ, Toker O. Autoinflammatory syndromes. Pediatr Clin N Am. 2012;59(2):447–70.

Herman MJ, Martinek M. The limping child. Pediatr Rev. 2015;36(5):184–97.

Higgins GC. Complications of treatments for pediatric rheumatic diseases. Pediatr Clin N Am. 2018;65(4):827–54.

Koné-Paut I, Shahram F, Darce-Bello M, Cantarini L, Cimaz R, Gattorno M, et al. PEDBD group. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis. 2016;75(6):958–64.

Koné-Paut I. Behçet's disease in children, an overview. Pediatr Rheumatol Online J. 2016;14(1):10.

Lee JY, Schneider R. Systemic juvenile idiopathic arthritis. Pediatr Clin N Am. 2018;65(4):691–709.

Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, Paediatric Rheumatology International Trials Organisation (PRINTO), 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. 2010;69(5):798–806.

Petty RE, Laxer RM, Lindsley CB, Wedderburn L, editors. Textbook of pediatric rheumatology. 7th ed. Philadelphia: Elsevier; 2016.

Russo RAG, Katsicas MM. Takayasu arteritis. Front Pediatr. 2018;6:265.

Shenoi S. Juvenile idiopathic arthritis—changing times, changing terms, changing treatments. Pediatr Rev. 2017;38(5):221–32.

Stanton BF. Pediatric rheumatology: a field of great progress. Pediatr Clin N Am. 2018;65(4):xiii–xiv.

Tarvin SE, O'Neil K. Systemic lupus erythematosus, Sjögren syndrome, and mixed connective tissue disease in children and adolescents. Pediatr Clin N Am. 2018;65(4):711–37.

Vehe RK, Riskalla MM. Collagen vascular diseases: SLE, dermatomyositis, scleroderma, and MCTD. Pediatr Rev. 2018;39(10):501–15.

Weiss PF. Pediatric vasculitis. Pediatr Clin N Am. 2012;59(2):407–23.

Weiss PF, Colbert RA. Juvenile spondyloarthritis a distinct form of juvenile arthritis. Pediatr Clin North Am. 2018;65(4):675–90.

West SG. Behçet disease and Cogan's syndrome. In: West SG, editor. Rheumatology secrets. 3rd ed. Philadelphia: Elsevier Mosby; 2015. p. 248–52.

Neurology

16

Ivet Hartonian, Jong W. Yoo, and Jason T. Lerner

SEIZURES AND EPILEPSY

Classification of Seizure Types

- Simple partial (focal) seizures
  - No impairment of consciousness
  - Can have motor, sensory, or autonomic features
  - Can evolve to a complex partial seizure
- Complex partial seizures (focal seizure with altered consciousness)
  - Impairment of consciousness
- Both simple and complex partial seizures can secondarily generalize
- Generalized seizures
  - Absence (*petit mal*)
  - Myoclonic
  - Clonic
  - Tonic
  - Tonic–clonic (*grand mal)*
  - Atonic

Febrile Seizures

- Affects 2–5% of children
- Most common childhood seizure type (6 months to 5 years)
- Simple febrile seizure
  - Brief generalized seizure
  - Less than 15 min
  - Does not recur within 24 h
  - Febrile illness not involving the central nervous system (CNS)
- Complex febrile seizure
  - Can have focal features
  - Prolonged (> 15 min)
  - Recurs within 24 h of febrile illness
- Evaluation
  - Depends on clinical presentation
  - Ask about vaccination history
  - Consider meningitis/encephalitis if child is very sick; mental status changes, meningeal signs, focal exam
  - Lumbar puncture if meningitis or encephalitis is suspected at any age
  - Strongly consider lumbar puncture in children younger than 12 months because the signs and symptoms of bacterial meningitis may be minimal or absent in this age group
  - Blood work for evaluation of the febrile illness, not the seizure
  - Electroencephalogram (EEG) not necessary for simple febrile seizure
  - Neuroimaging is also not routinely needed for simple febrile seizure

Management

- Supportive
- Treatment of underlying febrile illness

I. Hartonian
Pediatric Neurology, Department of Pediatrics, Adventist Health White Memorial, Los Angeles, CA, USA

J. W. Yoo · J. T. Lerner (✉)
Pediatric Neurology, Department of Pediatrics, UCLA Mattel Children's Hospital, Los Angeles, CA, USA
e-mail: jlerner@mednet.ucla.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_16

Prognosis
- Approximately 1 in 3 patients will have recurrence after experiencing first febrile seizure
- Approximately 2–10% will likely be diagnosed with epilepsy after experiencing a febrile seizure

Neonatal Seizures

Background
- Incidence of neonatal seizures in term infants is 1–3.5 per 1000 births in the USA
- The incidence is much higher in preterm infants

Causes
- Hypoxic ischemic encephalopathy
- Intracranial hemorrhage (intraventricular, subdural, subarachnoid)
- Ischemic stroke
- Infections (meningitis)
- Hypoglycemia
- Hypo or hypernatremia
- Hypocalcemia
- Hypomagnesemia
- Related to underlying inborn error of metabolism
- Certain genetic disorders

Clinical presentation
- Often not obvious
- Subtle tonic or clonic movements of one limb
- Automatisms also possible (lip-smacking)

Diagnosis
- Laboratory evaluation to look for metabolic abnormalities, hypoglycemia, or infection
- EEG
- Neuroimaging to look for underlying structural abnormality
- Jitteriness can sometimes be associated with hypoglycemia

Treatment
- Try to treat the underlying etiology such as electrolyte abnormality or hypoglycemia
- Phenobarbital

Prognosis
- The consequence of neonatal seizures is in part dependent on the underlying etiology, response to treatment, and gestational age
- There is higher mortality rate
- Depending on etiology, there can also be increased risk of developing motor and cognitive delays
- "Fifth day fits" is a subset of benign familial neonatal convulsions with seizures occurring on the 5th or 6th day of life; self-limited

Infantile Spasms

Background
- Typical age of onset is between 4 and 7 months
- Typically involve rapid flexion of the trunk, neck, and extremities, followed by a tonic phase
- Often occur in clusters, and in between the spasms, the child may cry
- More common after an arousal, including after a nap
- West syndrome: Triad of infantile spasms, hypsarrhythmia on EEG, and developmental regression

EEG—hypsarrhythmia
- Triad of: High amplitude, disorganized background, multifocal discharges

Treatment
- Adrenocorticotropic hormone (ACTH)
- Vigabatrin if the spasms are symptomatic in a patient with tuberous sclerosis complex

Prognosis
- If not treated early or effectively → increased risk of developmental delay and intellectual disability

Childhood Absence Epilepsy

Background
- Typical onset between 4 and 10 years of age
- Staring and behavioral arrest

- Can have eye blinking or eye flutter
- Automatisms
- Usually will last a few seconds with rapid return to baseline
- Typically occur daily, multiple times per day
- During brief episodes, there is memory lapse → academic decline
- Often can be provoked with 2–3 min of hyperventilation

EEG

- 3 Hz generalized spike-wave discharges (Fig. 16.1)

Treatment

- Ethosuximide

Prognosis

- The majority will become seizure-free during adolescence

Benign Epilepsy with Centrotemporal Spikes (BECTS)

Background

- Previously known as benign rolandic epilepsy (BRE)
- Typical onset between 4 and 11 years of age
- Simple focal motor seizures (mostly involving the face but can spread to arm and leg, and can also secondarily generalize)
- Can also have sensory features (paresthesias) involving the corner of the mouth, cheek, or tongue
- There can be increased salivation and speech arrest
- Majority of seizure events are nocturnal
- Patients typically have normal neurocognitive development

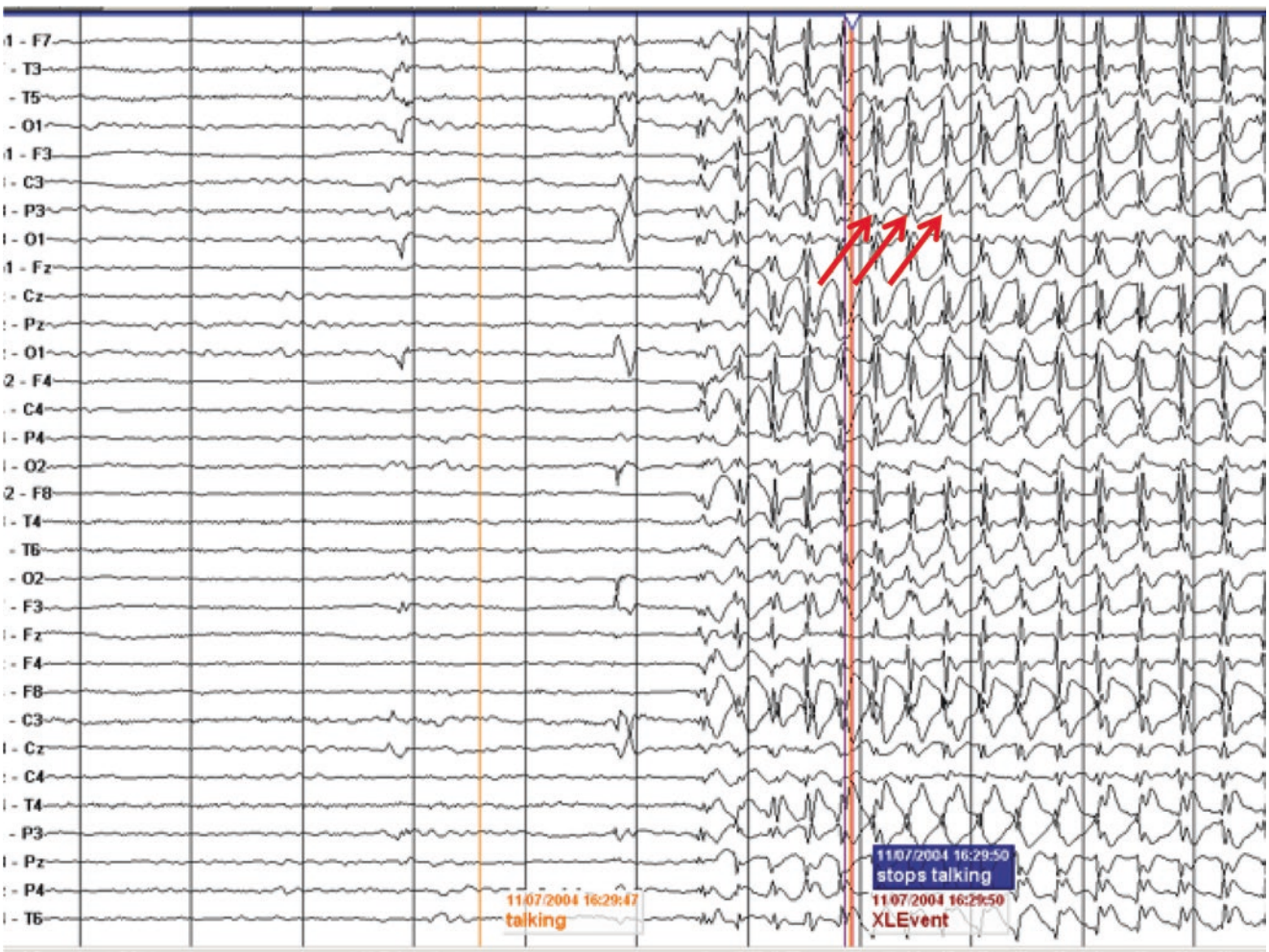


Fig. 16.1 Generalized 3 Hz spike-wave discharges seen in childhood absence epilepsy

EEG
- Focal discharges in the centrotemporal (rolandic) region with activation during sleep over a normal background

Treatment
- Low seizure frequency
- Because seizures are typically nocturnal and infrequent, there is no absolute indication to treat
- If treatment is considered, first-line is carbamazepine

Prognosis
- May be associated with developmental delays
- Spontaneously remits in mid-adolescence

Juvenile Myoclonic Epilepsy

Background
- Typical onset between 12 and 18 years of age
- Often presents with generalized tonic–clonic seizures
- Risk factors include sleep deprivation (from a sleepover), stress, and alcohol use
- Will often report jerking movements (myoclonic seizures) of the upper extremities upon awakening

EEG
- Generalized "atypical" spike or polyspike-and-wave discharges at 4–6 Hz
- Photosensitivity is common

Treatment
- Valproic acid
- Risk of neural tube defects
- May consider lamotrigine or levetiracetam

Prognosis
- Lifelong risk of seizures

Lennox–Gastaut Syndrome

Background
- Often have multiple seizure types (tonic, tonic–clonic, myoclonic, atypical absence, atonic "drop seizures")
- Seizures are often frequent and difficult to treat
- Begins in childhood

EEG
- Diffuse slow spike-and-wave discharges at 1.5–2.5 Hz (Fig. 16.2)

Treatment
- Usually requires multiple medications
- Consider ketogenic diet
- Surgical options
- Consider corpus callosotomy in patients with refractory drop seizures
- Vagal nerve stimulator placement

Prognosis
- Refractory epilepsy
- Intellectual disability

Landau–Kleffner Syndrome

Background
- Onset between 3 and 7 years of age
- Acquired aphasia after development of normal language skills
- 25% of patients do not have clinical seizures

EEG
- Spikes, sharps, and spike-and-wave discharges typically seen over bilateral temporal areas
- Presence of electrical status epilepticus during slow-wave sleep (ESES)
- Continuous spike-wave discharges during 85% of slow-wave sleep

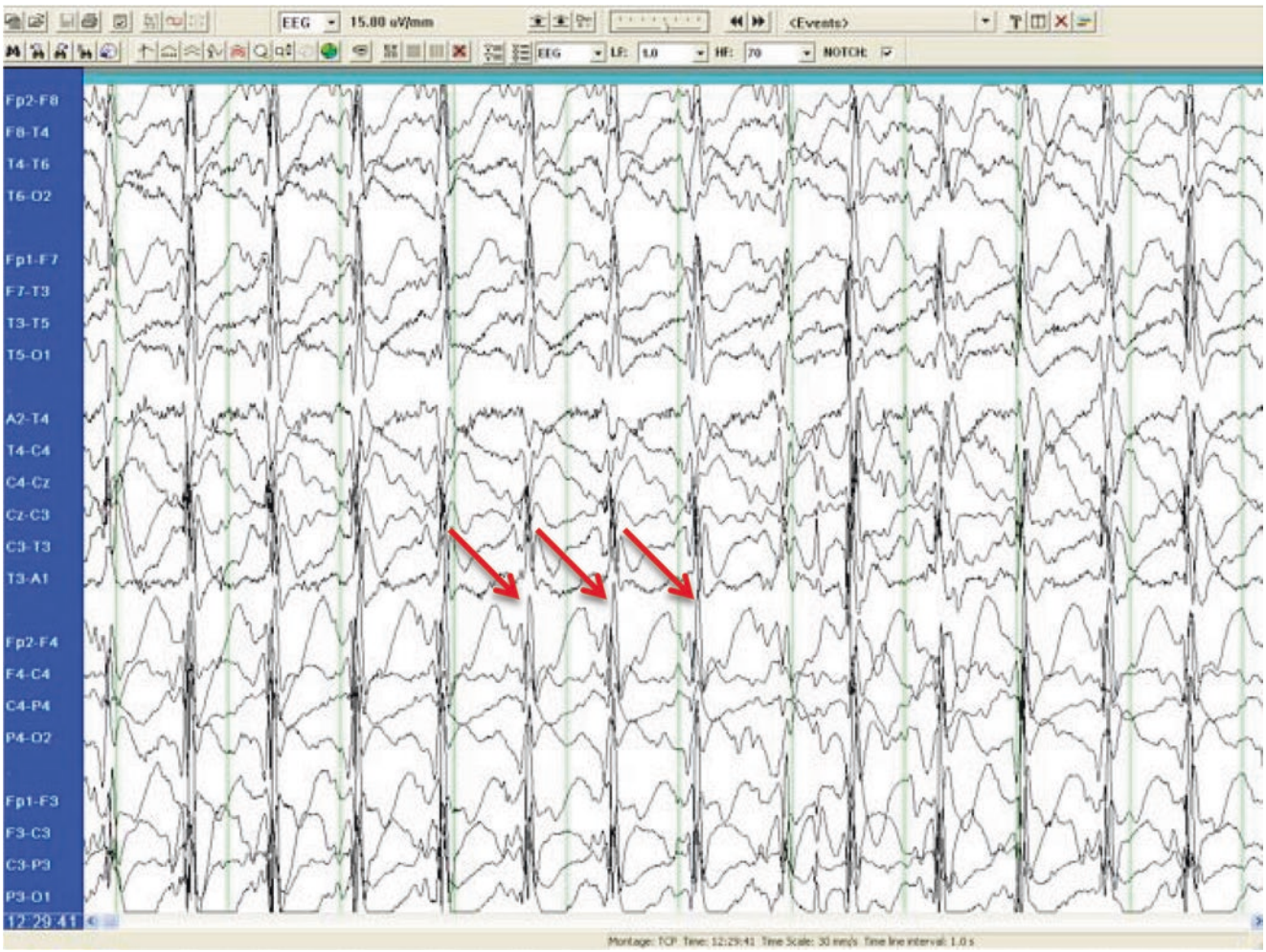


Fig. 16.2 Generalized 1 Hz slow spike-wave seen in Lennox–Gastaut syndrome

Treatment

- Anticonvulsants
- Corticosteroids
- Benzodiazepines

Prognosis

- Often, clinical seizures have good response to medications
- Language recovery is variable

Rasmussen Encephalitis

- Progressive encephalopathy, often leading to refractory partial seizures, cognitive decline, and hemiparesis
- Imaging shows eventual atrophy in the affected cerebral hemisphere
- Neuropathology possibly related to perivascular lymphocytic infiltrates (no clear explanation why it is unilateral)
- Anti-glutamate receptor antibodies have been found in patients, suggesting an autoimmune process
- Medical treatment includes high-dose steroids and intravenous immunoglobulin (IVIG) (only a temporary solution, as the process is progressive)
- Definitive treatment is functional hemispherectomy (disconnecting the affected cerebral hemisphere)
- Varying degrees of focal deficits are to be expected after hemispherectomy (hemiparesis, speech difficulties)

Type of seizure and treatment of choice (Table 16.1)

Common side effects of antiepileptic drugs (Table 16.2)

Table 16.1 Type of seizure and treatment of choice

Seizure type	Treatment of choice
Partial seizures	Carbamazepine
	Oxcarbazepine
	Levetiracetam
Absence	Ethosuximide
	Valproic acid
	Lamotrigine
Generalized tonic–clonic	Valproic acid
	Levetiracetam
	Lamotrigine
Infantile spasms	Adrenocorticotropic hormone (ACTH)
	Vigabatrin (tuberous sclerosis)

Table 16.2 Common side effects of antiepileptic drugs

Antiepileptic drugs (AEDs)	Common side effects
Ethosuximide	Gastrointestinal upset
	Leukopenia
	Sedation
Carbamazepine	Rash ➔ Stevens–Johnson syndrome
	Drug interaction (oral contraceptives)
	SIADH/hyponatremia
	Leukopenia, hepatotoxicity
	Teratogenicity
	Dizziness/ataxia
Phenytoin	Zero-order kinetics
	Hirsutism, ataxia, gum hypertrophy, rash, teratogenic: fetal hydantoin syndrome
Phenobarbital Commonly used in (neonates and infants)	Cognitive slowing Behavioral changes
Lamotrigine	Rash
	Stevens–Johnson syndrome
Levetiracetam	Irritability
	Behavioral changes
	Hyperactivity
Valproic acid	Weight gain
	Tremor
	Hair loss
	Hepatotoxicity
	Pancreatitis
	Teratogenicity
All AEDs	Suicidal ideation (literature is not clear)

SIADH Syndrome of inappropriate antidiuretic hormone secretion

Status Epilepticus

Background

- Status epilepticus (SE) is defined as repeated seizures without regaining consciousness between attacks, or prolonged seizure for at least 5 or 30 min (evidence is based on animal data and incomplete)
- Although SE is seen throughout the life span, it tends to be more common in children under 1 year of age and adults older than 60 years
- The etiology of SE is dependent on age group; 50% of SE in children occurs with febrile illness; SE in this setting has a 5% mortality rate

Clinical presentation

- SE can occur with multiple seizure types
- Generalized tonic–clonic (primary or secondary generalization)
- Myoclonic (often seen following anoxic brain injury)
- Tonic (primarily in children, especially those with Lennox–Gastaut syndrome)
- Clonic (primarily in children)
- Epilepsia partialis continua (in cases of Rasmussen encephalitis)
- Absence

Management

- Noninvasive airway protection (0–2 min)
- Intubation if airway compromise, poor oxygenation, or increased intracranial pressure (ICP) (0–10 min)
- Vital signs assessment (0–2 min)
- Vasopressor support if needed (5–15 min)
- Neurologic exam (0–5 min)
- IV access for meds and fluids (0–5 min)
- Send blood (complete metabolic panel, complete blood count, calcium, magnesium; consider toxicology screen and antiepileptic drug levels)
- Check finger-stick glucose (0–2 min)
- Start IV fluids
- In adults, give thiamine before giving glucose if there is hypoglycemia
- 3 equivalent first-line options:
  - Intramuscular (IM) midazolam

  - IV lorazepam
  - IV diazepam
- If seizures persist, second therapy options:
  - IV fosphenytoin
  - IV valproic acid
  - IV levetiracetam
- If none of the above are available, IV phenobarbital
- If seizures continue, choices include (no clear evidence for one therapy over another):
  - Continuous infusion of thiopental, midazolam, pentobarbital, or propofol
- With any of the above, the patient should be on continuous EEG monitoring
- Admit patient to intensive care unit
- Urgent EEG or, if possible, continuous EEG monitoring if patient is not waking up after clinical seizures have stopped
- Additional evaluations once patient is stable can include lumbar puncture if patient is febrile or infection is suspected, as well as neuroimaging

Complications from SE

- Neurologic: Neuronal damage, elevated ICP, cerebral edema
- Respiratory: Hypoxia, aspiration, hypercapnia
- Cardiovascular: Tachycardia, cardiac arrhythmia
- Renal: Acute renal insufficiency, myoglobinuria, or rhabdomyolysis
- Autonomic: Hyperthermia
- Metabolic: Lactic acidosis, electrolyte disturbances

Prognosis

- Early mortality from SE in children is 3%
- Longer duration of SE is associated with worse outcome
- Etiology of SE is also related to prognosis

Keywords of high yield cases of epilepsy syndromes (Table 16.3)

Clinical approach to first-time seizure

- It is estimated that in the USA, between 25,000 and 40,000 children per year have a first unprovoked seizure
- First nonfebrile seizure without obvious provoking factors (head trauma, intracranial infection, or tumor)
- Immediate evaluation: Stabilize the child, and obtain detailed history to determine if seizure has occurred and if it is the child's first seizure

Table 16.3 Keywords of high-yield cases of epilepsy syndromes

Keywords	Epilepsy syndromes
Infant with rapid repetitive clusters of seizures or head nodding, hypsarrhythmia on EEG, and neurodevelopmental arrest/regression	West syndrome
Behavioral arrest, staring, eye flutter, automatisms, lack of a postictal state, 3 Hz spike-wave discharges on EEG (4–10 years of age)	Childhood absence epilepsy
Seizures soon after sleep onset or just before awakening, paresthesia of the mouth/tongue, facial twitching, and drooling (onset 4–11 years)	Rolandic epilepsy with centrotemporal spikes
Ictal vomiting, eye deviation, convulsions less common, events often prolonged (> 5 min) (onset 3–6 years)	Panayiotopoulos syndrome
Myoclonic seizures (jerks) involving the upper extremities upon awakening, GTCs, sensitive to sleep deprivation, EEG 4–6 Hz (spike and polyspike-wave)	Juvenile myoclonic epilepsy
Language regression or acquired aphasia after normal language development + electrographic status epilepticus in sleep (ESES)	Landau–Kleffner syndrome "Acquired epileptic aphasia"
Intractable epilepsy, multiple seizure types, intellectual disability, slow spike-wave EEG < 3 Hz	Lennox–Gastaut syndrome
Progressive partial seizure, difficult to treat, positive antibodies, atrophic hemisphere	Rasmussen's encephalitis
Gelastic seizures: sudden burst of mirthless laughter, cooing, giggling, or smiling	Hypothalamic hamartoma

GTC generalized tonic–clonic *seizure*, *EEG* electroencephalogram

- Laboratory evaluation should be based on individual clinical history such as vomiting, diarrhea, and dehydration
- Toxicology screen if any concern of drug exposure or substance abuse
- Lumbar puncture has limited value unless there is concern for meningitis or encephalitis
- EEG is recommended to help determine seizure type, epilepsy syndrome, and risk for recurrence
- Emergent neuroimaging should be performed in children with postictal focal deficits or prolonged altered mental status. Magnetic resonance imaging (MRI) is the preferred imaging modality in children
- Risk of seizure recurrence is higher in individuals with remote symptomatic etiology (history of head trauma or cerebral palsy) and abnormal EEG
- Treatment with antiepileptic drugs (AED) after first seizure compared to second seizure has not been shown to impact prognosis for long-term seizure remission
- Treatment with AED may be considered based on individual circumstances where the benefit of preventing a second seizure outweighs the risks of AED side effects

Neurodiagnostic studies of choice

- Head ultrasound—Preterm periventricular hemorrhagic infarction (although MRI more sensitive)
- Computed tomography (CT)—Skull fracture, epidural hematoma, subdural hematoma
- MRI—Diffuse axonal injury, subarachnoid hemorrhage, child abuse, hypoxic–ischemic encephalopathy, developmental brain malformations, stroke

Epilepsy Mimics

Breath-holding spells

- Typical age of onset is between 6 and 18 months
- Cyanotic breath-holding episodes often triggered by emotional stimuli (anger, frustration); the breath-holding occurs in expiration
- Pallid breath-holding episodes often provoked by sudden fear (after injury, surprise)
- With both spells, there can be loss of consciousness followed by limpness and movements that can look similar to tonic posturing or myoclonic jerks
- By age 6, most children will no longer have episodes
- Iron deficiency anemia is highly associated with breath-holding spells. Check complete blood count and ferritin. Supplement if necessary

Sandifer syndrome

- Involves tonic neck extension and dystonic posturing of trunk
- Commonly associated with gastroesophageal reflux disease (GERD)
- The posturing is believed to be related to the discomfort from reflux
- Infants typically have normal neurologic exam, and clinical history reveals a relationship between feeding and the posturing

Syncope

- Definition: Brief loss of consciousness as well as postural tone secondary to a transient decrease in cerebral perfusion with rapid recovery back to baseline
- Most common etiology of syncope is neurocardiogenic (vasovagal)
- Cardiovascular-mediated syncope includes arrhythmias (supraventricular tachycardia) and cardiac structural problems (aortic stenosis)
- If patient has recurrent syncope, family history of syncope, or sudden unexplained death, then cardiology referral is indicated

Night terrors

- Non-rapid eye movement disorder
- A type of parasomnia

- Most commonly occur in the first one-third of the night
- Clinically can see facial flushing and agitation
- Child will have amnesia for the event
- Night terrors can occur throughout first decade of life and usually will spontaneously remit

Movement disorders

- The movements associated with various movement disorders can be perceived as epileptic in nature
- Examples include tic disorder, sleep myoclonus, and paroxysmal dyskinesia

NEUROCUTANEOUS DISORDERS

Neurofibromatosis Type 1

Genetics

- Autosomal dominant
- Chromosome 17
- Most common with incidence of 1/3000
- Childhood onset

Diagnosis made by 2 or more of the following: (Table 16.4)

- > 6 *café au lait* spots: 5 mm prepubertal and 15 mm in pubertal children (hallmark of NF1)
- Axillary or inguinal freckling
- 2 neurofibromas or > 1 plexiform neurofibroma

Table 16.4 Age of onset of major clinical manifestations of neurofibromatosis 1

Clinical finding in NF1	Age of onset
Café au lait spots	Birth to 12 years
Axillary or inguinal freckling	3 years to adolescence
Lisch nodules	> 3 years
Optic glioma	Birth to 7 years (up to 30 years)
Cutaneous neurofibromas	> 7 years (usually late adolescence)
Plexiform neurofibromas	Birth to 18 years

- Distinctive bony lesion (sphenoid dysplasia, thinning of long bone cortex)
- Optic nerve glioma
- First-degree relative with NF1

Common associations

- Learning disabilities
- Migraines
- Seizures
- Skeletal abnormalities: Scoliosis, short stature

Increased risk

- Pilocytic astrocytoma
- Meningioma
- Leukemia

Treatment

- Genetic counseling
- Early detection of malignancies
- Prevention of future complications

Neurofibromatosis Type II

Genetics

- Autosomal dominant
- Chromosome 22
- Incidence of 1/40,000
- Onset in adolescence

Diagnosis with one of the following:

- Bilateral vestibular schwannomas (cranial nerve [CN] VIII)
- First-degree relative with NF2 and unilateral vestibular schwannoma
- Any 2 of the following: meningioma, schwannoma, neurofibroma, glioma, or subcapsular cataracts

Common associations

- Hearing loss
- Tinnitus
- Gait abnormalities

Increased risk

- Multiple inherited schwannomas

- Meningioma
- Ependymoma

Treatment
- Genetic counseling
- Annual hearing screen
- Early detection of malignancies

Tuberous Sclerosis

Genetics
- Autosomal dominant
- Chromosome 9 and 16
- 1/6000 live births
- 50% may be spontaneous mutations

Diagnosis/findings
- Ash leaf spots (Fig. 16.3a)
- Shagreen patch
- Periungual fibromas
- Facial angiofibromas (Fig. 16.3b)
- Cardiac rhabdomyoma
- Renal and pulmonary angiomyolipomas
- Cortical tubers
- Subependymal giant cell astrocytomas (SEGA)
- Minor features: Dental pits, rectal polyps, bone cysts, "confetti" skin lesions, white matter radial migration lines, gingival fibromas, nonrenal hamartomas, multiple renal cysts

Common associations
- Seizures (most common presenting symptom)
- Infantile spasms
- Intellectual disability

Increased risk
- Rhabdomyomas found in 50% of cases may spontaneously regress or may lead to congestive heart failure
- Angiomyolipomas can lead to spontaneous pneumothorax
- Polycystic kidney disease
- Intellectual disability when presenting with severe seizures

Treatment
- Seizure control
- Echocardiogram (ECHO)
- Blood pressure check/renal ultrasound
- Neuroimaging every 1–3 years
- CT chest in adolescent females

Sturge–Weber Syndrome

Genetics
- Spontaneous mutation
- Incidence of 1/50,000

Diagnosis/findings
- Facial port-wine stain in V1 or V2 distribution
- Seizures

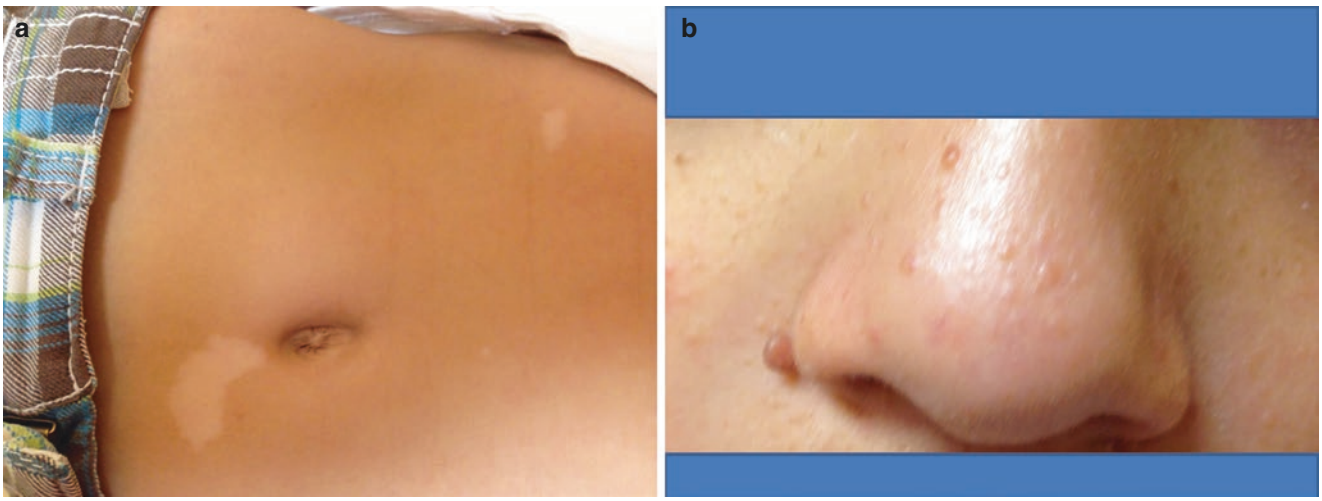


Fig. 16.3 (**a**) Typical ash leaf macules: Hypomelanotic macules round and oval in shape and vary in size from a few mm to as much as few cm in length. (**b**) Facial angiofibromas (adenoma sebaceum): Multiple papular lesions varying in size clustered on and around the nose and cheeks

- Ipsilateral cerebral leptomeningeal angioma which calcifies over time (tram-track/railroad calcifications on CT)

Common associations
- Intellectual disability
- Seizures
- Contralateral hemiparesis and hemianopia

Increased risk
- Glaucoma
- Seizures
- Hemiparesis
- Hemiatrophy

Treatment
- Seizure control—may require hemispherectomy
- Annual eye screening

HEADACHE

Epidemiology
- Prevalence of headache in children up to the age of 20 years is approximately 58%
- Female:male ratio of 1.5:1 in this same age group
- Migraines in this population are seen 7.7–7.9% in females and 6% in males
- In young children, boys have more migraines, but this reverses at puberty
- Younger children often have more atypical symptoms

Types of headaches
- Migraine
- Tension
- Chronic nonprogressive
- Chronic progressive

Migraine Headache

Clinical presentation
- Acute intermittent headache
- Duration of pain can be 30–60 min but up to 72 h
- Unilateral (frontal/temporal) location (may be bilateral in children)
- Typically has a pulsating quality
- Nausea and/or vomiting
- Photophobia and/or phonophobia
- Vertigo
- May have associated aura
- Child will typically seek a quiet and dark place to rest
- Sleep can often relieve the pain
- Periodic syndromes in children such as cyclic vomiting (recurrent bouts of vomiting) or benign paroxysmal vertigo (recurrent episodes of dizziness) often become typical migraines as child gets older

Features of aura
- Fully reversible visual symptoms
- Flickering lights, spots, lines, and even loss of vision
- Fully reversible sensory symptoms—pins and needles or numbness
- Fully reversible dysphasic speech disturbance
- Aura symptoms develop over ≥ 5 min
- Each symptom typically lasts ≥ 5 min and ≤ 60 min
- Headache typically develops during the aura or follows aura within 60 min

Tension Headache

- Milder headache
- Less disabling than migraine headaches
- Usually, there is no nausea or vomiting
- Can have either photophobia or phonophobia but usually do not have both
- Pain often described as "band-like" around the head
- Often responsive to over-the-counter analgesics

Chronic Nonprogressive Headache

- Also called new daily persistent headache
- Definition: Headache present for ≥ 4 months for ≥ 15 days/month

- Common in adolescents
- Usually, there is a normal neurologic exam
- Often, there are psychosocial factors involved

Treatment

- Multidisciplinary approach is best
- Pharmacologic interventions (preventative treatment such as amitriptyline)
- Lifestyle modifications (adequate sleep, moderate exercise, regular meals)
- Biobehavioral strategies (relaxation exercises)
- Psychiatric and/or psychological interventions

Chronic Progressive Headache

- Gradual increase in frequency of headache
- Gradual increase in severity of headache
- Consider the presence of increasing ICP
- Differential diagnosis includes brain tumor, hydrocephalus, chronic meningitis, brain abscess, subdural hematoma, and idiopathic intracranial hypertension (pseudotumor cerebri)

Headache "Red Flags"

Clinical presentation

- Sudden severe headache
- Occipital headache
- Early morning headache
- Pain that awakens the child from sleep
- Worsening of pain with changes in position
- Increasing frequency and intensity of headache

Physical exam

- Change in mental status
- Cranial nerve palsies
- Visual field defects
- Papilledema
- Abnormal pupillary responses
- Focal neurologic deficits
- Ataxia, gait disturbance

Diagnosis of Primary Headache Syndromes

- Clinical history
  - Ask about family history of headaches
  - Impact on school (days missed, drop in grades)
  - Ask about anxiety, depression, other psychiatric comorbidities
  - Ask about extracurricular activities
- Imaging
  - Low-yield imaging in an isolated headache unaccompanied by other neurological findings
  - CT only indicated in acute cases such as high suspicion for subarachnoid hemorrhage
  - MRI indicated for chronic progressive headache, even in absence of focal neurologic symptoms
- Typically no indication for EEG or skull films
- No routine blood work

Treatment of Primary Headache Syndromes

General

- Lifestyle modifications (regular meals, consistent sleep, exercise, hydration)
- Methods to cope with stress
- Treat pain early
- Set realistic goals

Acute treatment

- Acetaminophen
- Ibuprofen, naproxen, and other NSAIDs
- Triptans (only rizatriptan and almotriptan are approved by the US Food and Drug Administration for pediatrics)
- Consider promotility agents, as gastroparesis can delay medication absorption (prochlorperazine, metoclopramide)

Chronic treatment (preventative therapy)
- Lifestyle change
- Exercise, regular sleep pattern, good balanced diet, hydration
- Avoid overuse of analgesic medications; may cause analgesic headache
- Try to use medications that will address comorbidities
- Amitriptyline for patients with sleep problems
- Cyproheptadine for patients with allergies, poor appetite, or thin
- Topiramate for obese patients
- Avoid propranolol in patients with asthma

Alternative therapies
- Behavioral therapies (biofeedback)
- Acupuncture
- Natural supplements (magnesium, riboflavin, butterbur)

Posttraumatic or Postconcussion Headaches

- Posttraumatic headache is common in association with other postconcussive symptoms such as dizziness, sleep disturbance, and mood changes

Risk factors for posttraumatic headache
- Preexisting headache (migraine)
- Age (adolescence)
- Psychological factors (maladaptive coping strategies, high-risk psychological traits)

Assessment
- Thorough history and neurologic exam
- Ask about preexisting headaches
- Ask about frequency, severity, and characteristics of posttraumatic headaches as well as other postconcussion symptoms
- Laboratory evaluation usually not indicated unless there is concern for other underlying condition (hypothyroidism, anemia)
- Neuroimaging (CT or MRI) is typically not indicated if neurologic exam is normal

Treatment
- Abortive medications: NSAIDs; triptans if posttraumatic headaches have migraine features; opioids should be avoided
- Preventive treatments: Lifestyle modifications; typical prophylactic medications used to treat primary headaches (riboflavin, magnesium, amitriptyline, topiramate, propranolol); comorbid symptoms should also be addressed (psychiatric conditions, sleep problems, cognitive issues)

Idiopathic Intracranial Hypertension

Background
- Previously called pseudotumor cerebri
- Important consideration in the differential diagnosis in a patient with chronic daily headache
- Incidence of 3.5–19 per 100,000
- Majority of patients are female

Clinical features (Table 16.5)
- Will often have diffuse pounding headache
- Can also complain of neck stiffness and transient visual disturbances
- Key features of exam include papilledema and visual field testing to evaluate for an enlarged blind spot
- Neuroimaging is often normal (CT scan must be performed before lumbar puncture)
- Diagnostic approach includes basic cerebrospinal fluid (CSF) evaluation plus obtaining opening pressure during lumbar puncture (pressure will exceed 200 mm H_2O)

Table 16.5 Signs of increased intracranial pressure according to age

Age	Signs of increased intracranial pressure
Infants	Poor oral intake, irritability, wide sutures, bulging fontanel, downward deviation of eyes, hydrocephalus
Children	Headache, diplopia, papilledema, abducens nerve paralysis, hypertension, and bradycardia

- Lumbar puncture will also often help with headache symptoms by relieving the pressure

Treatment

- Carbonic anhydrase inhibitors such as acetazolamide
- Ophthalmological follow-up if visual symptoms are prominent
- If necessary, optic nerve sheath fenestration can be performed

MALFORMATIONS OF THE BRAIN

Arnold–Chiari Malformation Type I (Table 16.6)

Definition

- Most common type of Chiari malformation. Herniation of the cerebellar tonsils through the foramen magnum into the cervical canal can be associated with syringomyelia but is not associated with hydrocephalus

Symptoms

- Generally asymptomatic in early childhood. During adolescence or adult life can cause recurrent headaches, urinary frequency, neck pain, and progressive lower extremity spasticity

Treatment

- Asymptomatic patients can be monitored clinically and with MRI to evaluate progress as needed. Symptomatic patients can undergo surgery as necessary

Arnold–Chiari Malformation Type II

Definition

- Classic form of Chiari malformation. Cerebellar tonsillar and lower medullary herniation through the foramen magnum into the upper cervical canal. Associated with progressive hydrocephalus due to obstruction of outflow of CSF through the posterior fossa and lumbosacral meningomyelocele

Symptoms

- Some can present in infancy with dysphagia, stridor, apnea, and weak cry. Can also present later with gait abnormalities and incoordination

Table 16.6 Difference between Chiari malformation type I and type II

Chiari malformation type I	Chiari malformation type II
Herniation of the cerebellar tonsils > 0.5 cm below the foramen magnum into the cervical canal	Herniation of cerebellar tonsils and lower medulla, pons, fourth ventricle through the foramen magnum into the upper cervical canal
Most common and least severe	Less common and more severe
	Can involve the cranial nerve
Can be associated with syringomyelia (Spine MRI is diagnostic)	Usually associated with hydrocephalus, and myelomeningocele
Asymptomatic during childhood	Infants
During adolescence	Dysphagia
Neck pain	Apnea
Recurrent headaches	Weak cry
Sleep apnea	Older children
Bowel/bladder dysfunction	Gait abnormalities
Lower extremities spasticity	
Observation	Observation
Surgical decompression as necessary	Serial MRI follow-up
	Surgical decompression as necessary

MRI magnetic resonance imaging

Treatment

- Clinical observation and serial MRIs to evaluate for any progression. Surgical decompression as necessary

Lissencephaly

Definition

- Smooth brain without sulci. (Agyria refers to portions of the brain lacking gyri; pachygyria refers to the presence of broad gyri and shallow sulci)
- Caused by incomplete or failure of neuronal migration, resulting in a lack of development of gyri and sulci
- Type 1 is associated with facial dysmorphism and sometimes with deletion of chromosome 17
- Type 2 is associated with hydrocephaly and dysgenesis of the cerebellum

Symptoms/exam

- Microcephaly, results in neurologic impairment

Diagnosis/treatment

- CT or MRI of brain, supportive care

Polymicrogyria

Definition

- Presence of large number of small gyral convolutions separated by shallow sulci. Usually an acquired defect

Clinical presentation

- Depends on location, extent, and severity. Seizures are common sequelae

Diagnosis/treatment

- CT or MRI of the brain, supportive care, and treatment of seizures

Agenesis of Corpus Callosum

Definition

- Complete or partial, depending on the stage of development at which growth was arrested
- Isolated, incidental finding in some patients
- When accompanied by other malformations, can result in severe seizures and intellectual disability
- Chromosomal mutations (8, 9, 13, 18), inborn errors of metabolism (nonketotic hyperglycinemia, neonatal adrenoleukodystrophy, pyruvate dehydrogenase deficiency), and teratogens (maternal alcohol and cocaine use)

Symptoms/exam

- Intellectual disability, seizures, hypo- or hypertelorism
- Aicardi syndrome: Combination of agenesis of corpus callosum, chorioretinal lacunae, and infantile spasms
- Recurrent hypothermia (Shapiro syndrome)
- Development can be normal if it is the only neurologic manifestation

Diagnosis/treatment

- MRI brain, supportive care, and treatment of neurologic sequelae

Dandy–Walker Malformation

Definition

- Cystic expansion of the fourth ventricle in the posterior fossa. Majority of cases have hydrocephalus
- Malformation is also often associated with agenesis of corpus callosum and agenesis or hypoplasia of cerebellar vermis

Symptoms/diagnosis

- Wide range of neurodevelopmental outcomes. Can see rapid increase in head circumference and prominent occiput due to hydrocephalus,

cerebellar ataxia, delayed motor, and cognitive development. Can also be associated with orofacial deformities and with congenital abnormalities of the cerebrovascular, gastrointestinal, and genitourinary systems
- MRI of the brain shows cystic structure in posterior fossa

Treatment
- VP shunt for hydrocephalus, treatment of neurologic sequelae

DISORDERS OF HEAD GROWTH

Microcephaly

Definition
- Head circumference > 2 standard deviations below the mean for age and gender

Etiology
- Primary—genetic syndromes, chromosomal abnormalities (trisomy 13, 18, 21)
- Secondary (acquired)
  - Intrauterine infection—TORCH which includes Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections
  - Postnatal infections—meningitis, encephalitis
  - Hypoxic ischemic encephalopathy
  - Stroke
  - Traumatic brain injury
  - Malnutrition

Diagnosis
- Ask about family history
- Obtain TORCH titers
- Consider karyotype
- Neuroimaging

Treatment
- Genetic counseling
- Monitor for developmental delays (refer for appropriate interventions such as physical, occupational, and speech therapy)

Macrocephaly

Definition
- Head circumference > 2 standard deviations above the mean for age and gender; megalencephaly (large brain)

Etiology
- Familial
- Sporadic
- Associated with neurofibromatosis, tuberous sclerosis, or achondroplasia
- Certain metabolic disorders (Alexander disease, Canavan disease, Soto syndrome)

Diagnosis
- Ask about family history
- Check for evidence of increased ICP
- If concern for elevated ICP → neuroimaging

Treatment
- Treat underlying etiology
- Monitor development and refer to appropriate services if indicated

Hydrocephalus

Definition
- Disturbance of formation, flow, or absorption of CSF that leads to an increase in volume within the cerebral ventricles and an elevation in ICP

Ventricular system (CSF flow)
- Unilateral flow
- CSF is mostly made in choroid plexus within ventricles (total volume produced is about 400–500 mL/day)
- CSF flows from lateral ventricles → foramina of Monro → third ventricle → cerebral aqueduct → fourth ventricle → foramina of Luschka and foramen of Magendie → cisterna magna → reabsorbed in the arachnoid granulations

Obstructive (noncommunicating) hydrocephalus

- CSF is obstructed within the ventricular system or in its outlets to the arachnoid granulations
- Most common etiology is congenital aqueductal stenosis
- Other causes include posterior fossa tumors, Arnold–Chiari type II malformations, and Dandy–Walker syndrome

Nonobstructive (communicating) hydrocephalus

- Flow within ventricular system is intact, but the cisterns and arachnoid villi cannot absorb CSF
- Typically related to accumulation of blood or infectious material
- Causes include subarachnoid hemorrhage, intraventricular hemorrhage (premature infants), and meningitis

Clinical features

- Signs and symptoms of increased ICP
- Altered mental status, irritability
- In infants: Full fontanel, rapid head growth, poor feeding, downward deviation of eyes (sunset sign)
- Vomiting
- Headache
- Increased tone or reflexes

Diagnosis

- Consider head ultrasound in infants (through the anterior fontanel)
- Head CT or MRI

Treatment

- If possible, treat underlying etiology
- Medical treatment with acetazolamide
- Definitive treatment is surgical with placement of ventriculoperitoneal (VP) shunt
- Shunt complications
  - Infection (persistent fever, headache)
    - Antibiotic and shunt replacement
  - Shunt malfunction (headache without fever)
    - Consult neurosurgery for shunt adjustment
  - Epilepsy: Occurs in 1/3 patients 10 years post-shunt
    - Subacute/chronic shunt dysfunction can occasionally present with worsening seizures or status epilepticus

Craniosynostosis

Definition

- Premature fusion of one or more sutures → abnormal skull shape
- Incidence is about 3.4 per 10,000 births
- Most common is closure of sagittal suture (50–60%)

Etiology

- Typically sporadic
- Secondary causes
  - Certain metabolic disorders (hyperthyroidism)
  - Storage disease (mucopolysaccharidosis)
  - Genetic disorders (Crouzon, Apert, and Pfeiffer syndromes)
  - Hematological disorders (thalassemia)
  - Brain malformations (holoprosencephaly, microcephaly)
  - Teratogen exposure (valproic acid)

Diagnosis

- Palpation of skull
- Skull films
- Head CT if considering surgery

Treatment

- Surgery in moderate to severe cases to restore normal skull/facial growth and development
- Surgical intervention is mandatory if there is increased ICP

VASCULAR ANOMALIES

Stroke

Background
- Incidence is about 2–3 per 100,000 children annually
- About 1 infant in 4,000 live births

Causes
- Ischemic stroke includes congenital heart disease, coagulation disorders, infections (meningitis), sickle cell disease, vasculopathies, and arterial dissection
- Hemorrhagic stroke includes congenital vascular anomalies (arteriovenous malformations), brain tumors, head trauma, and thrombocytopenia

Clinical presentation
- Acute onset of hemiparesis
- Seizures
- Severe headache with focal neurologic symptoms most commonly present in hemorrhagic stroke
- Additional signs and symptoms include irritability, lethargy, and behavioral changes

Diagnosis
- Neuroimaging
  - CT is good in cases of hemorrhagic stroke (acute blood)
  - MRI/magnetic resonance angiography, including diffusion-weighted imaging is more sensitive for ischemic stroke
  - Conventional angiography is the gold standard if noninvasive evaluation is inconclusive
  - Consider Echo and hypercoagulable evaluation

Treatment
- Treat the underlying etiology
- Aspirin is the main antiplatelet agent used in children
- Neurosurgical intervention may be needed in cases of hemorrhagic stroke

Prognosis
- Mortality rates are higher with hemorrhagic stroke compared to ischemic stroke, but long-term comorbidities are less common with hemorrhagic stroke
- There is low recurrence rate after neonatal stroke

Arteriovenous Malformations (AVMS)

- Result from failure of normal capillary bed development between cerebral arteries and veins
- Most are sporadic and isolated
- Tend to cause supratentorial intracranial hemorrhages
- Patients can present with sudden headache, seizures, and focal neurologic deficits if an AVM bleeds
- CT will show acute blood
- Conventional angiography will provide a more detailed assessment of the AVM
- Surgical treatment often required given high recurrence rate

Vein of Galen Malformation

- Arteriovenous shunt between cerebral arteries and the vein of Galen
- Typically presents in neonatal period with high-output congestive heart failure
- There can also be progressive macrocephaly from hydrocephalus due to increasing venous pressure
- Diagnose with neuroimaging
- Treatment includes management of heart failure and embolization

Cerebral Venous Thrombosis

Background
- Incidence of about 1 in 100,000 children annually
- Highest risk is in the neonatal period

Causes
- Infection, especially involving head and neck (sinusitis, mastoiditis, meningitis)
- Dehydration
- Perinatal events
- Prothrombotic disorders
- Head trauma
- Malignancy
- Cardiac disease
- Chronic systemic disease

Clinical presentation
- Diffuse neurologic deficits but can also have focal deficits
- Seizures
- Headache
- Lethargy
- Nausea/vomiting
- Signs of increased ICP

Diagnosis
- Need venous imaging
- Imaging goal should be to assess blood flow and filling defects within the venous system
- MRI/magnetic resonance venography is often the modality of choice in children because of lack of radiation exposure

Treatment
- Anticoagulation
- Treat underlying etiology

SPINAL CORD DISEASES

Tethered Cord

- Occurs when the distal part of the spinal cord is thickened and is anchored in the spinal canal
- As the child grows, the distal part of the spinal cord is stretched and can become ischemic

Clinical features
- Cutaneous lesion in lower back (tuft of hair, dimple, hemangioma, lipoma)
- Lower extremity weakness, spasticity, or numbness
- Scoliosis
- Low back pain

Diagnosis
- Lumbosacral MRI

Treatment
- Transection of filum terminale

Prognosis
- Neurologic deficits are often irreversible

Spina Bifida Occulta

- Mildest form of spina bifida
- Spinal film will show incomplete closure of some vertebrae
- May see midline sacral tuft of hair or dimple on exam
- No neurological symptoms
- Often no need for intervention

Meningocele

- Protrusion of meninges from the back
- Does not contain nervous tissue
- Typically will not have neurological symptoms
- Treatment is surgical closure of the back

Myelomeningocele

- More severe form of spina bifida
- Broad-based defect in back with protruding sac containing meninges and spinal cord

- Neurological deficits are based on level of spinal cord involved
- Significant number of patients will develop hydrocephalus over time (more common when the lesion is in the thoracolumbar area)
- Treatment involves closure of the back as well as supportive care, including placement of VP shunt if hydrocephalus develops

Transverse Myelitis

Definition

- Inflammation of the spinal cord, typically involving ≤ 3 vertebral segments Includes both motor and sensory abnormalities

Causes

- Postinfectious or postvaccination
- Viral myelitis
- Autoimmune vasculitis
- Spinal cord trauma

Clinical features

- Acute/subacute onset
- Thoracic cord most often involved
- Weakness and often flaccid paralysis and areflexia initially, followed by spasticity and hyperreflexia
- Paresthesias common in the legs
- Sensory level
- Bowel and bladder dysfunction
- Back pain around the involved spinal segments

Diagnosis

- Spinal MRI (assess the extent of lesion)
- If lumbar puncture performed, CSF typically shows lymphocytic pleocytosis; protein may be elevated or normal; glucose is typically normal

Treatment

- Corticosteroids
- Supportive therapy

Spinal Epidural Abscess

- Causes: Bacteremia, direct extension from local infection
- Clinical presentation typically like transverse myelitis
- Most common organism: *Staphylococcus aureus*
- MRI with contrast is the study of choice
- Lumbar puncture is usually contraindicated
- If no neurologic deficits, can consider treatment with antibiotics only
- Surgical intervention and appropriate antibiotic therapy mainstay of treatment

Spinal Cord Trauma

- Causes: Birth injury; falls; motor vehicle accident; sport injury, including diving/trampoline; gunshot/stab wounds; infection (abscess)
- Complete spinal cord injury
  - Spinal shock: Complete loss of spinal cord function
  - Truncal + extremity muscles below level of lesion flaccid, deep tendon reflexes are depressed or absent, Babinski reflex absent, anesthesia to all modalities, autonomic dysfunction (hypotension + bradycardia)
  - If injury more permanent ➔ Hyperreflexia, muscle spasticity, permanent motor and sensory deficits, and autonomic dysfunction can persist for months
  - Recovery rare and prognosis poor

Atlantoaxial Instability

- Excessive movement between C1 (atlas) and C2 (axis)
- Ligaments mainly provide stability to the upper cervical spine
- Causes: Down syndrome, osteogenesis imperfecta, neurofibromatosis, skeletal dysplasias, mucopolysaccharidoses, trauma, tumors

- Neurologic symptoms occur when there is impingement to the spinal cord
- Plain radiography is the main diagnostic tool, preferably in an awake patient sitting or standing
- CT and MRI usually reserved for a more detailed evaluation of congenital anomalies or neurological impairment
- Posterior C1–C2 fusion if there are neurological impairments

DISORDERS OF NEUROMUSCULAR JUNCTION (TABLE 16.7)

Myasthenia Gravis

Neonatal

- Maternal anti-acetylcholine receptor (AChR) antibody transferred transplacentally
- Ptosis, feeble cry, poor suck during the first few days
- Usually resolves within 3–5 weeks

Table 16.7 Difference between upper and lower motor neuron lesions

Upper motor neuron lesions (UMNL)	Lower motor neuron lesions (LMNL)
Interruption of neural pathways in the brain and spinal cord before anterior horn cells	Interruption of neural pathways outside the brain and spinal cord
Weakness in all muscle group	Weakness more distal
(Less muscle wasting)	(More muscle wasting)
Spasticity	Hypotonia (flaccid)
Reflexes are increased	Reflexes are reduced
Babinski reflex; extensor plantar response	Fasciculations
Upgoing toe (Normal in < 3 years)	
Study of choice:	Study of choice:
CT scan (brain)	Nerve conduction studies
MRI (brain/spine)	Electromyogram
	Creatine kinase

CT computed tomography, *MRI* magnetic resonance imaging

Congenital

- Familial, not transferred via mother
- No antibodies, multiple subtypes
- Can be presynaptic (packaging, release) or postsynaptic (slow-channel syndrome, etc.)

Juvenile

- Females > males
- Onset > 10 years
- Clinical symptoms include generalized weakness, fatigability of muscles, ptosis, and ophthalmoplegia
- Diagnosis can be made by edrophonium test, ice pack test, EMG (electromyography), normal nerve conduction study (NCS), and antibodies in serum
- Treatment can involve prednisone, anti-acetylcholinesterase (AChE) drugs, thymectomy in severe cases, IVIG, and immunosuppression

Botulism

- Toxin from *Clostridium botulinum* (anaerobe)
- Two most common sources of ingestion of spores are from honey and soil
- Gradual onset of hypotonia, constipation, poor suck and swallow, feeble cry, sluggish pupils

Diagnosis

- Isolation of toxin from stool. EMG shows fibrillation potentials and decremental response on repetitive nerve stimulation

Treatment

- Botulism immune globulin (BIG), supportive care. Many patients go on to respiratory paralysis and intubation

PRIMARY MUSCULAR DISEASES (MYOPATHIES)

Duchenne Muscular Dystrophy

Genetics

- X-linked recessive disorder (affects only males) resulting in an absence of dystrophin. 30% of cases are spontaneous mutations. Incidence is 1 in 3500 male births

Symptoms/exam

- Normal newborn, develops waddling, poor head control, difficulty standing or climbing (Gowers' sign), hypertrophic calves (pseudohypertrophy), generally unable to walk after 12 years of age, death in 75% by age of 20—dilated cardiomyopathy

Diagnosis

- Creatine phosphokinase (CPK) elevated even prior to muscle weakness. Muscle biopsy is diagnostic. Genetic testing for dystrophin gene. EMG shows characteristic myopathic features. Echo, EKG, and CXR to evaluate cardiac function

Treatment

- Supportive care and physical therapy. Corticosteroids are sometimes recommended to delay wheelchair use

Becker Muscular Dystrophy

Genetics

- Defect is at same locus as Duchenne muscular dystrophy, but patients have later onset and milder course

Symptoms/exam

- Symptoms onset later than Duchenne patients, but also present with pseudohypertrophy of calves and wasting of thigh muscles. Patients ambulatory until late adolescence and early adulthood. Becker patients can also present with cardiomyopathy

Diagnosis

- CPK elevated, muscle biopsy is diagnostic. Genetic testing for dystrophin gene. Echo, EKG, and CXR to evaluate cardiac function

Treatment

- Supportive care, physical therapy

Congenital Myotonic Dystrophy

Genetics

- Autosomal dominant. CTG trinucleotide repeat expansion of chromosome 19. Inheritance is generally from mother, and symptoms become more severe with each successive generation (genetic anticipation)

Symptoms/exam

- Hypotonia in the newborn, "floppy infant," hollowing of temporal bones, tenting of upper lip, feeding issues, respiratory distress due to intercostal and diaphragmatic weakness, arthrogryposis; some patients have cataracts

Diagnosis

- DNA testing for CTG repeats, CPK not useful

Treatment

- Supportive care, physical therapy

NEUROPATHIES

Acute Inflammatory Demyelinating Polyneuropathy (Guillain–Barré Syndrome, GBS)

- Postinfectious polyneuropathy that results in paresthesias and ascending symmetric peripheral neuropathy. Early calf pain is also common. Occurs in healthy individuals, days to weeks after an antecedent illness
- Miller Fisher variant presents with facial weakness, ophthalmoplegia, ataxia, and areflexia

Causes

- Strongest association with bacteria *Campylobacter jejuni*, also associated with *Mycoplasma pneumoniae*
- Autoimmune conditions, surgery, and vaccinations

Clinical presentation

- Weakness
  - Refusal to walk, walking on a wide base, or difficulty with running or climbing stairs
  - Usually begins distally in the legs and ascends
- Symmetric diminished or absent reflexes early in the course
- Cranial nerve abnormalities are frequent; facial nerve is the most commonly affected cranial nerve, and the weakness is often bilateral
- Paresthesias
- Autonomic instability: Arrhythmia, orthostatic hypotension, hypertension, bladder dysfunction
- Acute illness usually peaks in severity 2 weeks after onset; recovery may take weeks to months

Diagnosis

- Primarily on basis of clinical appearance. CSF shows elevated protein without an elevated cell count (albuminocytologic dissociation); EMG can take weeks to show positive findings, and first abnormality is the F wave; nerve conduction studies are slow with evidence of conduction block

Treatment

- IVIG and plasmapheresis—treatment should begin as soon as clinical diagnosis is determined
- Supportive care and hospitalization until patient is stabilized and ICU care if there are symptoms of bulbar palsy, vital capacity is compromised, and/or autonomic instability

Course and prognosis

- Prognosis for childhood GBS generally is excellent
- Full recovery within 6–12 months, with the majority of those who do not fully recover having only mild disabilities

Hereditary Motor Sensory Neuropathy (HMSN) (Charcot–Marie–Tooth Disease)

- Most common inherited peripheral neuropathy. Group of disorders characterized by defective peripheral nerve myelination. Deep tendon reflexes are markedly diminished or absent; vibration sense and proprioception are significantly decreased. Pain and temperature sense intact
- HMSN I: Charcot–Marie–Tooth type 1
  - Autosomal dominant: Demyelinating condition. Asymptomatic until late childhood or adolescence. Palpable enlargement of nerves
- HMSN II: Charcot–Marie–Tooth type 2
  - Autosomal dominant or recessive: Axonal condition. Onset in childhood and associated with severe wasting of calf muscles with pes cavus and wasting of dorsal interossei of hands, foot drop; ankle–foot orthosis to help with the foot drop
- HMSN III: Dejerine–Sottas disease
  - Autosomal dominant or recessive: Onset early in infancy; delayed milestones. Peripheral nerves thicken due to myelin loss, followed by remyelination in layers. Cross section looks like onion bulb
- HMSN IV: Refsum disease
  - Autosomal recessive: Peroxisomal disorder. Problem of phytanic acid storage. Retinitis pigmentosa, hearing loss

Diagnosis

- Genetic testing, EMG/NCS

Spinal Muscular Atrophy (SMA)

- Autosomal recessive condition affecting the anterior horn cell. Characterized by three different types ranging in severity: SMA type 1 (Werdnig–Hoffmann), SMA type 2 (no eponym), and SMA type 3 (Kugelberg–Welander)

Clinical presentation

- Severe hypotonia; SMA type 1 presents prior to 6 months of age
- Frog-leg position
- Difficulty feeding
- Tongue fasciculations, atrophy with progression of disease
- No sphincter loss, sensory loss, or cognitive loss

Diagnosis

- Gene mutation screening

Management

- Respiratory, nutritional, orthopedic support
- Gene therapy [1]

Familial Dysautonomia (Riley–Day Syndrome)

- Inherited neuropathy affecting sensory and autonomic nerves
- Symptoms
  - Insensitivity to pain, temperature dysregulation, difficulty feeding, blood pressure instability, vomiting, sweating spells

Bell's Palsy (Table 16.8)

- Idiopathic facial nerve (CN VII) paralysis. Can occur after viral upper respiratory infection. Usually unilateral and self-limiting

Table 16.8 Difference between upper and lower motor neuron lesion in facial nerve palsy

Upper motor neuron facial nerve palsy	Lower motor neuron facial nerve palsy
Causes: Stroke	Causes: Idiopathic, viral infection
The angle of the mouth falls	The angle of the mouth falls
Eye closure and blinking are not affected	Weak or absent eye closure and blinking

Ramsay Hunt Syndrome

- Infectious neuropathy caused by herpes zoster oticus infection in the geniculate ganglion leading to peripheral CN VII paresis and/or other cranial nerve involvement

Clinical presentation

- Peripheral facial nerve paresis
- Deafness
- Vertigo
- Nausea
- Pain

Diagnostic criteria

- Herpes zoster oticus lesions present in the ear and on the face
- Peripheral facial nerve paresis with taste disturbance and reduction of tear secretion
- Sensitivity disturbances in the innervation area of CN V
- Sensitivity disturbance in the cervical dermatomes (usually C2–C4)
- Lesion of CN VIII (impaired hearing)

Treatment

- Acyclovir
- Corticosteroid
- Gabapentin (pain control)
- Earlier treatment (within 3 days) associated with improved outcomes

Tick Paralysis

- Uncommon, noninfectious, neurologic syndrome characterized by acute ataxia progressing to ascending paralysis
- Caused by salivary neurotoxins of several species of ticks
- Neurotoxin causes impaired neurotransmitter release at synaptic terminals

Clinical presentation
- Fatigue and weakness: Starts in legs and progresses rapidly within 2–7 days
- Irritability
- Muscle pain
- Paresthesias

Evaluation
- Serum studies and neuroimaging are usually normal

Treatment
- Removal of tick (usually found on scalp) leads to rapid improvement
- Provide respiratory support if required
- Increased risk of mortality with missed diagnosis due to respiratory failure

DISORDERS OF MOVEMENT

Ataxia

- Definition: "…disturbance in the smooth performance of voluntary motor acts" [2]

Differential diagnosis (broad spectrum)
- Infectious or postinfectious
- Posterior fossa tumors
- Neuroblastoma (opsoclonus myoclonus syndrome)
- Acute hemorrhage
- Toxic (i.e., alcohol, benzodiazepines)
- Congenital (i.e., progressive hydrocephalus, Chiari malformation, Dandy–Walker syndrome)
- Genetic and/or degenerative (i.e., ataxia telangiectasia, Friedreich ataxia, spinocerebellar ataxia)

Acute Cerebellar Ataxia

- Relatively common in children, often in the second decade of life
- Most commonly associated with viral illness (varicella, Epstein–Barr virus)
- Thought to be due to molecular mimicry

Clinical features
- Rapid onset of ataxia, over hours to days
- Typically manifests as a gait disturbance
- Can also see ataxia (e.g., when reaching for objects) or dysarthria
- Mild CSF pleocytosis
- MRI may show enhancement

Prognosis
- Usually self-limiting
- May take several weeks or months for complete resolution of symptoms

Ataxia Telangiectasia

- Autosomal recessive
- Frequency of approximately 1 per 40,000 births
- Causative gene—ataxia telangiectasia mutated (ATM) gene located on chromosome 11

Clinical features (Fig. 16.4)
- Symptom onset by 2–3 years old
- Impairment in coordinated muscle movements involving gait, trunk, and limbs
- Progressive symptoms lead to loss of ambulation in childhood
- Movement disorder precedes the oculocutaneous telangiectasias
- Jerking eye movements and oculomotor apraxia are common

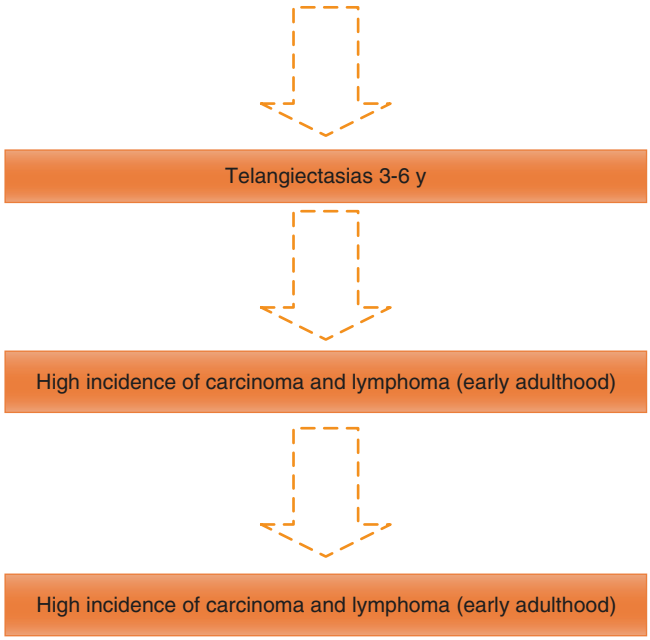


Fig. 16.4 Sequence of major symptoms in ataxia telangiectasia

- Immunologic deficiencies—increase in sinopulmonary infections
- Cerebellar degeneration
- Increased sensitivity to radiation
- Increased risk of lymphoreticular neoplasms (leukemia, lymphoma)

Diagnosis

- Elevated levels of serum alpha-fetoprotein
- Decreased serum immunoglobulins (IgA, IgG, and IgE)

Prognosis

- Often wheelchair-bound by 10 years of age
- Median survival is about 25 years

Friedreich Ataxia (Table 16.9)

- Autosomal recessive
- 98% of patients are homozygous for a GAA trinucleotide repeat expansion in intron 1 of frataxin gene (FXN)

Table 16.9 Difference between ataxia telangiectasia and Friedreich ataxia

Ataxia telangiectasia	Friedreich ataxia
Autosomal recessive	Autosomal recessive, trinucleotide repeat
1 per 40,000–100,000	1–2 per 100,000
Age of onset: 2–3 years	Age of onset: Early adolescence
Elevated levels of serum alpha-fetoprotein	Normal levels of serum alpha-fetoprotein
Decreased serum immunoglobulins (IgA, IgG, and IgE)	Normal immunoglobulins
Oculocutaneous telangiectasias	No oculocutaneous telangiectasias
Ataxia, ocular apraxia, pulmonary infections	Ataxia, nystagmus, diabetes mellitus, kyphoscoliosis, weakness, loss of deep tendon reflexes
Negative Romberg sign, intact sensation	Positive Romberg sign, poor sensation
No cardiomyopathy	Cardiomyopathy
Normal arch foot	High arched foot

Clinical features

- Onset of symptoms typically during early adolescence
- Progressive trunk and limb ataxia
- Muscle weakness
- Dysarthria
- Loss of deep tendon reflexes
- Upgoing plantar responses
- Sensory neuropathy (loss of vibration sense and proprioception)
- Scoliosis is common
- Cardiomyopathy
- Diabetes mellitus (seen in up to 30% of patients)

Diagnosis and management

- Specific genetic testing
- Typically wheelchair-bound within 10 years of symptom onset
- Supportive care with symptomatic treatment (i.e., cardiomyopathy, diabetes mellitus, scoliosis)

Tics

Definition

- Intermittent, sudden, discrete, repetitive, nonrhythmic movements or vocalizations. Tics typically occur multiple times per day. With typical tics, the anatomic location can change over time, as can their frequency, type, and severity

Types

- Motor: Involves skeletal muscle (simple or complex)
- Vocal: Involves the diaphragm or laryngeal–pharyngeal muscles (simple or complex)
- Simple motor tic: Involves a single muscle or localized group (eye blinks, facial grimacing, shoulder or head jerks)
- Simple vocal tic: Throat clearing, sniffing, coughing, or grunting
- Complex motor tic (often prolonged and can appear purposeful): Head shaking, trunk flexion, finger tapping, jumping
- Complex vocal tic: Involves uttering words or phrases; coprolalia (uttering swear words) or echolalia (repeating the words or phrases of others)

Epidemiology

- Approximately 20% prevalence in the population
- Tends to be familial; males > females
- Typically appears in first decade of life with median age of onset being 6–7 years
- There is usually significant improvement by late teens or early adulthood
- Most common presenting tic is eye blinking

Clinical features

- Tics are often preceded by an urge or sensation, sometimes manifested as nonspecific anxiety
- Performing the tic relieves the urge or anxiety
- Tics can often be suppressed for short periods of time
- Tics can be exacerbated by environmental stimuli, stress, and poor sleep
- Tics typically do not occur in sleep
- Comorbid behavioral symptoms: Attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety disorders, mood disorders, sleep disorders, conduct, and oppositional behavior

Cause

- Exact pathophysiology not completely understood
- Likely involves the basal ganglia
- Most common is transient tic disorder (tics for at least 4 weeks that resolve before 1 year)
- For primary tic disorder—diagnosis is based on history plus normal neurologic exam aside from tics

Treatment

- Reassurance
- Anticipatory guidance and education
- Often no medications needed
- If sufficient morbidity—typical first-line agents are alpha-2-agonists (clonidine or guanfacine)
- Behavioral therapies
- Treatment of comorbidities such as ADHD, OCD, anxiety, or mood disorders

Tourette Syndrome

Diagnostic indications

- Presence of both motor and vocal tics
- Duration of tics > 12 months
- No tic-free interval > 3 month's duration
- Age of onset < 21 years
- Tourette syndrome is one entity in a spectrum of disorders
- Coprolalia occurs in possibly < 10% of patients.
- Male to female ratio of 3:1
- Associated behavioral problems: ADHD, OCD, anxiety, depression, episodic outburst (rage), learning disabilities, sleep disorders

Treatment—symptomatic

- Nonpharmacologic—variety of behavioral treatments
- Pharmacologic:
  - Milder tics—alpha-adrenergics (clonidine, guanfacine)
  - More severe tics—typical and atypical neuroleptics
- Surgical—Deep brain stimulation

Sydenham Chorea

Definition of chorea

- Frequent, brief, purposeless movement that are chaotic and unpredictable and that flow from one body part to another
- Sydenham chorea is one of the major Jones criteria for diagnosis of acute rheumatic fever (ARF)
- Seen in 10–40% of children with ARF
- Most common between ages 5 and 15 years
- Typically, the chorea begins several weeks to months after a group A beta-hemolytic streptococcal infection
- Gradual progression with behavioral changes (impulsivity, aggression, OCD behaviors) along with emotional lability

Diagnosis

- Clinical history and laboratory data; 25% of patients serologically negative

Treatment

- Studies have failed to confirm benefits of treatment with IVIG, corticosteroids, or plasma exchange for the presumed autoimmune process

Dystonic Reactions

Definition of dystonia

- Involuntary, sustained, and often painful muscle contractions
- Caused by an imbalance between cholinergic and dopaminergic stimulation
- Types include: Oculogyric crisis, torticollis, opisthotonus, macroglossia

Causes

- Medication adverse effect (gastrointestinal medications, antipsychotics, antiepileptics, sedatives)
- Can be caused by the medications that treat dystonia (see below)
- Head trauma

Treatment

- Anticholinergic agent, benzodiazepine, antihistamine

DEVELOPMENTAL DISORDERS

Cerebral Palsy (Table 16.10)

Definition

- A group of disorders that involve the development of movement and posture leading to limitations in activity, attributable to nonpro-

Table 16.10 Etiology and risk factors for cerebral palsy

Perinatal brain injury	**Toxins**
Hypoxia, ischemia	In utero alcohol exposure
Asphyxia	Methyl mercury
Neonatal stroke (ischemic perinatal infarction, sinovenous thrombosis)	Congenital infections (TORCH)
Prematurity	**Postnatal**
Periventricular leukomalacia	Neonatal meningitis
Intraventricular hemorrhage	Bilirubin toxicity (kernicterus)
Developmental abnormalities	**Other**
Congenital brain malformations	Male gender
Genetic disorders; metabolic disorders	Multiple gestation
Prenatal	
Maternal chorioamnionitis	
Intrauterine growth restriction	
Prothrombotic abnormalities	
Infertility	

Adapted from Swaiman et al. [1], with permission

gressive disturbances that occurred in the developing fetus or infant brain
- Incidence of cerebral palsy is approximately 2.5 per 1000 births
- Key aspects:
  - Disorder of motor function
  - Clinical manifestations may change over time, but the causative lesion is static
  - The lesion occurs in the brain at some point during the brain's developmental period

General manifestations of cerebral palsy
- Delayed motor milestones
- Abnormal muscle tone
- Hyperreflexia
- Hand preference before 1 year of age: A red flag for possible hemiplegia
- Growth disturbances: Especially failure to thrive
- Persistence of developmental reflexes
- Presence of pathological reflexes
- Failure to develop maturational reflexes such as the parachute response
- Clinical manifestations may change with maturation
- No evidence of disease progression or developmental regression

Diagnosis of cerebral palsy
- History and physical examination (including thorough neurologic exam)
- Review pregnancy and delivery records
- Neuroimaging (preferably MRI)
- Ophthalmologic and auditory evaluation
- Speech and language evaluation
- Metabolic and genetic testing should not be done routinely unless there is an atypical clinical presentation and nonspecific neuroimaging
- EEG if concern for seizures

Management/complications of cerebral palsy
- Family-centered care
- Multidisciplinary approach
- Symptomatic treatment of seizures
- Symptomatic treatment of spasticity (oral baclofen, baclofen pump, botulinum toxin, diazepam)
- Orthopedic management of contractures, including surgery
- Use of orthotics
- Therapies to improve functional gains and slow the progression of contractures (physical and occupational therapy)
- Learning and cognitive evaluations (speech therapy, individualized educational plan [IEP] in school, special education)
- Growth and nutrition, including monitoring of swallowing and gastroesophageal reflux
- Respiratory monitoring for obstructive sleep apnea, risk of chronic aspiration, development of restrictive lung disease secondary to scoliosis
- Management of sleep problems
- Dental care—increased risk of malocclusion, dental caries, and gingivitis

Types of cerebral palsy
- Spastic
  - Hemiplegia
  - Diplegia
  - Quadriplegia
- Dyskinetic
  - Choreoathetoid
  - Dystonic
- Hypotonic
- Mixed

Spastic Hemiplegia

Causes
- Most common cause is perinatal stroke
- More commonly involving the left hemisphere (affecting right side of body)
- Represents approximately 30% of all cases of cerebral palsy

Clinical presentation
- Early hand preference
- Difficulty using the affected hand—trouble with pincer grasp
- Growth arrest of abnormal side—more prominent in distal arm and leg
- Facial involvement is rare
- Circumduction gait with toe walking

- Signs of upper motor neuron involvement on affected side—hyperreflexia, ankle clonus, and extensor plantar response
- Seizures

Spastic Diplegia

Causes

- Most commonly seen in preterm infants
- Often associated with periventricular leukomalacia
- Bilateral leg involvement and commonly may have some degree of arm impairment

Clinical presentation

- May have asymmetric impairment
- Scissoring of legs when held in vertical position
- Toe walking in older children
- Spasticity of hip muscles may lead to femur subluxation
- Signs of upper motor neuron involvement in the legs—hyperreflexia, ankle clonus, and extensor plantar responses

Spastic Quadriplegia

Causes

- White matter damage (periventricular leukomalacia)
- Abnormal brain development
- Intracranial hemorrhage
- Hypoxic–ischemic encephalopathy or asphyxia
- Kernicterus
- Perinatal CNS infections

Clinical presentation

- Generalized increase in muscle tone
- Legs involved more than the arms
- Decreased limb movements
- Difficulties in swallowing—predisposing to aspiration pneumonia
- Spasticity
- Signs of upper motor neuron involvement—hyperreflexia in upper and lower extremities, ankle clonus, and extensor plantar responses
- Spasticity of hip muscles may lead to femur subluxation
- Flexion contractures of elbows and wrists
- Visual and hearing impairment more common in spastic quadriplegic children
- Learning and intellectual disabilities also more common
- Seizures

Dyskinetic Cerebral Palsy

Causes

- Presence of extrapyramidal signs; choreoathetoid or dystonic
- Problems with posture and involuntary movements
- Usually caused by damage or malformation of basal ganglia or cerebellum
- Often associated with hypoxic–ischemic brain injury or kernicterus

Clinical Presentation

- Choreoathetoid
  - Large-amplitude, involuntary movements
  - Athetosis usually involves the distal limbs
  - Chorea may involve the face, limbs, and possibly the trunk
  - Difficulty with speech
  - Upper motor neuron involvement
  - Seizure and intellectual disability can also be present
- Dystonic
  - Trunk muscles and proximal limbs more involved
  - Uncommon form of cerebral palsy

Rett Syndrome

- X-linked
- Mutation in *MECP2* gene

- Affects approximately 1 in 10,000 live female births
- Males with the mutation typically die before or soon after birth.

Clinical Features

- Neurologic regression starting between 1.5 and 3 years of age with loss of acquired hand skills and spoken language
- Can also have autistic features with social withdrawal, decreased eye contact, and decreased response to visual and auditory stimuli
- Extreme irritability and anxiety
- After regression, there is stabilization of skills
- Severe intellectual disability (although with the severe communication impairment, accurate assessment is difficult)
- Movement abnormalities—repetitive hand stereotypies, gait (ataxia and apraxia), dystonia, axial hypotonia (initially), increased tone with rigidity (later)
- Seizures are common
- Acquired microcephaly
- Gastrointestinal abnormalities (GERD, constipation)
- Scoliosis
- Sleep disorders
- Bruxism

Diagnostics

- Specific genetic testing
- Abnormal EEG
- MRI initially normal but will later show generalized atrophy of the cerebral hemispheres

Treatment

- No curative treatment available
- Symptomatic treatments only (i.e., anticonvulsants for seizures, reflux medications for GERD)

Table 16.11 Primitive reflexes

Reflex	Response	Age at disappearance
Sucking	Sucking response when something touches the roof of the mouth	3–4 months
Rooting	Turning the head toward the cheek being stroked	3–4 months
Stepping	Stepping movements when soles of feet touch a flat surface	6–8 weeks
Palmar grasp	Finger flexion	6 months
Plantar grasp	Toe flexion	15 months
Asymmetric tonic neck (fencer posture)	Extension of extremities on side of head turn and flexion of extremities on the opposite side	3–4 months
Moro	Abduction of upper extremities followed by flexion	4–6 months
Parachute	Extension of arms as infant is projected toward the floor	Appears ≈ 8–9 months; permanent

Primitive Reflexes (Table 16.11)

PEARLS AND PITFALLS

- Complex febrile seizures are focal and prolonged (> 15 min) or occur multiple times in 24 h.
- 1 Hz spike-wave discharges are seen in Lennox–Gastaut syndrome, 3 Hz spike-wave discharges are seen in childhood absence epilepsy, and 4 Hz spike-wave discharges are seen in juvenile myoclonic epilepsy.
- Guillain–Barré syndrome should be recognized as a neurologic emergency, because patients are at risk for respiratory failure during the course of illness.

- Gene therapy is now available for patients with spinal muscular atrophy that has led to improvement in motor milestones [1].
- Consider possible underlying immunodeficiency with a new diagnosis of Ramsay–Hunt syndrome.
- Patients with NF1 are at risk for hypertension secondary to renal artery stenosis and pheochromocytoma.
- NF1 patients should be monitored for precocious puberty, because optic pathway gliomas can extend into the hypothalamus.
- Vigabatrin is the treatment of choice for infantile spasms secondary to tuberous sclerosis.
- Tuberous sclerosis patients should be monitored for symptoms of increased intracranial pressure, because subependymal giant cell astrocytomas can lead to obstructive hydrocephalus.
- Sturge–Weber syndrome can be a cause of epilepsia partialis continua or simple motor status epilepticus.
- Patients with lissencephaly can present with seizures in the neonatal period but can also present with infantile spasms later during infancy.
- Be sure to account for parents' head circumference because familial macrocephaly is one of the most common causes of macrocephaly.
- Microcephaly in a female 6–18 months of age should lead to evaluation of Rett syndrome.
- Acquired microcephaly associated with Rett syndrome is when an infant initially has a normal head circumference at birth, but the head circumference does not grow appropriately on a typical growth curve.
- The presence of Cushing's triad (hypertension, bradycardia, irregular respiration) should prompt urgent management of increased intracranial pressure.
- Overdrainage of VP shunts can also be a cause of headaches that worsen upon sitting or standing.
- Tics can be suppressed for a period of time and do not occur during sleep.
- For a diagnosis of Tourette syndrome, patients must have had both motor and vocal tics, and the tics have to be present for > 1 year.
- Early hand preference (< 1 year) is a red flag for possible hemiplegia and cerebral palsy.
- Kernicterus (damage to the brain from significantly elevated bilirubin) is associated with dyskinetic cerebral palsy.

Acknowledgments The authors gratefully acknowledge the contributions of Rujuta Bhatt Wilson, MD, Semel Institute for Neuroscience and Human Behavior, UCLA, Los Angeles, California, to the first edition of this chapter, many of which have been incorporated into this edition as well.

References

1. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, ENDEAR Study Group, et al. Nusinersin versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377(18):1723–32.
2. Swaiman KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, et al. Swaiman's pediatric neurology: principles and practice. 6th ed. Edinburgh: Elsevier; 2018.

Suggested Reading

Abend N, Loddenkemper T. Management of pediatric status epilepticus. Curr Treat Options Neurol. 2014;16(7):1–16.

Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. J Child Neurol. 2012;27(11):1460–9.

Beslow LA, Jordan LC. Pediatric stroke: the importance of cerebral arteriopathy and vascular malformations. Childs Nerv Syst. 2010;26(10):1263–73.

Chadehumbe MA, Greydanus DE, Feucht C, Patel DR. Psychopharmacology of tic disorders in children and adolescents. Pediatr Clin N Am. 2011;58(1):259–72.

Choe MC, Blume HK. Pediatric posttraumatic headache: a review. J Child Neurol. 2015;31(1):76–85.

Delatycki MB, Corben LA. Clinical feature of Friedreich ataxia. J Child Neurol. 2012;27(9):1133–7.

Dodge NN. Cerebral palsy: medical aspects. Pediatr Clin N Am. 2008;55(5):1189–207.

Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, ENDEAR Study Group, et al. Nusinersin versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377(18):1723–32.

Forsyth R, Newton R. Paediatric neurology, Oxford specialist handbooks in paediatrics. 3rd ed. Oxford: Oxford University Press; 2018.

Ghanem I, El Hage S, Rachkidi R, Kharrat K, Dagher F, Kreichati G. Pediatric cervical spine instability. J Child Orthop. 2008;2(2):71–84.

Gothe R, Kunze K, Hoogstraal H. The mechanisms of pathogenicity in the tick paralyses. J Medical Entomol. 1979;16(5):357–69. Review.

Guerrini R, Pellacani S. Benign childhood focal epilepsies. Epilepsia. 2012;53(Suppl 4):9–18.

Hirtz D, Ashwal S, Berg A, Bettis D, Camfield C, Camfield P, et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. Neurology. 2000;55(5):616–23.

Hirtz D, Berg A, Bettis D, Camfield C, Camfield P, Crumrine P, Quality Standards Subcommittee of the American Academy of Neurology, Practice Committee of the Child Neurology Society, et al. Practice parameter: treatment of the child with a first unprovoked seizure: report of the quality standards subcommittee of the American Academy of Neurology and the practice committee of the Child Neurology Society. Neurology. 2003;60(2):166–75.

Jacobs H, Gladstein J. Pediatric headache: a clinical review. Headache. 2012;52(2):333–9.

Katz DM, Berger-Sweeney JE, Eubanks JH, Justice MJ, Neul JL, Pozzo-Miller L, et al. Preclinical research in Rett syndrome: setting the foundation for translational success. Dis Models Mech. 2012;5(6):733–45.

Knoch J, Kamenisch Y, Kubisch C, Berneburg M. Rare hereditary diseases with defects in DNA-repair. Eur J Dermatol. 2012;22(4):443–55.

Lerner JT, Matsumoto JH, Wu JY. Infantile spasms. In: Sirven J, Stern J, editors. Atlas of video-EEG monitoring. New York: McGraw Hill; 2010. p. 329–40.

Matsumoto JH, Lerner JT. First steps to epilepsy syndrome diagnosis. In: Auvin S, Sankar R, editors. Acute seizures in children in the emergency setting. Montrouge: John Libbey Eurotext; 2013. p. 175–85.

Menkes JH, Sarnat HB, Maria BL, editors. Child neurology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

Nussinovitch M, Prais D, Volovitz B, Shapiro R, Amir J. Post-infectious acute cerebellar ataxia in children. Clin Pediatr. 2003;42(7):581–4.

Pearl PL. Epilepsy syndromes in childhood. Continuum (Minneap Minn). 2018;24(1, Child Neurology):186–209.

Roser T, Bonfert M, Ebinger F, Blankenburg M, Ertl-Wagner B. Primary versus secondary headache in children: a frequent diagnostic challenge in clinical routine. Neuropediatrics. 2013;44(1):34–9.

Sarnat HB. Disorders of segmentation of the neural tube: Chiari malformations. Handb Clin Neurol. 2008;87:89–103.

Schlaggar BL, Mink JW. Movement disorders in children. Pediatr Rev. 2003;24(2):39–51.

Sheehan JP, Jane JA, Ray DK, Goodkin HP. Brain abscess in children. Neurosurg Focus. 2008;24(6):E6. https://doi.org/10.3171/FOC/2008/24/6/E6. Review.

Singer HS, Mink JW, Gilbert DL, Jankovic J, editors. Movement disorders in childhood. 2nd ed. London: Elsevier; 2016.

Solmaz I, Izci Y, Albayrak B, Cetinalp E, Kural C, Sengul G, et al. Tethered cord syndrome in childhood: special emphasis on the surgical technique and review of the literature with our experience. Turk Neurosurg. 2011;21(4):516–21.

Subcommittee on Febrile Seizures. Clinical practice guidelines – febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 2011;127(2):389–94.

Swaiman KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, et al., editors. Swaiman's pediatric neurology: principles and practice. 6th ed. Edinburgh: Elsevier; 2018.

Wagner G, Klinge H, Sachse M. Ramsay Hunt syndrome. J Dtsch Dermatol Ges. 2012;10(4):238–44. [Article in English and German].

Waterhouse E. Status epilepticus. Continuum (Minneap Minn). 2010;16(3 Epilepsy):199–227.

Williams VC, Lucas J, Babcock MA, Gutmann DH, Korf B, Maria BL. Neurofibromatosis type 1 revisited. Pediatrics. 2009;123(1):124–33.

Wirrell E, Nickels KC. Pediatric epilepsy syndromes. Continuum (Minneap Minn). 2010;16(3 Epilepsy):57–85.

Zamora C, Castillo M. Neuroradiology companion: methods, guidelines, and imaging fundamentals. 5th ed. Philadelphia: Wolters Kluwer; 2017.

Ophthalmology

17

Kyle E. Miller and Shira L. Robbins

VISION SCREENING [1]

- Screening of vision at routine intervals can prevent lifelong blindness
- All ages: Ocular history, external inspection, red reflex testing, pupil examination
- Six months and older: Add ocular motility assessment
- Instrument-based screening, if available, should be started by 12 months of age
- Visual acuity should be tested with age-appropriate optotypes in cooperative 3-year-olds and older
- Preferred optotypes for younger children include LEA® or HOTV symbols with advancement to letter optotypes for those who can distinguish letters
- Fixation and following visual behavior descriptors are used in those under 3

Performing visual acuity screening

- Ensure eye chart is in a well-lit area with minimal distractions
- Ensure child is not peeking through fingers. Consider using a patch
- Test each eye individually; a child who is blind in one eye can be missed if both eyes are tested simultaneously

Painful Erythematous Eye

Presentation

- Unilateral or bilateral red eye with pain and/or photophobia
- Discharge presence and type can give insight into diagnosis

Clinical evaluation

- Unilateral vs. bilateral
- Discharge? Watery vs. mucoid. Amount? Frequency?
- Pain vs. itch. An itchy eye is frequently a sign of allergy or infection
- History of trauma or foreign object/chemical exposure
- Visual acuity

Ophthalmia Neonatorum

- Conjunctivitis occurring in the 1st month of life

Ophthalmia Neonatorum due to *N. gonorrhoeae*

Clinical presentation

- Hyperacute conjunctivitis with hyper-purulent discharge in the first 3–5 days of life

K. E. Miller
Department of Ophthalmology, Naval Medical Center Portsmouth, Portsmouth, VA, USA

S. L. Robbins (✉)
Department of Ophthalmology, Ratner Children's Eye Center, University of California San Diego, La Jolla, CA, USA
e-mail: srobbins@ucsd.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_17

Diagnosis
- Culture and Gram stain of eye discharge will reveal Gram-negative intracellular diplococci *Neisseria gonorrhoeae*
- Sepsis workup and evaluation for disseminated systemic infections are critical
- Infants should be tested also for HIV, chlamydia, and syphilis

Treatment of gonococcal conjunctivitis
- Parenteral ceftriaxone 25–50 mg/kg, not to exceed 125 mg, must be given immediately
- Delay in treatment can cause corneal perforation and permanent vision loss
- Frequent lavage of the fornices with normal saline is recommended
- Topical antibiotics may be indicated if there is corneal involvement

Prophylaxis
- Erythromycin topical ointment is effective prophylaxis after birth
- Silver nitrate is rarely used today and can cause a chemical conjunctivitis

Ophthalmia Neonatorum due to Chlamydia

Background
- Onset occurs around 1 week of age
- Associated with infantile pneumonitis

Clinical presentation
- Minimal-to-moderate mucopurulent discharge
- Eyelid edema
- Papillary conjunctivitis
- Pseudomembrane formation in tarsal conjunctiva

Diagnosis
- Culture of conjunctival scrapings, direct fluorescent antibody test, and enzyme immunoassays are also available

Management
- Oral erythromycin for a minimum of 14 days
- No effective prophylaxis is currently available
- Ensure source of infection (i.e., mother and her sexual partners) are treated as well

Ophthalmia Neonatorum due to Herpes Simplex

Background
- Onset usually around 2nd week of life, typically later than chlamydia or gonorrhea
- Most frequently associated with maternal herpes simplex virus (HSV)-2 infection with increased risk with active lesions in vaginal delivery in the neonatal setting

Clinical presentation
- Watery discharge
- Eyelid lesions (usually vesicles), conjunctivitis, keratitis, and cataracts are all possible

Diagnosis
- Clinical presentation +/− viral cultures

Management
- Systemic workup necessary to rule out central nervous system involvement
- Systemic acyclovir for 14 days. Topical antiviral eye drops may be added in some cases

Acute Bacterial Conjunctivitis

Background
- Acute bacterial nongonococcal conjunctivitis is usually benign and self-limited; however, antibiotics can expedite the return to normal activities

Bacterial causes
- *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Pseudomonas* are common causes

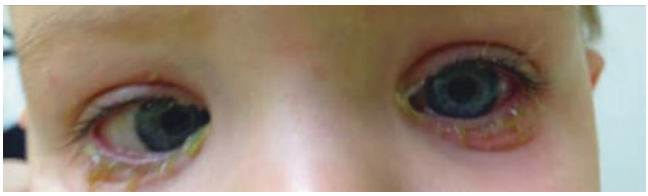


Fig. 17.1 A 13-month-old child presents with fever, bilateral eye discharge, and ear infection

- School-aged children: *Streptococcus pneumoniae, Haemophilus,* and *Moraxella*

Clinical presentation
- Mild hyperemia
- Scant purulent discharge (Fig. 17.1)
- May have significant conjunctival injection with moderate purulent discharge

Management
- Empiric topical antibiotic agents (e.g., sulfacetamide, trimethoprim polymyxin B, tobramycin, erythromycin ointment, fluoroquinolones, azithromycin) to shorten the duration and reduce the amount of contagion of the disease [2]
- Fourth-generation fluoroquinolones (moxifloxacin, gatifloxacin, besifloxacin) have more rapid effectiveness and simplified dosing regimen but are considerably more expensive and should perhaps be reserved for more severe or recalcitrant infections

Parinaud Oculoglandular Syndrome

Background
- Most frequently by *Bartonella henselae* (cat-scratch disease)
- Many other causes, e.g., Chlamydia trachomatis, Francisella tularensis, and *Mycobacterium tuberculosis*

Clinical presentation
- Unilateral granulomatous conjunctivitis
- Swollen ipsilateral preauricular lymph node
- Submandibular lymphadenopathy

Management
- Treatment of the cause

Acute Hemorrhagic Conjunctivitis

Causes
- Coxsackievirus A24
- Enterovirus 70

Clinical presentation
- Highly contagious disease
- Large subconjunctival hemorrhage, can involve the entire subconjunctival space
- Patients also may present with fever and headache

Management
- Treatment is supportive, and complications are rare

Pharyngoconjunctival Fever

Background
- Highly infectious illness affecting the eye and pharynx
- Adenovirus types 3, 4, 5, and 7 (the most common cause)
- Often affects young children
- May lead to community outbreak

Clinical presentation
- Fever
- Pharyngitis
- Follicular conjunctivitis
- Regional lymphoid hyperplasia with tender, enlarged preauricular adenopathy
- May cause punctate lesions in the corneal epithelium (best seen with fluorescein staining) that warrant an ophthalmologic referral

Treatment
- Supportive care
- The conjunctivitis is self-limited, usually lasting no more than 10 days

Molluscum Contagiosum Conjunctivitis

Background

- Common viral infection in children
- Lesions may be anywhere on the body, including the eyelid
- Classic dome-shaped, umbilicated lesions
- Lesions shed viral particles into eyes, causing irritation

Clinical Presentation

- Red, irritated eye with follicular conjunctival reaction
- Molluscum lesions around lid
- May present as a recurrent red eye initially treated as viral or bacterial conjunctivitis

Treatment

- Conservative monitoring may be appropriate
- Surgical excision, cryotherapy, and curettage may be therapeutic but require general anesthesia in the pediatric population

Herpes Simplex Virus (HSV) Conjunctivitis

Causes

- HSV type 1 or 2
- Most cases of primary eye involvement are caused by HSV-1 and are associated with gingivostomatitis or recurrent orolabial infection (cold sores)
- HSV-2 is associated with genital infection and is a more common cause of neonatal HSV eye infections transmitted via direct contact in the vaginal canal during birth

Clinical presentation

- Concurrent herpetic skin vesicular eruption, usually somewhere on the face
- Unilateral follicular conjunctivitis
- Palpable preauricular lymph node
- Ocular infection can affect the eyelids, conjunctiva, or cornea

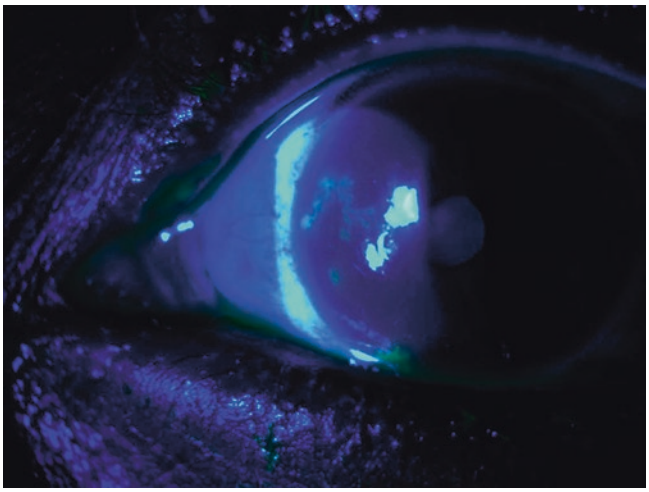


Fig. 17.2 Fluorescein staining. (Photo courtesy of Kyle Miller, M.D., Naval Medical Center Portsmouth, Portsmouth, VA) of corneal herpetic dendrite. Can be seen with Woods lamp

- Corneal epithelial dendrites (linear branching lesions with terminal bulbs) can be seen with fluorescein stain (Fig. 17.2)

Diagnosis

- Based on the clinical findings
- HSV corneal disease will usually have significant pain
- In atypical cases, culture, ELISA, or polymerase chain reaction (PCR) testing can be used to confirm the diagnosis

Treatment

- If HSV conjunctivitis or corneal involvement is suspected, immediate referral to an ophthalmologist is recommended
- Oral antivirals (e.g., acyclovir)
- Topical antiviral therapy (e.g., trifluridine 1 % drops, ganciclovir ophthalmic gel) is less frequently used due to toxicity
- NOTE: The use of steroids alone in herpetic infections is contraindicated
- Children with a history of HSV-related eye disease should always seek care for any future cases of "pink eye," as the rate of recurrence is high
- Given the higher than adult recurrence rate for corneal herpetic infections, oral prophylaxis for 1 year after the initial infection should be considered

Chemical Conjunctivitis

Background
- Acute noninfectious conjunctivitis after chemical exposure

Clinical presentation
- Acute onset of pain
- History of chemical exposure: Cleaners, pool chlorine, some medications, etc.
- Usually red eye; however, severe injuries may actually have white eyes
- Photophobia or decreased spontaneous opening of the affected eye(s)

Diagnosis
- Clinical findings and history of exposure are nearly pathognomonic
- pH test of the eye should be performed

Treatment
- Primary goal is to stop further injury
- Neutralize pH through irrigation
- Referral to ophthalmologist for further evaluation and treatment

Parasitic Conjunctivitis

Background
- Pediculosis may cause a follicular conjunctivitis in adults with pubic lice

Clinical presentation
- Intense itching of the eyelids
- Conjunctival and lid margin injection
- **Know** that pubic lice (*Pthirus pubis*) and nits in the cilia (eyelashes) in children are due to sexual abuse unless proven otherwise

Management
- Referral to an ophthalmologist
- Ophthalmic ointment (e.g., erythromycin) to smother the lice
- Pediculicide lotions and shampoos should also be applied

Atopic (Seasonal) Allergic Conjunctivitis

Background
- Immunoglobulin E (IgE)-mediated immediate hypersensitivity reaction
- Dust, molds, spores, pollens, and animal dander are common triggers

Clinical presentation
- Itching
- Conjunctival chemosis, which manifests as pale edema; eyelid edema
- Watery discharge
- Giant papillae assume a flat top appearance, often described as "cobblestone papillae" (Fig. 17.3)

Treatment
- Should be based on severity of symptoms
- Allergen avoidance
- Cold compresses
- Artificial tears
- Topical antihistamines or mast cell stabilizers
- Systemic antihistamines

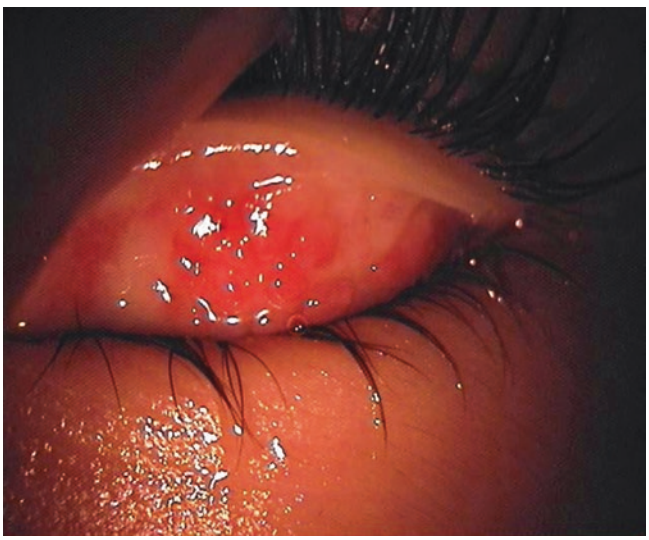


Fig. 17.3 Allergic conjunctivitis. Multiple giant papillae in the superior tarsus. (Courtesy of Violeta Radenovich MD, MPH, Children's Eye Center; Department of Ophthalmology, Texas Tech University, El Paso, Texas)

- Topical nonsteroidal anti-inflammatory agents in nonresponsive cases
- Selective use of topical corticosteroids for severe cases treated by an ophthalmologist
- Allergic rhinitis and asthma are often present as well and must be treated accordingly
- Severe cases may benefit from referral for allergy testing

Anterior Uveitis

Background

- Uveitis usually associated with systemic diseases, e.g.,
  - Juvenile idiopathic arthritis (JIA)
  - Sarcoidosis
  - Kawasaki syndrome
  - Reiter syndrome
  - Herpes
  - Syphilis
  - Lyme disease
  - Idiopathic
  - Trauma

Clinical presentation

- Conjunctival injection
- Pain
- Tearing
- Photophobia
- Decreased vision

Management

- Refer to ophthalmologist
- Topical steroids
- Cycloplegic agents
- Treat the underlying cause

Juvenile Idiopathic Arthritis (JIA)

Background

- Ocular involvement in JIA is common
- JIA-related uveitis can cause permanent vision loss
- Uveitis may be presenting sign for JIA or may be caught on ocular screening exams in these cases
- Systemic arthritis (Still's disease) has the least propensity for ocular involvement

Clinical presentation

- May be asymptomatic
- Pain
- Photophobia
- Unilateral or bilateral eye redness
- Normal to decreased vision

Management

- Symptomatic patients should be referred to ophthalmology
- Topical steroids
- Topical cycloplegics
- Systemic steroids or immunobiologics

Screening

- All children with JIA should be referred for routine ophthalmologic screening, which can be as often as every 3 months per current guidelines [3]
- Any child with a history of JIA and complaining of a red eye or diagnosed with pink eye should be referred to ophthalmology for urgent evaluation
- The highest-risk JIA subgroup for ocular involvement is antinuclear antibody (ANA)-positive oligoarthritis

Preseptal Cellulitis

Background

- Infection of periorbital soft tissues *anterior* to the orbital septum
- Usually results from extension of external ocular infections such as:
  - Hordeolum (stye)
  - Dacryocystitis/dacryoadenitis
  - Rhinosinusitis
  - Dental abscess
  - Insect bite
  - Post-traumatic puncture, laceration, or abrasion of the eyelid skin. Direct penetrating injury to the orbit and hematogenous seeding
  - Severe conjunctivitis
  - Skin infections: Impetigo or herpes zoster

Causes
- *Staphylococcus* and *streptococcus* have become the two most common (75%) pathogens responsible for pediatric orbital cellulitis

Clinical presentation
- Erythema
- Eyelid swelling
- No limitation of eye movement
- The globe should be white and essentially unaffected
- Eyelids can be severely swollen, causing difficulty in spontaneous opening

Diagnosis
- Clinical
- No imaging studies are necessary

Management
- Choice of antibiotic depends on the source of infection, e.g.,
  - Dental abscess: Cover for anaerobes, e.g., clindamycin or amoxicillin–clavulanate
  - Insect bite or stye: Cover for staph, e.g., first-generation cephalosporin
  - Sinusitis: Cover for *S. pneumoniae*, e.g., high-dose amoxicillin–clavulanate, oral second- or third-generation cephalosporins
- Admit to hospital children who do not respond to oral antibiotics

Orbital Cellulitis

Background
- Infection of orbital soft tissue posterior to orbital septum
- The most common association is ethmoid sinusitis

Clinical presentation
- Orbital pain
- Severe swelling
- Chemosis
- Proptosis
- Ophthalmoplegia: Limited ocular movement
- Decreased visual acuity
- Fever

Diagnosis
- *CT scan with intravenous (IV) contrast* is the most important diagnostic test distinguishing preseptal from postseptal (orbital) cellulitis

Management
- IV antibiotic therapy should have empiric coverage against *staphylococcal* and *streptococcal* species
- Vancomycin or clindamycin (MRSA) plus a second- or third-generation cephalosporin is a reasonable initial regimen
- Orbital cellulitis requires antibiotic therapy for a total of 10–14 days
- Mucormycosis can occur in patients with diabetic ketoacidosis or severe immunosuppression and is often fatal
  - The treatment should include debridement of necrotic and infected tissue plus amphotericin B
- Urgent consult to ophthalmology and otorhinolaryngology

Complications
- **Cavernous sinus thrombosis** is the most serious complication
- **Loss of vision** and meningismus or meningitis may be late complications

Hordeolum (Stye) and Chalazion

HORDEOLUM
- Acute focal infection (usually *staphylococcal*) involving the glands of Zeis or the hair follicle

CHALAZION
- Granulomatous inflammation of the meibomian glands that results from the obstruction of the gland duct and is usually in the midportion of the tarsus or eyelid away from the lid border

Clinical Presentation

- Hordeolum
  - Local, tender, erythematous swelling on the eyelid margin (Fig. 17.4)
- Chalazion
  - Firm, tender, or nontender swelling of the eyelid (Fig. 17.5)
  - Eye discomfort, if large or internal
  - May cause refractive errors and possible amblyopia if chronic

Management is the same for both hordeolum and chalazion

- Frequent warm compresses
- Topical antibiotics (eye drops or ophthalmic ointment) if associated infection
- Oral antibiotic if complicated by preseptal cellulitis

Fig. 17.4 A 5-year-old with tender erythematous subcutaneous nodule near the eyelid margin

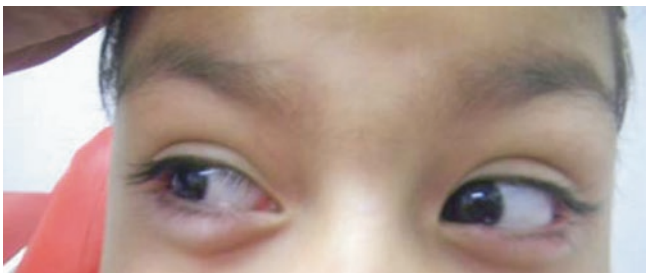


Fig. 17.5 Chalazion in the right lower eyelid. (Courtesy of Violeta Radenovich MD, MPH, Children's Eye Center; Department of Ophthalmology, Texas Tech University, El Paso, Texas)

- If patient does not respond to conservative therapy, consult with an ophthalmologist
- Incision and drainage and/or steroid injection is indicated if the hordeolum is large or if it is refractory to medical therapy and is done by the ophthalmologist
- Most surgical cases require general anesthesia in pediatric patients

Nasolacrimal Duct Obstruction (Congenital Dacryostenosis)

Background

- Tearing and mucoid or mucopurulent discharge, often noticed to be worse after sleeping as the mucus can cause eyelids to stick together
- Normal conjunctiva, but they may develop acute inflammation
- Digital pressure near medial canthus results in retrograde discharge of mucopurulent material
- Congenital glaucoma must be ruled out by history and physical examination. Classic triad of photophobia, tearing, and blepharospasm (involuntary hard blinking)

Management

- Digital massage of the lacrimal sac
- Topical antibiotics if conjunctivitis, e.g., erythema and exudates
- Duct probing in persistent cases
- Most cases (> 90%) will self-resolve by 1 year of age
- Early probing reduces the duration of bothersome symptoms and the potential of chronic infections

When to refer

- If persists to 1 year of age; however, in some areas, the ophthalmologist may prefer to perform early in-office probing at an earlier age
- If develops dacryocystitis, will require IV antibiotics

Congenital Ptosis

Background
- Congenital droopy eyelid from birth
- Isolated abnormality of levator muscle in one or both eyelids

Clinical presentation
- Droopy eyelid since birth (Fig. 17.6)
- The child compensates by lifting the chin or the forehead/eyebrow muscles
- Often associated with strabismus and anisometropia
- Amblyopia may occur

Management
- Ophthalmology evaluation is important within the first few months of life
- Surgical correction if causing occlusion amblyopia
- If complete ptosis after a few days of life, urgent ophthalmology consultation is required

Acquired Ptosis

Causes
- Horner syndrome; ptosis, miosis, anhidrosis
- Myasthenia gravis
- Kearns–Sayre syndrome (progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction abnormalities)
- Orbital tumor
- Third cranial nerve palsy
- Neurofibroma from neurofibromatosis
- Leigh syndrome

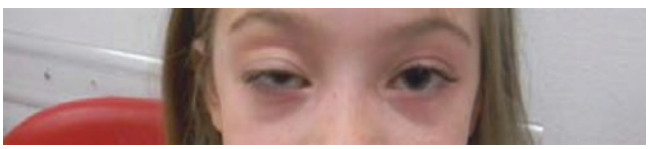


Fig. 17.6 Congenital ptosis of the right eye. Drooping eyelid covering part of the pupil. (Courtesy of Violeta Radenovich MD, MPH, Children's Eye Center; Department of Ophthalmology, Texas Tech University, El Paso, Texas)

Management
- Any child with ptosis requires full ophthalmologic evaluation and possibly neurologic referral if concerns for systemic involvement

Anisocoria

Background
- Difference in the size of the pupils
- May be harbinger of significant neurologic disease

Causes
- Small differences (1 mm or less) may be physiologic and of no consequence
- Aneurysm affecting cranial nerve III
- Horner syndrome: Neuroblastoma, mediastinal tumors, brainstem lesions
- Pharmacologic pupil change
- Adie tonic pupil

Management
- Measure size of pupils in light and in dark
- Neurologic evaluation to exclude any other neurologic involvement
- Referral to an ophthalmologist for neuro-ophthalmologic evaluation
- Urgent referral for any patients with anisocoria and additional neurologic deficits such as third nerve palsy

Coloboma

Background
- Incomplete closure of the embryonic fissure
- May be found in association with systemic syndromes or in isolation
- CHARGE syndrome (**c**oloboma of the eye, **h**eart defects, **a**tresia of the choanae, **r**etardation of **g**rowth and development, and **e**ar abnormalities and deafness) is the most common multisystem disease associated with coloboma

Clinical findings

- Timing of incomplete closure determines the extent of involvement
- Early failure of closure leads to more posterior involvement with the retina or optic nerve being involved or possibly complete microphthalmia
- Late failure may result in an isolated iris coloboma (keyhole appearance)
- Effect on visual acuity can be none to severe, depending on structures involved

Management

- Referral to an ophthalmologist for complete ocular examination to determine extent of coloboma and evaluation of visual function
- Treatment will be aimed toward minimizing amblyopia; however, those with more extensive colobomas will likely continue to have profound vision loss
- No current therapies are available to repair posterior eye colobomas
- If unilateral involvement, protection of the good eye is important

Congenital Glaucoma

Definition

- A progressive optic neuropathy usually related to intraocular pressure

Clinical presentation

- Corneal cloudiness
- Increased corneal diameter/large-appearing eye
- Conjunctival injection (late finding)
- Excessive tearing, photophobia, and blepharospasm (eye squeezing) should alert you to the development of glaucoma
- Myopia may develop as the eye elongates

Management

- Referral to ophthalmologist
- Congenital glaucoma often requires surgical intervention as the first-line treatment

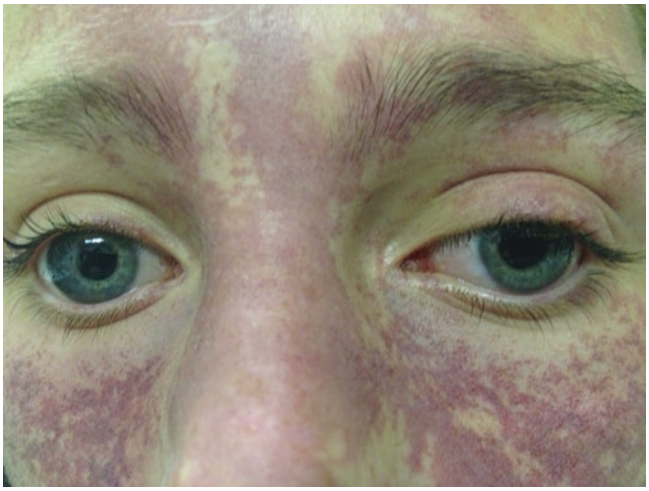


Fig. 17.7 Skin appearance of Sturge–Weber syndrome

Conditions associated with glaucoma

- Sturge–Weber syndrome (Fig. 17.7)
- Intraocular hemorrhage (hyphema)
- Inflammation or tumor
- Aniridia (WAGR syndrome—**W**ilms tumor (a tumour of the kidneys), **a**niridia (absence of the colored part of the eye, the iris), **g**enitourinary anomalies, and mental **r**etardation
- Lowe syndrome
- Aphakia
- Marfan syndrome
- Homocystinuria
- Neurofibromatosis
- Steroid treatment: Any steroid use can affect the intraocular pressure

Congenital Cataract

Background

- Cataracts may occur at any age

Causes

- Approximately 50% of congenital cataracts are idiopathic
- Hereditary: Autosomal dominant are always bilateral. X-linked and autosomal recessive can also occur
- Prematurity is sometimes a cause of a cataract-like condition from remnants of the fetal vasculature and may resolve spontaneously

- **Rubella** is the most common infectious cause of congenital cataracts (TORCH syndrome—**t**oxoplasmosis, **o**ther agents [including HIV, syphilis, varicella, and fifth disease], **r**ubella, **c**ytomegalovirus, **h**erpes simplex) worldwide
- Metabolic diseases must be considered, e.g., galactosemia and diabetes
- Teratogens such as alcohol and corticosteroids may also cause congenital cataracts
- Associated syndromes include trisomies 13, 18, and 21, as well as Alport, Lowe, and Marfan syndromes

Clinical presentation (Fig. 17.8)
- Absent or asymmetric red reflex
- Any irregularity or asymmetry of the pupils
- Dark spots in the red reflex
- White reflex
- Occasional nystagmus

Management
- **Immediate** referral to a pediatric ophthalmologist
- Optimally, surgical intervention for unilateral congenital cataracts should occur within 6 weeks and bilateral cases within 10 weeks [4]

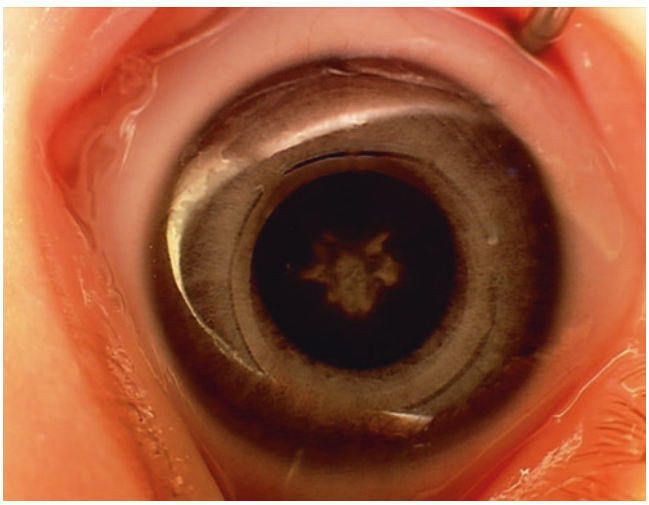


Fig. 17.8 Central cataract in a 4-month-old child

Retinoblastoma (RB)

Background
- RB is the most common malignant intraocular tumor in childhood
- Usually presents before 5 years of age
- One of the most common (47%) causes of leukocoria in childhood
- RB gene *RB1* is passed as autosomal dominant trait
- Risk of recurrence is lower in unilateral than bilateral cases of RB

Clinical presentation
- Leukocoria and strabismus are the most common presenting findings
- Average age at the time of diagnosis is 2 years in unilateral cases and 1 year in bilateral cases

Diagnosis
- Magnetic resonance imaging (MRI) and ultrasound are the best diagnostic testing, often noting calcification within the mass

Management
- All children with a new leukocoria should be referred to an ophthalmologist
- Primary systemic chemotherapy (chemoreduction) followed by local therapy (laser photocoagulation, cryotherapy, thermotherapy, or plaque radiotherapy), or even enucleation (surgical removal of the eye), depending on the stage of the disease (Fig. 17.9)
- Intra-arterial chemotherapy is a new modality of treatment in certain cases
- Immediate referral to an ophthalmologist and subsequently an oncologist after diagnosis confirmation

Papilledema

Background
- Papilledema is a swelling of optic discs secondary to increased intracranial pressure

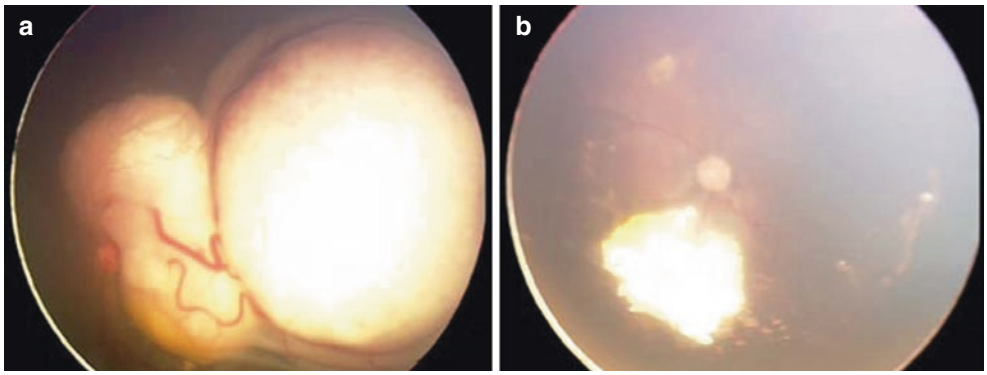


Fig. 17.9 (**a**) Retina photo showing large retinoblastoma covering part of the optic nerve. (**b**) Retinoblastoma after systemic chemotherapy and laser therapy. (Courtesy of Violeta Radenovich MD, MPH, Children's Eye Center; Department of Ophthalmology, Texas Tech University, El Paso, Texas)

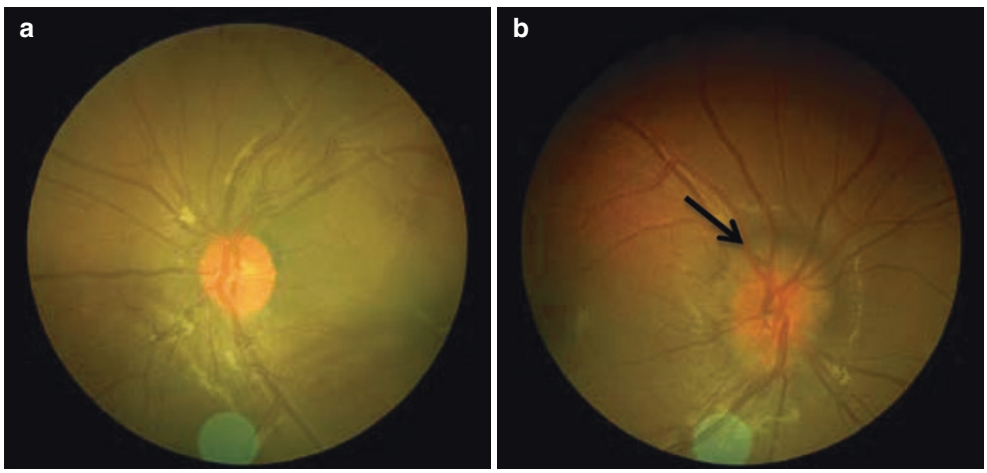


Fig. 17.10 (**a**) Normal optic disc with sharp margins and pink rim. (**b**) Fundus photograph showing optic nerve edema due to elevated intracranial pressure in the right eye, peripheral elevation of nerve, and blurred disc margins (*arrow*). (Courtesy of Violeta Radenovich MD, MPH, Children's Eye Center; Department of Ophthalmology, Texas Tech University, El Paso, Texas)

Causes

- Hydrocephalus, mass lesion, neuroblastoma, meningitis, or idiopathic intracranial hypertension (IIH), aka Pseudotumor cerebri

Clinical presentation

- Severe headaches with possible nausea and vomiting
- Cranial nerve palsies are usually a late sign
- Esotropia and double vision may result from cranial nerve VI paralysis, which is the most likely involved oculomotor nerve due to its anatomic course
- Transient visual obscurations
- Blurred margins of optic disc (Fig. 17.10a) showing normal optic disc with sharp margin for comparison (Fig. 17.10b)

Management

- Head imaging computed tomography (CT)/MRI must be performed
- MRI/magnetic resonance venography (MRV) is better for IIH and some other processes; however, CT may be faster to obtain and can rule out many emergent diagnoses in urgent situations
- If CT is negative, lumbar puncture should be performed for possibility of IIH

Optic Neuritis

Background
- Optic neuritis implies an inflammatory process involving the optic nerve
- Most cases of optic neuritis in children are due to an immune-mediated process

Causes
- Presents often after systemic infections such as measles, mumps, chicken pox, and viral illnesses
- Vaccinations have been associated with onset due to upregulation of the immune system.
- It can occur as an isolated neurologic deficit or as component of more generalized neurologic disease, such as acute disseminated encephalomyelitis, neuromyelitis optica, or multiple sclerosis

Clinical presentation
- Vision loss, can be asymmetric
- Decreased color vision
- Painful eye movements
- Optic disc edema
- Afferent pupillary defect if asymmetric involvement

Management
- Brain and orbital MRI with addition of spinal MRI if peripheral neuropathy present
- Consider lumbar puncture
- Intravenous steroids should be considered in order to hasten visual recovery but does not lessen the risk of recurrence

Retinitis Pigmentosa (RP) [5]

Background
- Progressive vision loss starting in childhood from loss of photoreceptor function
- One in 4000 worldwide prevalence

Causes
- Inherited in dominant, recessive, and X-linked forms
- Sometimes associated with Usher or Bardet–Biedl syndromes
- Treatable forms of RP can be found in abetalipoproteinemia (Bassen–Kornzweig), phytanic acid oxidase deficiency (Refsum disease), and familial isolated vitamin E deficiency

Clinical presentation
- Usually presents initially in adolescence
- Complaints of difficulty with night vision (seeing stars, difficulty in movies)
- Visual acuity can remain normal for many years
- Progressive peripheral visual field loss leading to tunnel vision and blindness
- Classic triad: Pigmentary retinopathy ("bone spiculing"), waxy pallor of the optic nerve, and retinal vessel attenuation
- Cataracts may also be seen

Treatment
- No definitive treatment exists
- Vitamin A supplementation may be beneficial
- Referral to low vision specialist at time of diagnosis allows a child to learn how to use low vision aids prior to losing vision (e.g., Braille)
- Some forms are amenable to gene therapy

Retinal Hemorrhage

Background
- Bleeding within the layers of the retina
- Can be asymptomatic or cause profound vision loss, depending on location and type
- Location and appearance of hemorrhages can give clue as to cause

Causes
- Trauma, in particular nonaccidental
- Birth via vaginal delivery and occasionally C-section can sometimes produce small, self-resolving hemorrhages
- Roth spots (retinal hemorrhages with white center) can be seen most commonly in leukemia or bacterial endocarditis
- Retinopathy of prematurity (ROP) or regressing fetal vasculature in neonates (Fig. 17.11)

Retinal Hemorrhages in Nonaccidental Trauma

- Scattered to diffuse retinal hemorrhages in multiple layers of the retina (Fig. 17.12)

Treatment

- Varies based on type and severity
- Close monitoring
- Head of bed elevation is useful in some cases
- Intraocular surgery may be necessary in severe cases
- Attempts should be made to photo document these cases due to the legal ramifications

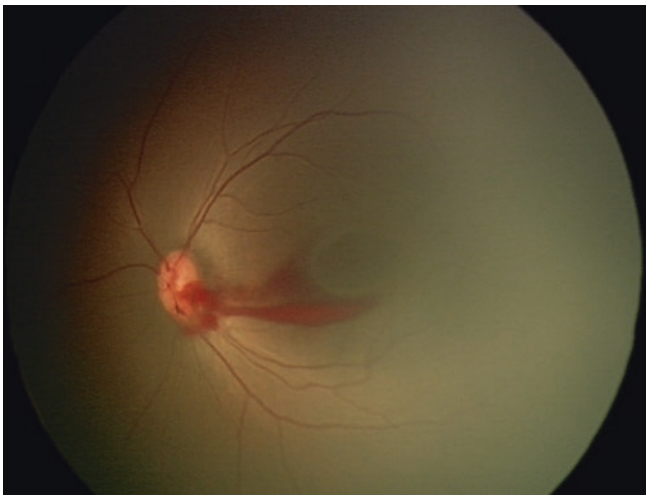


Fig. 17.11 Boat-shaped retinal hemorrhage secondary to regressed fetal vasculature

Retinopathy of Prematurity (ROP)

Background

- Vasoproliferative disease of the retina mediated through the release of vascular endothelial growth factor (VEGF)
- ROP is a disease of the retina in a premature infant due to neovascularization: Fragile vessels that break, bleed, and form scar tissue causing retinal detachment and blindness
- First described in preterm infants
- Annually, a total of 15 million infants are born premature worldwide, 1 in 10 [6]
- Annually, an estimated 50,000 children go blind secondary to ROP worldwide [7]

Causes

- First epidemic
  - 1940s and 1950s
  - Primary cause: oxygen unmonitored
  - Few small (750–1000 g) infants survived (< 8 %)
- Second epidemic
  - 1970s to present
  - Oxygen closely monitored
  - Primary cause: Many small (500–1000 g) infants survived (> 80 %)
- Third epidemic
  - 2000s to present
- Primary cause: Oxygen unmonitored

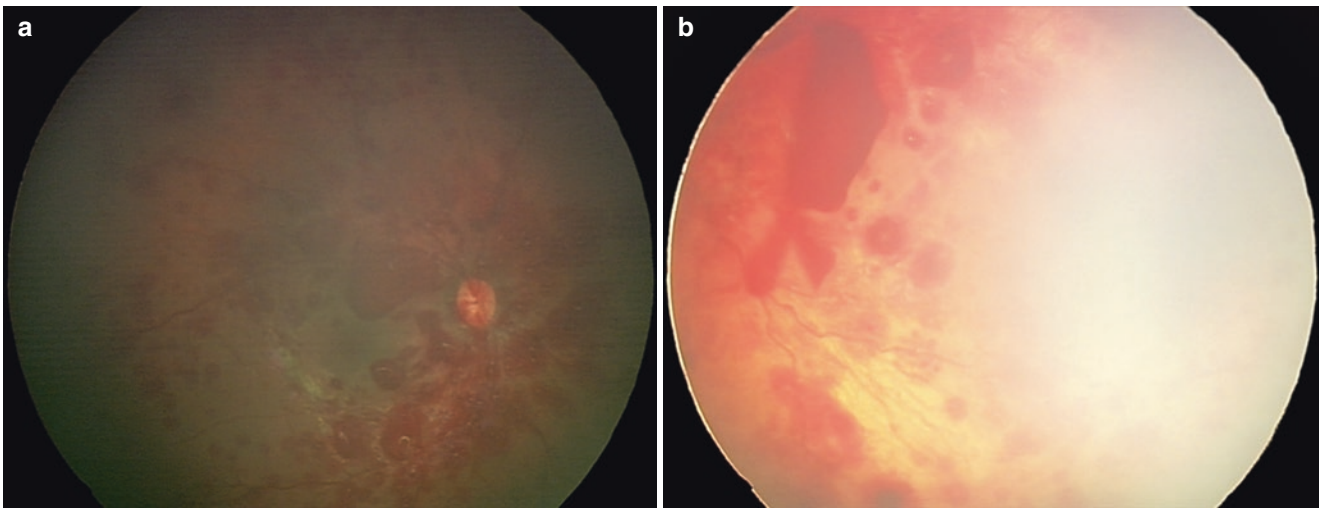


Fig. 17.12 (**a**, **b**) Diffuse retinal hemorrhages in various layers of the retina. Some hemorrhages have white central dot

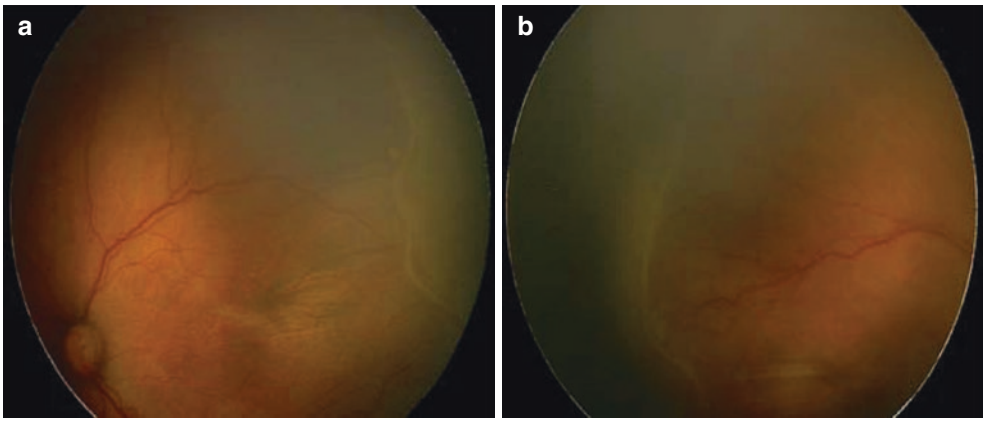


Fig. 17.13 Retinopathy of prematurity (ROP). (**a**) Retina photo showing stage 2 ROP or ridge. (**b**) Retina photo showing popcorn disease, small extravascular fibroproliferation or early stage 3, posterior to the ridge. (Courtesy of Violeta Radenovich MD, MPH, Children's Eye Center; Department of Ophthalmology, Texas Tech University, El Paso, Texas)

- Many infants (750–2000 g infants) survived (> 90%)
- ROP is multifactorial
- Smallest, most immature, and sickest infants in NICU are at the highest risk

Risk factors

- Low birth weight
- Low gestational age
- Hypoxia
- Hyperoxia
- Oxygen fluctuations
- Blood transfusions
- Intraventricular hemorrhage
- Bronchopulmonary dysplasia
- Sepsis
- Necrotizing enterocolitis
- Infant of a diabetic mother

Complication of ROP

- Mild/transient to severe proliferative neovascularization with scarring, retinal detachment, and blindness (Figs. 17.13 and 17.14)

Initial retinal screening [8]

- Premature infants of 30 weeks gestation or less
- Birth weight of 1500 g or less
- Older or heavier infants with an unstable clinical course or believed by the pediatrician to be at high risk
- Examination at 4 weeks postnatal age or 31 weeks adjusted age (whichever is later)

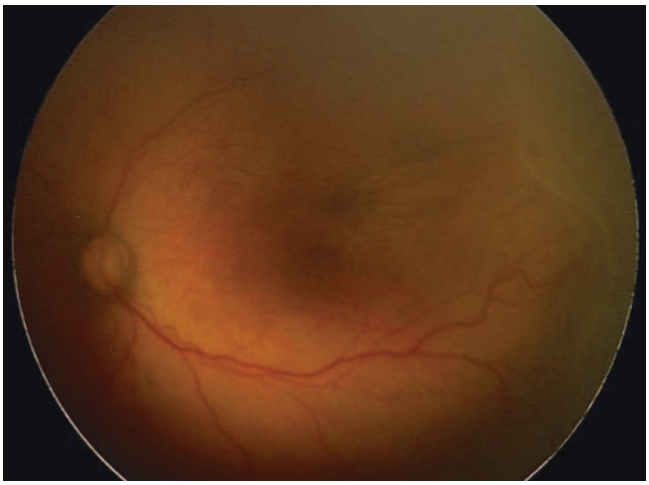


Fig. 17.14 Retina photo showing sectorial plus disease, mild dilation, and tortuosity of central retina vessels. (Courtesy of Violeta Radenovich MD, MPH, Children's Eye Center; Department of Ophthalmology, Texas Tech University, El Paso, Texas)

Current management

- Prevention: Appropriate oxygenation and nutrition
- Robust screening program

Screening Descriptions [9]

- 3 zones
  - Zones are annotated I, II, and III with I being the zone that is most posterior and includes the optic nerve
- Six stages
  - Stages are annotated 0 through 5 with 0 being immature vessels and 5 indicating a

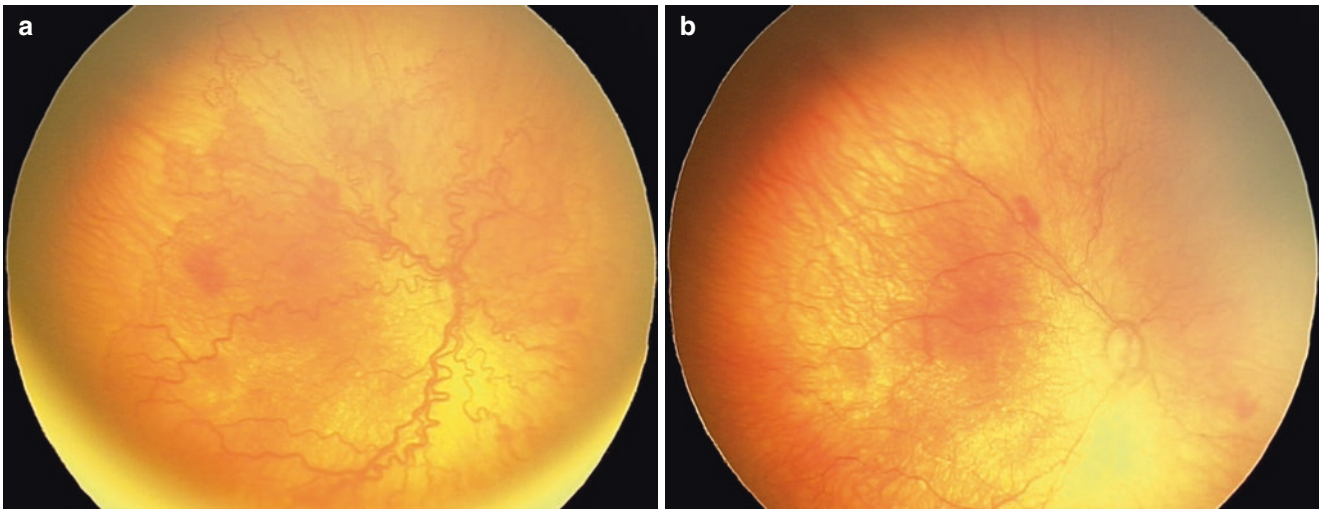


Fig. 17.15 Retinal photo showing aggressive posterior retinopathy of prematurity. (**a**) Note extensive vessel dilation and tortuosity in the posterior pole with flat neovascularization at the terminal ends of the vessels. (**b**) Same patient 1 week after treatment with bevacizumab injection into the vitreous

total retinal detachment (best ➔ worst visual prognosis)

- Plus disease: An additional descriptor relating to presence of central retinal venule dilation and arteriolar tortuosity
- Aggressive posterior ROP (AP-ROP). An aggressive form of ROP that is seen in the most posterior zone and portends a poor outcome even if treated (Fig. 17.15)

Treatment programs

- Goal of treatment is to downregulate release of VEGF to reduce neovascularization
- Laser surgery has overtaken cryotherapy as the mainstay of treatment
- Anti-VEGF therapy
- Retinal surgery for those infants with retinal detachments

Early treatment

- Laser ablation to peripheral avascular retina to prevent retinal detachment by pediatric ophthalmologist or retina specialist
- Anti-VEGF therapy (bevacizumab) is becoming more widespread and has shown to have good outcomes, especially for those children with very posterior disease (zone 1)
- The injection of anti-VEGF medications frequently does not require sedation or general anesthesia; however, the medication does become systemic. Early data suggest that there are no systemic or neurologic deficits due to this systemic absorption; however, studies are ongoing
- Blindness due to ROP can often be prevented with adequate nutrition, oxygenation, and timely treatment
- Despite being vision-saving, the treatment for ROP, as well as the disease itself, will often lead to high myopia, strabismus, and other ocular conditions throughout life

EYE TRAUMA [10]

Background

- Eye trauma can lead to permanent vision loss
- 840,000 cases of pediatric ocular trauma occur yearly in the USA
- Can be broadly defined as open-globe or closed-globe injury
- Prevention saves vision. Encourage protective eyewear

Evaluation

- Visual acuity: Presenting visual acuity is a key factor in predicting final visual outcome
- Pupil size, shape, and reactivity

- A tadpole-shaped pupil is a sign of an open globe

Open-globe injuries
- Penetrating injury to the eye
- Tend to have a poorer visual acuity outcomes
- Must be ruled out in any trauma to the eye
- Mechanism of injury and abnormal pupil shape are quickly available for assessment
- If an open-globe injury is suspected, emergent referral to an ophthalmologist is indicated
- If an open-globe injury is suspected, consider administering a broad-spectrum antibiotic and making patient *non per os* (NPO)

Closed-globe injuries
- Any injury to the eye *not* resulting in open globe
- Corneal abrasions, hyphema, burns, conjunctival laceration
- If appropriately treated, usually have favorable visual outcomes

Treatment
- Referral to ophthalmologist. If concern for open globe, then shield the eye and consult

Traumatic Iritis

Background
- Inflammation in the front chamber of the eye
- Most commonly seen with a history of blunt trauma

Clinical presentation
- History of trauma
- Photophobia (can be severe)
- Conjunctival injection, usually 360°
- Variable vision, but usually at least slightly decreased in affected eye
- No corneal staining with fluorescein evaluation
- Under high magnification with a slit lamp microscope, one can see white cells floating in the anterior chamber

Diagnosis
- Requires the use of a slit lamp microscope to evaluate anterior chamber cell and flare

Management
- Referral to ophthalmologist
- Topical steroid and dilating drops
- Frequent evaluation until resolved

Retinal Detachment

Background
- Occurs when the retina separates from its underlying supporting tissue, the choroid
- Spontaneous detachments in children are rare

Causes
- ROP
- Trauma
- High myopia
- Diabetes
- Sickle cell disease
- Stickler syndrome
- Marfan syndrome

Clinical presentation
- Dark curtains, floaters, and flashes of light are possible presenting complaints
- Preverbal and early verbal children may not be able to express symptoms
- Preverbal and nonverbal children may display reactionary signals of vision change such as poking the eye (oculodigital reflex) or rubbing the eye
- Visual acuity may be completely intact
- Red reflex may be abnormal if retinal detachment involves the central retina

Management
- Immediate referral to ophthalmologist
- Retinal detachments require surgery. Can be vitrectomy or scleral buckling, depending on the type of detachment and surgeon
- Children may need amblyopia treatment following repair

Orbital Fracture

Background
- Blunt trauma to the face or directly to eye

Clinical presentation
- Periorbital ecchymosis
- Eye/face pain
- Limitation of upward gaze
- May have decreased ipsilateral cheek or upper lip sensation
- Epistaxis
- Bradycardia from oculocardiac reflex
- Diplopia

Diagnosis
- Thin-cut coronal CT of the orbit is the best imaging study
- Associated globe injury 10–50 %
- Orbital floor is most common fracture
- Beware the white-eyed blowout fracture, which presents with minimal eye redness, but has a "trapdoor" or a greenstick fracture of the orbital floor, which can cause subtle findings on CT

Management
- Discourage blowing of nose. Give nasal decongestants
- Must be evaluated by facial trauma team (ophthalmology, ENT, plastic surgery, maxillofacial surgeon, or others, as standard in particular location)
- If primary team is not ophthalmology, then will also require ophthalmologic evaluation
- Surgical repair is not indicated in every case; many are managed conservatively
- Bradycardia, nausea, and vomiting are signs of muscle entrapment, which may require urgent surgical intervention

Corneal Abrasion

Clinical presentation
- Eye tearing
- Foreign body sensation
- Discomfort with blinking, sharp pain, and photophobia
- In infants, corneal abrasions can present as initially unexplained, inconsolable crying
- A child may be continually rubbing an eye, which is watery and red

Diagnosis
- Topical fluorescein, which is available in paper strip or drop forms
- May apply topical anesthetic in solution to facilitate the eye exam
- The area of abrasion will fluoresce under a cobalt blue filter light (Wood's lamp)
- A vertically oriented abrasion may herald a foreign body under the eyelid

Management
- Topical eye antibiotic ointment, for example, erythromycin or bacitracin ophthalmic, should be applied four times daily to prevent infection
- Ointment is preferred, as it creates a lubricating effect; however, it also blurs the vision much more than topical drops
- Antibiotics are continued until the epithelial defect is closed
- Daily examination is recommended for children

Important to know
- Corneal abrasions heal rapidly, often within 24 h for smaller injuries
- Patients who wear contact lenses or have a history of ocular herpes should be referred urgently to an ophthalmologist for consultation
- The usual recommendation is to avoid contact lenses until the injured eye has felt normal for at least 1 week
- Patients with large or central abrasions should be referred to an ophthalmologist
- The use of patching should be avoided unless directed by an ophthalmologist

Eye Foreign Body

Clinical presentation

- Sudden onset of eye pain after exposure, particularly with flying debris or wind
- Associated with intraocular foreign body in 18–41% of cases

Diagnosis

- History and physical exam
- Topical anesthetic will facilitate the exam
- Fluorescein exam
- Evert the upper eyelid at exam. Foreign bodies (FBs) tend to hide under the upper eyelid
- Retract the lower eyelid to inspect the inferior conjunctiva
- **Orbital CT scan,** if intraocular FB is suspected

Management

- **Best initial management** is gentle eye irrigation or gentle swabbing
- Eye irrigation can be performed by hanging an IV and holding the tubing over the eye. Irrigating contact lenses can cause more injury in some cases
- Refer to ophthalmology any patient with an intraocular FB when FB cannot be removed or has caused large corneal abrasion or if discoloration of tissue is noted after the FB is removed

Hyphema

Background

- Hyphema is blood in the anterior chamber usually after blunt trauma
- Paintballs, small foam missiles, other projectiles like bungee cords are common causes

Clinical presentation

- Blurring of vision to complete loss of vision
- Photophobia
- Eye pain is common

Management

- Bed rest with elevation of the head of the bed and eye shield on the affected eye
- Emergent ophthalmology consultation
- May require admission if unable to reliably complete bed rest
- Sickle cell disease status should be tested in high-risk populations due to the association of complications

Complications

- Internal corneal staining
- Increased intraocular pressure, which can cause glaucoma and optic nerve damage if untreated
- Cataract

STRABISMUS

Background

- Strabismus is a misalignment or deviation of the eye or deviation; it may be congenital or acquired
- -Tropia: Deviation with binocular viewing, may be intermittent or constant (e.g., red reflex, cover–uncover testing)
- -Phoria: Deviation present only when binocular viewing is interrupted (e.g., alternate cover testing)
- **Esotropia** is an inward deviation (Fig. 17.16)
- **Exotropia** is an outward deviation (Fig. 17.17)
- **Hypertropia** is an upward deviation
- **Hypotropia** is a downward deviation

Congenital esotropia

- Onset within first 6 months of age
- Associated with large-angle strabismus and usually a constant deviation
- Amblyopia in 50% of patients
- Poor stereovision (includes depth perception)
- Treatment: Early referral to ophthalmologist with surgery within first 12 months of life

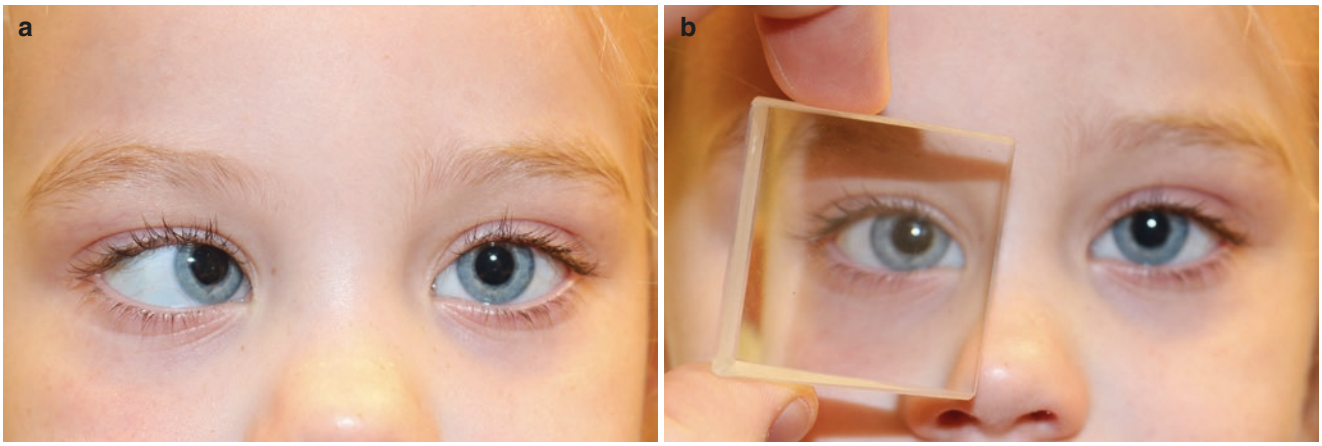


Fig. 17.16 (**a**) External photo showing right eye esotropia or crossing. (**b**) External photo showing recentration of corneal light reflex through the use of prism to measure amount of esotropia, in this case 35 prism diopters (Krimsky test)

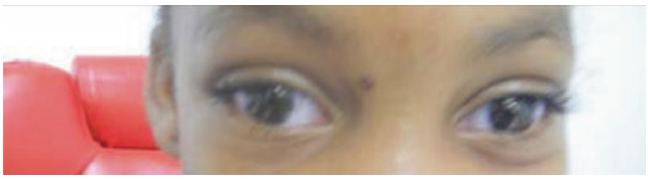


Fig. 17.17 External photo showing right eye exotropia, outward deviation. (Courtesy of Violeta Radenovich MD, MPH, Children's Eye Center; Department of Ophthalmology, Texas Tech University, El Paso, Texas)

Accommodative esotropia

- Onset usually between 3 and 5 years of age
- Directly related to hypermetropia (i.e., farsightedness)
- Attempt to accommodate to see clearly causes the eyes to cross
- Typical crossing at near is greater than at distance
- Treatment: Full-time wear of eyeglass correction
- Some subtypes require bifocals or surgery in addition to the eyeglasses

Intermittent exotropia

- Most commonly occurring between ages 2 and 8 years
- Patient may squint one eye
- Treatment is to correct any refractive error with eyeglasses, and some may require strabismus surgery
- Patching therapy may help in some cases

Vertical misalignment

- Congenital fourth nerve palsy is the most common nontraumatic cause in children
- May be cause of torticollis that is not responsive to physical therapy
- Orbital floor fracture can cause hypotropia, worse on attempted upgaze

Pseudostrabismus

- An appearance of esotropia when one does not actually exist
- Frequently seen in children with wide nasal bridges or large epicanthal folds
- Diagnosis: Central corneal light reflex. No misalignment on cover testing

Diagnosis

- Visual acuity test, cover test, light reflex test
- Corneal light reflex (Hirschberg) is a good initial testing
- An asymmetric red reflex may indicate strabismus with the brighter eye having misalignment
- The best test to differentiate heterophoria from heterotropia is cover–uncover test

Remember

- Occasional eye deviation in newborns can be observed; if it persists beyond 4 months, should be referred to pediatric ophthalmologist

- Refer to pediatric ophthalmologist all patients with strabismus

Critical to know
- New-onset strabismus can be a manifestation of eye or brain tumor and should be investigated immediately
- Amblyopia is a common complication in untreated cases
- Strabismus is treated by the ophthalmologist with eyeglasses, patching, or surgery

Amblyopia

Background
- A unilateral or bilateral reduction of best-corrected visual acuity that cannot be attributed directly to the effect of any structural abnormality of the eye or the posterior visual pathways
- It is a consequence of diminished visual input into the visual cortex, which leads to impairment of neuro-ophthalmologic pathways

Causes
- Strabismus (the most common cause)
- Anisometropia (unequal refractive errors) or high refractive errors
- Stimulus deprivation: Cataracts, corneal opacities, vitreous hemorrhage, lid hemangiomas

Diagnosis
- Vision screening

Management
- Patients who failed vision screening need to be referred to an ophthalmologist

Ophthalmology treatment
- Eliminate any obstacle to vision such as cataracts
- Correct any refractive errors
- Patching or occlusion therapy. Atropine eye drops may be used in some cases
- Amblyopia should be detected early
- Vision screenings in children under five are very important
- Occlusion therapy is more effective under the age of 8 but can still be done in older children
- Studies in older children with amblyopia have shown that treatment can still be beneficial beyond the first decade of life, especially if never treated previously
- Compliance can be a problem with children

VISION DEVELOPMENT AND VISUAL ACUITY [11, 12]

- Visual pathways begin to develop around the day 23 of gestation
- Ocular lens placode develops by day 27
- Embryonic fissure of the optic stalk closes by day 33 (important for colobomas)
- The fovea (retinal anatomy responsible for best vision) starts to differentiate at around 15–17 weeks and continues through 32 weeks
- Myelination of optic nerve starts at approximately 7 months and continues after term birth
- Visual acuity matures somewhere between ages 5 and 15
- Eye alignment should be consistently straight after 3–4 months of age
- Infants can differentiate shape and size by 4.5 months and contours/edges by 6 months of age

DISORDERS OF REFRACTION

- Types: Myopia (nearsighted), hyperopia (farsighted), astigmatism
- Without adequate screening programs for children, can easily be missed
- Unless objectively evaluated, children may not complain of any subjective visual difficulties for many years
- Uncorrected refractive error can cause difficulty in school

- Uncorrected refractive errors can cause permanent vision loss through amblyopia if not diagnosed and referred in early childhood
- Screening visual acuity should occur at yearly well-child visits beginning at age 3 [1]
- Referral criteria is based on age of child:
  - Age 3–4: 20/50 or worse
  - Age 4–5: 20/40 or worse
  - Over 5: 20/32 or worse
  - Any age: Asymmetry between the two eyes

Contact lens-related problems

- Sleeping in contact lenses exponentially raises risk of infection
- A red eye with a lesion on the cornea (seen best with fluorescein and magnification) in a patient with contact lens use needs immediate referral to an ophthalmologist
- Broad-spectrum ophthalmic antibiotics (e.g., topical moxifloxacin) is a commonly used option for contact lens-related ulcers/keratitis

Nystagmus

Background

- Nystagmus is involuntary rhythmic eye movement
- May signify important eye or central system pathology
- Can be hereditary
- Any internal eye problem can cause sensory nystagmus, e.g., cataract, optic atrophy or aniridia, corneal opacities, retinal dystrophies, optic nerve hypoplasia, etc.

Clinical presentation

- Infantile nystagmus syndrome usually before 2 months
  - Horizontal, jerky oscillations, bilateral
  - Visual function is highly variable from normal to significantly impacted
  - It is not associated with other central nervous system abnormalities
  - Anomalous head position often leads to a slowing of the eye movements (null point)
  - Surgery is indicated to correct the head position and slow the eye movements

Congenital sensory nystagmus

- Horizontal nystagmus, sometimes pendular
- Begins in the first 3 months of life
- Associated with ocular abnormalities that may affect visual development: Bilateral cataracts, glaucoma, corneal opacities, aniridia, retinal dystrophy, optic nerve hypoplasia, foveal hypoplasia

Acquired nystagmus

- Brain imaging is necessary to rule out any intracranial lesions

Spasmus nutans

- Bilateral nystagmus, horizontal, vertical, or rotary
- Abnormal head movement (nodding or bobbing) or torticollis
- Rarely starts before 4 months of age
- MRI to rule out chiasmal or suprachiasmatic tumors (glioma)

Management

- Children with nystagmus need to be referred to a pediatric ophthalmologist

ORBITAL MASSES

Periorbital Tumor or Hemangioma

Background

- Periorbital masses may cause vision loss through ptosis or compressive mechanisms
- May be isolated or a harbinger of systemic disease
- Many causes: Neurofibroma, hemangioma, dermoid cyst, neuroblastoma, tumor

Clinical presentation

- Ptosis—usually unilateral
- Proptosis

- Increased resistance to retropulsion
- Asymmetric astigmatism
- Neuroblastoma can present as sudden-onset eyelid ecchymosis

Treatment
- Urgent MRI for concern of neuroblastoma
- Referral to ophthalmologist
- Treat amblyopia
- Hemangioma: Consider topical or oral beta-blocker
- Possible surgical excision

Orbital Rhabdomyosarcoma [13]

Background
- Highly malignant neoplasm of embryonal striated muscle cells
- Orbital involvement is one of the most common locations, accounting for 10–20% of all rhabdomyosarcoma cases
- Most common soft tissue sarcoma in children

Clinical Presentation
- Proptosis, possibly rapidly changing
- Ptosis
- Globe displacement, most frequent inferotemporally

Diagnosis
- Orbital imaging with CT or MRI is mandatory
- Biopsy should be performed promptly if a mass is noted on radiographic evaluation

Management
- Urgent referral to an ophthalmologist
- Treatment usually includes a combination of chemotherapy, irradiation, and/or surgical excision

PEARLS AND PITFALLS

- Visual acuity screening with linear testing methods should be attempted at age 3 years.
- Vision screening is important, as many vision problems become more difficult or impossible to improve as children approach age 8 years.
- Ophthalmia neonatorum is a vision-threatening process in which the timing of onset can help provide clues to the diagnosis.
- Ocular involvement in juvenile idiopathic arthritis may be asymptomatic, and children should have routine screening exams.
- Congenital glaucoma must be ruled out in cases of excess tearing such as nasolacrimal duct obstruction and can possibly be identified through a classic triad of tearing, photophobia, and blepharospasm.
- Congenital cataracts have a variety of etiologies but must be identified and treated as early as 4 weeks of life.
- Retinal hemorrhages from trauma are usually diffuse and found in multiple layers of the retina.
- In evaluating for papilledema with a lumbar puncture, the opening pressure must be carefully measured.
- The goal of treatment in ROP is to downregulate the expression of VEGF, which is now most frequently accomplished through laser treatment, with anti-VEGF injections becoming an option in many centers.
- Beware of the white-eyed blowout orbital fracture. Child will present with a white eye, but may have bradycardia, nausea, vomiting, and/or diplopia. This condition requires urgent surgical evaluation.

Acknowledgment The authors gratefully acknowledge the contributions of Violeta

Radenovich MD, MPH, Children's Eye Center of El Paso, El Paso, Texas, to the 1st edition of this chapter, many of which have been incorporated into this edition as well.

SLR was supported by an unrestricted grant from Research to Support Blindness (New York, NY).

Disclaimer The views expressed in this chapter are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government. CDR Miller is a military service member. This work was prepared as part of his official duties. Title 17 U.S.C. 105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 U.S.C. 101 defines a United States Government work as a work prepared by a military service member as part of that person's official duties.

References

1. Committee on Practice and Ambulatory Medicine, Section On Ophthalmology, American Association of Certified Orthoptists; American Association For Pediatric Ophthalmology and Strabismus; American Academy of Ophthalmology. Visual system assessment in infants, children, and young adults by pediatricians. Pediatrics. 2016;137(1):28–30.
2. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. 2013;310(16):1721–9.
3. Cassidy J, Kivlin J, Lindsley C, Nocton J, Section on Rheumatology; Section on Ophthalmology. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. Pediatrics. 2006;117(5):1843–5.
4. Davenport KM, Patel AA. Cataracts. Pediatr Rev. 2011;32(2):82–3. Review.
5. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet. 2006;368:1795–809.
6. World Health Organization. Preterm birth. http://www.who.int/news-room/fact-sheets/detail/preterm-birth. Accessed 21 Sep 2018.
7. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008;84(2):77–82.
8. Fierson WM, American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131(1):189–95.
9. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol. 2005;123(7):991–9.
10. Miller KE. Pediatric ocular trauma: An update. Current Ophthalmology Reports. 2017;5(2):107–13.
11. American Academy of Ophthalmology. Growth and development of the eye. In: AAO basic and clinical science course. Pediatric ophthalmology and strabismus. San Francisco: American Academy of Ophthalmology; 2011. p. 167–71.
12. Siu CR, Murphy KM. The development of human visual cortex and clinical implications. Eye Brain. 2018;10:25–36.
13. Shields JA, Shields CL. Rhabdomyosarcoma: review for the ophthalmologist. Surv Ophthalmol. 2003;48(1):39–57.

Suggested Reading

American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus Panel. Preferred practice pattern guidelines: pediatric eye evaluations. San Francisco: American Academy of Ophthalmology; 2017. p. 189–227.

American Academy of Pediatrics, Section on Ophthalmology, Council on Children with Disabilities, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, and American Association of Certified Orthoptists. Joint statement—learning disabilities, dyslexia, and vision. Pediatrics. 2009;124(2):837–44.

Donahue SP, Nixon CN, Section on Ophthalmology, American Academy of Pediatrics; Committee on Practice and Ambulatory Medicine, American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Visual system assessment in infants, children, and young adults by pediatricians. Pediatrics. 2016;137(1):28–30.

Ehlers JP, Shah CP. Corneal abrasion. In: Ehlers JP, Shah CP, editors. The Wills eye manual: office and emergency room diagnosis and treatment of eye disease. 5th ed. Baltimore: Lippincott; 2008. p. 15–6.

Harrison JR, English MG. Chlamydia trachomatis infant pneumonitis: comparison with matched controls and other infant pneumonitis. N Engl J Med. 1978;298(13):702–8.

Rapoza PA, Chandler JW. Neonatal conjunctivitis: diagnosis and treatment. In: Focal points 1988: clinical modules for ophthalmologists. San Francisco: American Academy of Ophthalmology; 1988. p. 5–6.

Ear, Nose, and Throat

18

Kara D. Meister and Anna H. Messner

EARS

Preauricular Pits/Sinus (PPS)

- Small indentations located anterior to the helix and superior to the tragus
- Can occur unilaterally (~50%) or bilaterally (~50%)
- Prevalence ranges between 1% and 10% depending on ethnicity
- Can occur in isolation with no increased risk of hearing impairment or renal issues
- Can be associated with hearing impairment and organ malformations
- Branchio-oto-renal (BOR) syndrome:
  - Most common inherited syndrome causing hearing loss (autosomal dominant)
  - Clinical presentation: preauricular pits, sensorineural hearing loss (SNHL), branchial cysts (may present as holes/pits in the side of the neck or as tags/pits in front of the ear), renal anomalies
- Beckwith-Wiedemann syndrome:
  - Clinical presentation: macroglossia, asymmetric ear lobules or creases, omphalocele, Wilms tumor, hepatoblastoma.
  - Hearing loss can present later in childhood as conductive or mixed hearing loss
- PPS do not require surgical excision unless they are frequently draining or infected
- Passing of prenatal hearing screen should be confirmed in all patients
- Audiogram should be performed if there are other outer ear deformities or any evidence of genetic syndromes
- Wang et al. [1] suggest that a renal ultrasound be performed in children with ear anomalies accompanied by any of the following:
  - Other known organ malformations
  - Family history of deafness and auricular and/or renal malformation
  - Maternal history of gestational diabetes mellitus

Otalgia

Definition

- Ear pain may be primary or referred in origin

Clinical Presentation

- Must consider potential sources of referred pain as well as sources of primary ear pain
- Primary: otitis externa, foreign body, acute otitis media (AOM), chondritis, ear canal laceration, mastoiditis
- Referred: temporomandibular joint (TMJ) disorders, larynx infection or pathology, deep neck space infection, cervical spine disorders
  - Very common after oropharyngeal surgery (such as tonsillectomy)

K. D. Meister
Department of Otolaryngology-Head & Neck Surgery, Pediatrics Division, Lucile Packard Children's Hospital, Stanford University, Stanford, CA, USA

A. H. Messner (✉)
Professor of Otolaryngology/Head & Neck Surgery, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA
e-mail: annamessner@stanford.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_18

Otitis Externa

Definition

- Inflammation of the external auditory canal (EAC) due to bacterial (most commonly *Pseudomonas aeruginosa*, followed by *Staphylococcus* species) or fungal infections

Clinical Presentation

- Pain and tenderness with tragal pressure/pulling pinna; pruritic, erythematous, and edematous EAC; debris in the EAC; malodorous otorrhea
- Differential diagnosis: necrotizing otitis externa, otitis media with perforation, Ramsay Hunt syndrome, furuncle, atopic dermatitis, EAC foreign body, chondritis

Treatment

- Pain control and anti-inflammatories.
- Topical ear drops (ensured *Pseudomonas* coverage)
- Keep ears dry with water precautions (child either should swim with a neoprene headband to keep the ears dry or should not swim) and/or with ear dryer (hair dryer)
- Ears drops of solution made of 50:50 white vinegar and rubbing alcohol can provide prophylaxis (if there's **no** tympanic membrane perforation). Commercial ear drops to prevent swimmer's ear are also available over the counter

Indications for Ear, Nose, and Throat (ENT) Referral

- Significant debris in the EAC—will require debridement.
- If unable to visualize the tympanic membrane due to canal edema, patient will require a temporary ear wick
- Immunocompromised or diabetic patient

Foreign Body in the External Ear

- Beads, insects, toys, popcorn, beans, and button batteries are common ear foreign bodies.
- Presentation: drainage, cough, pain, pruritus, child pulling at ear, incidentally noted during exam
- Most foreign bodies do not require emergent removal
- Emergent removal for button batteries.
- Indication for ENT referral:
  - Presence of tympanic membrane perforation
  - Foreign body wedged in the canal that cannot be grasped
  - Trauma/bleeding in the ear canal
  - Failed attempt at removal

Hematoma of the External Ear (Pinna)

- Commonly due to trauma
- Can cause avascular necrosis (blood supply lifted away from the cartilage by the hematoma) and permanent damage to the underlying cartilage (Fig. 18.1)

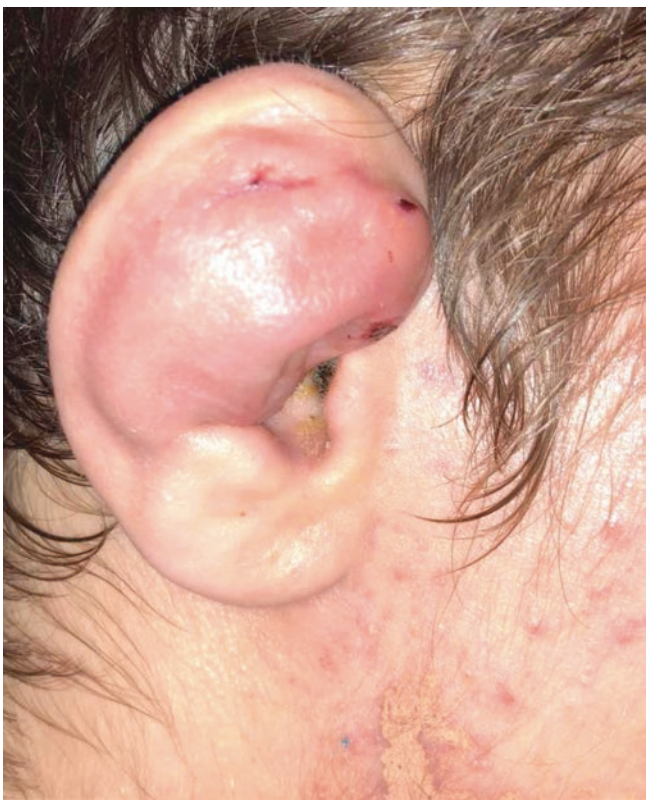


Fig. 18.1 Auricular hematoma of the right ear

Management

- Urgent aspiration of hematoma to prevent pinna deformity (i.e., wrestler's ear or cauliflower ear)
- Pressure dressing applied after evacuation
- Close follow-up to monitor for reaccumulation

Acute Otitis Media (AOM)

Background

- Signs of an acute infection associated with middle effusion and inflammation (bulging tympanic membrane)
- 80% of children have at least one AOM before 1 year of age; 90% of children have at least two AOM by the age of 3

Risk Factors

- Age (6–18 months), positive family history of otitis media, daycare attendance, lack of breastfeeding, exposure to tobacco smoke, pacifier use/bottle propping, race/ethnicity (native Americans and the Inuit are at higher risk) [2]

Common Pathogen

- Bacterial: *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes* (group A *Streptococcus*) are the most common causes.
- Viral: respiratory syncytial virus (RSV), picornavirus, coronavirus, influenza, adenovirus

Clinical Presentation

- Fever, irritability, apathy, anorexia, vomiting, diarrhea, otalgia, otorrhea, hearing loss
- Frequent nighttime awakening

Diagnosis

- Pneumatic otoscopy showing decreased tympanic membrane mobility remains the best method for diagnosing the presence of middle ear fluid

Management

- 2013 American Academy of Pediatrics guidelines [3]:
  - Immediate antibiotic treatment for the following:
    - Children < 6 months of age
    - Children with moderate to severe otalgia
    - Otalgia lasting longer than 48 h
    - Temperature > 39 °C (102.2 °F)
    - Bilateral AOM and less than 24 months of age
  - Antibiotic treatment or observation with pain control:
    - 6 to 24 months of age with unilateral non-severe AOM.
    - > 24 months of age with unilateral or bilateral non-severe AOM.
    - When observation is chosen, child must be followed up. Initiate antibiotics within 48–72 h should the child worsen or fail to improve

Antimicrobial Therapy

- First line: amoxicillin (90 mg/kg/day divided twice a day) × 10 days
- Second line, amoxicillin-clavulanate:
  - Children who failed first-line therapy
  - Children with increased risk of beta-lactam resistance
  - Beta-lactam use within the past 30 days
  - Concomitant purulent conjunctivitis (likely *H. influenzae*)
  - Recurrent AOM unresponsive to amoxicillin
- For patients with hypersensitivity to penicillin:
  - Macrolides
  - Cefdinir, cefuroxime, ceftriaxone

Complications

- Intratemporal: conductive hearing loss (CHL), tympanic membrane perforation, ossicular erosion, labyrinthitis, facial nerve paralysis, mastoiditis, subperiosteal abscess, petrous apicitis, sigmoid sinus thrombosis

- Intracranial: meningitis, epidural/subdural/parenchymal abscess, cavernous sinus thrombosis, otitic hydrocephalus

Recurrent Acute Otitis Media

- 3 episodes in 6 months or 4 episodes in 1 year with 1 episode in the preceding 6 months [3]
- Associated conditions overlap with risk factors for Eustachian tube dysfunction: age < 2 years, allergic rhinitis/sinusitis, mucociliary dysfunction, craniofacial abnormalities, immunodeficiency.
- Hallmark on physical exam is tympanosclerosis (a.k.a. myringosclerosis): white plaques on the tympanic membrane, which represent a form of scarring (Fig. 18.2)
- Recommendations to decrease risk: pneumococcal conjugate vaccine, annual influenza vaccine, exclusive breastfeeding for at least 6 months, avoidance of tobacco smoke exposure
- Prophylactic antibiotics are **not** recommended

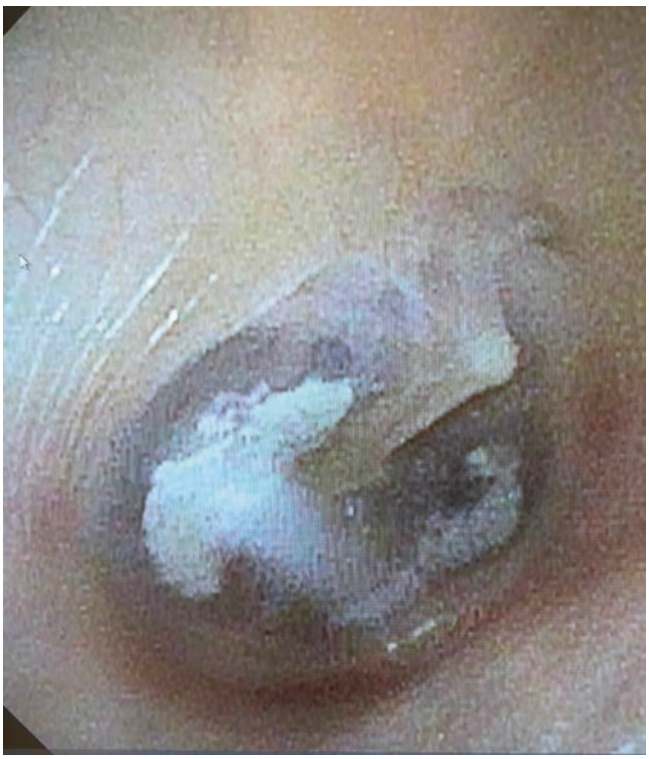


Fig. 18.2 Right tympanic membrane demonstrating tympanosclerosis

Suggested Follow-Up

- < 2 years of age: 8–12 weeks after diagnosis/treatment of AOM
- < 2 years of age with language or developmental delay: 8–12 weeks after diagnosis/treatment of AOM
- > 2 years of age with no comorbidities/language or development delay: next routine visit

Otitis Media with Effusion (OME)

- Middle ear effusion without signs of acute infection

Etiology

- After AOM (typically):
  - In the presence of Eustachian tube dysfunction in the absence of AOM
- It is estimated up to 90% of OME will resolve spontaneously within 3 months.
- 30% to 40% of patients will have recurrent episodes of OME.
- Most common cause of pediatric hearing loss.
- Frequency decreases as children age.
- More common in patients with Eustachian tube dysfunction:
  - Craniofacial abnormalities (cleft palate and others): weak Eustachian tubes secondary to palate abnormalities
  - Mucociliary dysfunction: primary ciliary dyskinesia
  - Concurrent blockage of the Eustachian tube opening: adenoidal hypertrophy, allergic rhinitis/sinusitis

Investigations

- Hearing evaluation:
  - Children with OME > 3 months

  - Children at risk of speech, language, and learning delay
- Speech language evaluation:
  - In children at risk of speech, language, and learning delay

Treatment

- Observation, "watchful waiting"
  - In children with OME with low risk of speech, language, and learning delays with speech awareness thresholds showing hearing loss less than 20 dBs.
  - Monitor every 3 months to ensure resolution of effusion
- Myringotomy and tympanostomy tube insertion
  - See **Indication for Myringotomy and Tympanostomy Tubes for Acute Otitis Media (AOM) and Otitis Media with Effusion (OME)**

Chronic Suppurative Otitis Media (CSOM)

Definition

- Otorrhea (> 6 weeks or recurrent) from a middle ear and/or mastoid infection in the presence of tympanic membrane perforation (or ventilation tube)

Common Pathogen

- Mixed infections:
  - Gram-negative bacilli (*Pseudomonas*, *Klebsiella*, *Proteus*, *Escherichia coli*)
  - *Staphylococcus aureus*
  - Anaerobes

Clinical Presentation

- Otorrhea, TM perforation, inflamed middle ear mucosa, conductive hearing loss

Treatment

- Keep the ear clean and dry:
  - Water precautions (avoid getting water in ear)
  - Refer to otolaryngology if debridement is required.
- Topical antimicrobials/corticosteroids (must cover *Pseudomonas* and methicillin-resistant *Staphylococcus aureus* [MRSA]):
- If topical antibiotics failed, consider systemic antibiotics (broad spectrum covering *Pseudomonas* and MRSA)

Indication for Myringotomy and Tympanostomy Tubes for Acute Otitis Media (AOM) and Otitis Media with Effusion (OME) [4, 5]

- Bilateral myringotomy and tympanostomy tubes are indicated for a patient with the following:
  - Bilateral OME for 3 months or more and documented hearing difficulties
  - Unilateral or bilateral OME for 3 months and symptoms likely related to OME, for example, vestibular symptoms, poor school performance, behavioral difficulties, ear discomfort, and decreased quality of life
  - Recurrent AOM and unilateral or bilateral middle ear effusion at the time of assessment
  - At-risk children (such as those having craniofacial abnormalities or having only one hearing ear), with unilateral or bilateral OME that is unlikely to resolve quickly as reflected by a type B tympanogram (flat) or persistent effusion for 3 months or longer
- **Complications of Tympanostomy Tubes**
  - Tube otorrhea (most common)
  - Blockage of the tube
  - Granulation tissue formation
  - Displacement of the tube in the middle ear
  - Tympanic membrane changes: myringosclerosis, atrophy, atelectasis, retraction pocket
  - Persistent tympanic membrane perforation (may require surgical repair)
  - Anesthesia-related complications

Acute Mastoiditis

Background

- Suppurative infection of the middle ear (acute otitis media) that spreads to the mastoid cavity, resulting in osteitis of the mastoid bone
- May become purulent and lead to bony breakdown within the mastoid bone (acute coalescent mastoiditis)

Common Presentation

- Erythema, tenderness, and edema over the mastoid bone (postauricular region)
- Protuberant ear
- Fever, adenopathy, otitis media

Assessment

- Complete blood count (CBC), inflammatory markers, audiometric evaluation
- Imaging: computed tomography (CT) of the temporal bones (look for bony breakdown within the mastoid suggestive of coalescence)
  - If there's any concern for intracranial complication, use of contrast is recommended.

Treatment

- Immediate otolaryngology consultation
- Systemic antibiotics (usually requires intravenous antibiotics)
- Possible myringotomy (tympanocentesis/culture) and ventilation tube (use topical antimicrobial if the tube is present)
- Cortical mastoidectomy for cortical erosion of the mastoid or intracranial complications

Cholesteatoma

Definition

- Squamous epithelium in the middle ear and mastoid cavities (misnomer as there's no cholesterol)
- Risk of leading to recurrent infections, as well as bone and soft tissue erosion

Types

- Congenital
  - Presents as a white mass, most often in the anterior-superior middle ear space with an intact tympanic membrane
- Acquired
  - Squamous epithelium which enters the middle ear via the retraction pocket (invagination), migration through tympanic membrane perforation, or iatrogenic implantation

Clinical Presentation

- Conductive hearing loss
- Persistent otorrhea
- Tympanic membrane retraction pocket filled with squamous epithelial debris/crusts
- Possible whitish mass behind the TM (not always seen)

Complications

- Erosion/destruction of the ossicular chain, chronic otitis media, labyrinthine fistula, intracranial complications/abscess, facial nerve paralysis

Treatment

- Otolaryngology consultation is mandatory.
- Requires surgery (tympanomastoidectomy, possible ossicular chain reconstruction)
- Long-term follow-up required by otolaryngology

Labyrinthitis

- Extremely rare in children
- Bacterial or viral invasion into the inner ear/cochlear labyrinth; may be associated with permanent hearing loss, vestibular dysfunction, or meningitis

Clinical Presentation

- Vertigo, hearing loss, tinnitus, possible middle ear infection:

  - Labyrinthitis causes vertigo and hearing loss, whereas vestibular neuritis causes vertigo but spares hearing.

Diagnosis
- Clinical presentation, often preceded by an upper respiratory infection (URI)
- Obtain an urgent audiogram (sensorineural hearing loss)

Treatment
- Treat underlying infectious process:
  - Bacterial (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*): systemic antibiotics
  - Viral (cytomegalovirus [CMV], mumps, varicella-zoster virus, rubeola, influenza, parainfluenza, etc.): bed rest and hydration
  - +/− Myringotomy/ventilation tube if acute otitis media is present

Vertigo

Definition
- Illusion of rotational, linear, or tilting movement (i.e., "spinning," "turning") of the patient or their surroundings

Types of Vertigo
- Central/systemic:
  - Vascular (i.e., migraines, autoimmune disorders, stroke); anemia; brain tumor; medications, toxin, and chemotherapy; neurologic disorders (i.e., seizures, multiple sclerosis); metabolic disorders (i.e., thyroid disease, diabetes); anxiety and panic attack
- Peripheral (related to the ear):
  - Benign positional vertigo of childhood (most common), vestibular neuritis due to viral infections (Epstein-Barr virus [EBV] most common), perilymph fistula (abnormal connection between the inner ear and middle ear), trauma to the vestibular system/concussion, Ménière disease, cerebellopontine angle tumors/acoustic neuroma

Physical Exam
- Vital signs
- Head and neck: complete exam, inspection of the middle ear/TM, pneumatic otoscopy
- Neurologic: complete cranial nerve exam, extraocular movements/nystagmus, coordination (finger-to-nose testing), gait, Romberg's test, gross vision testing
- Audiometric evaluation

Treatment
- Varies based on etiology.
- Refer to an otolaryngologist if suspicious of peripheral cause of vertigo; consider neurology referral if suspicious of central cause of vertigo

Benign Paroxysmal Vertigo of Childhood

Definition
- Most common peripheral vestibular disorder, typically self-limiting, can be recurrent
- Distinctly different from benign paroxysmal positional vertigo (BPPV), which is common in adults but not in children

Causes
- Spontaneous, posttraumatic, post-viral
- Thought to be a migraine equivalent

Clinical Presentation
- Brief recurrent episodes of vertigo lasting seconds to less than 1 min
- Can be pale and sweaty, vomits during an episode and then appears back to normal
- No hearing loss or tinnitus

Diagnosis
- Clinical history essential; physical exam and vestibular testing usually normal:
  - Rule out other more sinister causes of vertigo as directed by history and exam.
  - Often a family history of migraines.

Treatment

- Usually self-limiting
- Counsel on risk of typical migraine headaches later in life

Meniere Disease

Background

- Rare in children, but the prevalence ranges from 1.5% to 4% among children diagnosed with vertigo

Clinical Presentation (Triad)

1. Episodic vertigo (minutes to hours)
2. Episodic fluctuating sensorineural hearing loss (typically unilateral)
3. Tinnitus +/− aural fullness in the affected ear

Diagnosis

- Clinical.
- Obtain an audiogram at time when patient reports hearing loss.

Management

- Refer to an otolaryngologist if suspicious of Meniere disease

HEARING LOSS AND AUDIOLOGY

Three Main Types of Hearing Loss

- **Conductive hearing loss** (CHL):
  - Normal bone conduction threshold with abnormal air conduction thresholds
  - Presence of an air-bone gap (ABG)
  - Indicative of a middle ear issue, for example, abnormalities with the tympanic membrane, ossicles, or middle ear space (i.e., effusion; Fig. 18.3)
- **Sensorineural hearing loss** (SNHL):
  - When the air conduction is the same as the bone conduction with both showing abnormal hearing thresholds, this is suggestive of an inner ear issue resulting in sensorineural hearing loss (e.g., damage to cochlear, neural pathways and others)
  - No ABG (Fig. 18.4)
- **Mixed hearing loss** (CHL + SNHL):
  - Presence of conductive hearing loss and sensorineural hearing loss at the same time (Fig. 18.5)

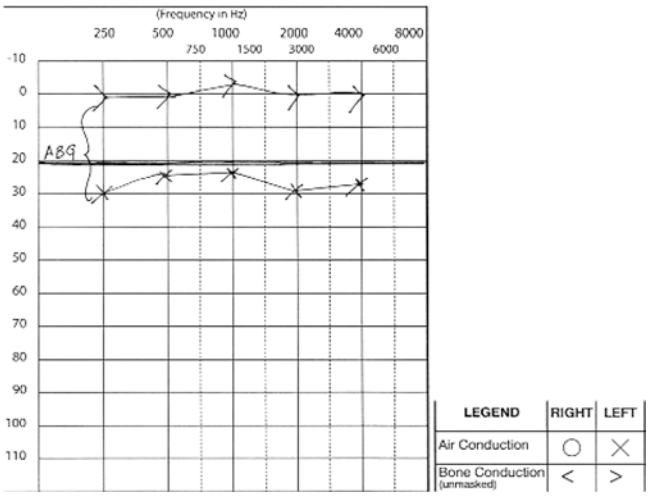


Fig. 18.3 Audiogram of mild conductive hearing loss

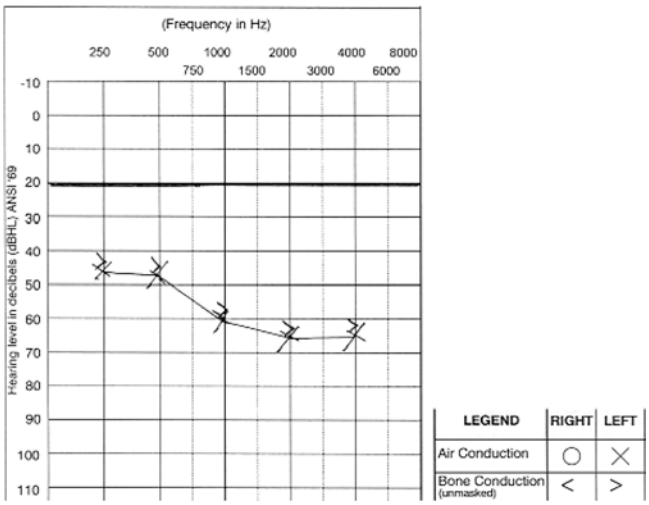


Fig. 18.4 Audiogram of moderate to moderate to severe sensorineural hearing loss

Congenital Hearing Loss

- Congenital hearing loss can be divided into two main categories, environmental and genetic. This is further described in Table 18.1 [6]

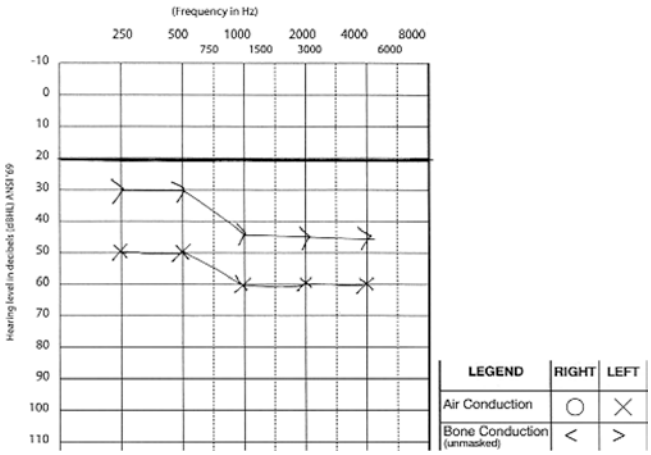


Fig. 18.5 Audiogram of mild to moderate sensorineural hearing loss with ~20 dBs conductive hearing loss

Table 18.1 Causes of congenital hearing loss [6]

50% environmental	Cytomegalovirus (CMV)	
	Neonatal icterus	
	Meningitis	
	Rubella	
	Prematurity	
	Ototoxicity	
	Other infections	
50% genetic	30% syndromic	*Autosomal recessive*:
		Usher syndrome
		Pendred syndrome
		Jervell and Lange-Nielsen syndrome
		Alport syndrome (sometimes X-linked)
		Autosomal dominant:
		Waardenburg syndrome
		Stickler syndrome
		Branchio-oto-renal syndrome
		Treacher Collins syndrome
	70% nonsyndromic	Connexin mutations most common

Genetic Syndromic Hearing Loss

- More than 500 syndromes are associated with hearing loss. The most common are listed as follows:

Autosomal Dominant

- *Waardenburg syndrome*: SNHL, hypertelorism, pigmentary abnormalities
- *Stickler syndrome*: SNHL, ocular abnormalities (myopia, retinal detachment), Marfanoid habitus, Pierre Robin sequence
- *Branchio-oto-renal syndrome*: mixed hearing loss (sensorineural and conductive hearing loss), pinna deformities, preauricular or neck pits/fistulas/tags, kidney abnormalities
- *Treacher Collins syndrome* (mandibulofacial dysostosis): CHL (malformed ossicles), aural atresia/stenosis, zygomatic/mandibular hypoplasia
- *Others:* neurofibromatosis type II, Apert syndrome (acrocephalosyndactyly), Crouzon syndrome (craniofacial dysostosis)

Autosomal Recessive (mnemonic "PUJ")

- Usher syndrome:
  - Leading cause of deafness and blindness
  - SNHL, blindness (retinitis pigmentosa), vestibular dysfunction
- *Pendred syndrome*: SNHL, goiter, enlarged vestibular aqueducts
- *Jervell and Lange-Nielsen syndrome*: SNHL, cardiac defects (prolonged QT), syncope, sudden death

X-Linked

- *Alport syndrome*: X-linked, hearing loss, progressive nephritis, occasional ocular lesions

Genetic Nonsyndromic Hearing Loss

Connexin Mutations

- Most common cause of hereditary nonsyndromic hearing loss.
- Connexin 26 mutations (*GJB2* gene) account for ~80%
- Testing done as part of the workup for bilateral SNHL.

Universal Newborn Hearing Screening

- Implemented across all states in the USA and provinces in Canada.
- Tests hearing with otoacoustic emission (OAE) screening or with an automated auditory

brainstem response (ABR) shortly after birth (usually before the neonate leaves the hospital)
- Any infant who fails the initial screen should be referred to an audiologist for a full evaluation no later than 3 months of age.
- For all children in whom hearing loss is established by full audiologic evaluation, intervention must begin as soon as possible and no later than 6 months of age

Clues to Hearing Loss in a Child Visit
- Speech delay
- Social and behavioral challenges
- A child asking people to repeat themselves, not hearing instructions
- Listening to loud television or music
- Clumsiness—may be a clue to middle ear fluid

Pediatric Audiometric Testing

Evoked Otoacoustic Emission (OAE)
- OAE detects the sound coming from the cochlea in response to clicks or tones.
- OAE affected by external or middle ear debris (high false-positive rate)
- Used for all ages
- No infant cooperation is required.

Auditory Brainstem Response (ABR)
- ABR measures the electroencephalographic waveform response from the vestibulocochlear nerve to higher central nervous system auditory centers.
- ABR minimally affected by external or middle ear debris.
- Can be used at any age.
- Patient must be asleep or very still—may require sedation.
- Often used to confirm abnormal OAE results.

Testing Methods

Behavioral Observation Audiometry (BOA)
- Birth—6 months of age
- Sound presented via speakers. Skilled examiner observes for patient response (i.e., startling or head turning toward sound)
- Grossly assessed auditory thresholds of "better" ear (tests both ears at the same time)

Visual Response Audiometry (VRA)
- Six months to 3 years of age.
- Toddler encouraged to look for auditory stimulus (i.e., lights, toys, motion for reinforcement)
- Each ear may be tested individually—potential to provide complete audiogram

Play Audiometry
- 3 to 5 years of age.
- Child performs tasks in response to auditory stimulus (e.g., "Pick up a block and place it in the bucket when you hear the beep")
- Each ear is tested individually, frequency specific

Conventional Audiometry
- 4 to 6 years of age and older
- Child instructed to push a button or raise a hand when a tone is heard
- Complete audiogram, ear specific, frequency specific

Hearing Loss Classification
- Classified by hearing threshold levels (may vary slightly based on sources):
  - Normal: < 19 dB
  - Mild: 20–40 dB
  - Moderate: 41–55 dB
  - Moderate to severe: 56–70 dB
  - Severe: 71–90 dB
  - Profound: 91 dB

Tympanometry
- Age: all ages except newborn.
- Detects the mobility of TM and external auditory canal volumes.
- Normal canal volumes range between 0.2 and 1.5 ml:
  - Type A
    - Normal peak between −150 and +50 deka pascals

- Type B
  - Flat, no peak
  - Suggestive of:
    - Middle ear effusion (normal to low volumes)
    - Tympanic membrane perforation (high canal volumes)
    - Patent ventilation tube (high canal volumes)
- Type C
  - Peak negatively shifted (< −150)
  - Suggestive of a retracted tympanic membrane or Eustachian tube dysfunction

Patterns of Hearing Loss

Interpreting an Audiogram

- *Y*-axis = hearing level in decibels (dBs) or the "loudness" of sound
- *X*-axis = frequency of sound presented measured in Hertz (low pitch to high pitch)
- "x" = responses from the left air conduction line
- ">" = responses from the left bone conduction line
- ABG = difference between air conduction and bone conduction lines

Common Clinical Scenarios

- Tympanic membrane perforation (Fig. 18.6):
  - Audiometric findings:
    - ABG
    - Flat tympanogram
    - High canal volumes
    - Mild conductive hearing loss
- Middle ear effusion (Fig. 18.7):
  - Audiometric findings:
    - ABG
    - Flat tympanogram
    - Low or normal canal volumes
    - Mild conductive hearing loss
- Ototoxicity (Fig. 18.8):
  - Ototoxic medications cause hearing loss by damaging the hair cells within the cochlea, resulting in sensorineural hearing loss, primarily in the high frequencies.

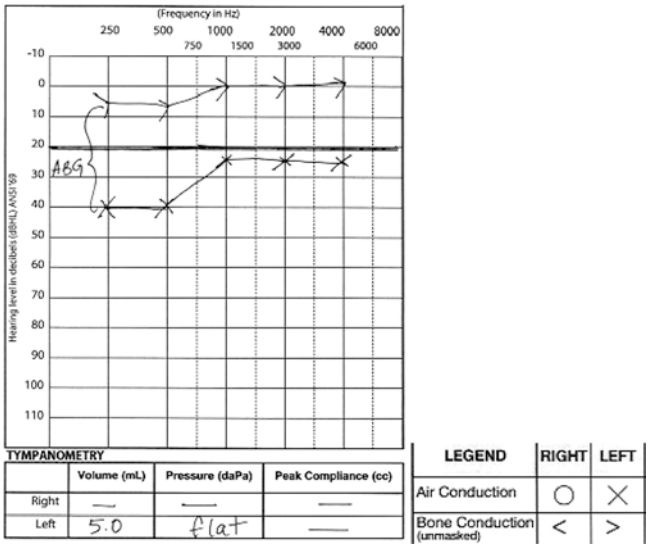


Fig. 18.6 Audiogram of tympanic membrane perforation

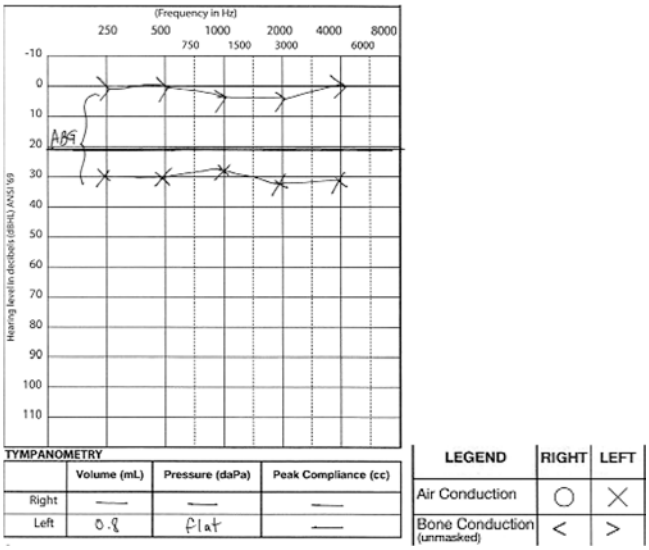


Fig. 18.7 Audiogram of middle ear effusion

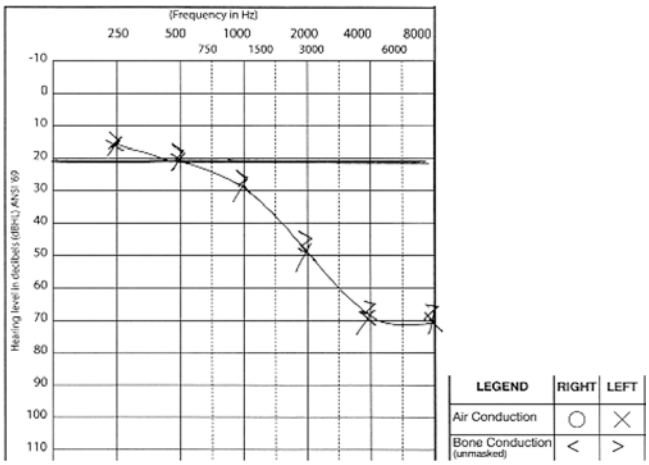


Fig. 18.8 Audiogram of ototoxicity

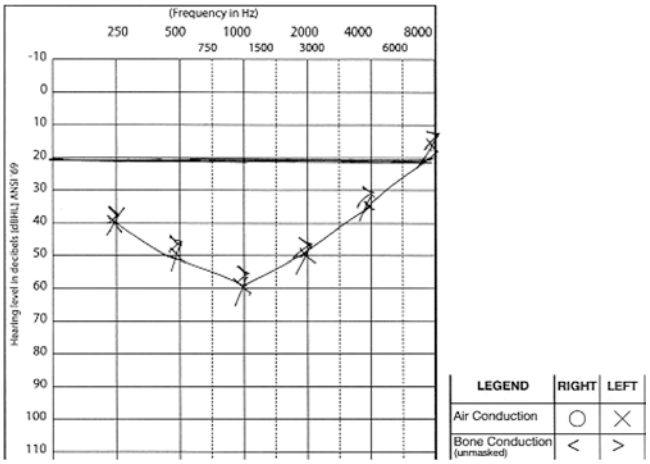


Fig. 18.9 Audiogram of hereditary hearing loss

  - Most commonly caused by cisplatin/carboplatin.
  - Audiometric findings:
    - High-frequency sensorineural hearing loss (moderate to moderate to severe)
    - No ABG
    - Normal tympanogram and volumes (typically)
- Hereditary hearing loss (Fig. 18.9):
  - Cookie bite (U-shape) pattern of sensorineural hearing loss
  - No ABG, normal tympanogram, normal canal volumes

Sound Amplification Devices

- Early identification and intervention is required to maximize hearing and speech development, as well as to achieve developmental milestones.
- Refer to an otolaryngologist when an abnormal hearing screen is identified.
- Hearing interventions are dependent on type and severity of hearing loss.

Hearing Aids

- Non-implantable external hearing device that amplifies frequency-specific sounds.
- Used for unilateral or bilateral CHL, SNHL, and mixed hearing losses.
- Wide variety available, depending on hearing needs and preferences.
- Fitting and programming processes are complex and completed by an audiologist

Bone-Anchored Hearing Aid (Osseo-integrated Auditory Implant)

- Titanium implant surgically placed in mastoid bone behind the ear.
- Sound processor is placed externally on the implant and conducts sounds via bone contact and vibration.
- Primarily used in patients with unilateral or bilateral CHL with congenital ear malformation (i.e., atresia, canal stenosis)

Cochlear Implants

- Convert sound to an electrical signal that stimulates the cochlear nerve.
- External component captures sound and converts it to an electrical signal.
- Internal component delivers frequency-specific electrical signal to the cochlear nerve
- Multiple cochlear implant devices are available, depending on hearing loss pattern and patient preferences
- Cochlear implant criteria are very specific and include a multidisciplinary team (otolaryngologist, speech pathologist, audiologist, social worker, psychologist, etc.)
- In general, indicated for children (US Food and Drug Administration [FDA] approved for 12 months of age or older, though children are often implanted younger than 12 months of age) with pre- or postlingual severe to profound bilateral high-frequency SNHL
- Fitting and programming is a complex process performed by a specialized cochlear implant audiologist and requires multiple audiology visits
- There is increasing evidence regarding the benefits of binaural hearing

NOSE AND NASOPHARYNX

Choanal Atresia

Background

- Congenital obstruction of the choana (posterior nasal aperture—connects the nasal cavity to the nasopharynx):
  - Diagnosis is suspected with the inability to pass a 5F suction catheter through the nose into the nasopharynx
- It may be mixed (60%), bony (30%), or membranous (10%) (CT scan can help to confirm and identify the type of atresia)
- Unilateral or bilateral 2:1 ratio.
- Syndromic association with congenital anomalies is associated with unilateral choanal atresia 50% of the time, and there is a syndromic association 75% of the time if the atresia is bilateral:
  - Can be associated with syndromes (e.g., **c**oloboma of the eye, **h**eart defects, **a**tresia of the nasal choanae, **r**etardation of growth and/or development, **g**enital and/or urinary abnormalities, and **e**ar abnormalities (CHARGE) and deafness, trisomy 21, trisomy 18, Treacher Collins syndrome, Apert syndrome, Crouzon syndrome, velocardiofacial syndrome)

Clinical Presentation

- Bilateral:
  - Severe respiratory distress at birth, cyclical cyanosis—pink with crying, cyanotic when not crying
  - Requires immediate oral airway or intubation; refer to otolaryngology once airway is secured for surgical repair in the first few days of life
  - Patients with bilateral atresia and those with syndromes (e.g., CHARGE) are at greater risk of restenosis
- Unilateral:
  - Identified at birth due to inability to pass 6F catheter or later in childhood with unilateral symptoms of rhinorrhea, decreased nasal patency, or stertor
  - Surgical repair based on symptoms and growth, often around 1 year of age and nearly all before 4 years of age

Epistaxis

Background

- In children, 90% of epistaxis occurs from the anterior septum (Kiesselbach plexus)
- Posterior epistaxis is rare in children and should prompt further evaluation.
- Most common causes: trauma (i.e., nose picking), mucosal irritation and drying, foreign body, and medications (e.g., nasal steroids)

Other Causes

- Tumors, e.g., juvenile nasopharyngeal angiofibroma (occurs in pubescent males), pyogenic granuloma
- Vascular malformation: hemangioma, telangiectasia, Osler-Weber-Rendu syndrome (+ family history)
- Bleeding diathesis: von Willebrand disease, leukemia, liver disease

Management

- Usually self-limiting with application of constant pressure for 5 min by squeezing the sides of the nose shut
- Discourage nose picking/rubbing.
- Avoid mucosal dryness—humidifier in the bedroom; apply small amount of nasal lubricant to the anterior septum
- If severe, it will need IV access and formal nasal packing +/− airway management +/− hemodynamic resuscitation
- Refer to an otolaryngologist if suspicious for a foreign body, tumor, recurrent epistaxis, or severe epistaxis

Nasal Trauma

Background

- Nasal fractures are the most common facial fracture in children (followed by the mandible)
- Most commonly secondary to falls, sporting collisions, motor vehicle accidents.

Presentation

- External nasal deformity, nasal obstruction, epistaxis, anosmia, septal deviation, edema, bruising

Assessment

- Pediatric Advanced Life Support (PALS); rule out injuries to the cervical spine, central nervous system, and chest, orbit/vision problems, midface stability, malocclusion, presence of telecanthus, cerebrospinal fluid leak, etc.
- Nasal x-rays not useful.
- Must evaluate for septal hematoma/abscess.

Clinical Presentation

- Boggy asymmetrical swelling of the nasal septum not responsive to topical vasoconstriction
- Management of nasal hematoma: requires urgent drainage by an otolaryngologist +/− bolster dressing to prevent nasal cartilage necrosis

Management

- If there's cosmetic deformity +/− functional issues (e.g., decreased nasal patency), refer to otolaryngology for reduction of nasal fracture.

SINUSES

Acute Rhinosinusitis

Definitions

- Sinusitis: mucosal inflammation of paranasal sinuses typically caused by a viral illness

Table 18.2 Clinical characteristics of viral vs. bacterial rhinosinusitis

Clinical feature	Viral rhinosinusitis	Bacterial rhinosinusitis
Fever	Absent or occurs early (first 24 h)—low grade, resolves in 2 days	Present, > 39 °C (102 °F) × 3 days, may develop or recur on days 6–7 of illness
Nasal discharge	Peaks on days 3–6 and then improves	Fails to improve or worsens
Cough	Peaks on days 3–6 and then improves	Fails to improve or worsens
Ill-appearance	Absent	If severe or complicated
Severe headache	Absent	If severe or complicated
Clinical course	Peaks on days 3–6 and then improves	> 10 days, without improvement

- Acute bacterial rhinosinusitis (ABRS): sinusitis secondary to bacterial infection
- Acute: < 90 days

Risk Factors

- URI
- Daycare
- Allergic rhinitis
- Anatomic anomalies (e.g., septal deviation)

Presentation

- Congestion, purulent rhinorrhea, tenderness over sinuses:
  - Clinical presentation may be variable based on the pathogen, as described in Table 18.2.
- Virology/microbiology:
  - Viruses: rhinovirus, parainfluenza, influenza, adenovirus
  - Bacteria: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*
  - Risk of antimicrobial resistance [7]:
    - Age < 2 years, daycare antibiotics in the past month, hospitalization within 5 days

Treatment

- Over-the-counter cold medications or decongestants (either systemic or intranasal) are not recommended for children under 12 years of age.

- Supportive therapies: hydration, saline nasal rinses, acetaminophen/ibuprofen.

Treatment of ABRS [8]
- Saline nasal rinses.
- Antibiotics:
  - First line: amoxicillin/clavulanic acid 45 mg/kg divided BID × 10–14 days
  - If at risk of resistance (see above), 90 mg/kg divided BID × 10–14 days
  - Third-generation cephalosporins if there's penicillin hypersensitivity
- Surgery:
  - No role in ABRS, unless there's evidence of complication (i.e., orbital or intracranial)
- Monitor for complications:
  - Orbital
  - Preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, cavernous sinus thrombosis
  - Intracranial
  - Meningitis, epidural abscess, subdural abscess, parenchymal abscess, etc.
  - Osteomyelitis (typically of frontal bones)

Imaging
- CT scan of the sinuses is only indicated for the following:
  - If suspicious for sinusitis complications (e.g., orbital or intracranial)
  - Failure of antibiotic treatment × 48 h
  - Immunocompromised patient
- Findings: opacification of sinuses, mucosal thickening, air-fluid levels
  - Note: These findings are also present with the common cold.

Chronic Sinusitis

Definition
- Persistence of symptoms > 12 weeks.
- Symptoms include nasal congestion, facial pressure, nasal obstruction, rhinorrhea/postnasal drip, and altered sense of smell.

Risk Factors
- Young age (developing immune system), URI, ciliary dysfunction, allergic rhinitis, gastroesophageal reflux disease (GERD), immune deficiency, cystic fibrosis

Microbiology
- Aerobes: *S. pneumoniae*, *M. catarrhalis*, *H. influenzae*, *Staphylococcus aureus*, *Pseudomonas*
- Anaerobes: *Peptococcus*, *Peptostreptococcus*, *Bacteroides*

Diagnosis
- Clinical diagnosis (imaging not required for diagnosis)
- Plain X-ray films are generally NOT helpful.
- CT scan indicated when failed medical management and surgical intervention is being considered.

Treatment
- Medical management:
  - Saline nasal rinses.
  - Antibiotics: amoxicillin-clavulanic acid × 3–4 weeks.
  - Topical nasal steroids.
  - Consider treatment of gastroesophageal reflux disease (GERD) if suspicious.
- Surgical:
  - Only considered if there's failure of long-term medical management.
  - Adenoidectomy is first line of surgery.
  - If symptoms are persistent following adenoidectomy and the patient continues to fail medical management, functional endoscopic sinus surgery (maxillary antrostomy and ethmoidectomy usually sufficient unless clinical symptoms or imaging suggests other sinuses involved) may be considered.
- Ancillary tests:
  - If medical management fails, consider allergy testing if suspicious for allergies.
  - If negative, consider workup for primary immunodeficiency disorder if suspicious.

Frontal Sinus Trauma

- Rare in children, as frontal sinuses begin forming around 6–7 years of age.
- Associated with high-impact injury—must rule out cervical spine injuries and intracranial injury.
- May present with forehead lacerations or swelling, palpable frontal defect, pain, epistaxis, cerebrospinal fluid leak.
- CT scan optimal for identifying fractures, magnetic resonance imaging (MRI) considered in addition to assessing intracranial involvement.
- If frontal sinus fracture is present, consult otolaryngology for further management.
- Conservative or surgical depending on fracture pattern.
- If suspicious for intracranial involvement, consult neurosurgery.

THROAT AND OROPHARYNX

Tonsillitis/Pharyngitis

Etiology

- Infectious (most common), allergy, GERD [9]
- Viral (most common):
  - Rhinovirus, coronavirus, adenovirus, herpes simplex virus (HSV), EBV, coxsackie virus
  - Usually associated with symptoms of cough, sneezing, rhinorrhea, low-grade fever
- Bacterial (streptococci, pneumococci, *H. influenzae*):
  - Bacteria are responsible for 5–10% of pharyngitis.
  - Group A b-hemolytic *Streptococcus* (GABHS)—most common bacterial cause [10]
  - Usually associated with symptoms of high-grade fever, tonsillar/palatal petechiae, exudative tonsils, tender lymphadenopathy; rarely seen with cough or rhinorrhea; most common in children 5–12 years of age.
  - GABHS pharyngitis should be treated to reduce the risk of rheumatic fever and scarlet fever.
  - Other bacterial causes: syphilis, pertussis, gonorrhea, diphtheria, *Fusobacterium*.
  - Untreated *Fusobacterium* infections may lead to Lemierre syndrome: thrombus of the internal jugular vein with potential for septic emboli.

Symptoms

- Sore throat, pain with swallowing, ear pain (referred), malaise, fever, oropharyngeal erythema, cervical lymphadenopathy

Diagnosis

- Based on history and physical exam
- Throat cultures, the diagnostic standard:
  - A positive posttreatment culture represents the asymptomatic chronic carrier state (not a significant source for the spread of GABHS, no treatment needed)
  - If there are recurrent symptoms and persistently positive culture, consider compliance failure, exposure, immunosuppression, and penicillin-resistant organism (consider second-line therapy, such as amoxicillin-clavulanate)
- GABHS rapid antigen test:
  - Sensitivity/specificity: enzyme immunoassay in children, pooled sensitivity estimated at 86% and the pooled specificity estimated to be 92%; for immunochromatographic assay in children, pooled sensitivity estimated at 88% and the pooled specificity estimated to be 86%
  - Throat culture should follow negative rapid antigen test when diagnosis of GABHS infection is strongly suspected.
- Monospot test (EBV)
- Streptococcal antibody titers not recommended

Treatment

- Ensure airway safety.
- Supportive:
  - Hydration, humidity, analgesia
- Antibiotics if bacterial infection is suspected (confirm with cultures):
  - Treatment proposed to decrease symptoms within ~16 h, decreased rates of peritonsillar abscess (PTA) and retropharyngeal abscess.
  - Modified Centor score may be used to help physicians decide which patients need no testing, throat culture/rapid antigen detection testing, or empiric antibiotics.

Peritonsillar Abscess (PTA)

Definition

- Peritonsillar space defined:
  - Space between the palatine tonsil, superior constrictors, and tonsillar pillars

Etiology

- More common in adolescents
- Spread of infection from the tonsil
- Pathogens: aerobes (*Streptococcus pyogenes*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Neisseria* species) and anaerobes

Clinical Presentation

- Sore throat, painful swallowing, uvular deviation to the contralateral side (medialization), trismus, asymmetrical swelling on the soft palate, "hot potato" voice, fevers, referred otalgia.
- Symptoms are typically present for at least 3 days before abscess is formed; double worsening phenomenon is common.

Diagnosis

- History and physical examination.
- CT for atypical cases or if there are concerns for retropharyngeal/parapharyngeal space involvement.

Table 18.3 Clinical features of peritonsillar abscess vs. retropharyngeal space abscess

Retropharyngeal abscess	Peritonsillar abscess
< 6 years old	Adolescent
Fever, throat pain, neck stiffness	Fever, throat pain, trismus
Purulence of retropharyngeal lymph node	Purulence of tonsillar fossa
May need imaging studies	Usually diagnosed clinically

- Clinical features of PTA and retropharyngeal space abscess are outlined in Table 18.3.
- PTA and retropharyngeal abscess can occur concurrently.

Management

- Surgical incision and drainage.
- Antibiotic therapy (penicillin or clindamycin)
- Two or more PTAs may require a future tonsillectomy (bilateral) once infection resolves.
- "Quinsy tonsillectomy"—tonsillectomy at the time of infection may be considered in younger children but is rare in practice secondary to acute inflammation of the tonsils.

Retropharyngeal Abscess

Definition

- Space between pharyngeal constrictors and the alar fascia (skull base to the mediastinum)

Etiology

- Presents most commonly in children
- Spread of infection from the tonsils, sinuses, and/or nasopharynx
- Polymicrobial flora (most commonly *Staphylococcus aureus, Streptococcus* species, and anaerobes)

Clinical Presentation

- Fevers, "hot potato voice," painful swallowing, drooling, decreased neck range of motion (typically limited neck extension), trismus

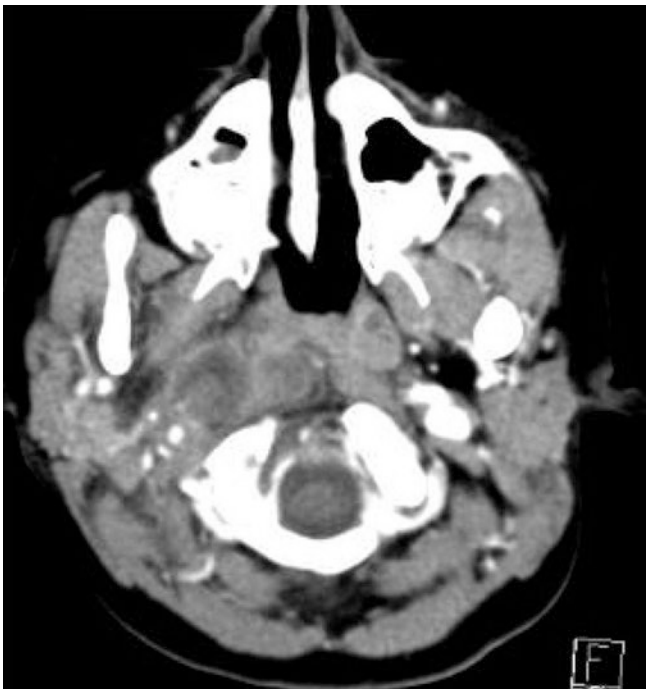


Fig. 18.10 Concurrent peritonsillar abscess on the right and retropharyngeal abscess in a 10-year-old boy as seen on axial computed tomography scan

possible if there's pterygoid inflammation, possible airway compromise/stridor if severe

Diagnosis

- Lateral neck radiograph: abnormally increased thickness of the prevertebral soft tissue (greater than half thickness of the adjacent vertebral body)
- CT scan with contrast useful for localization, extension, phlegmon, or abscess (Fig. 18.10)

Treatment

- Airway management if required and/or ongoing airway monitoring
- Hydration and analgesia
- Antibiotics (may consider third-generation cephalosporin, clindamycin, or ampicillin/sulbactam for first line)
- Surgical drainage indicated for failed medical management, well-defined rim-enhancing abscess, systemic illness, and/or airway compromise

Indication for Tonsillectomy (+/– Adenoidectomy) [11, 12]

Absolute Indications

- Moderate to severe obstructive sleep apnea
- Suspicions of tonsillar malignancy, including posttransplant lymphoid proliferative disorder (PTLD)

Relative Indications

- Mild obstructive sleep apnea
- Recurrent tonsillitis—must meet criteria:
  - Frequency:
    - Seven or more episodes in 1 year
    - Five or more episodes per year for 2 years
    - Three or more episodes per year for 3 years
- Associated with *one or more* of the following:
  - Temperature > 38.3 ° C (101 °F)
  - Cervical lymphadenopathy
  - Tonsillar exudate
  - Positive test for GABHS
- Chronic tonsillitis unresponsive to antimicrobial therapy
- Severe halitosis
- PTA (greater than one episode)
- PFAPA syndrome (periodic fever, aphthous ulcers, pharyngitis, cervical adenitis)
- PANS/PANDAS syndrome: a controversial indication (pediatric acute-onset neuropsychiatric syndrome/pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection)

Indication for Adenoidectomy Alone

- Moderate to severe nasal obstruction with persistent symptoms
- Refractory chronic sinusitis
- Recurrent acute otitis media or otitis media with effusion in a child who had prior tympanostomy tubes that have now extruded (e.g., repeat surgery when indicated would

consist of adenoidectomy plus myringotomy ± insertion of ventilation tube) and is over 4 years of age

Postsurgical Complications of Adenotonsillectomy

- Anesthesia related
- Pain: moderate to severe lasting 7–14 days, requiring analgesia
- Hemorrhage:
  - Bimodal timing
  - < 24 h postoperative: ~< 2%
  - 5 to 7 days postoperative (sloughing of eschar): ~3%
- Dehydration secondary to decreased oral intake
- Halitosis (expected)
- Immediate postoperative airway obstruction (due to anesthesia, analgesia, or sleep apnea)
- Persistence of obstructive sleep apnea
- Velopharyngeal insufficiency (VPI):
  - New onset or worsening of existing VPI.
  - High-risk patients: cleft palate, submucous cleft palate, impaired baseline palatal movement (e.g., neurogenic), very large adenoid pad, velocardiofacial syndrome. Risk is decreased by conservative approach to surgery.

Obstructive Sleep Apnea (OSA) Syndrome

Definition

- Sleep-disordered breathing (SDB): a pathophysiologic continuum that includes snoring, upper airway resistance syndrome, obstructive hypopnea syndrome, and OSA.
- OSA: episodes of complete or partial upper airway obstruction during sleep, often resulting in gas exchange abnormalities and arousals. True OSA results in detrimental clinical sequelae such as failure to thrive, behavior problems, learning problems, and cardiovascular disease.
- Criteria for OSA: clinically relevant symptoms *and* an apnea hypopnea index (AHI) > 1 or hypoventilation (CO_2 > 50 mmHg for > 25% total sleep time) as determined on polysomnogram (PSG)

Etiology

- OSA syndrome affects 2–10% of children; adenotonsillar hypertrophy as a primary driver of OSA is most common between ages 2 and 6 years of age.

Clinical Presentation

- Nocturnal—snoring, mouth breathing, pauses in breathing, enuresis, gasping or choking, restless/awakenings:
  - Children may still have OSA without snoring.
- Daytime: inappropriate sleepiness, inattention/learning problems, hyperactivity/aggression, irritability.
- Children with OSA during infancy are more likely to have a risk factor other than adenotonsillar hypertrophy or obesity, such as craniofacial abnormality, neurologic problems, and genetic syndrome.

Diagnosis

- The American Academy of Pediatrics recommends screening by history (snoring, daytime symptoms) during well-child checks.
- Focused sleep history.
- Physical exam—vitals including blood pressure; craniofacial, oral, nasal, and oropharyngeal exams; growth curve; and BMI should be recorded:
  - Adenotonsillar hypertrophy and obesity are the major causes in otherwise healthy children.
  - Usually there is evidence of large tonsils, but small tonsils may cause symptoms during sleep; adenoids are best visualized by nasal endoscopy.
  - Strongest risk factor for OSA in adolescence is obesity.
  - If there's normal weight and small tonsils/adenoids, otolaryngology will look for more rare causes of obstruction such as

laryngeal masses, lingual tonsillar hypertrophy, macroglossia, abnormal pharyngeal tone, and nasoseptal obstruction.
- PSG—gold standard for definitive diagnosis (also requires presence of clinical symptoms) and can help to inform treatment decisions and counsel caregivers:
  - If there's clinical suspicion without high-risk features (see below), offer PSG rather than referral (otolaryngology, pulmonology, sleep medicine physician)
  - If there are high-risk features, PSG in a facility experienced with children and referral are recommended:
    - Obesity, craniofacial abnormalities, mucopolysaccharidoses, Prader-Willi syndrome, sickle cell disease, Down syndrome, neuromuscular disorders, congenital hypoventilation syndrome, etc.
- Classification based on AHI: mild OSA (1–4.9), moderate OSA (5–9.9), severe (greater than 10)

Treatment
- Tonsillectomy and adenoidectomy—otherwise healthy children with OSA and adenotonsillar hypertrophy:
  - Consideration of clinical symptoms, OSA severity, comorbidities.
  - Obese children may experience weight gain after surgery.
- Supportive care with watchful waiting—mild OSA, mild symptoms, and reevaluation in 6 months:
  - Data based on Childhood Adenotonsillectomy Trial (CHAT) [13]
- Positive airway pressure therapy: minimal anatomic reason for obstruction, poor surgical candidate, need to stabilize/optimize the patient prior to surgery, persistent OSA after tonsillectomy/adenoidectomy
- Rapid maxillary expansion

MOUTH AND ORAL CAVITY

Aphthous Ulcers

- Aphthous ulcer is the most common oral ulcer.

Etiology
- Idiopathic (most common); other causes include immune disorders, infections, hormonal cause, stress, trauma, and nutrition.
- Painful white ulcers on keratinized gingiva surrounded by erythematous border.

Types
- Minor: most common, < 1 cm in diameter, painful, burning/tingling prodrome
- Major: more painful, 1–3 cm in diameter, 1 to 10 ulcers at one time, scarring potential
- Herpetiform: multiple small ulcers (1–3 mm in diameter)
- Sutton's disease: recurrent aphthous ulcers (major type)

Treatment
- Observation (self-limiting course)
- May also consider analgesia, anti-inflammatories, antibiotics if superinfected, and antivirals

Bifid Uvula

- 2% of population (up to 10% in some ethnic groups)
- Clinical presentation ranges from split to duplication.
- May be a marker of submucous cleft palate:
  - Lucency of the midline soft palate, palpable notch of the midline hard palate
  - Associated with speech problems, VPI, dysphagia
- Rarely, may be associated with genetic syndromes:

- Cornelia de Lange syndrome
- Loeys-Dietz syndrome: increased risk of aortic aneurysm

Cold Panniculitis

- Lobular, erythematous, acute eruption in adipose tissue following exposure to cold and subsequent inflammation.
- Cheeks and forehead often affected in infants.
- **Differential:** adiponecrosis subcutanea (subcutaneous fat necrosis of the newborn, cold panniculitis of the newborn), sclerema neonatorum (often fatal, needle-shaped crystals), post-steroid panniculitis, frostbite, and group A streptococcal bacteremia.
- **Diagnosis** is clinical; biopsy if needed will show lobular panniculitis with occasional deposition of mucin.
- **Treatment** is symptomatic, with slow rewarming.

Ankyloglossia

- Abnormally short frenulum limiting effective tongue mobility
- In infants, if severe, may present with suckling difficulties and painful latch (if breastfeeding)
- In older children, may result in speech articulation issues, social mechanical issues (i.e., difficulty in licking an ice-cream cone, keeping teeth clean, playing wind instruments, "French" kissing)
- Surgical intervention indicated for problematic symptoms

Mucocele

- Painless, bluish submucosal lesion appearing on the lower lip (Fig. 18.11)
- Typically secondary to trauma (i.e., biting lower lip)

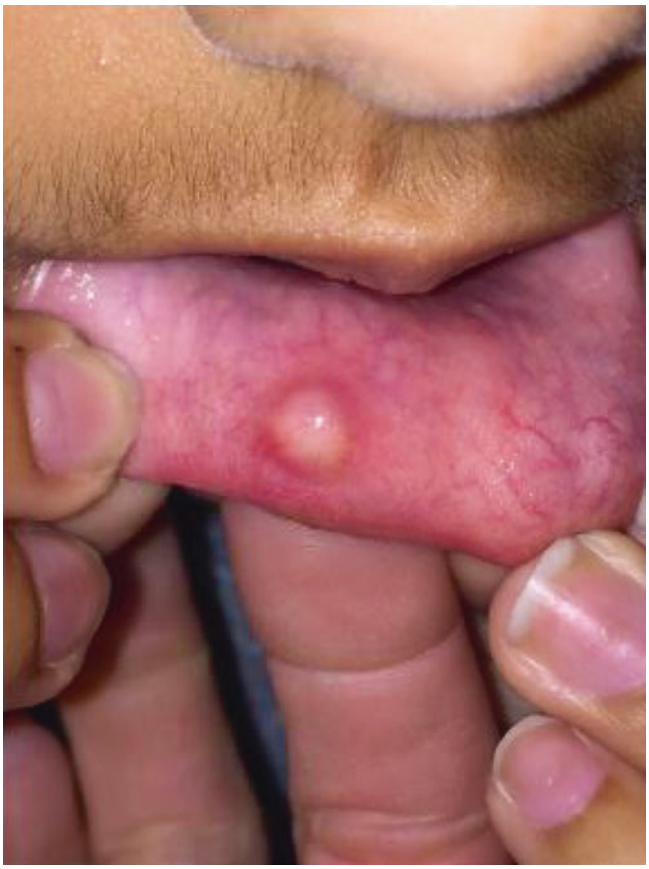


Fig. 18.11 Mucocele of the lower lip

- Can slowly grow in size
- Treatment: observation if not bothersome, surgical excision

Parotitis

Etiology

- Salivary stasis, obstruction (usually unilateral; stone, mass/tumor), retrograde bacterial migration, idiopathic
- Bacteria: *Staphylococcus aureus* (most common), *Streptococcus viridans*, *H. influenzae*, *Streptococcus pyogenes*, *E. coli*
- Viruses (usually bilateral): HIV, mumps, influenza, coxsackie
- Recurrent parotitis of childhood:
  - Unknown etiology
  - Episodes occurring every 1–3 months
  - May alternate sides

  - Typically resolves spontaneously
  - No antibiotic therapy needed unless there's presence of systemic symptoms

Symptoms
- Tender, red, warm parotid gland
- Purulence at Stensen's duct with "milking" of gland

Diagnosis
- History and physical exam
- Cultures of purulent discharge to help guide antibiotic therapy

Treatment
- Conservative: rehydration, warm compresses, parotid massage, sialogogues.
- Antibiotics (based on cultures)
- If there's no improvement with above treatment, consider parotid imaging (CT or ultrasound) for evaluation of abscess, stone, or obstructing lesion.

Cleft Lip and Palate (CLP)

Epidemiology
- Second most common malformation (after clubfoot)
- Cleft lip and palate (CLP): 1/1000 births.
- Cleft palate (CP): 1/2000 births (Fig. 18.12)

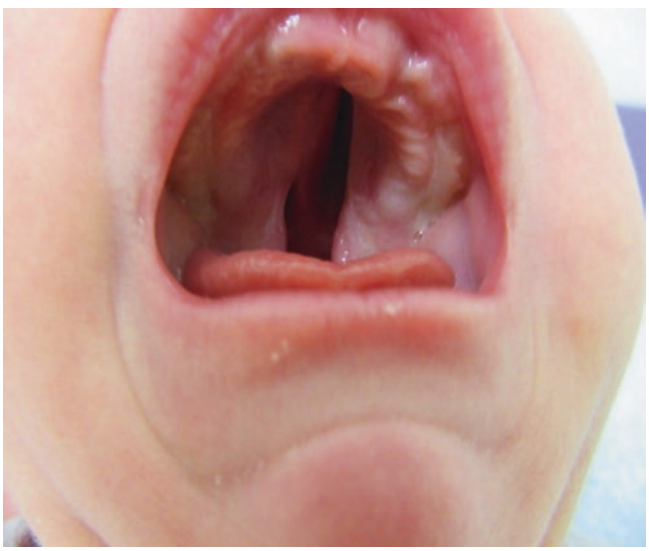


Fig. 18.12 Young patient with cleft palate

- Cleft lips (+/− cleft palate) and isolated cleft palate occur in distinct genetic lines.
- Higher prevalence in Asians and Native Americans.
- Cleft lip (CL): Males > females.
- Isolated cleft palate: Females > males.

Risk Factors
- Teratogens (ethanol, thalidomide)
- Maternal diabetes
- Amniotic band syndrome

Genetic Evaluation
- 8% of isolated cleft palates are associated with a syndrome.
- Over 200 syndromes are associated with CL/CLP, which most commonly include:
  - Stickler syndrome: CP, retinal detachment, cataracts
  - Treacher Collins syndrome: CP, midface hypoplasia, eyelid colobomas, ossicular abnormalities
  - Apert syndrome: CP, acrocephaly, fused digits, stapes fixation

Feeding Difficulties
- Infants experience difficulty with "seal"—often requires specialized nipple (i.e., Mead Johnson crosscut, McGovern's nipples)
- Often require feeding in more upright position with frequent rests and burping.

Otologic Disease
- Increased risk of developing Eustachian tube dysfunction resulting in OME with CP/CLP
- Often requires myringotomy/ventilation tubes

Timing of Surgical Intervention
- CL generally is surgically repaired between the ages of 10 and 12 weeks:
  - "Rule of tens"—10 pounds, 10 weeks old, and hemoglobin of 10.0 g/dL (100.0 g/L)
- CP is usually repaired between 9 and 12 months of age.

For Follow-Up
- Difficulty in feeding and growth
- Recurrent ear infections/possible hearing loss

- Dysfunctional speech and communication (i.e., velopharyngeal dysfunction)
- Dental problems
- Social struggles because of the child's appearance

Robin Sequence (RS)

- Sequence defined as micrognathia, cleft palate, and glossoptosis.
- Occurs in isolation or with associated syndrome (i.e., trisomy 18 or Stickler syndrome)
- Infants with RS are at high risk to develop respiratory distress and potentially have "difficult airways," given their anatomy. These infants require close airway monitoring in the postnatal period.
- Management of respiratory distress in RS:
  - Prone positioning.
  - Place suture at the tip of the tongue and pull the tongue forward.
  - Intubate if needed. If unable to intubate, place a laryngeal mask airway.
  - If patient fails extubation, patient may require:
    - Mandibular distraction
    - Tracheostomy

Delayed Dental Eruption

- Normal range for dental eruption is between 8 and 18 months.
- Delayed dental eruption is considered when teeth fail to erupt within 12 months of "normal range."
- Possible etiologies include hypothyroidism, hypopituitarism, ectodermal dysplasia, and rickets.

Odontogenic Infection

Etiology

- Caries are typically the primary cause of odontogenic infections.
- Polymicrobial:
  - *Streptococcus mutans* (most common cause of initial caries infection)
  - Alpha-hemolytic streptococci
  - Anaerobes (*Peptostreptococcus*, *Bacteroides*, *Fusobacterium*)

Clinical Presentation

- Localized pain, edema, erythema, purulence
- Sensitivity to temperatures and palpation, loose tooth
- Orofacial swelling:
  - Swelling below the jaw (mandibular abscess)
  - Periorbital swelling (maxillary abscess)

Imaging

- Evaluate airway compromise, gas-producing organisms, presence of abscess, and extent of involvement.
- Panorex.
- CT scan.

Treatment

- Remove source of infection (i.e., tooth)
- Analgesia.
- Antibiotics.
- Incision and drainage if an abscess is present.

Early Childhood Caries

Definition

- Caries affecting the primary dentition, especially in the first 3 years of life

Caries Formation

- Chronic infectious disease.
- Pathogenesis: Tooth-adherent bacteria (most commonly *Streptococcus mutans*) metabolize sugars to produce acid that leads to demineralization of the tooth structure.

Risk Factors

- Bottle propping (affects predominantly central incisors)

- Low-income households
- Excessive consumption of sugar
- Genetic factors

Prevention

- Dental visit within the first 6 months of first tooth eruption and no later than 1 year of age.
- Tooth brushing is suggested twice daily with an age-appropriate size of fluoridated toothpaste (discourage swallowing toothpaste to prevent fluorosis)
- Avoid high-frequency consumption of high-sugar liquids/solid foods.
- Recommend weaning from bottle between 12 and 18 months and transitioning to a cup.

Fluoride Supplementation

- Dental fluorosis occurs during the development of the tooth (critical ages between 0 and 6 years of age, with most important being between 15 and 30 months) [14]
- Be aware that access to fluoridated water may be limited in some areas in the USA.
- Optimal water fluoridation is 0.7 ppm of fluoride.
- If there's limited access to fluoridated water, supplementation may be considered, especially for patients between 15 and 30 months of age.

Dental Trauma and Avulsions

Primary Tooth Avulsion

- Refer to the dentist for follow-up to rule out any associated problems.
- Avoid reimplantation of primary avulsed tooth.
- Permanent tooth avulsion (it is a true dental emergency) [15]:
  - Reimplantation of tooth:
    - If reimplanted within 5 min, tooth survival rate is 85–97%
    - If reimplanted after 1 h of injury, tooth is unlikely to survive.
  - Instructions for avulsed permanent tooth:
    - Gently wash the avulsed tooth with no rubbing or brushing.
    - Reimplant the tooth into the socket as soon as possible.
    - If not possible, preserve the tooth in saliva, milk, or normal saline.
    - The goal is to maintain viability of the periodontal ligament fibers.
    - Child should be transported to a dental office or the nearest emergency room.

NECK

Cervical Lymphadenitis

Pathogens

- Viral: EBV (most common virus), CMV, HSV, adenovirus, enterovirus, roseola, rubella, HIV
- Bacterial: group A *Streptococcus* (most common), *Staphylococcus aureus*

Clinical Presentation

- Fevers (typically low grade for viral), malaise, tender and mobile cervical nodes (Fig. 18.13)

Diagnosis

- History and physical examination
- Possible aspiration for culture and sensitivity

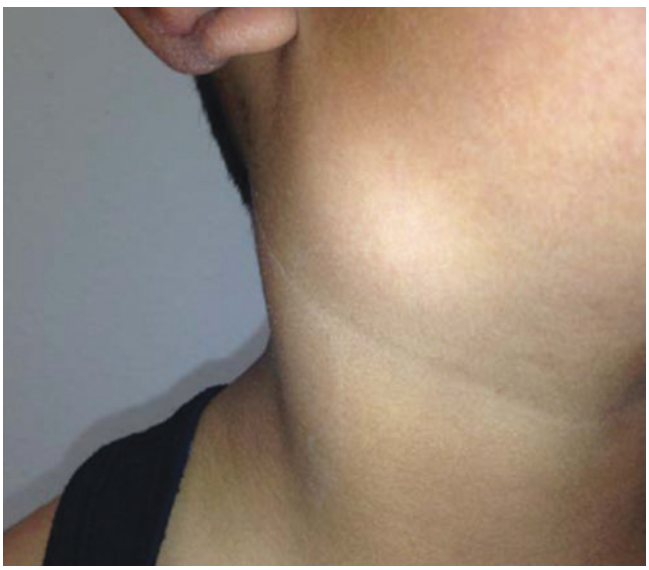


Fig. 18.13 9-year-old boy presenting with a high fever of 104 ° F, malaise, and tender large bacterial cervical lymphadenopathy

Complications
- Cellulitis, abscess, internal jugular vein thrombosis, mediastinitis, sepsis

Treatment
- Viral: supportive
- Bacterial:
  - Antibiotics
  - Incision and drainage if there is an abscess formation

Infectious Mononucleosis

- Caused by EBV

Clinical Presentation
- Fever, pharyngitis, and lymphadenopathy.
- Symmetric cervical adenopathy (most commonly, posterior triangle nodes)
- Axillary and inguinal nodes may also be involved.
- Fatigue, malaise, splenomegaly.

Diagnostic Tests
- Monospot test ("heterophile antibody"):
  - High false-negative rate if obtained early on in illness or in children under 4 years of age
- Elevated immunoglobulin M titer to viral capsid antigen (IgM-VCA) indicates acute infection.

Cat Scratch Disease

- Pathogen: *Bartonella henselae*

Clinical Presentation
- Present ~2 weeks after cat scratch or bite (usually from a kitten)
- Papular lesion at primary scratch site associated with cervical lymphadenopathy (tender initially and then becomes painless)—may ulcerate and form fistula
- Fever (often mild), malaise

Diagnosis
- Serology (IgG henselae titers), culture (Warthin-Starry stain), polymerase chain reaction (PCR) assay, histopathology

Treatment
- Supportive (typically self-limiting)
- Antibiotic therapy in immunocompromised patients
- Surgical aspiration for culture, but avoid formal incision and drainage to prevent fistula/sinus formation

Atypical Mycobacteria
- Pathogen: *Mycobacterium avium* complex, *M. scrofulaceum*, M. kansasii

Risk Factors
- Young children, immunocompromised.
- If patient is less than 1 year old, consider alternative diagnosis such as Langerhans histiocytosis.

Clinical Presentation
- Asymptomatic.
- Unilateral cervical lymphadenopathy, preauricular adenopathy, commonly located on the face over body of mandible.
- Adhesive to overlying skin; overlying skin is erythematous in advanced disease.
- Lesions often described as having "violaceous" coloring.

Diagnosis
- Acid-fast stain, culture (requires 2–4 weeks for results)

Treatment
- Watchful waiting (typically takes months to resolve)
- Excision or incision and curettage (avoid incision and drainage, as fistula can result)

Other Causes, Lymphadenitis

- Tuberculosis: in children, less common than atypical mycobacterium
- Kawasaki disease (mucocutaneous lymph node syndrome):
  - Acute vasculitis affecting multiple organs in children
  - Diagnosis:
    - Must have five of the following:
      - Fever > 5 days (high)—absolute criteria
      - Erythematous rash
      - Conjunctival injection
      - Oropharyngeal changes
      - Peripheral extremity changes (induration or desquamation)
      - Cervical lymphadenopathy
      - Echocardiogram
      - High risk of developing coronary aneurysm or myocardial infarction (consider IVIG and aspirin therapy, along with EKG and echo)

Kikuchi

- Rare disease of unknown etiology
- Presentation: young women, cervical and generalized lymphadenopathy, fever, night sweats, rash, weight loss, nausea, and vomiting
- Diagnosis: lymph node biopsy—histiocytic necrotizing lymphadenitis
- Treatment:
  - No effective treatment, typically resolves within 1–4 months.
  - Symptom control with steroids.
  - Follow-up is necessary, as patients with Kikuchi are at higher risk of developing systemic lupus.

Tularemia

- **Pathogen:** *Francisella tularensis*
- Transmission: contact with infected animal (i.e., rabbits or hamsters)
- Presentation: febrile illness, ulceroglandular syndrome (painful regional lymphadenopathy and an ulcerated skin lesion)
- **Treatment:** streptomycin

Castleman's Disease

- Lymphoproliferative disorder localized to a single node (unicentric) or systemically (multicentric)
- Polyclonal proliferation of B-lymphocytes
- Unicentric:
  - Typically asymptomatic—presents with an enlarged lymph node (20% in the neck)
  - CT scan shows a well-circumscribed mass.
  - Pathology demonstrates nodal expansion.
  - Surgical removal is curative 90% of the time.
- Multicentric:
  - May be associated with HIV, Kaposi sarcoma-associated herpesvirus, and/or human herpesvirus type 8.
  - No standard treatment. May include antivirals, chemotherapy, corticosteroids, and monoclonal antibodies.
  - Refer to oncology.

Lymphoma

- Most common pediatric malignancy of the head and neck.
- Lymphoproliferative disorder.
- Hodgkin and non-Hodgkin lymphoma may present with cervical lymphadenopathy.

Clinical Presentation

- Nodal masses—may present with cervical nodes
- Hodgkin: contiguous lymph nodes
- Non-Hodgkin lymphoma: may present with extranodal involvement (i.e., enlarged tonsils, base of tongue, enlarged thyroid, etc.)
- Constitutional symptoms: fevers, night sweats, weight loss

Diagnosis
- History and physical examination
- Evaluation of all nodal sites
- Open biopsy (rather than fine needle biopsy)—fresh tissue is required for immunochemistry

Management
- If positive for lymphoma, refer to oncology.

Thyroglossal Cyst

Definition
- Failed obliteration of the thyroglossal duct (embryologic tract from the foramen cecum of the tongue to the thyroid)

Clinical Presentation
- Midline neck mass (often cystic, may be solid, mixed, or inflamed)—surrounding the hyoid bone and superior to the thyroid (Fig. 18.14)

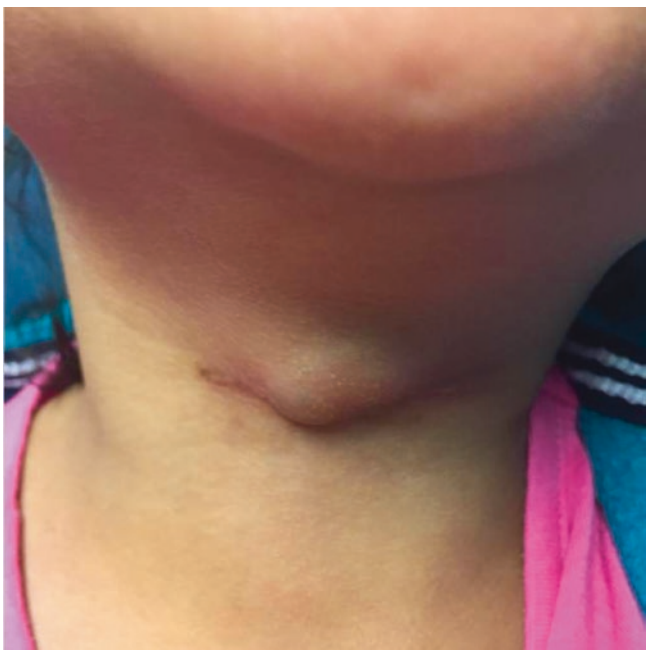


Fig. 18.14 Typical appearance of a neck mass associated with underlying thyroglossal duct cyst. It is important to obtain an ultrasound of the neck to confirm the presence of a normal thyroid gland prior to removal of the thyroglossal duct cyst in order to avoid inadvertent removal of the only thyroid tissue

- Elevates with tongue protrusion (pathognomonic)

Complications
- May become infected
- Rare malignant potential

Treatment
- Treat infection with antibiotics (avoid incision and drainage)
- Surgical removal when not infected (Sistrunk procedure)

Branchial Cleft Cyst

- Alterations of the branchial apparatus resulting in cysts, sinuses, or fistula

Presentation
- Unilateral (most common)
- Anterior, lateral neck mass (typically anterior to sternocleidomastoid muscle), sinus, or fistula
- May become infected with drainage (associated with URI)

Treatment
- Treat infection with antibiotics (avoid incision and drainage)
- Complete surgical excision of cyst, sinus, and fistula tract once infection resolves.

Lymphatic Malformation
- Also known as cystic hygroma and lymphangioma (outdated terms)
- Etiology: abnormal lymphatic development

Presentation
- May occur anywhere in the body
- Soft, painless, multiloculated, compressible mass that transilluminates:
  - In the cervical region, posterior triangle is most common.
- Present at birth or shortly thereafter:
  - Often enlarges after URI

- Associated symptoms related to mass compression of nearby structures

Imaging: MRI preferred
Management
- Observation if small and with no associated complications
- Sclerosing agents
- Surgical excision

Thyroid Carcinoma

Presentation
- Midline anterior mass, may have associated lateral neck masses (lymph nodes):
  - Painless, solid, fixed, asymptomatic mass.
  - Thyroid nodules in children reportedly have a ~25% incidence of malignancy.
  - Neck metastasis is frequently the presenting symptom.
- More common in females (2 to 3 times), adolescents, and those with personal history of autoimmune thyroid disease.
- History should include radiation exposure and family history.
- May be associated with genetic syndromes:
  - Multiple endocrine neoplasia type 2 (MEN2) syndromes: medullary thyroid carcinoma (MTC):
    - MEN2A: MTC, pheochromocytoma, parathyroid adenoma, or hyperplasia
    - MEN2B: MTC, pheochromocytoma, Marfanoid habitus, mucosal neuromas
    - Familial medullary thyroid cancer: MTC only, affects 5–35% of MEN2 families
  - Familial adenomatous polyposis: papillary form, may be in younger age
  - Cowden syndrome (*PTEN* hamartoma tumor syndrome): papillary or follicular form
- Associated symptoms related to mass compression (dysphagia, dyspnea) or invasion of nearby structures (hoarseness) are very rare in children.

Workup
- Ultrasound of the thyroid and neck preferred as initial imaging, often with fine needle aspiration (plus molecular studies) of thyroid mass
- Thyroid function tests and thyroid antibody studies (in consultation with endocrinology)
- Complete metabolic panel (including calcium)
- Chest radiograph (lung metastasis, most common site of distant disease)

Pathology
- Papillary (most common), follicular, medullary, anaplastic

Management
- Multidisciplinary care team referral (endocrinology, genetics, otolaryngology/pediatric surgery)
- Treatment is surgical, with additional therapy pending the pathology results and patient factors.

Acute Laryngitis

Etiology
- Infectious (most commonly viral, may have secondary bacterial infection)
- Fungal infection (immunocompromised child, steroid inhaler use)
- Vocal strain (secondary to screaming/yelling)

Management
- Generally self-limiting.
- Optimize hydration.
- Humidification.
- Saltwater gargles.
- Treat with antibiotics or antifungals if bacterial or fungal infection is suspected.
- Referral to otolaryngology if it persists > 4 weeks.

Chronic Laryngitis/Hoarseness

- Definition: symptoms of hoarseness, dysphonia, and/or vocal fatigue for > 3 months
- Associated symptoms: chronic cough, frequent throat clearing, postnasal drip sensation

Etiology
- Typically noninfectious causes (most common vocal fold screamers' nodules)
- Gastroesophageal reflux disease/laryngopharyngeal reflux disease
- Recurrent respiratory papillomatosis (caused by HPV 6 and HPV 11)
- Environmental irritants (second-hand smoke, vape, huffing)
- Environmental allergies
- Postnasal drip/rhinitis
- Medications (e.g., inhaled steroids, chemotherapy, anti-cholinergic medications)
- Rarely, chronic systemic disease (e.g., amyloid, granulomatosis with polyangiitis), lymphovascular malformation, or malignancy

Diagnosis
- ENT referral for flexible nasolaryngoscopy

Management
- Treat underlying cause.
- Empiric treatment of GERD/ laryngopharyngeal reflux (LR) is often considered if clinical history is suggestive.

Vocal Fold Paralysis

Background
- One of the most common laryngeal abnormalities in childhood
- Unilateral or bilateral paralysis of the vocal fold
- Congenital or acquired

Etiology
- Iatrogenic (most common in pediatric patients): patent ductus arteriosus ligation, cardiothoracic surgery, tracheoesophageal fistula repair, thyroidectomy
- Idiopathic (most common in newborns/ infants)
- Neurologic (e.g., Arnold-Chiari malformation, posterior fossa tumor)
- Viral
- Autoimmune
- Pulmonary lesion or cor pulmonale (Ortner's syndrome)

Diagnosis
- Refer to ENT for flexible laryngoscope, which will assess for vocal fold mobility, mucosal lesions, and laryngeal masses.

Workup of Vocal Fold Paralysis
- Observation (if known iatrogenic cause)
- Chest radiograph
- Modified barium swallow (to assess for aspiration)
- MRI brain
- CT for the neck and chest

Treatment
- Observation:
  - Monitor for signs of aspiration or respiratory distress.
  - Monitor for signs of recovery.
- Surgery:
  - Tracheostomy (bilateral)
  - Vocal fold surgery
  - Hypoglossal to recurrent laryngeal nerve reanastomosis

Stridor

- Noisy breathing, which often implies turbulent airflow through an extrathoracic airway obstruction

- Stertor: Distinct from stridor. Stertor is more often a muffled, congested upper airway noise emanating from the nose, nasopharynx, or oropharynx.

Etiology

- Inspiratory: most often above the level of the vocal folds
- Expiratory: most often in the trachea
- Biphasic: most often at the level of the vocal folds (glottis) or the subglottis

Differential Diagnosis

- Acute—most often of infectious or inflammatory cause: number 1, croup (parainfluenza virus); influenza virus type A or B, RSV, rhinovirus, epiglottitis, bacterial tracheitis, angioedema, foreign body
- Chronic—most often of an anatomic cause: number 1, laryngomalacia; vocal fold immobility (unilateral or bilateral), vascular ring, tracheomalacia, papilloma, subglottic stenosis, laryngeal web, tracheal stenosis, subglottic hemangioma

Diagnosis

- History: Symptoms related to positioning, feeding; apparent life-threatening events (ALTEs)/brief, resolved, unexplained events (BRUEs), cyanotic episodes, crying/agitation, and trajectory are especially important.
- Physical exam: vitals including pulse oximetry, growth curve, complete head and neck evaluation; cardiopulmonary evaluation including inspection for retractions, abdominal breathing, respiratory distress.
- ENT referral for flexible nasolaryngoscopy and further evaluation.
- If pathology is thought to be below the level of the vocal folds (e.g., subglottic stenosis), operative laryngoscopy and bronchoscopy are also needed to evaluate the airway.
- If there's suspicion of vascular ring, refer to cardiology and consider of CT angiography of the chest.

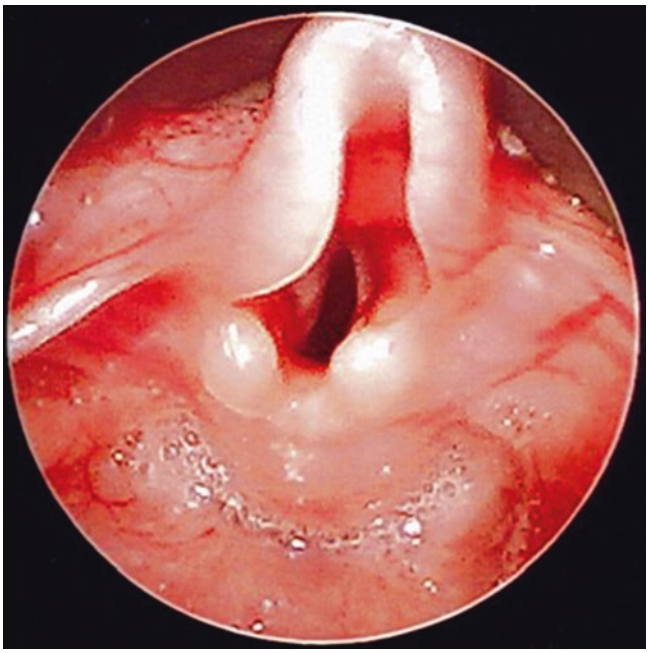


Fig. 18.15 Mild to moderate laryngomalacia as evidenced by tubular ("omega-shaped") epiglottis, knobby, or bulky arytenoid cartilages and tight aryepiglottic folds

Management

- Treat underlying cause.
- Empiric treatment of GERD/LPR often considered if clinical history is suggestive.

Laryngomalacia

- Collapse of the supraglottic airway (epiglottis, arytenoid cartilages, or both) during inspiration secondary to immature framework (Fig. 18.15)
- Most common congenital lesion of the larynx.
- High-pitched inspiratory stridor usually begins around 4–6 weeks, peaks around 6–8 months, and resolves by 24 months of age.
- Higher incidence of GERD

Symptoms

- Stridor, feeding difficulty, sleeping difficulty, need for frequent repositioning (increased when supine), increased work of breathing/retractions, failure to thrive, cyanotic episodes (rare); may worsen in the setting of URI

Management

- 90% of patients treated with conservative management and time; referral to ENT for flexible nasolaryngoscopy and consideration of surgical management (airway evaluation, possible supraglottoplasty) if symptoms are moderate/severe
- Surgery considered for failure to thrive, hypoxemia, severe retractions, sleep apnea

PEARLS AND PITFALLS

- Otalgia is an expected phenomenon for up to 2 weeks following tonsillectomy.
- Hematoma of the external ear (pinna) necessitates same-day referral for emergency care because of the potential for permanent deformity secondary to avascular necrosis of the cartilage.
- First-line therapy for AOM is amoxicillin (90 mg/kg/day divided twice a day) × 10 days.
- Caregivers should be instructed to warm ear drops in their hands prior to administration to decrease patient discomfort.
- Patients with benign paroxysmal vertigo of childhood are at increased risk of typical migraine headache as adolescents and adults.
- CHARGE is the most commonly associated congenital anomaly with choanal atresia.
- In children, 90% of epistaxis occurs from the anterior septum (Kiesselbach plexus), and the most frequent cause is digital trauma.
- Nasal fractures are the most common facial fracture in children.
- Presence of nasal polyps in children should prompt testing for cystic fibrosis.
- Nasal saline rinses should be used with caution in children with history of aspiration.
- The most common cause of a neck mass in the pediatric population is cervical lymphadenitis.
- If there is clinical suspicion for lymphoma, systemic steroids should be avoided, as these may interfere with flow cytometry results.
- Midline neck mass is most likely a thyroglossal duct cyst secondary to the embryologic derivative at the base of the tongue (foramen cecum). Ultrasound should be performed to confirm the presence of a normal thyroid in its expected location.
- The most common congenital lesion of the larynx is laryngomalacia; most children will outgrow the diagnosis by 24 months of age.
- Cough, rhinorrhea, and diarrhea are more common with viral than with bacterial pharyngitis.
- The diagnostic gold standard for bacterial pharyngitis is a throat culture.
- Diagnosis of PTA is a clinical diagnosis based on history (double worsening, URI symptoms > 5 days prior to new symptoms) and physical exam (hot potato voice, trismus, uvular deviation)
- The American Academy of Pediatrics recommends screening for OSA by history (snoring, daytime symptoms) during well-child checks. Symptoms may include irritability, hyperactivity, daytime sleepiness, and nocturnal enuresis; this is a different constellation of symptoms than in adult patients.
- Ankyloglossia often manifests as discomfort in the mother's nipples.
- Children with cleft palate are at an increased risk of developing Eustachian tube dysfunction resulting in OME and recurrent AOM.
- Eruption cysts present as blue or purple compressible cysts at the site of an erupting deciduous or permanent tooth. These are often self-limiting but may require treatment if they become infected or limit feeding.

Acknowledgement The authors gratefully acknowledge the contributions of Josee Paradis, MD, Paediatric Surgery, London Health Sciences Centre—Victoria Hospital, London, Ontario, Canada, to the first edition of this chapter, many of which have been incorporated into this edition as well.

References

1. Wang RY, Earl DL, Ruder R, Graham JM Jr. Syndromic ear anomalies and renal ultrasounds. Pediatrics. 2001;108(2):E32.
2. Uhari M, Mantysaari K, Niemela M. A meta-analytic review of the risk factors for acute otitis media. Clin Infect Dis. 1996;22(6):1079.
3. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–99. *Erratum* Pediatrics. 2014;133(2):346. Dosage error in article text.
4. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: otitis media with effusion (update). Otolaryngol Head Neck Surg. 2016;154(1 Suppl):S1–S41.
5. Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg. 2013;149(1 Suppl):S1–S35.
6. Alford RL, Arnos KS, Fox M, Lin JW, Palmer CG, Pandya A, ACMG Working Group on Update of Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss; Professional Practice and Guidelines Committee, et al. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. Genet Med. 2014;16(4):347–55.
7. Wald ER, Applegate KE, Bordley C, Darrow DH, Glode MP, Marcy SM, American Academy of Pediatrics, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013;132(1):e262–80.
8. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al. Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–e112.
9. Choby BA. Diagnosis and treatment of streptococcal pharyngitis. Am Fam Physician. 2009;79(5):383–90.
10. Stewart EH, Davis B, Clemans-Taylor BL, Littenberg B, Estrada CA, Centor RM. Rapid antigen group a streptococcus test to diagnose pharyngitis: a systematic review and meta-analysis. PLoS One. 2014;9(11):e111727.
11. Baugh RF, Archer SM, Mitchell RB, Rosenfeld RM, Amin R, Burns JJ, American Academy of Otolaryngology-Head and Neck Surgery Foundation, et al. Clinical practice guideline: tonsillectomy in children. Otolaryngol Head Neck Surg. 2011;144(1 Suppl):S1–30.
12. Ramos SD, Mukerji S, Pine HS. Tonsillectomy and adenoidectomy. Pediatr Clin N Am. 2013;60(4):793–807.
13. Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, Childhood Adenotonsillectomy Trial (CHAT), et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med. 2013;368(25):2366–76.
14. Hong L, Levy SM, Broffitt B, Warren JJ, Kanellis MJ, Wefel JS, Dawson DV. Timing of fluoride intake in relation to development of fluorosis on maxillary central incisors. Community Dent Oral Epidemiol. 2006;34(4):299–309.
15. Andersson L, Andreasen JO, Day P, Heithersay G, Trope M, Diangelis AJ, et al. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: avulsion of permanent teeth. Dental Traumatol. 2012;28(2):88–96.

Cardiology

19

Grace Kung, Allison Hill, and Jennifer Su

CHEST PAIN

Background

- Chest pain in children is rarely due to cardiac disease
- The history and physical examination can establish the diagnosis of noncardiac chest pain in the majority of cases
- 20% to 45% of cases of pediatric chest pain are idiopathic

Red Flags for Cardiac Chest Pain

- **History**
  - Exertional symptoms (chest pain, syncope, fatigue)
  - Pain associated with palpitations or fever
  - Pain that radiates to the back, jaw, and left arm/shoulder or increases when supine
  - Cocaine/amphetamine use
  - Family history of sudden unexplained death, cardiomyopathy, or inherited arrhythmias such as long QT syndrome
- **Abnormal cardiac exam**
  - Ill-appearing
  - Tachycardia
  - Narrow pulse pressure
  - Hypotension
  - Pulsus paradoxus (PP)
  - Distant heart sounds or pericardial friction rub
  - Murmur:
    - Harsh systolic ejection murmur
    - Pansystolic murmur
    - Continuous murmur
  - Gallop rhythm
  - Peripheral edema

Cardiac Disorders Associated with Chest Pain

- Coronary artery diseases (ischemia or infarction)
  - History of Kawasaki disease (coronary arteritis)
  - History of transposition of great arteries s/p arterial switch
  - Anomalous origin of the coronary arteries
  - Coronary artery fistula
  - Cocaine abuse
  - Coronary calcinosis
  - Takayasu arteritis
- Infections/autoimmune disorders
  - Pericarditis
  - Myocarditis
  - Systemic lupus erythematosus, juvenile rheumatoid arthritis
- Arrhythmias
  - Supraventricular tachycardia (SVT)
  - Ventricular tachycardia
- Other cardiac abnormalities
  - Aortic stenosis

G. Kung (✉) · A. Hill · J. Su
Division of Cardiology, Department of Pediatrics, Children's Hospital of Los Angeles, USC Keck School of Medicine, Los Angeles, CA, USA
e-mail: gkung@chla.usc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_19

  - Aortic dissection (collagen vascular disease such as Marfan syndrome)
  - Hypertrophic cardiomyopathy (HCM)
  - Pulmonary hypertension
  - Severe pulmonary stenosis

Noncardiac Causes of Chest Pain

- Musculoskeletal causes of chest pain: one of the most common diagnoses in children who have chest pain:
  - Costochondritis
  - Strained chest wall muscles following coughing, exercise, sports participation, or carrying heavy books or backpack
  - Direct trauma causing sternal or rib contusion or rib fracture
- **Clinical presentation:**
  - Chest wall tenderness with palpation.
  - History of trauma.
  - Pain may be pleuritic, bilateral, sharp, and exaggerated by physical activity.
  - Pain may persist for several months.
  - Quality of pain is unchanged with exertion.

Respiratory Causes of Chest Pain

- Asthma
- Pneumonia
- Pulmonary embolism:
  - History of oral contraceptive use
  - Hypercoagulable state
- Pneumothorax:
  - Marfan syndrome
- Pleural effusion/hemothorax
- **Clinical presentation:**
  - Tachypnea
  - Dyspnea
  - Hypoxia
  - Fever
  - Pleuritic pain
  - Cough
  - Hemoptysis

Gastrointestinal Causes of Chest Pain

- Recent foreign body ingestion
- Reflux esophagitis
- **Clinical presentation:**
  - Burning, substernal in location
  - Worsened by reclining or eating spicy foods
  - Pain related to meals

Psychogenic Causes of Chest Pain

- Anxiety
- Stress

Miscellaneous Causes of Chest Pain

- Sickle cell disease may lead to vaso-occlusive crises or acute chest syndrome.
- Shingles may result in severe chest pain.

Clinical Approach to Chest Pain

- **Comprehensive history:**
  - Characteristics of the pain:
    - Frequency, location, quality, and severity of the pain
    - Timing: daily activity, sleep, exercise
  - Associated symptoms: exercise intolerance, fatigue, palpitations, shortness of breath, dizziness, or syncope
  - Family history for heritable diseases affecting the heart or lungs, i.e., sudden death, deafness, seizures, cardiomyopathy, or asthma
  - A prior history of structural or acquired heart disease
  - Prior history of cardiac surgery
  - Medication or drug use
- **Physical examination:**
  - Vital signs
  - Signs of heart failure or congestion

  - Abnormal cardiac findings
  - Chest wall palpation
- **Electrocardiogram (ECG):**
  - Further testing as indicated: echocardiogram, exercise stress testing, 24 h Holter monitor, pulmonary function testing, blood tests, chest radiography (CXR), toxicology screen

SYNCOPE

Background

- Syncope is a temporary loss of consciousness that may be due to cerebral hypoperfusion or neurologic disorders.
- Anoxic seizures may rarely occur.

Causes of Syncope

- Vasovagal/neurocardiogenic: impaired response of the autonomic nervous system.
- The most common form of syncope in children.
- Mechanism is an exaggerated reflex in vasomotor tone and heart rate causing vasodilation, hypotension, and bradycardia.
- Clinical presentation:
  - Triggers:
    - Standing from a supine/seated position.
    - Prolonged standing.
    - Dehydration/heat.
    - Urination (micturition syncope).
    - Hairbrushing.
    - Intense emotion or pain (blood draw).
    - Pregnancy.
  - Prodrome (lightheadedness, dizziness, weakness, pallor, nausea, cold sweat, blurred vision, or hearing loss) precedes syncope.
  - Relief from all symptoms usually occurs if the patient lies down during prodrome.
  - Brief period of unconsciousness.
  - Normal physical examination ± orthostatic hypotension.
- Cardiac disorders:
  - Hypertrophic obstructive cardiomyopathy
  - Aortic stenosis
  - Pulmonary hypertension
  - Coronary artery anomalies
  - Myocarditis
  - Arrhythmias
  - Sinus node dysfunction
  - Complete heart block
  - Rapidly conducting supraventricular tachycardia
  - Ventricular tachycardia (*torsades de pointes*) or fibrillation
- Noncardiac mechanisms: breath-holding spells, hyperventilation, heat stroke, hypoglycemia, anaphylaxis, intoxication.
- Conditions that mimic syncope: migraines, seizures, narcolepsy, or psychological disorders.

Initial Evaluation

- History (including preceding events, description of the event, past history, family history)
- Physical exam: vitals, including orthostatic vital signs
- ECG
- Red flags for cardiac syncope:
  - No prodrome
  - Sudden onset of palpitations, shortness of breath, or chest pain before syncope
  - Syncope during exertion, swimming, or supine
  - Episode brought on by sudden startle
  - Exercise intolerance and fatigue
  - Young age, < 10 years (especially less than 6 years)
  - Previous heart disease
  - Family history of cardiomyopathy, channelopathy, or sudden death in a close relative < 50 years old
  - Abnormal physical examination
  - Abnormal ECG

Further Evaluation

- 24-hour Holter or 30-day event monitoring if history suggests arrhythmia
- Echocardiogram if physical examination or ECG is abnormal or if family history is concerning

Treatment of Vasovagal Syncope

- Increase fluid and salt intake—results in no further episodes in 90% patients.
- Postural awareness; avoid venous pooling.
- Fludrocortisone.
- Midodrine
- Beta-blockers

CARDIAC ARRHYTHMIAS (FIGS. 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 19.10, 19.11, AND 19.12)

Background

- Although most childhood arrhythmias are benign, prompt and correct diagnosis of a serious rhythm disturbance in a child can be lifesaving.
- Key history for arrhythmias:
  – Initiation/termination of tachycardia:

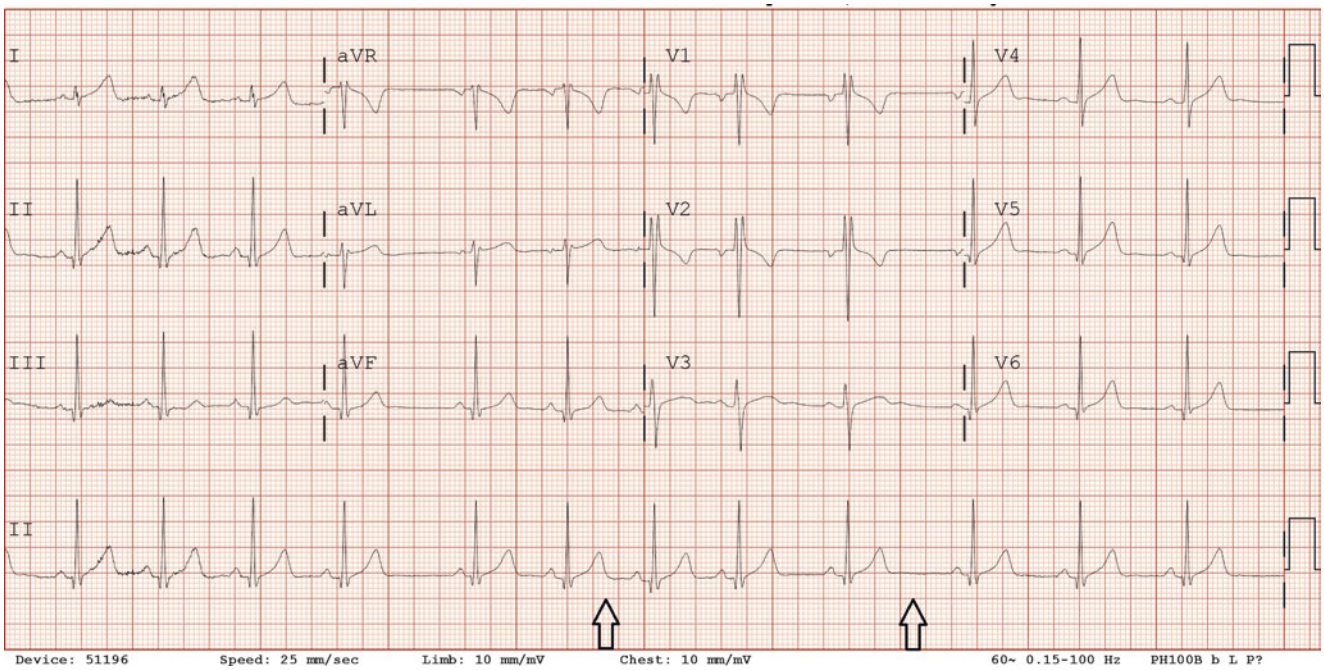


Fig. 19.1 13-year-old child with sinus arrhythmia. *Arrows* show the acceleration and deceleration of heart rate

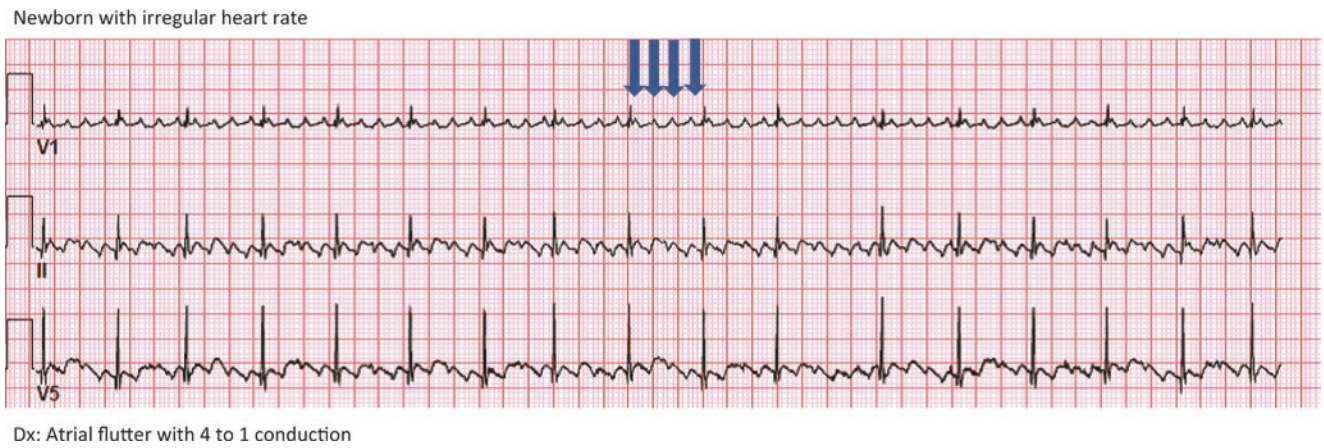
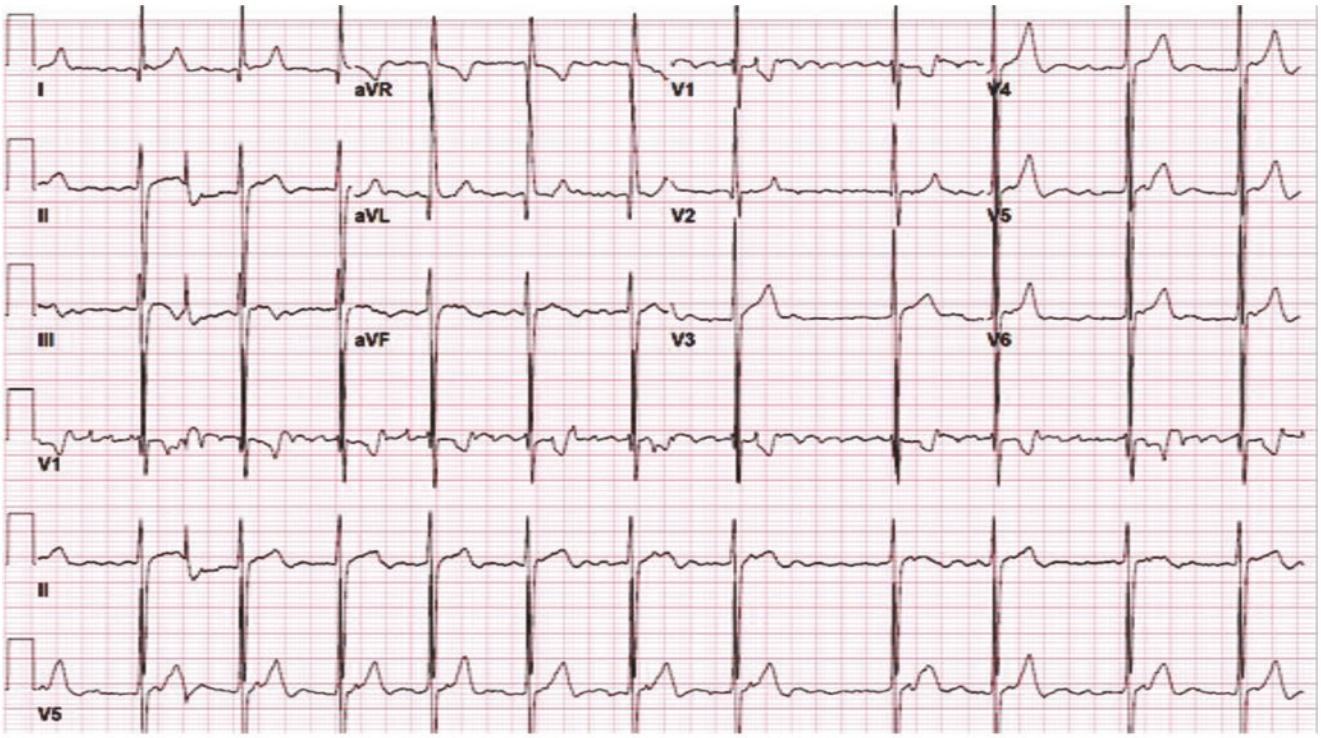
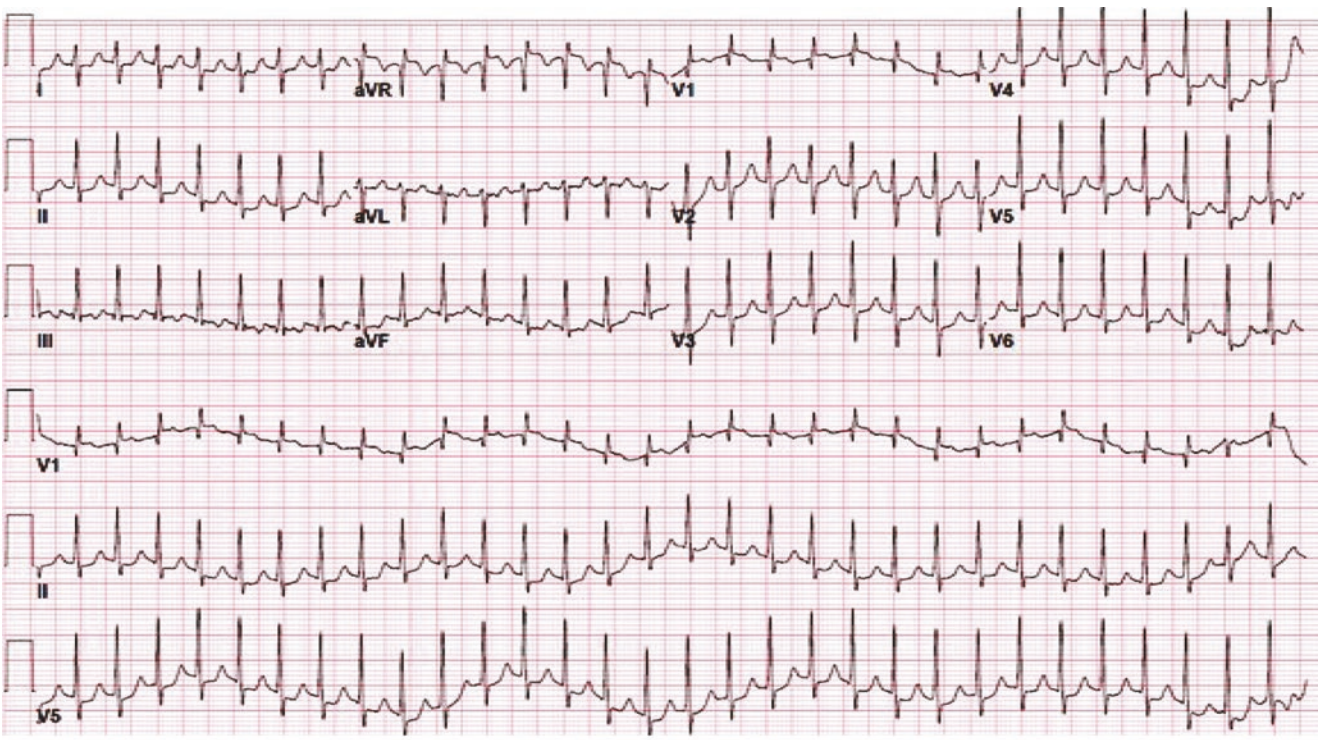


Fig. 19.2 Newborn with irregular heart rate. Diagnosis: atrial flutter with 4:1 conduction



Dx: Atrial fibrillation (irregularly irregular with no clear P wave)

Fig. 19.3 15-year-old child with atrial septal defect. Diagnosis: atrial fibrillation (irregularly irregular with no clear P-wave)



Dx: Supraventricular tachycardia (Narrow complex tachycardia regular)

Fig. 19.4 12-year-old child with palpitations. Diagnosis: supraventricular tachycardia (regular narrow complex tachycardia)

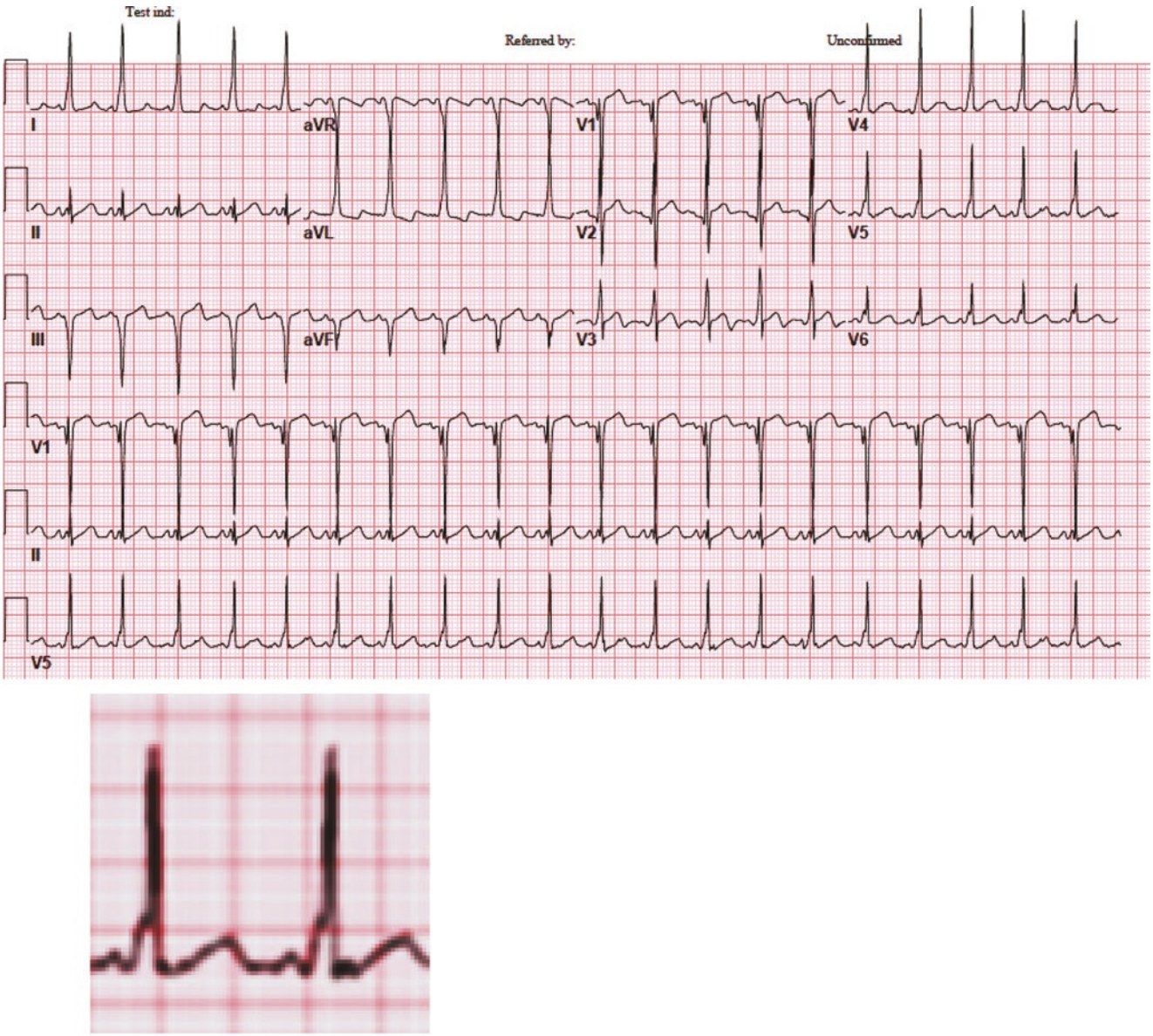


Fig. 19.5 8-year-old boy with palpitation. Diagnosis: Wolff-Parkinson-White syndrome (short PR with delta wave)

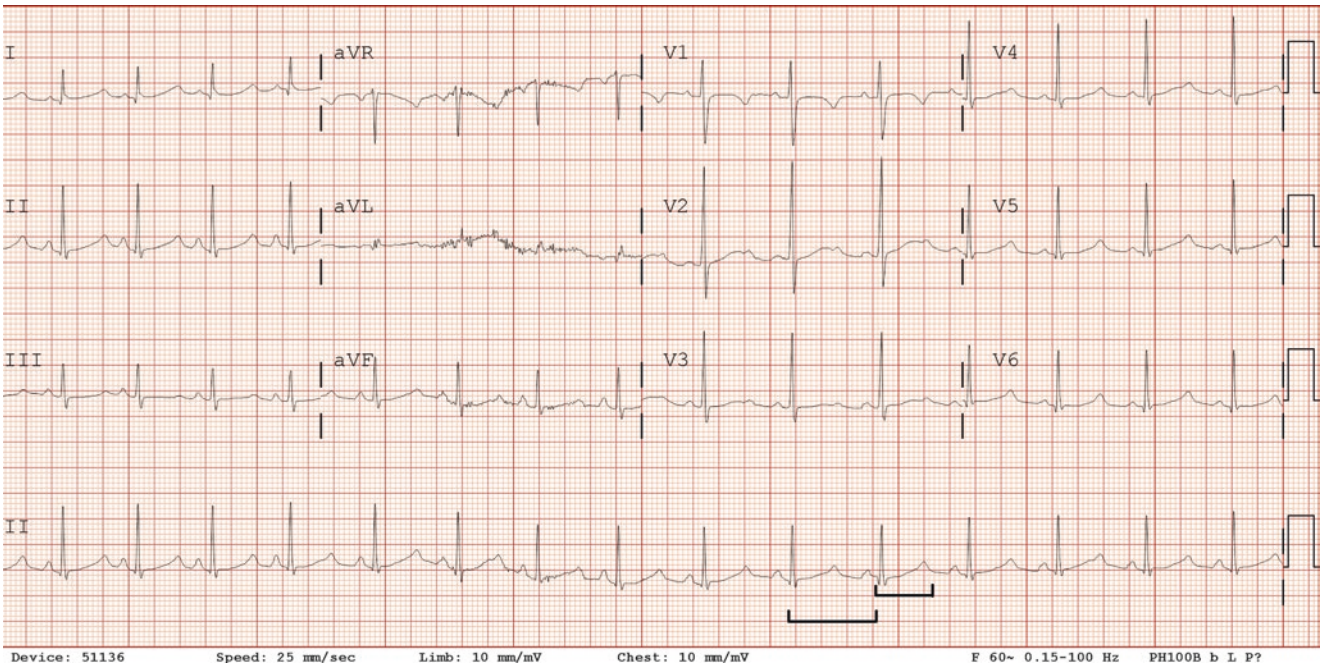


Fig. 19.6 11-year-old with long QT syndrome. *Brackets* point out the RR and QT intervals used to calculate the prolonged QTc

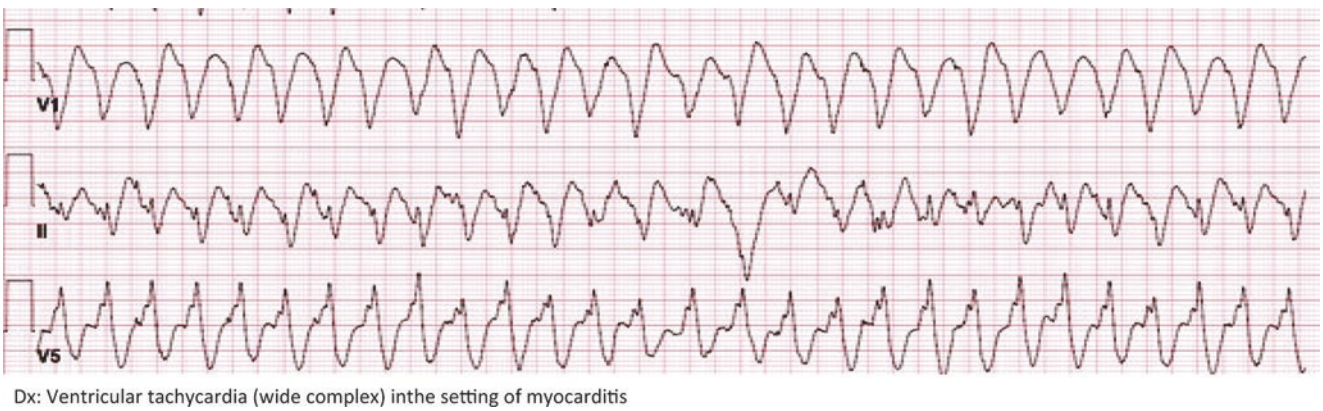


Fig. 19.7 6-year-old child presented with difficulty in breathing. Diagnosis: ventricular tachycardia (wide complex) in the setting of myocarditis

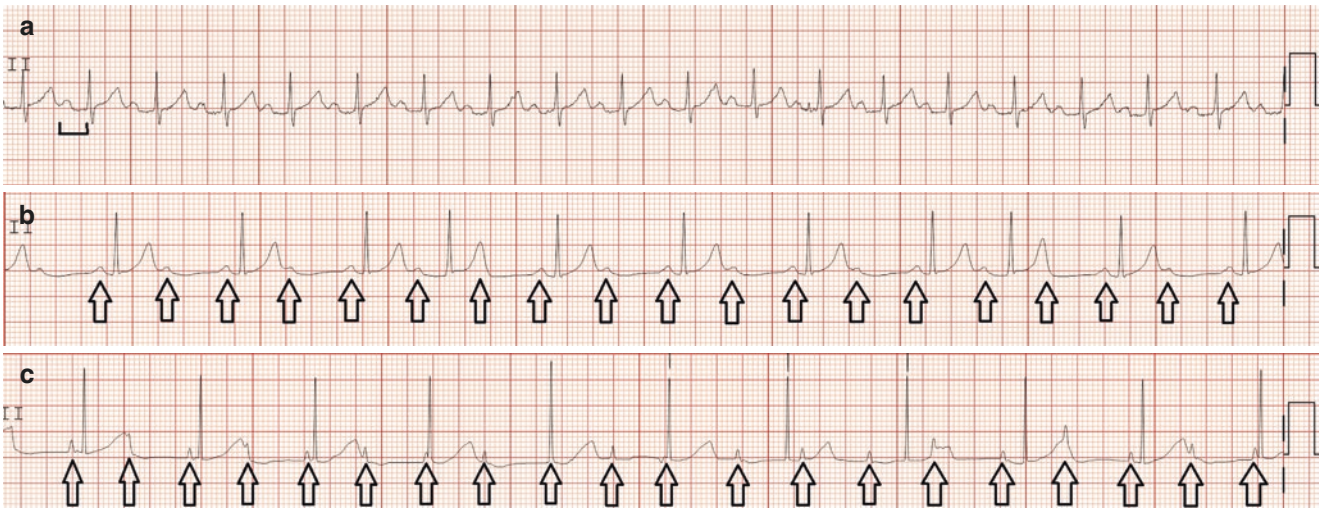


Fig. 19.8 Rhythm strips demonstrating (**a**) first-degree atrioventricular (AV) block (prolonged PR interval shown with a *bracket*), (**b**) Wenckebach conduction (progressive PR prolongation prior to dropped QRS) with *arrows* pointing to the P-waves, (**c**) complete heart block (complete AV dissociation) with *arrows* pointing to the P-waves

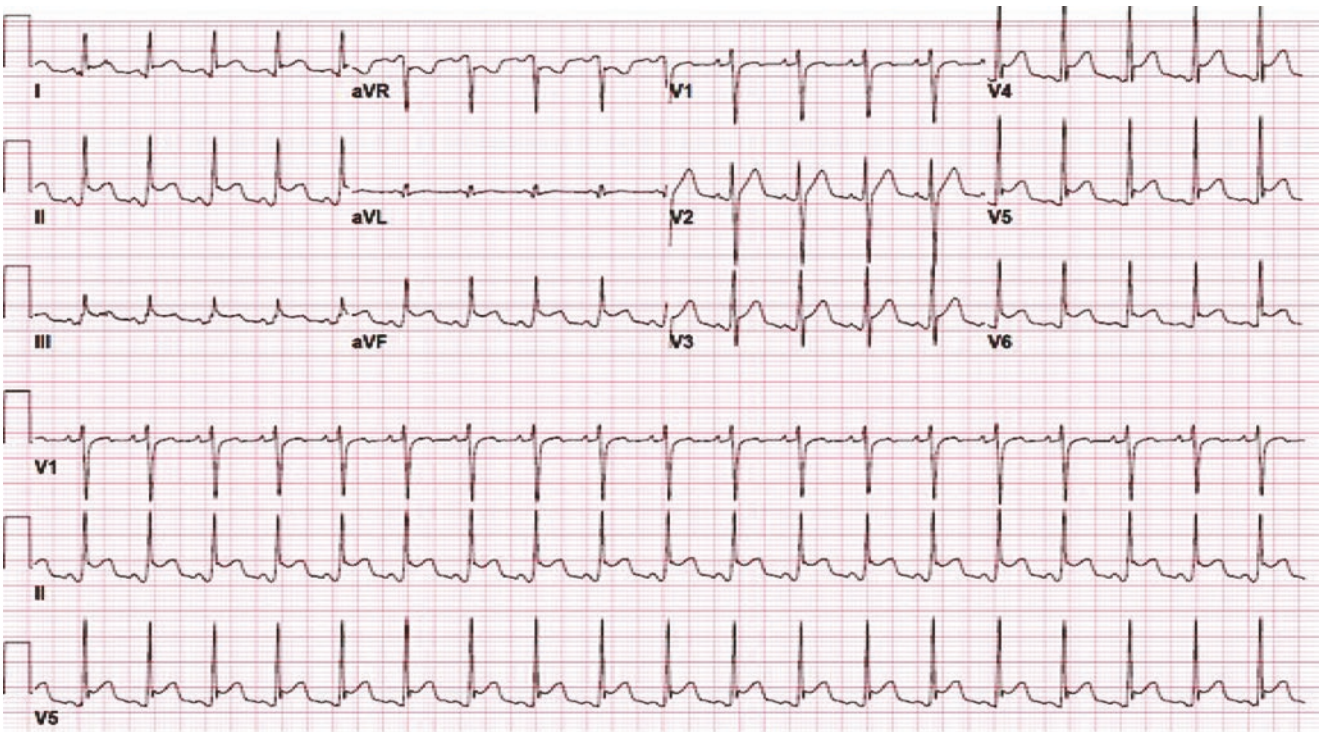


Fig. 19.9 14-year-old child with chest pain. Diagnosis: Diffuse ST elevation, perimyocarditis

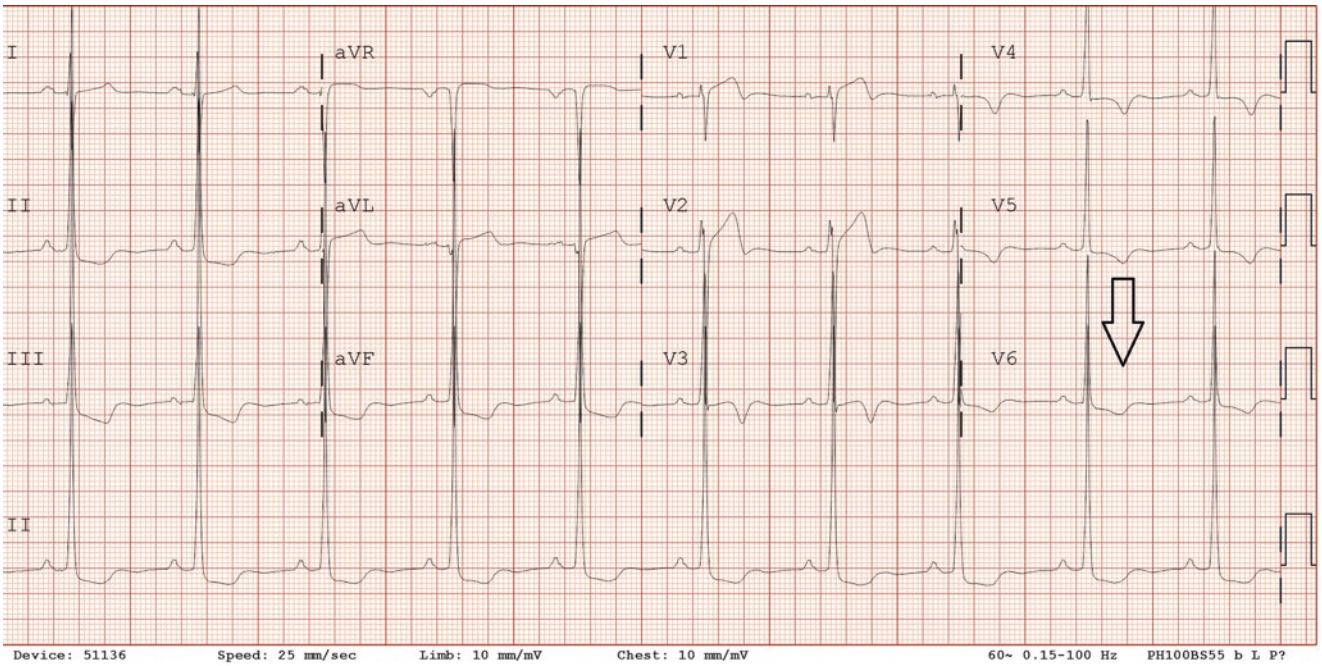


Fig. 19.10 17-year-old child with hypertrophic cardiomyopathy (LVH with abnormal T-waves shown by an arrow in lead V6)

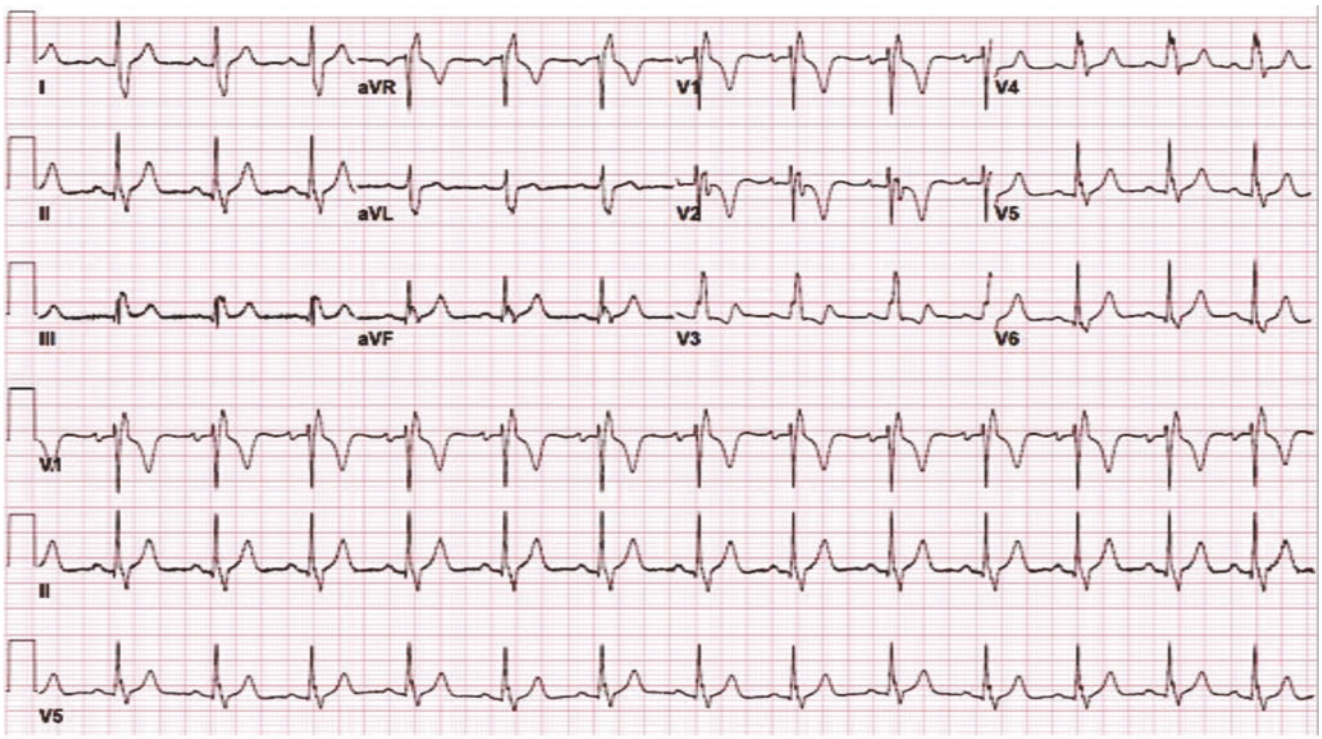


Fig. 19.11 16-year-old patient with tetralogy of Fallot repaired in infancy. Diagnosis: normal sinus rhythm with right bundle branch block

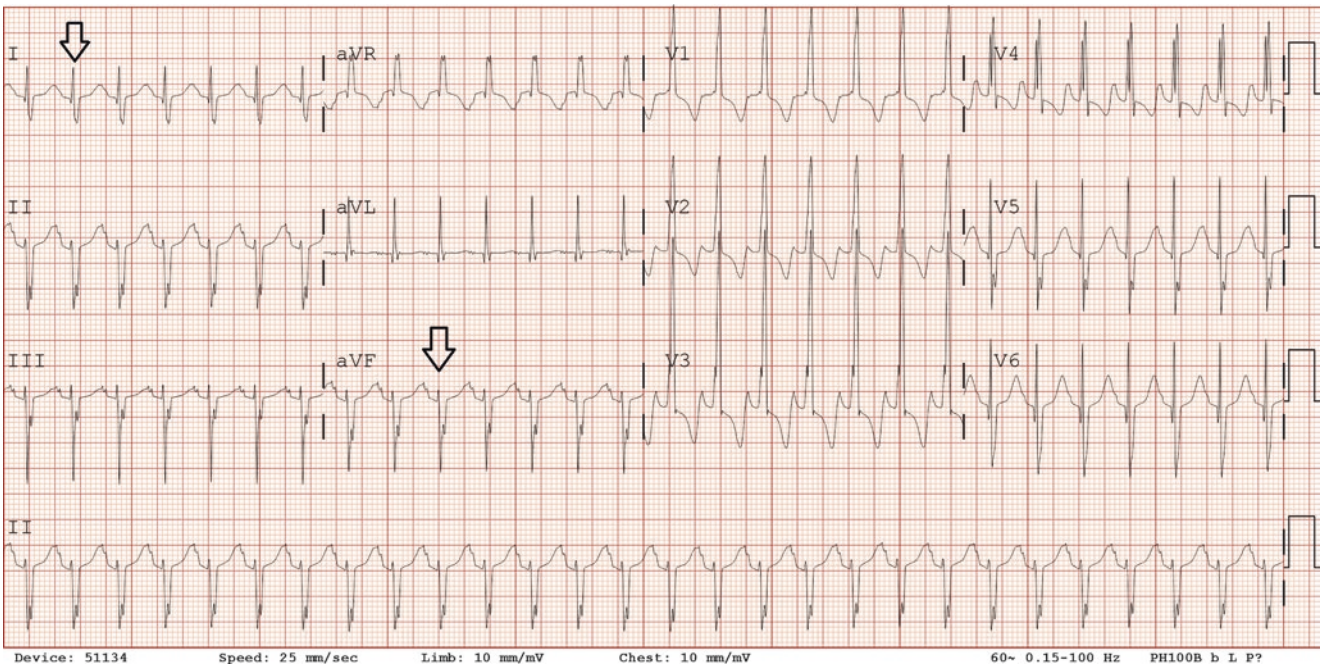


Fig. 19.12 5-month-old infant with atrioventricular canal (northwest axis shown in leads I and aVF with *arrows*)

- Abrupt onset and termination are suggestive of an arrhythmia.
- Gradual onset and termination are suggestive of normal variation.

– Symptoms: syncope, dizziness, fatigue, shortness of breath, chest discomfort
– Arrhythmia triggers: exercise, startle/loud noises, swimming
– History of heart disease
– Medication history
– Family history: sudden death, pacemaker, deafness, seizures

- ECGs—the key to interpretation is systematic review:
  – Rate
  – Rhythm (P-wave axis, atrioventricular [AV] synchrony, premature beats, irregularity)
  – QRS axis
  – Presence of atrial enlargement
  – Intervals: PR, QRS, and QT corrected
  – Presence of left ventricular hypertrophy (LVH) or right ventricular hypertrophy (RVH)
  – ST and T-wave abnormalities

Sinus Rhythm and Sinus Arrhythmia

Background

- Sinus arrhythmia is a normal finding in healthy children.
- Decrease in SA node firing subsequent to activation of the vagus nerve by exhalation.

Clinical Presentation

- Asymptomatic.
- The heart rate varies with respiration.
- ECG shows sinus rhythm with a prolongation of the RR interval during exhalation.

Premature Atrial Contractions (PACs)

Background

- Premature atrial contractions (PACs) are very common in pediatric patients and are benign when isolated (i.e., only single beats with no consecutive or sustained tachycardia).

Causes

- Idiopathic (most common)
- Electrolyte imbalances

- Intracardiac lines (peripherally inserted central catheter [PICC] or central lines with the tip in the right atrium [RA])

Clinical Presentation
- Asymptomatic or feeling a "skipped beat" or "pause," often followed by a strong beat

ECG
- Premature, inverted, or oddly shaped P-waves

Management
- No additional evaluation is necessary.
- If the patient is bothered by PACs, reassure and avoid triggers.

Atrial Flutter

Background
- Atrial rates usually 300–400 beats/min (can be slower in older children or those with atrial scars from cardiac surgery) with variable conduction so that the ventricular rate is slower than the atrial rate.
- Atrial flutter is caused by a reentrant circuit in the atrium.

Clinical Presentation
- Infants may present with congestive heart failure.
- Older children may have palpitations, dizziness, syncope, chest pain, and shortness of breath.
- The major clinical clue is usually a fixed rapid heartbeat that is between 150 and 200 bpm (flutter with 2:1 conduction).
- Prolonged atrial flutter or fibrillation (usually > 24 h) can result in thrombus formation within the left atrium.
- Can be seen in certain types of inherited arrhythmias (Brugada syndrome).

Diagnosis
- Classic inverted "sawtooth" pattern on ECG, best seen in leads II, III, and aVF.
- Can be difficult to see when the AV node is conducting 1:1 (i.e., with ventricular rates of > 200) or 2:1 (i.e., with ventricular rates of 150–200 bpm).
- Adenosine will not terminate the atrial flutter but can aid in diagnosis by temporarily blocking the AV node and unveiling the sawtooth pattern on ECG.

Management
- Urgent cardiac evaluation and treatment.
- If the patient is unstable, initiate synchronized cardioversion.
- If the patient is stable, evaluate for thrombus by echo (depending on suspected duration of flutter).
- Synchronized electrical cardioversion if no thrombus is present.
- Antiarrhythmic drugs can be used to control the ventricular rate during a course of anticoagulation if a thrombus is present.
- Radiofrequency catheter ablation can be curative for recurrent episodes of atrial flutter.

Atrial Fibrillation (AF)

Background
- AF is uncommon in young children.

Causes
- Other types of supraventricular tachycardia (SVT) can degenerate into AF.
- Hyperthyroidism.
- Electrolyte disturbance such as hypomagnesemia.
- Substance abuse.
- Hypertrophic cardiomyopathy.
- Inherited arrhythmias (long QT/Brugada/short QT syndromes).

Clinical Presentation
- AF generally is not life-threatening except if the patient has a rapidly conducting accessory bypass tract (i.e., Wolff-Parkinson-White [WPW] syndrome on baseline ECG).

- Palpitations.
- Chest pain.
- Syncope.
- Irregularly irregular rhythm.
- Prolonged atrial fibrillation or flutter (usually > 24 h) can result in clot development within the left atrium.

Diagnosis

- Absent or very low-voltage (i.e., small), fast, and irregular P-waves with irregularly irregular RR intervals on ECG

Management

- Urgent cardiac evaluation and treatment.
- If the patient is unstable, initiate synchronized cardioversion.
- If the patient is stable, evaluate for thrombus by echo (depending on suspected duration of atrial fibrillation).
- Synchronized electrical cardioversion if no thrombus is present.
- Antiarrhythmic drugs can be used to control the ventricular rate during a course of anticoagulation if a thrombus is present.
- Radiofrequency catheter ablation can be considered to evaluate and treat other SVT substrates that may have induced atrial fibrillation.

Supraventricular Tachycardia (SVT)

Background

- SVT is defined as a rapid tachycardia originating above the bundle of His.
- It occurs in as many as 1 in 250 children but is often misdiagnosed due to the variety of presentations.

Pathogenesis

- Reentrant tachycardia using an accessory pathway
- AV nodal reentrant tachycardia (AVNRT), typically seen in adolescents
- Ectopic atrial tachycardia

Clinical Presentation of Typical SVT

- **Infant:**
  - Heart rates of 200–270 beats/min
  - Poor feeding/vomiting, pallor, irritability, and lethargy
  - Congestive heart failure with hemodynamic decompensation if prolonged
- **School-aged children:**
  - Sudden-onset palpitations, heart or throat/neck pounding, "beeping in the chest"
  - Chest discomfort
  - Shortness of breath
  - Exercise intolerance
  - Heart rate: 180–240 beats/min

Diagnosis

- ECG:
  - Usually narrow complex (< 80 ms) tachycardia with a fixed rapid rate.
  - P-waves are often difficult to see but may be seen as sharp deflections within the T-waves.
  - Baseline ECG can be normal or can have WPW (in accessory pathway-mediated SVT).

Management

- Acute management of an SVT episode:
  - If patient is stable:
    - Vagal maneuvers, i.e., place an ice bag on the face over the forehead/eyes (raccoon distribution) for 5–15 s or Valsalva.
    - Adenosine will terminate reentrant SVTs that involve the AV node.
    - Remember to administer adenosine quickly (via push with a flush quickly thereafter) through a large-bore IV as centrally as possible to avoid breakdown of adenosine by red blood cells prior to reaching the heart.
    - Verapamil can be used if > 1 year of age, but avoid calcium channel blockers in infants due to the risk of hypotension and shock.
  - If patient is unstable, direct-current (DC) cardioversion

- Chronic management:
  - Pediatric cardiology referral.
  - Ambulatory ECG monitoring devices (24 h Holter monitors or event recorders) are useful for diagnosing SVT in patients who have sporadic episodes.
  - Medical management: beta-blocker, calcium channel blocker (in non-infants), digoxin (in the absence of an accessory pathway), or other antiarrhythmic medications.
  - Electrophysiology (EP) study with ablation procedure is the definitive treatment of choice.

Wolff-Parkinson-White (WPW) Syndrome

Background

- WPW is a pattern seen on ECG due to an aberrant accessory pathway that allows electricity to pass to the ventricles prior to going through the AV node.
- Associated conditions: cardiomyopathy (hypertrophic and LV noncompaction), Ebstein anomaly, corrected transposition of the great arteries (TGA).
- Presentation is an incidental finding on an ECG or with suspected or documented SVT.
- If the accessory pathway can conduct electricity in a bidirectional fashion (both from the atrium to the ventricle and from the ventricle to the atrium), then patients can have episodes of SVT.
- If the accessory pathway is robust (i.e., can conduct electricity from the atrium to the ventricle at very fast atrial rates), then patients are at risk of sudden death (via rapidly conducted atrial fibrillation leading to ventricular fibrillation).

ECG

- Shortened PR interval
- Slurring and slow rise of the initial upstroke of the QRS complex (delta wave)
- Widened QRS complex (total duration > 0.12 s)
- ST segment T-wave changes, generally directed opposite the major delta wave and QRS complex

Treatment

- SVT treatment, as described before
- Asymptomatic WPW:
  - Risk stratification (with exercise test or Holter monitor) of the accessory pathway to determine risk of sudden death
  - Electrophysiology (EP) study and ablation if high risk or preferred by the patient

Sick Sinus Syndrome (SSS)

Background

- This rhythm is a result of sinus node dysfunction.
- Most often in patients who had prior cardiac (especially extensive atrial) surgery or cardiomyopathy.
- Can be seen in patients with inherited arrhythmias (long QT syndrome, Brugada syndrome).

Clinical Presentation

- Asymptomatic (most common)
- Exercise intolerance/fatigue
- Syncope/seizure

ECG

- Sinus or junctional bradycardia ± sinus pauses.
- Long periods of inactivity in the atrium (i.e., sinus bradycardia or sinus pauses) can cause disorganization of rhythm and induce tachyarrhythmias such as atrial fibrillation/flutter.

Management

- Patients suspected of having SSS should be referred to a cardiologist for evaluation and assessment of need for pacemaker

Premature Ventricular Contractions (PVCs)

Background

- Ectopic beats originating from the ventricle
- Occurs commonly in healthy, normal hearts
- Can occur with electrolyte disturbances
- Can rarely be a presenting sign of myocarditis or cardiomyopathy
- Occurs more frequently in patients with structural heart disease and certain inherited arrhythmias

Clinical Presentation

- Usually asymptomatic
- Feeling that the "heart skips" and then resumes with a strong beat

ECG

- Premature, wide QRS complex not preceded by a P-wave and often followed by a compensatory pause.
- Frequent PVCs may occur with every other beat (bigeminy) or every third beat (trigeminy).

Management

- No treatment for PVCs for the following:
  - Single, uniform in appearance
  - Suppressed by exercise
  - No evidence of underlying heart disease or family history of sudden death

Prolonged QT Interval

Background

- Corrected QT (QTc) = $QT / \sqrt{RR}$.
- QT interval corrected between 340 and 450 ms is normal.
- QT interval corrected > 450 ms may be abnormal; > 470 is abnormal.
- QTc may be prolonged in normal neonates < 7 days of age.

Causes

- Acquired long QT:
  - Drugs (e.g., tricyclic antidepressants, antimicrobials, antiarrhythmics)
  - Electrolyte disturbances (hypocalcemia, hypomagnesemia, hypokalemia)
  - Hypothermia
- Congenital long QT syndrome (see below)

Clinical Presentation

- May cause ventricular tachyarrhythmias (*torsades de pointes*)
- Syncope/seizures
- Cardiac arrest/sudden death

Congenital Long QT Syndrome (LQTS)

Background

- Caused by mutations in ion channel genes.
- Can be an inherited or a spontaneous mutation.
- Remember that not every patient who has a prolonged QTc has congenital LQTS.
- There exist many different types of long QT syndrome.

Clinical Presentation

- Family history of unexplained sudden death.
- Previously healthy patient usually presents with fainting spells or seizures while swimming, startling from loud noises, or exercising. Can also present with seizures, palpitations, or cardiac arrest.
- As many as 10% have episodes of sudden cardiac arrest.
- Congenital deafness in the family is associated with a particularly malignant and rare form of hereditary LQTS (Jervell and Lange-Nielsen syndrome).

ECG

- Prolonged QTc and abnormal T-wave morphology.

- Can also see sinus bradycardia.
- Exercise testing can help to evaluate QTc response to exercise.

Treatment

- Beta-blockers are very effective in preventing cardiac events, particularly in the most common type of LQTS (type 1)
- Magnesium or DC cardioversion can treat *torsades de pointes*
- Implantable cardioverter-defibrillator (ICD) is highly effective in preventing sudden cardiac death in high risk patients
- Patients should avoid QT-prolonging medications
- Lifestyle modifications (exercise restriction, loud noise avoidance, evaluation and treatment for electrolyte disturbances in the setting of illness)

Ventricular Tachycardia (VT)

Background

- VT in children is defined as a tachycardia of at least three successive ventricular beats
- Nonsustained if the rhythm lasts < 30 s and terminates spontaneously
- Sustained > 30 s, usually requires therapeutic intervention

Causes

- Drugs
- Electrolyte imbalances
- Underlying cardiac disease
- Prior cardiac surgery
- Cardiomyopathy
- Inherited arrhythmia syndromes

Clinical Presentation

- Some patients are asymptomatic
- Syncope
- Palpitations
- Dyspnea on exertion, fatigue
- Congenital or acquired cardiac disease

ECG

- Bizarre, wide QRS complex (> 120 ms) tachycardia:
  - Can be monomorphic:
    - Most commonly arising from the RV outflow tract (RVOT)
  - Less commonly polymorphic (multiple different morphologies):
    - More likely to be associated with underlying electrical or cardiomyopathic disease
- P-waves may or may not be visible, depending on the ventricular rate

Management

- Any patient identified as having VT should be assessed immediately for hemodynamic instability
- Once clinically stable, he or she will require a cardiac evaluation, including ECG, echocardiography, exercise stress testing, and Holter monitoring
- May require medications or ablation, depending on the underlying cause of VT

Ventricular Fibrillation (VF)

Background

- VF is a rare pediatric cardiac emergency caused by uncoordinated activity of the cardiac muscle fibers, resulting in cardiac arrest
- The heart quivers rather than contracts; therefore, pulses are not palpable

ECG

- Bizarre, random waveform without clearly identifiable P-waves or QRS complexes and a roaming baseline

Management

- Any patient suspected of having VF requires advanced cardiac life support intervention (defibrillation) because circulation ceases within seconds of onset

Atrioventricular Block (AVB)

Background

- AVB is a sign of impairment of the normal conduction system (AV node or His-Purkinje system)

Causes

- Idiopathic
- Myocarditis
- Lyme disease
- Exposure to maternal lupus antibodies in utero
- Congenital heart disease (particularly postoperative)

Types of AV Block

- First-degree heart block:
  - PR interval > 95th percentile for age and heart rate (typically > 200 ms)
- Second-degree heart block:
  - Mobitz I—Wenckebach:
    - Progressive prolongation of PR interval until there is a dropped beat
  - Mobitz II—normal, stable PR interval, but periodically there is 1 (or more) dropped QRS
- Third-degree heart block:
  - No conduction through the AV node
  - P and QRS have independent but regular (fixed) rates with a faster atrial (P-wave) rate than ventricular (QRS) rate

Management of Heart Block

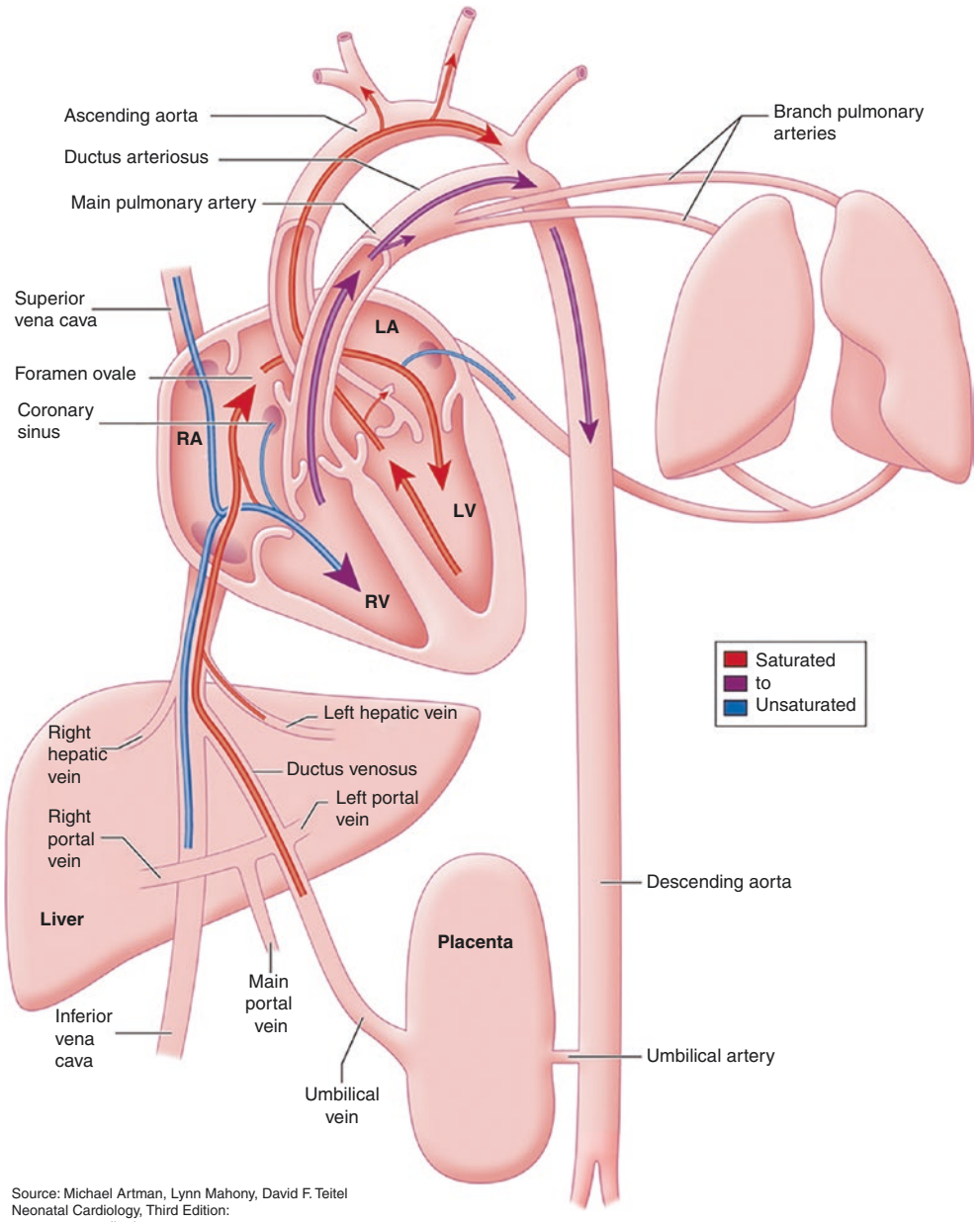
- First-degree and second-degree Mobitz I: depends on cause. If idiopathic and asymptomatic, it can be observed
- Second-degree Mobitz II and complete heart block:
  - Temporary transcutaneous or transvenous pacing is the treatment of choice for emergency situations caused by AV block
  - Atropine administration (0.5–1.0 mg) may improve AV conduction (although can worsen if block is in the His-Purkinje system)
  - Isoproterenol may increase the ventricular rate
  - Permanent pacemaker may be necessary if the cause of heart block is not temporary

ECG Tips

- Sinus tachycardia and sinus bradycardia are rarely due to a primary cardiac problem
- Sinus arrhythmia is a normal finding
- Left superior axis: can be from AV canal defect, tricuspid atresia, or ostium primum atrial septal defect (ASD)
- Anomalous left coronary artery from pulmonary artery (ALCAPA): deep Q-wave I and aVL and ↓ voltage V3–V5 ± LAD (left axis deviation) ± LVH
- Hypertrophic cardiomyopathy: LVH with "strain" (T-wave inversions), deep Q-wave V3–V6, left atrial enlargement (LAE)
- Right bundle branch block (RBBB):
  - More common in children particularly after open heart surgery
  - Wide QRS (> 120 ms)
  - rSR' (rabbit ears) in V1 and wide S-wave in V6
- Left bundle branch block (LBBB):
  - Rare in children
  - Wide QRS (> 120 ms)
  - rSR' notched or slurred in the lateral leads I, aVL, and V6
  - SRS' in V1

FETAL PHYSIOLOGY (FIG. 19.13) [1]

- Fetal cardiac output is defined as a combined cardiac output (CCO) and is directly proportional to heart rate, contractility, and preload:
  - Fetus is less able to increase its CCO
  - HR operates along the top of the Starling curve, and fetus has limited reserve with stress
- Due to non-inflation of the lungs, the pulmonary vascular resistance (PVR) is high, and there is little flow to the lungs



Fetal circulation, showing blood flow patterns throughout the central blood vessels, and cardiac chambers. Poorly oxygenated blood streams through the right ventricle to the placenta and lower body, and well-oxygenated blood streams through the left ventricle to the heart and brain.

Fig. 19.13 Fetal physiology (From Artman et al. [1], ©McGraw Hill Education, with permission)

- Majority of blood flow out the RV is directed R->L across the patent ductus arteriosus (PDA) into the descending aorta
- The patent foramen ovale (PFO) directs the umbilical vein (UV) flow from the ductus venosus, which is highly saturated from the placenta, R->L to flow out the aorta, delivering the highly saturated blood to the brain
- With initiation of ventilation at birth, the PVR drops
- PFO shunts (left to right) L->R with the increased pulmonary venous return to the LA

- PDA eventually shunts L->R as the PVR drops and then constricts
- If L->R PDA shunting is noted in utero, there's concern for inadequate antegrade pulmonary blood flow

MURMURS

Background

- A murmur is heard in most children at one or more examinations
- Because most murmurs are innocent (i.e., normal), it is important to differentiate those that are a manifestation of cardiac disease
- In general, history and physical examination permit the caregiver to determine if heart disease is present

Innocent Murmurs

- **Still's murmur:**
  - Early systolic ejection
  - Short duration
  - Low intensity (grade 1–2/6)
  - Vibrating (or musical) quality
  - Located at the left lower sternal border, non-radiating
- **Peripheral pulmonary artery stenosis of the newborn:**
  - Murmur is related to the acute take-off angle of the branch pulmonary arteries in the newborn
  - A murmur louder in the axillae or back than the anterior chest is highly suggestive of the diagnosis of peripheral pulmonary artery stenosis of the newborn
  - Characteristics:
    - Systolic ejection murmur of low intensity
    - Heard best at the left upper sternal border and radiates bilaterally to the axillae and back
    - Split S2 of normal intensity
    - Murmur disappears, usually in 3–6 months, when the angles remodel overtime with increased pulmonary blood flow
- **Venous hum:**
  - The murmur is caused by blood flowing down the jugular vein
  - Typically, louder in diastole as the atrium empties
  - Characteristics:
    - Continuous murmur
    - Heard in the infraclavicular region
    - Usually right-sided
    - Best heard sitting or standing
    - Disappears when the patient lies down
    - Diagnostic if it disappears when the examiner applies gentle pressure over the jugular vein

Pathologic Murmurs

- **Systolic murmurs:**
  - Systolic ejection murmurs: crescendo-decrescendo murmur heard best with the diaphragm:
    - Ejection murmurs are generated when blood flows through a stenotic area or if there is relative stenosis from increased flow through a normal area
    - Aortic stenosis (right upper sternal border, RUSB)
    - Pulmonary stenosis (left upper sternal border)
    - Atrial septal defect (relative stenosis from increased blood flow through the pulmonary valve)
    - Coarctation of the aorta (left clavicle or back),
- **Pansystolic murmurs: murmur of the same intensity throughout systole and heard best with the diaphragm:**
  - Ventricular septal defect (VSD): high pitched, harsh at the left lower sternal border
  - Mitral regurgitation: low pitched, blowing at the left lower sternal border radiating to the left axilla, louder with the patient in left lateral decubitus position
  - Tricuspid regurgitation: low pitched, blowing at the left and right lower sternal border

- **Diastolic murmurs:**
  - Early decrescendo murmur heard best with the diaphragm and loudest at the left mid-sternal border:
    - Aortic insufficiency (high pitched) heard best when the patient is leaning forward in expiration
    - Pulmonary insufficiency (low pitched)
  - Mid-diastolic rumble heard best with the bell
    - Tricuspid stenosis: right lower sternal border
    - Mitral stenosis: axilla
- **Continuous murmur:**
  - Heard best with the diaphragm throughout systole and through S2 to diastole, but not necessarily present throughout diastole, similar to a bruit:
    - PDA (left clavicular region)
    - Coronary artery fistula (can be heard anywhere in the precordium)
- **Heart sounds:**
  - S1: heard best at the left lower sternal border
  - S2: heard best at the left mid-upper sternal border; physiologically, splitting occurs because the aortic valve closes prior to the pulmonary valve:
    - Split S2 normally widens with inspiration
    - Loud S2: anterior aorta
    - Loud, single S2: pulmonary hypertension
    - Fixed split S2: atrial septal defect
    - Paradoxically split S2: aortic stenosis
  - Systolic click:
    - Aortic or pulmonary valve stenosis (PS): heard best at the left mid-sternal border
    - Mitral valve prolapse: mid-systolic click in axilla
  - S3: heard best with the bell at the left lower sternal border, anterior axillary line in mid-diastole
  - S4: heard best with the bell at the left lower sternal border, anterior axillary line immediately prior to S1
  - Rub: irregular, crackling sound not related to heart rate heard best with the diaphragm anywhere in the precordium
- **Thrills:**
  - Felt best with the palm of the hand
  - Aortic stenosis: Suprasternal notch thrill is diagnostic
  - Aortic or pulmonary stenosis: left mid-sternal border; thrill indicates increased severity of stenosis
  - Ventricular septal defect: left mid- or lower sternal border; thrill may indicate small, restrictive VSD
- **Heave:**
  - Indicates RVH or LVH

CONGENITAL HEART DEFECTS

Acyanotic Shunt Lesions

- **Left-to-right shunts (ASD, VSD, PDA):**
  - Physiology:
    - Shunting from the systemic (aorta) to pulmonary bed
    - Degree of shunting depends on the balance between systemic and pulmonary resistances
    - Shunting increases as the PVR decreases postnatally

Cyanotic Lesions

- **Right-to-left shunts:** Tetralogy of Fallot (TOF), tricuspid atresia (TA), transposition of the great arteries (TGA), truncus arteriosus, Ebstein anomaly, totally anomalous pulmonary venous return (TAPVR)
  - Physiology:
    - Central cyanosis due to desaturated blood entering systemic circulation with cyanosis noted of the tongue and oral mucous membranes
    - Acrocyanosis due to poor circulation in extremities due to vasoconstriction; other parts of the body are not cyanotic
    - Cyanosis due to congenital heart defect is constant, not significantly improved by the administration of oxygen; improved saturation close to normal is

more likely related to primary pulmonary disease
- Clinical cyanosis depends on hemoglobin and amount of desaturated blood present
- Degree of right-to-left shunting will also depend on the PVR as well as any obstruction to pulmonary flow
- If there's insufficient antegrade pulmonary blood flow, rely on L->R PDA for additional flow (TOF, tricuspid atresia, pulmonary atresia)
- In TA and TAPVR, mixing of the systemic venous return and pulmonary venous return occurs by default as the result of the anatomy, not usually dependent on PVR
- Chronic hypoxia results in polycythemia and clubbing of extremities on exam
- R->L shunt lesions are at high risk of cerebral vascular accidents

Obstructive Lesions

- Hypoplastic left heart syndrome (HLHS), coarctation, aortic stenosis, pulmonary stenosis:
  - Physiology:
    - Obstruction to either systemic or pulmonary blood flow, depending on lesion
    - If significant obstruction, may need to rely on PDA for either additional systemic or pulmonary flow

LEFT-TO-RIGHT SHUNTS

Atrial Septal Defect (ASD)

Anatomy
- Communication between right and left atria in various locations (primum, secundum, sinus venosus, coronary sinus)

Physiology
- Obligate left-to-right shunt due to difference in atrial compliance; does not depend on PVR, resulting in right-sided volume overload overtime

Ostium Secundum Defect
- The most common type of ASD, deficiency of the septum primum
- Located in the midportion of the atrial septum.
- Associated syndromes:
  - Holt-Oram syndrome
  - Upper limb anomalies (radius)
- Closure can be performed with transcatheter or surgical approach

Ostium Primum Defect
- Located in the lower portion of the atrial septum adjacent to the AV valves, deficiency of the septum secundum:
  - May be associated with a cleft mitral valve and partial AV canal defect
  - If there is an associated inlet VSD and common AV valve, the defect is known as a complete AV canal (CAVC) defect or endocardial cushion defect
  - Associated syndrome: Down syndrome.
  - Closure is not amenable to transcatheter closure and is performed surgically; it may include closure of the mitral valve cleft

Sinus Venosus Defect
- Located by the superior vena cava (SVC) and at the junction of the pulmonary veins and the posterior-superior wall of the atrium (superior type) or less commonly by the inferior vena cava (IVC) to the right atrium (RA) junction (inferior type):
  - Superior type often associated with anomalous drainage of the right pulmonary veins to the SVC
- Closure is performed surgically and usually includes baffling of right pulmonary veins to the left atrium

Description
- Clinical presentation is similar regardless of location of the defect.
- Most often asymptomatic in the pediatric population

Clinical Presentation
- Mostly asymptomatic; initial presentation may be murmur and abnormal CXR or ECG.

Physical Examination
- Systolic ejection murmur due to increased flow across the pulmonary valve (relative pulmonary stenosis) best heard in the left upper sternal border
- Second heart sound is wide with a fixed split without respiratory variation.
- Mid-diastolic rumble murmur can be heard at the left lower sternal border due to increased flow across the tricuspid valve (relative tricuspid stenosis)

CXR
- Varying degrees of right atrial and ventricular enlargement
- Increased pulmonary vascular markings

ECG
- Right axis deviation
- RV conduction delay with RSR1 pattern in lead V1
- RVH
- Right atrial enlargement
- Left superior axis seen in ostium primum defect

Treatment
- Mostly asymptomatic, rarely may need Lasix® (furosemide) if there are other comorbidities such as chronic lung disease

Indications for Closure
- Asymptomatic patients with 2:1 or more left-to-right shunt and evidence of RV volume overload
- Symptomatic patients (rare)
- Elective closure usually performed between 3 and 5 years of life
- Early closure indicated if the patient has other hemodynamically significant lesions or heart failure symptoms
- Depending on location, can be closed by transcatheter approach with an ASD device or traditional surgical approach

Ventricular Septal Defect (VSD)

- Most common cardiac malformation

Anatomy
- Communication between the right and left ventricles, various locations (perimembranous, muscular, inlet, outlet)
- Muscular type is located in the trabecular midportion of the LV or the apex and may be single or multiple type (Swiss cheese septum)
- Outlet (conoseptal, supracristal, subpulmonic) may be associated with aortic insufficiency.
- Inlet (AV canal defect).
- Can be multiple with a combination of locations

Physiology
- Degree of left-to-right shunting depends on PVR
- Large shunt results in left-sided volume load and dilated LA and LV
- If there is a pressure difference between the two ventricles > 30 mmHg, the defect is classified as restrictive; if there is a pressure difference between the two ventricles < 30 mmHg, the defect is classified as nonrestrictive
- Pulmonary hypertension if the VSD is not restrictive and can result in chronic changes and pulmonary vascular disease

Description
- Shunting increases as PVR drops overtime, which partially determines age of presentation.
- Heart failure and pulmonary overcirculation develop if there is a large left-to-right shunt and result in LV volume overload

Physical Examination
- Holosystolic murmur, best heard at the left lower sternal border

- Increased S2 or single S2 if pulmonary hypertension is present
- LV heave with hyperdynamic precordium
- Systolic ejection murmur at the left upper sternal border due to increased flow across the pulmonary valve (relative pulmonary stenosis)
- Mid-diastolic rumble in the mitral area heard best at the apex due to increased flow across the mitral valve (relative mitral stenosis) with a large shunt

CXR
- Minimal cardiomegaly and increased pulmonary vasculature with small shunts
- Cardiomegaly with prominence of the left atrium and left ventricle with large shunts

ECG
- LV or biventricular hypertrophy due to LV dilation
- Left atrial enlargement
- T-wave inversions in the left lateral leads due to LV dilation
- Left superior QRS axis with inlet VSD (similar to CAVC)

Course
- Small defects can close spontaneously up to 30–50%
- Small muscular type more likely to close up to 80% vs. membranous type, which is up to 35%
- Patients with outlet (conoseptal, supracristal, subpulmonic) are at higher risk to develop aortic valve regurgitation and usually undergo surgical closure despite small shunt

Treatment
- Diuretics
- Digoxin
- Afterload reduction with ACE inhibitor to promote more systemic flow and less pulmonary flow
- Nutritional supplementation (higher-calorie formula, nasogastric feedings)

Indications for Closure
- Heart failure symptoms with failure to thrive refractory to medical therapy
- Reactive pulmonary hypertension

Intervention
- Most cases are closed surgically; some muscular VSDs may be amenable to transcatheter device closure

Common Atrioventricular Canal Defects (AVCDs)

Anatomy
- Failure of development of the endocardial cushions resulting in a common AV valve, ostium primum ASD, and inlet VSD

Physiology
- Essentially that of a combined ASD and VSD with left-to-right shunting as the PVR falls

Description
- Common in trisomy 21, can sometimes be seen in combination with tetralogy of Fallot.
- Does not resolve spontaneously, requires surgical closure
- The AV valve tissue may be malformed, resulting in valvar regurgitation

Clinical Presentation
- Shunting increases as PVR drops overtime, which partially determines age of presentation
- Heart failure and pulmonary overcirculation develop if there is a large left-to-right shunt and results in LV volume overload, tachypnea, and difficulty in feeding

Physical Examination
- Active precordium if large shunt
- VSD is not pressure restrictive, so murmur will be of low frequency

- High-frequency systolic murmur may be present if there is significant valvar regurgitation
- Mid-diastolic rumble in the mitral area heard best at the apex due to increased flow across the mitral valve (relative mitral stenosis) with a large shunt

CXR
- Cardiomegaly with prominence of the left atrium and left ventricle with large shunts

ECG
- Superior QRS axis
- LV or biventricular hypertrophy due to LV dilation
- Left atrial enlargement

Course
- Progressive pulmonary overcirculation
- Requires surgical closure in the first year of life

Treatment
- Diuretics
- Afterload reduction with ACE inhibitor to promote more systemic flow and less pulmonary flow
- Nutritional supplementation (higher-calorie formula, nasogastric feedings)
- Indications for earlier surgical intervention
- Heart failure symptoms with failure to thrive refractory to medical therapy

Patent Ductus Arteriosus (PDA)

Anatomy
- Residual finding from normal fetal circulation

Physiology
- Depending on size, may be a significant left-to-right shunt with left-sided volume load and diastolic runoff into the pulmonary system, resulting in low diastolic systemic pressure.
- Tissue is responsive to high overall partial pressure of oxygen (PO2)

Description
- Common in preterm infants, patency as a result of hypoxia and immaturity, early pharmacological or surgical intervention usually not required (except if unable to manage heart failure), and spontaneous closure occurring in most instances
- PDA persisting > 1 week in term infant is very unlikely to close spontaneously or with pharmacological intervention.
- The wall is deficient in both the mucoid endothelial layer and muscular layer

Clinical Presentation
- Small PDA is usually asymptomatic.
- Large PDA will result in heart failure due to large left-to-right shunt

Physical Examination
- Continuous machinery murmur in neonate
- Continuous (bruit) in older child, heard best along the left clavicle
- Wide pulse pressure and bounding peripheral pulses
- LV heave

CXR
- Prominent pulmonary artery, with increased pulmonary vascular markings
- Cardiomegaly involving the left atrium and left ventricle

ECG
- LV or biventricular hypertrophy
- Left atrial enlargement
- T-wave inversions in left lateral leads

Treatment
- Indocin (more effective in premature infants) promotes closure
- Diuretics

- Nutritional supplementation (higher-calorie formula, nasogastric feedings)

Indications for Closure

- Heart failure, signs of significant pulmonary overcirculation refractory to medical management
- Reactive pulmonary hypertension.
- Closure is performed transcatheter or surgically, depending on PDA size and patient size

RIGHT-TO-LEFT SHUNT LESIONS

Tetralogy of Fallot

Anatomy

- Abnormal deviation of the conal septum that results in RVOT obstruction, VSD, overriding aorta, and RVH

Physiology

- The degree of RVOT obstruction will determine if and how much R->L shunting will occur across the VSD

Description

- Constellation of findings that are the result of abnormal development of the conotruncal area in fetal life
- Tetralogy:
  - Multiple levels of RVOT obstruction: infundibular, valvar, and supravalvar
  - VSD due to anterior deviation of the conal septum
  - Aortic override of the ventricular septum due to anterior deviation of the conal septum
  - RVH due to the RVOT obstruction
- Spectrum of presentation depending on the degree of RVOT obstruction, from those without much obstruction and minimal to no R->L shunting (pink tet) to severe cyanosis due to extreme RVOT obstruction.
- Extreme RVOT obstruction can result in pulmonary atresia, and these patients are dependent on the PDA or aortopulmonary collaterals.

Clinical Presentation

- It depends on degree of RVOT obstruction, but almost all will have systolic ejection murmur at birth.
- Cyanosis at birth if there's severe RVOT obstruction
- Paroxysmal hypercyanotic attack (or "blue" or "tet" spell)
- Older unrepaired children may squat to prevent a spell

Physical Examination

- Systolic ejection murmur along the left upper sternal border due to RVOT obstruction.
- Systolic ejection murmur may radiate to the axillae and back as in peripheral pulmonary stenosis
- RV heave
- Continuous murmur of PDA or aortopulmonary collaterals (heard best in the back)

Associated Syndrome

- 22q11.2 deletion (DiGeorge syndrome)

CXR

- Boot-shaped heart (*cœur en sabot*) due to upturned RV apex
- Decreased pulmonary blood flow
- Absent main pulmonary artery segment
- Possible associated right aortic arch

ECG

- Right axis deviation
- RVH

Treatment

- Neonates with severe obstruction maintain on prostaglandin E1 (PGE) infusion until intervention
- Surgical correction electively within the first year of life
- Hypercyanotic spells:

- Calming behavior (mother, pacifier, quiet room)
- Knee-chest position
- Squatting if older child
- Oxygen
- Fluid resuscitation
- Morphine
- Sodium bicarbonate
- Phenylephrine
- Esmolol

Surgery

- Some patients can have a palliative aortopulmonary shunt (modified Blalock-Taussig shunt) in infancy until full repair.
- Surgical repair eventually with closure of VSD and resection of sub-pulmonic muscle and opening of pulmonary valve (PV) as needed; in cases of pulmonary atresia, will need PV replacement.
- PV replacement often necessary in the third to fourth decade of life.

Tricuspid Atresia

Anatomy

- Abnormal development of the tricuspid valve without patency

Physiology

- Obligate right-to-left shunt across the atrial septum
- Varying degrees of antegrade pulmonary blood flow, depending on presence and size of an associated VSD

Description

- Classified by presence of VSD/pulmonary valve stenosis (PS) and relationship of great arteries
- If no VSD with antegrade blood flow, will be dependent on PDA flow from the aorta to the pulmonary artery

Clinical Presentation

- Presents with cyanosis in the newborn period

Physical exam

- Single S1; if pulmonary atresia, single S2 as well
- If murmur is present, usually related to VSD/PS

CXR

- Normal cardiac size
- Small pulmonary artery prominence if there's decreased pulmonary flow

ECG

- QRS with left axis deviation
- Diminished RV forces

Treatment

- Initiation of PGE if there's inadequate pulmonary blood flow and then aortopulmonary shunt
- Single-ventricle palliation with Glenn and Fontan procedures

Transposition of Great Arteries

Anatomy

- Abnormal conoseptal development results in the aorta arising from the RV and the pulmonary artery arising from the LV.

Physiology

- Parallel circulations result in desaturated systemic venous blood being recirculated into the systemic circulation.

Description

- Presents with cyanosis in the neonatal period.
- Associated VSD in 20% of cases.
- Atrial-level shunt allows for oxygenated blood to flow to the systemic circulation.

Clinical Presentation

- Severe hypoxemia immediately after birth if there's inadequate atrial mixing.
- Cyanosis and tachypnea within the first few days of life once the ductus begins to close:
  - Preductal saturation (right hand) may be lower than post-ductal saturation (foot) if pulmonary hypertension is present due to R->L shunting through the PDA.
- Hypoxemia is severe despite the oxygen therapy.

Physical Examination

- Parasternal heave may be present.
- Single and loud second heart sound with occasional split.
- Murmur is usually absent, or soft ejection murmur may be noted at the mid-left sternal border.

CXR

- Narrow mediastinum with small heart tipped on the side ("egg-on-a-string") due to abnormally related great arteries
- Normal pulmonary vascular markings

ECG

- Often normal for a newborn with RVH and right axis deviation

Treatment

- If transposition is suspected in a newborn, start PGE.
- If cyanosis is severe, balloon atrial septostomy is performed to improve mixing between the left and right sides of the heart.
- Arterial switch procedure is the surgical procedure of choice and performed within the first 2 weeks of life.
- Long-term survivors of early atrial switch operation may have RV failure and/or arrhythmias.

Ebstein Anomaly

Anatomy

- Abnormal delamination of the septal leaflet of the tricuspid valve results in deformity and varying degrees of tricuspid regurgitation.

Physiology

- Cyanosis due to atrial-level R->L shunting if there's severe tricuspid regurgitation and/or inadequate antegrade pulmonary blood flow.
- Worsening tricuspid regurgitation can result in right-sided heart failure.

Description

- Malformation of the tricuspid valve characterized by failure of the tricuspid valve apparatus to separate from the RV myocardium:
  - Displacement of the tricuspid valve annulus into the RV body and tricuspid insufficiency
  - Atrialization of a portion of the right ventricle
  - Massive dilation of the right atrium
  - Atrial septal defect or PFO

Clinical Presentation

- Newborn with severe form may have marked cyanosis and massive cardiomegaly, may have inadequate pulmonary blood flow, and may be PDA/PGE dependent.
- Cyanosis: Right-to-left shunting through the PFO because of severe tricuspid insufficiency causes elevated right atrial pressures.
- Atrial arrhythmias are common because of atrial enlargement and associated WPW.
- Sudden death can occur from the arrhythmias.

Physical Examination

- Holosystolic murmur in the tricuspid area
- Widely split S2
- Multiple systolic clicks
- Jugular venous distension
- Enlarged liver
- Cyanosis

CXR

- Varies from normal to massive box-shaped heart (cardiomegaly caused by enlargement of the right atrium and ventricle)

ECG

- Right atrial enlargement
- Incomplete right bundle branch block

- Unusual late QRS configuration
- Accessory pathways (WPW) with short PR interval and delta wave

Indications for Treatment
- Cyanosis limiting activity
- Heart failure
- Arrhythmias

Treatment
- Tricuspid valve repair or replacement
- Neonates: closure of the tricuspid valve with placement of an aortopulmonary shunt and conversion to a single-ventricle physiology

Truncus Arteriosus

Anatomy
- Embryological remnant of common arterial trunk arising from both the right and left ventricle.
- Malaligned VSD.
- Pulmonary arteries arise from the truncus as a main pulmonary artery or as separate right and left pulmonary arteries
- Truncal valve may have 3 to 6 leaflets and may be stenotic and regurgitant.

Physiology
- Due to common outlet, there is intracardiac mixing of desaturated systemic venous blood with oxygenated pulmonary venous blood.
- As PVR falls, left-to-right shunting increases.
- As shunting increases, overall saturations will increase.

Description
- Single arterial trunk supplying systemic, pulmonary, and coronary circulation

Clinical Presentation
- Cyanosis
- Murmur
- Heart failure

Physical Examination
- Systolic ejection murmur in the outflow region
- Wide pulse pressure
- Hyperdynamic precordium
- Aortic insufficiency
- Multiple valve clicks in systole

Associated Syndrome
- 22q11.2 deletion

CXR
- Right, left, or combined ventricular hypertrophy, prominent shadow of the ascending aorta and aortic knob, increased pulmonary vascularity in the first week of life

ECG
- Often normal

Treatment
- Heart failure treatment.
- Early surgical correction due to high risk of pulmonary vascular disease in infancy:
  - Closure of the VSD
  - Separation of the pulmonary arteries from the truncus with placement of a conduit or patch to connect pulmonary arteries to the right ventricle
- Repaired patients require reintervention for the RV to pulmonary artery connection, pulmonary artery stenosis, or truncal valve insufficiency.

Totally Anomalous Pulmonary Venous Return (TAPVR)

Anatomy
- Pulmonary veins drain to the common confluence, which does not communicate with the left atrium.
- Remnant of the primitive vessel remains to serve as a site of egress from the confluence to various sites.

Physiology
- All the pulmonary venous return eventually returns to and mixes with the blood in the RA.
- Obligate right-to-left shunt across ASD for systemic perfusion.
- If obstruction is noted, symptoms will vary depending on degree of obstruction.
- If there's severe obstruction, this results in severe hypoxemia and decreased cardiac output due to pulmonary venous congestion and lack of egress from the lungs to the body.

Description
- Types of TAPVR connections:
  - Supracardiac 50%:
    - Vertical vein to the left SVC
    - Right SVC
  - Coronary sinus or directly to the right atrium 25%
  - Infracardiac 20%, obstruction of the veins presenting 90–100% of these cases
  - Mixed 5%

Clinical Presentation
- Cyanosis
- No pulmonary venous obstruction:
  - No pulmonary hypertension and cyanosis absent or mild
  - Murmur of pulmonary stenosis
- Mild-to-moderate obstruction:
  - Infants can be severely ill because of pulmonary hypertension.
  - Tachypnea due to pulmonary edema from pulmonary venous congestion.
  - Cyanosis is mild.
- Severe obstruction:
  - Cyanosis and tachypnea may be prominent without murmur if there's severe obstruction, especially in the infracardiac group.
  - Severe hypoxemia with decreased cardiac output in the immediate neonatal period.

CXR
- Obstructed veins: small heart with ground-glass appearance to lung markings
- Supracardiac veins: large supracardiac shadow (snowman appearance) due to dilated SVC

ECG
- RVH
- Peaked T-waves

Treatment
- Obstructed TAPVR is a surgical emergency, with PGE usually ineffective.
- Other forms require surgical correction in infancy.

OBSTRUCTIVE LESIONS

Pulmonary Valve Stenosis (PS)

Anatomy
- Abnormal pulmonary valve leaflets, may be fused and dysplastic

Physiology
- Limits pulmonary blood flow, can be critical or minor

Description
- Critical pulmonary stenosis of the newborn:
  - Inadequate antegrade pulmonary blood flow because of severe stenosis.
  - PDA supplies pulmonary blood flow.
  - Right-to-left shunt through the atrial septal defect, which may result in cyanosis.
- Valvar pulmonary stenosis:
  - Often asymptomatic
- Associated syndromes:
  - Noonan syndrome
  - Williams syndrome
- If gradient < 30 mmHg, not likely to progress

Physical Examination
- Harsh systolic ejection murmur in the pulmonic area (left upper sternal border).
- Thrill may be present in severe stenosis.
- Valve click can be heard at the left mid-sternal border.
- S2 may be soft in severe stenosis.
- RV lift present in severe stenosis.

CXR
- Prominent main pulmonary artery
- Diminished pulmonary vascular markings (newborn with critical PS)

ECG
- Right axis deviation
- RVH

Treatment
- Relief of obstruction by transcatheter balloon dilation or surgical valvotomy.
- Pulmonary insufficiency following treatment may require intervention later in life.

Indication for Intervention
- Cyanosis and inadequate antegrade pulmonary blood flow
- Significant RVH or compromised function
- Estimated RV to PA gradient > 50 mmHg

Peripheral Pulmonary Stenosis (PPS)

Anatomy
- Single or multiple stenosis anywhere along the major branches of the pulmonary artery

Physiology
- Depending on severity of stenosis, may result in increased RV pressures

Description
- PPS associated with syndrome or presenting later in life may require balloon angioplasty or surgical intervention.
- Mild PPS is a normal finding in newborns and resolves spontaneously.

Clinical Presentation
- Most patients are asymptomatic and usually just present with a murmur.

Physical Exam
- Systolic ejection murmur best heard in the axillae and across the precordium and can radiate to the back

Associated Syndromes
- Williams syndrome
- Alagille syndrome
- Noonan syndrome

Treatment
- Benign PPS of the newborn resolves spontaneously usually by 1 year of life.
- May occur unilaterally on the left side once PDA closes due to constriction from ductal tissue around the left pulmonary artery.
- Syndromic patient may require balloon valvuloplasty or stenting if there's evidence of RV hypertension.

Aortic Stenosis

Anatomy
- Abnormal formation of aortic valve cusps, can be trileaflet with fusion of two cusps, bicuspid, or unicuspid/dysplastic

Physiology
- Varying degrees of stenosis, the most severe resulting in decreased cardiac output.
- Sudden death is significant in severe obstruction, during or immediately after exercise due to poor cardiac output.

Description
- Types of aortic stenosis:
  - Valvar aortic stenosis occurs due to fusion of the valve commissures or malformation of the valve leaflets and is more common in patients with a bicuspid or unicuspid aortic valve.

  - Bicuspid aortic valve is one of the most common congenital heart lesions identified in up to 2% of adults with aortic stenosis and is usually asymptomatic in childhood
  - Subvalvar stenosis is due to abnormal ingrowth of tissue in the left valve outflow tract (LVOT) separate from the valve but may be adherent to the valve:
    - Associated with other congenital heart defects
    - Can be discovered after correction of other anomalies
    - In childhood, may progress rapidly in severity and may recur even after surgical resection
    - Can lead to concomitant aortic insufficiency
  - Supravalvar aortic stenosis is the least common type, associated with Williams syndrome.
- Aortic stenosis is a progressive disease and can be associated with other left-sided obstructive lesions such as mitral stenosis, coarctation of the aorta, and interrupted aortic arch (IAA).
- VSD is a common association when there is an associated arch anomaly.

Associated Syndromes
- Williams syndrome (supravalvar aortic stenosis)
- Turner syndrome (bicuspid aortic valve)

Clinical Presentation
- Critical aortic stenosis of the newborn:
  - Inadequate flow across the aortic valve leading to decreased cardiac output.
  - PDA is needed to maintain blood flow to the body from R->L shunting.
  - LV failure can occur.
  - Heart failure symptoms.
- Valvar aortic stenosis in older child:
  - Often asymptomatic
  - Murmur
  - Chest pain
  - Dizziness or syncope with exercise
- Sudden death has been reported in children with aortic stenosis.

Physical Examination
- Systolic ejection murmur loudest in the aortic area (right upper sternal border, RUSB), radiating to the carotids.
- Subaortic stenosis murmur may be loudest at the left mid-sternal border.
- Thrill in the suprasternal notch.
- Valve click at the left mid-sternal border.
- Soft S2.
- LV heave.
- If there's associated aortic insufficiency, can have early diastolic murmur.

CXR
- Prominent ascending aorta
- Normal size of the heart or cardiomegaly

ECG
- LVH and strain
- Inverted T-wave in the left precordial leads

Indications for Treatment
- Symptoms
- LVH
- Estimated peak systolic gradient > 60 mmHg by echo
- Systolic gradient > 40 mmHg by direct catheter measurement
- For subaortic stenosis, associated aortic insufficiency

Treatment
- For neonatal critical aortic stenosis, initiation of PGE to maintain cardiac output and then balloon valvuloplasty of the aortic valve
- Surgical valvotomy
- Aortic valve replacement (artificial or tissue valve, Ross procedure)
- High rate of reintervention, particularly in neonates with critical aortic stenosis

Coarctation of the Aorta

Anatomy
- Discrete or diffuse narrowing of portions of the aortic arch

Physiology
- Results in compromised blood flow to the areas distal to the obstruction and elevated pressures proximally

Description
- Narrowing of the aorta of varying degrees may occur at any point from the transverse arch to the iliac bifurcation.
- 98% of instances occur just below the left subclavian artery at the origin of ductus arteriosus (juxta-ductal coarctation).
- Association with berry aneurysm and hypertension may cause cerebrovascular accidents.
- Severe cases result in interrupted aortic arch (IAA).

Clinical Presentations
- Neonates (critical coarctation):
  - Flow to the descending aorta is inadequate.
  - Rapidly symptomatic as soon as the PDA closes.
  - Lower body hypoperfusion.
  - Shock/metabolic acidosis.
  - Severe heart failure.
- Older children:
  - Asymptomatic.
  - Present with hypertension noted in upper extremity.
  - Children and adolescents may complain about weakness or pain in legs after exercise.

Physical Examination (in the Absence of PDA)
- Diminished femoral pulses.
- Differential blood pressures between the right arm and leg (right arm blood pressure > 10 mmHg higher than the leg).
- Radial-femoral delay is a very important sign.
- Systolic murmur is usually heard in the third and fourth intercostal spaces along the left sternal border and can be heard to the infrascapular area and occasionally to the neck.
- Continuous murmur may be heard to the back if there are intercostal collateral vessels present.

Associated Syndromes
- Turner syndrome (the most common lesion associated with Turner syndrome is bicuspid aortic valve)
- PHACE syndrome (face and heart) (posterior fossa anomalies, facial hemangioma, arterial anomalies, cardiac anomalies, aortic coarctation, eye anomalies): may have stroke
- DiGeorge syndrome in cases with IAA, which also has a high association with a concomitant VSD

CXR
- Cardiomegaly and pulmonary congestion in infants with severe coarctation.
- Enlarged left subclavian artery produces a prominent shadow in the left superior mediastinum (E sign).
- Notching of the superior border of the ribs in late adolescent due to intercostal collateral vessels.

ECG
- May be normal in young children and mild cases.
- Older patients may show LVH.

Indications for Treatment
- PDA dependency
- Hypertension
- LVH
- Gradient between arm and leg > 20 mmHg

Treatment

- In neonates with critical coarctation, initiation of PGE to reopen the PDA and then surgery.
- Transcatheter balloon angioplasty or stent placement in older children.
- Surgical excision is not amenable to transcatheter intervention.
- Rebound hypertension in the immediate postoperative period and late after repair can occur.
- Re-coarctation at the site of repair that can be treated with balloon angioplasty, stent, or surgery.

Hypoplastic Left Heart Syndrome (HLHS)

Anatomy

- Underdevelopment of the mitral valve, LV, and aortic valve
- Spectrum of severe mitral stenosis with aortic atresia to mitral/aortic atresia, all with small LV
- Associated aortic arch hypoplasia and coarctation

Physiology

- Obligate left-to-right shunt across ASD as egress from the left atrium
- No aortic antegrade flow, depends on R->L shunting across PDA for systemic perfusion

Description

- PDA dependent for systemic perfusion, may not present until PDA starts to close

Clinical Presentation

- Cyanosis
- Tachypnea
- Circulatory shock when the PDA closes
- Heart failure

Physical Examination

- Murmur of tricuspid insufficiency may be present.
- Flow murmur of increased volume across the pulmonary valve may be present.
- Poor peripheral perfusion if PDA is closing.

CXR

- Cardiomegaly
- Increased pulmonary vascular markings

ECG

- Diminished left-sided forces

Treatment

- PGE to maintain PDA
- Staged palliation (Norwood or hybrid, bidirectional Glenn, Fontan procedure)

CARDIOVASCULAR GENETICS

- Chromosomal abnormalities associated with congenital heart disease:
  - Trisomy 21: AV canal, VSD, ASD
  - Trisomy 18: VSD, PDA, PS
  - Trisomy 13: VSD, PDA
  - Wolf-Hirschhorn syndrome: ASD, VSD, PDA
  - *Cri-du-chat* syndrome: VSD, PDA, ASD
  - Turner syndrome: coarctation, aortic stenosis, ASD
- Microdeletion syndromes associated with cardiac disease:
  - 22q11 deletion (DiGeorge): tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, aortic arch anomalies
  - Williams syndrome: supravalvar aortic stenosis, supravalvar pulmonic stenosis
  - Single-gene disorders:
    - Marfan syndrome: aortic root dilation, mitral valve prolapse
    - Holt-Oram syndrome: ASD, VSD

- Noonan syndrome: pulmonary stenosis, hypertrophic cardiomyopathy, ASD, partial AV canal, coarctation
- Tuberous sclerosis: cardiac rhabdomyomas
- Cornelia de Lange syndrome: VSD
- Alagille syndrome: branch pulmonary artery stenosis

INFECTION/VASCULITIS

Acute Rheumatic Fever (ARF)

Background

- ARF is caused by previous group A streptococcal (GAS) pharyngeal infection.
- Due to immune-mediated inflammatory response to the infection.
- Most common among children aged 5–15 years.

Classified according to the Jones Criteria (2015) [2]

- Evidence of recent GAS infection:
  - Positive throat culture or rapid strep test.
  - Elevated or rising antistreptococcal antibody titer.
  - Initial diagnosis requires 2 major or 1 major and 2 minor.
  - Recurrent diagnosis requires same as initial or 3 minors.
- Minor criteria:
  - Fever ≥ 38.5 °C
  - Polyarthralgia
  - Erythrocyte sedimentation rate (ESR) ≥ 60 mm/h and/or C-reactive protein (CRP) ≥ 3 mg/dL
  - Prolonged PR interval
- Major criteria:
  - Polyarthritis
  - Carditis
  - Erythema marginatum
  - Subcutaneous nodules
  - Sydenham chorea

Diagnosis

- Evidence of a preceding GAS infection along with the presence of two major manifestations or one major and two minor manifestations
- Streptococcal antibodies: antistreptolysin O (ASO), antihyaluronidase (AHase), and anti-deoxyribonuclease B (anti-DNase B) antibodies

Treatment of ARF

- Aspirin 80–100 mg/kg/day, continued until all symptoms have resolved.
- Restricted activity/bed rest.
- Carditis is managed with therapies used for heart failure.
- Corticosteroids are used if carditis is severe.
- Eradication of GAS requires the same antibiotic regimens that are used to treat GAS pharyngitis.
- Household contacts should have throat culture and if positive for GAS should be treated.
- Prophylactic antibiotics should be started immediately after the therapeutic antibiotic course is complete:
  - Penicillin VK, sulfadiazine (or macrolides if allergic) for patients at lower risk of ARF recurrence.
  - Benzathine penicillin G intramuscularly every 4 weeks for patients at higher risk of ARF recurrence.
  - Prophylaxis should continue for several years, typically until a patient is an adult and recurrence-free for 10 years.
  - Longer prophylaxis is indicated if the patient has residual heart disease.

Kawasaki Disease (KD) [3]

Background

- Kawasaki disease is an acute vasculitis of childhood that leads to coronary artery aneurysms in ~25% of untreated cases.

- It is the most common cause of acquired heart disease in children in developed countries.
- The etiology of KD is unknown, but it occurs more commonly in winter and early spring in North America.
- Ratio of males to females is 1.5:1, with highest relative risk in Asian children.
- KD occurs most frequently in children < 5 years of age.

Clinical Presentation

Classic KD

- Presence of fever for at least 5 days (day of fever onset is the first day), with at least 4 of the 5 following principal clinical features:
  1. Erythema and cracking of lips, strawberry tongue, and/or erythema of the oral and pharyngeal mucosa
  2. Bilateral bulbar conjunctival injection without exudate
  3. Rash: maculopapular, diffuse erythrodermal, or erythema multiforme-like
  4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
  5. Cervical lymphadenopathy (≥ 1.5 cm diameter), usually unilateral
- Patients who lack full clinical features of classic KD may have incomplete KD.
- If coronary abnormalities are detected, the diagnosis of KD is considered confirmed.
- Other clinical findings:
  - Cardiovascular:
    - Myocarditis, pericarditis, valvular regurgitation, shock
    - Coronary artery abnormalities
    - Aneurysms of medium-sized noncoronary arteries
    - Peripheral gangrene
    - Aortic root enlargement
  - Respiratory:
    - Peribronchial and interstitial infiltrates on CXR
    - Pulmonary nodules
  - Musculoskeletal:
    - Arthritis, arthralgia (pleocytosis of synovial fluid)
  - Gastrointestinal:
    - Diarrhea, vomiting, abdominal pain
    - Hepatitis, jaundice
    - Gallbladder hydrops
    - Pancreatitis
  - Nervous system:
    - Extreme irritability
    - Aseptic meningitis (pleocytosis of cerebrospinal fluid)
    - Facial nerve palsy
    - Sensorineural hearing loss
  - Genitourinary:
    - Urethritis/meatitis, hydrocele
    - Others
    - Desquamating rash in the groin
    - Retropharyngeal phlegmon
    - Anterior uveitis by slit lamp examination

Incomplete KD

- A challenging subset of patients who do not meet the classic criteria of KD:
  - Children with fevers ≥ 5 days and 2 or 3 compatible clinical criteria
  - Infants with fevers ≥ 7 days without other explanations
- More common in infants and older children
- Important considerations:
  - Recommended: Infants younger than age 6 months who have had ≥ 7 days of fever of unclear etiology and elevated inflammatory markers undergo echocardiography.
  - Clinicians should not dismiss the diagnosis of KD in children who have symptoms that are attributed commonly to viral illnesses.
  - Coronary artery dilatation is generally not detected by echocardiography until after the first week of illness, and a normal echocardiogram in the first week of illness does not rule out the diagnosis of KD.

Laboratory Studies

- Laboratory tests are nonspecific but provide support for a diagnosis of KD in patients with suggestive but incomplete features. They are listed here in order of frequency of occurrence:
  - Erythrocyte sedimentation rate (ESR) ≥ 40 mm/h (in most cases of KD)
  - Serum C-reactive protein (CRP) ≥ 3 mg/dL (in most cases of KD)
  - Platelet count of ≥ 450,000/mm^3 after the seventh day of fever (in most cases of KD)
  - White blood cell count (WBC) ≥ 15,000/mm^3 (occurs commonly in KD)
  - Anemia (occurs commonly in KD)
  - Albumin ≤ 3 g/dL (occurs commonly in KD and is associated with a more severe and prolonged clinical course)
  - Urine 10 ≥ WBC/hpf (occurs in 80% of KD)
  - Elevated transaminases or gamma-glutamyl transpeptidase (occurs in 40–60% of KD)
  - Hyperbilirubinemia (occurs in 10% of KD)

Echocardiography

- Echocardiographic findings include as follows:
  - Coronary artery abnormalities
  - Valvular abnormalities (mitral and aortic valves)
  - Aortic root dilation
  - Myocardial dysfunction or myocarditis
- If the diagnosis is clear, treatment for KD should not be withheld while waiting to schedule or obtain the results of echocardiography.
- Echocardiography should be obtained at diagnosis, 1–2 weeks later, and 4–6 weeks after treatment.
- Children who have persistent or recrudescent fever or who have known coronary artery abnormalities need close follow-up with a pediatric cardiologist.

Treatment

- Once the diagnosis of KD is confirmed, treatment with high-dose intravenous immunoglobulin (IVIG) (2 g/kg) should be instituted promptly and continued until the patient is afebrile for 48 h. Treatment is administered within the first 10 days of illness onset but as soon as possible after diagnosis.
- Treatment with IVIG after day 10 of illness is reserved for those with ongoing fever and evidence of systemic inflammation on laboratory studies.
- Administration of high-dose aspirin (80–100 mg/kg/day) is reasonable until the patient is afebrile, although there is no evidence that this reduces coronary artery aneurysms.
- This may be changed to low-dose aspirin (3–5 mg/kg/day) once the child has been afebrile for 48–72 h.
- Low-dose aspirin is administered until 6–8 weeks after onset of illness and can then be discontinued if the echocardiographic findings are normal.
- Therapies used in IVIG resistance include corticosteroids or infliximab (a tumor necrosis factor inhibitor).
- Measles and varicella-containing vaccinations are contraindicated for 11 months after administration of IVIG.

Evaluation of Incomplete KD

- The American Heart Association (AHA) recommendations for incomplete KD:
  - If CRP < 3 mg/dL and ESR < 40 mm/h:
    - Continue monitoring (clinical symptoms and laboratory assessment) if fevers persist.
    - Echocardiogram if typical peeling develops
  - If CRP ≥ 3 mg/dL and/or ESR ≥ 40 mm/h:
    - Treat if there are positive echocardiogram findings or three or more laboratory findings:
      - Anemia for age

- Platelet count ≥ 450,000 after seventh day of fever
- Albumin ≤ 3 g/dL
- Elevated alanine transaminase (ALT) level
- WBC count of ≥ 15,000/mm^3
- Urine ≥ 10WBC/hpf

- Consultation with a KD expert if needed

Prognosis of KD

- Incidence of coronary artery involvement in treated children has fallen to less than 5%, and only 1% of children develop giant coronary aneurysms.
- Long-term prognosis is unclear. Increased risk of atherosclerotic heart disease in adulthood is possible.

Infective Endocarditis (IE)

Background

- The diagnosis can be obvious in the presence of persistently positive blood cultures with a predisposing cardiac lesion.
- Endocarditis in children is often associated with the presence of a predisposing cardiac lesion, an intravascular foreign body (central venous catheter, valve prosthesis, intracardiac device), and/or an immunocompromised host.

Clinical Presentation

- New regurgitant murmur or heart failure.
- Evidence of emboli to the fundi, skin, digits, or conjunctivae.
- Additional organ systems may be affected by emboli, including the kidneys, spleen, and brain.

The Duke Criteria

- Two major/one major and three minor/five minor criteria
- Major criteria:
  - Two positive blood cultures at least 12 h apart

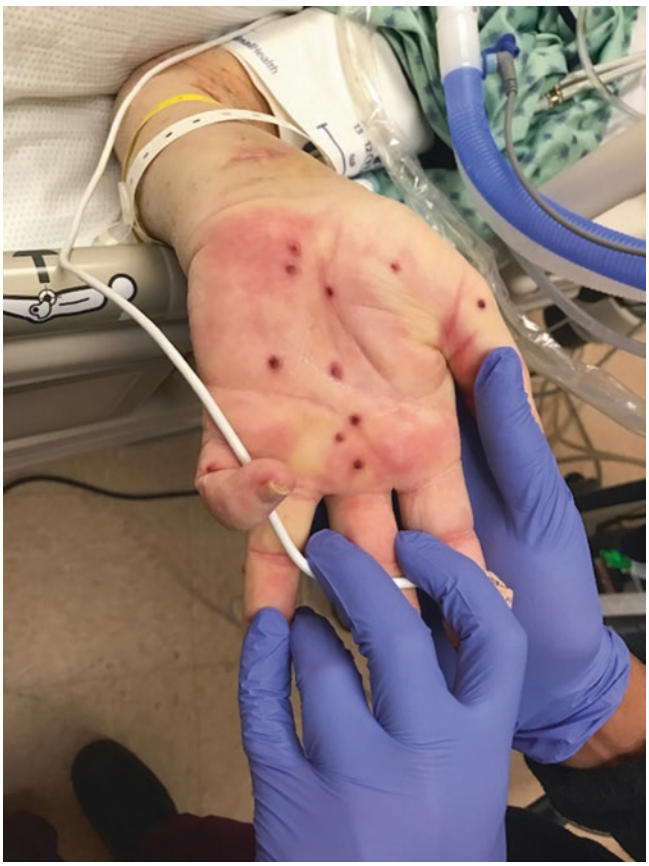


Fig. 19.14 Janeway lesions in a patient with infective endocarditis

  - Positive echocardiography for vegetation or new valvular regurgitation
- Minor criteria:
  - Predisposition to IE
  - Fever
  - Vascular phenomena (arterial emboli, septic pulmonary infarctions, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions (Fig. 19.14))
  - Immunologic phenomena such as glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
  - Single positive blood culture or serologic evidence of active infection with an organism consistent with IE

Antibiotic Prophylaxis

- Guidelines limit prophylaxis to cardiac conditions that have the highest risk of poor outcome from IE:

  - Prosthetic heart valves
  - Previous IE
  - Unrepaired cyanotic heart disease that includes palliative shunts and conduits
  - Completely repaired congenital heart disease with prosthetic material or device during the first 6 months following the procedure
  - Repaired congenital heart disease with residual defects at the site or next to the site of the prosthetic device
  - Valvulopathy in a transplanted heart

Indication for Prophylaxis

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
- Invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy or adenoidectomy
- Surgical procedures on infected tissue of skin or the musculoskeletal system

Prophylactic Antibiotics

- Ampicillin or first- or second-generation oral cephalosporins are recommended in nonallergic patients.

Treatment

- Antimicrobial therapy for IE should be administered in a dose designed to provide sustained bactericidal serum concentrations throughout the entire dosing interval.
- The minimum inhibitory concentration should be determined for all patients.
- The duration of intravenous antimicrobial therapy is approximately 4–6 weeks.

Acute Pericarditis

Background

- An inflammatory condition of the pericardium.
- Can present as chest pain in children.
- Pericarditis can be accompanied by myocarditis.

Causes

- Infection:
  - Viral is the most common cause in children.
  - Bacterial (staph, tuberculosis).
- Autoimmune disease
- Rheumatic fever
- Uremia
- Malignancy
- Reaction to a drug
- After cardiac surgery
- Idiopathic (one-third of the cases have no identifiable cause)

Clinical Presentation

- When viral, patients report a prodrome of fever or respiratory or gastrointestinal illness.
- Chest pain:
  - Substernal, sharp
  - Worse with inspiration
  - Relieved by sitting upright and leaning forward
  - Radiates to the scapular ridge due to irritation of the phrenic nerves

Physical Examination

- Friction rub (pathognomonic finding):
  - Scratchy, high pitched, to-and-fro sound
  - Loudest when the patient is upright and leaning forward
  - Heard best in the second to fourth intercostal spaces along the left sternal border or the mid-clavicular line
- If a large or rapidly developing pericardial effusion is present, patients can have the following:
  - Tachycardia
  - Pulsus paradoxus
  - Muffled heart tones

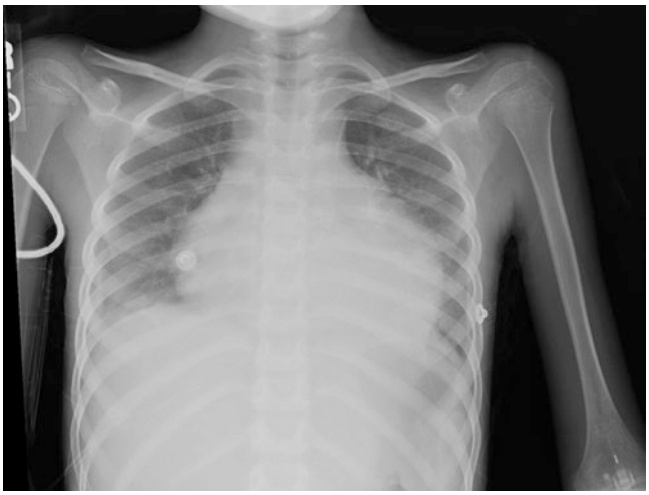


Fig. 19.15 8-year-old boy presenting with chest pain, tachycardia, and shortness of breath; *chest radiography* shows moderate cardiomegaly suggestive of pericardial effusion. Nonspecific increased central interstitial lung markings, presumably viral pneumonitis

Diagnosis

- Labs may show elevations of the WBC, ESR, and CRP.
- If there's myocardial involvement, the plasma troponin concentration also may be increased.

CXR

- Usually appears normal in patients who have acute pericarditis.
- When a significant pericardial effusion is present, the heart may have a triangular shape with a smooth border, known as a "water bottle heart" (Fig. 19.15).

ECG

- Diffuse ST segment elevation and PR segment depression
- *If* associated pericardial effusion:
  - Low-voltage QRS complex on ECG.
  - Amplitude of the QRS complex returns to normal after the pericardial effusion resolved or is drained.
- Echocardiography:
  - Pericardial effusion
  - Evidence of decreased RV filling (right atrial collapse, RV free wall compression, distended systemic veins)

Management

- Identify and, if possible, treat the underlying cause.
- Pericardiocentesis if there is evidence of tamponade.
- Symptoms tend to resolve within days for most patients.
- Ibuprofen is the preferred first-line agent because it has the lowest incidence of adverse effects.

Complications

- Recurrence (most likely with autoimmune causes)
- Constrictive pericarditis

Cardiac Tamponade

Background

- Pericardial effusion rapidly exceeds the pericardial reserve volume:
  - Effusion can be serous, hemorrhagic, chylous, or infectious.
- Rapidity of accumulation rather than volume more likely affects hemodynamics.
- Increases intrapericardial pressure, impairs cardiac filling, and results in decreased cardiac output.

Clinical Presentation

- Sudden onset of acute dyspnea/orthopnea
- Tachycardia
- Distant heart sounds
- Pulsus paradoxus (PP): > 10-mmHg drop in systolic blood pressure during nonmechanical inspiration
- If PP is significant, can be palpated on physical exam

CXR
- Water bottle heart
- New cardiomegaly

ECG
- Electrical alternans: cyclic variation in QRS caused by excessive motion of the heart within a fluid-filled pericardial sac
- Decreased voltages

Echocardiogram
- Effusion noted in the pericardial space, size itself not diagnostic, clinical diagnosis
- > 30% variation of mitral valve "E" Doppler with inspiration, correlates with PP
- RV/atrial collapse

Management
- Maintain adequate preload to maintain cardiac filling.
- Requires an emergent pericardiocentesis, can be done with echo guidance.

Constrictive Pericarditis

Background
- Obliteration of the pericardial space secondary to inflammation.
- Tuberculosis is the most common cause worldwide.

Clinical Presentation
- Signs and symptoms of right-sided heart failure
- Physical Examination
  - Faint friction rub
  - Diastolic knock
  - Jugular venous distention
  - Hepatomegaly

Myocarditis

Definition
- Inflammation of the myocardium

Causes
- Viral: most common, especially enteroviruses such as coxsackie B virus
- Bacterial: *Streptococcus pyogenes*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*
- May also be caused by fungi, protozoa, autoimmune diseases

Clinical Presentation
- Symptoms frequently may follow history of flu-like illness (fever, fatigue, malaise).
- Symptoms may range from mild to severe and may include the following:
  - Lethargy
  - Respiratory distress
  - Chest pain
  - Gastrointestinal symptoms
  - Other symptoms of heart failure
  - Shock
- Physical exam is variable according to severity and may include the following:
  - Resting tachycardia (sinus)
  - Tachypnea
  - Rales
  - Muffled heart sounds or gallop rhythm
  - Hepatomegaly
  - Lower extremity edema
  - Poor perfusion

CXR
- Pulmonary edema.
- Cardiomegaly may or may not be present.

ECG
- Low voltage.
- ST segment and T-wave abnormalities.
- Dysrhythmias may be present.
- Ischemic changes.

Echocardiogram
- Decreased ejection fraction.
- Ventricular dilation may or may not be present.
- Pericardial effusion.

Laboratory

- Elevated troponin and brain natriuretic peptide (BNP).
- CRP or ESR may be elevated.
- Positive viral studies may be supportive of myocarditis, although not definitive.
- Definitive diagnostic test is myocardial biopsy with polymerase chain reaction (PCR), although biopsy can be negative because of the patchy nature of myocarditis.

Management

- Supportive treatment (inotropic agents, diuretics, afterload-reducing medications).
- Evidence for IVIG or corticosteroids is lacking.
- If medications fail, mechanical support (extracorporeal membrane oxygenation [ECMO] or ventricular assist device) may be needed.
- Heart transplant for refractory heart failure.

HEART FAILURE

Congestive Heart Failure

Background

- Definition—cardiac output is insufficient to meet the metabolic demands of the body:
  - Low cardiac output: decreased stroke volume +/- decreased heart rate
  - High metabolic demand: increased blood volume, increased metabolic rate

Causes

- Congenital heart disease:
  - Left-to-right shunt causing excessive pulmonary blood flow—generally presents at 1–3 months of life when pulmonary vascular resistance falls to normal:
    - VSD
    - Atrioventricular canal defect (AVCD)
    - PDA
    - Transposition of the great arteries (TGA)
    - Truncus arteriosus (TA)
    - Totally anomalous pulmonary venous connection (TAPVC)
  - Valve insufficiency—depending on severity, may present anytime between infancy to adolescence. Generally, left-sided insufficiency will present earlier:
    - Tricuspid or pulmonary insufficiency: increased RV volume load
    - Mitral or aortic insufficiency: increased LV volume load
  - Obstructive lesions—generally presents in the newborn to early infancy period as the PDA begins to close:
    - Aortic, pulmonary, and mitral valve stenosis
    - Coarctation of the aorta
    - Interrupted aortic arch
    - Hypoplastic left heart syndrome (HLHS)
- Other intrinsic heart diseases:
  - Cardiomyopathies—depending on severity, may present anytime between infancy to adolescence:
    - Dilated cardiomyopathy
    - Restrictive cardiomyopathy
    - Hypertrophic cardiomyopathy
    - LV noncompaction
  - Dysrhythmias—variable timing of presentation, depending on etiology:
    - Supraventricular tachycardia
    - Ectopic atrial tachycardia
    - Atrial flutter/fibrillation with rapid ventricular response
    - Inappropriate bradycardia
    - Congenital heart block
- Acquired heart disease—variable timing of presentation, depending on etiology. Infections may occur at any time. The risks of anthracycline toxicity and failing Fontan circulation increase as the patient gets older:
  - Viral myocarditis
  - Other cardiac infections (endocarditis, pericarditis)
  - Pericardial effusion or tamponade
  - Anthracycline toxicity

  - Failing Fontan circulation
  - Myocardial infarction
- High metabolic demand (i.e., high-output heart failure):
  - Septic shock
  - Arteriovenous malformations
  - Anemia
  - Thyrotoxicosis

Clinical Presentation

- Neonate:
  - Lethargy
  - Respiratory distress
  - Irritability
  - Shock
- Infant:
  - Failure to thrive
  - Poor feeding
  - Increased fatigability
  - Respiratory distress or tachypnea
  - Irritability
- Older children:
  - Exercise intolerance
  - Gastrointestinal complaints: abdominal pain, anorexia, nausea, vomiting
  - Respiratory symptoms: cough, wheezing, dyspnea, orthopnea
  - Weight gain (from fluid accumulation)

Diagnostic Evaluation

- Vital signs:
  - Desaturation
  - Tachycardia
  - Tachypnea
  - Hypotension
  - Weight gain or loss
- Potential physical examination findings:
  - General: discomfort, agitation, cyanosis, pallor, diaphoresis, failure to thrive
  - Head, eyes, ears, nose, and throat (HEENT): jugular venous distension
  - Respiratory: tachypnea, rales, grunting, retractions
  - Cardiovascular: pansystolic mitral regurgitation murmur, gallop rhythm
  - Abdomen: hepatomegaly, ascites, abdominal pain
  - Extremities: peripheral edema, cool extremities, prolonged capillary refill time
- CXR:
  - Cardiac enlargement
  - Pulmonary congestion
- ECG:
  - Dysrhythmias
  - Atrial enlargement
  - Ventricular hypertrophy
  - Right or left bundle branch block
  - Abnormal repolarization pattern
- Echocardiography:
  - Structural heart disease
  - Systolic or diastolic ventricular dysfunction
  - Atrial or ventricular dilation
  - Valve regurgitation or stenosis
  - Effusions (both pericardial and pleural)
- Laboratory studies:
  - BNP and N-terminal pro-b-type natriuretic peptide (NT-proBNP)
  - Inflammatory markers: CRP, ESR
  - Markers of cardiac ischemia: troponin

Management

- Acute:
  - Assessment of fluid status and cardiac output:
    - Fluid overload:
      - Diuretics
      - Ultrafiltration
    - Low cardiac output:
      - Inotropic support (epinephrine, dopamine, milrinone)
      - Vasodilation and lusitropic support (milrinone)
      - Mechanical circulatory support
      - ECMO
      - Ventricular assist device
  - Prompt treatment of noncardiac causes of heart failure such as the following:
    - Anemia
    - Hypo-/hyperthyroidism
    - Sepsis/acidosis
    - Infection

  - Corrections of structural cardiac anomalies:
    - Closure of intracardiac shunts
    - Relief of left or right ventricular outflow tract obstruction
    - Relief of valvular regurgitation
    - Treatment of cardiac dysrhythmia
  - Cardiac transplantation
- Chronic:
  - Diuretics (typically with a loop diuretic such as furosemide): relieve signs and symptoms of volume overload
  - Afterload reduction:
    - Angiotensin-converting enzyme inhibitors
    - Beta-blockers
    - Angiotensinogen II receptor antagonist
  - Reverse remodeling agents:
    - Mineralocorticoid receptor antagonist
  - Cardiac glycosides (e.g., digoxin)

CARDIOMYOPATHIES

Dilated Cardiomyopathy

Description

- Disease of the myocardium characterized by ventricular dilation and decreased ejection fraction

Causes

- Idiopathic
- Familial with different genetic inheritance
- Cardiotoxic drugs, e.g., anthracyclines
- Neuromuscular diseases
- Metabolic/nutritional
- Autoimmune disease
- Severe anemia
- Thyrotoxicosis
- Tachyarrhythmia (supraventricular tachycardia, ectopic atrial tachycardia)

Clinical Presentation

- Heart failure
- Physical examination:
  - Murmur of mitral insufficiency
  - S3 gallop
  - Hepatomegaly
  - Jugular venous distention
  - Tachypnea and rales

CXR

- Cardiomegaly
- Pulmonary edema

ECG

- RVH and LVH
- Atrial enlargement
- Nonspecific ST segment or T-wave changes

Echocardiography

- Dilation of all the chambers and poor contractility

Treatment

- Treatment of congestive heart failure
- Treatment of the underlying cause
- Heart transplant for unresponsive cases

Restrictive Cardiomyopathy

Description

- Disease of the myocardium characterized by elevated diastolic filling pressures, dilated right and left atrium, and normal ventricular size and function

Causes

- Idiopathic
- Sarcoidosis
- Amyloidosis
- Mucopolysaccharidoses
- Radiation
- Malignancy

Clinical Presentation

- Heart failure
- Pulmonary hypertension
- Atrial arrhythmias
- Thromboembolism

CXR
- Mild to moderate atrial enlargement

ECG
- Biatrial enlargement
- Nonspecific T-wave abnormalities

Echocardiography
- Atrial enlargement
- Normal LV and RV size and function

Management
- Treatment of heart failure and arrhythmia
- Heart transplantation

Hypertrophic Cardiomyopathy (HCM)

Description
- Disease of the myocardium characterized by increased ventricular wall thickness and mass with normal or hyperdynamic ventricular function.
- HCM is the most common cardiac cause of sudden death in adolescents and young adults.
- HCM occurs in 1 out of 500 people (0.2% of the population).

Causes
- Genetic disorder:
  - Familial hypertrophic cardiomyopathy is autosomal dominant in 50% of cases.
- Idiopathic
- Metabolic

Clinical Presentation
- Sudden death (the most devastating presentation)
- Dyspnea (the most common presenting symptom in adults)
- Syncope or presyncope
- Angina
- Palpitation
- Dizziness
- Physical examination:
  - Double apical impulse
  - S4 gallop
  - Systolic ejection crescendo-decrescendo murmur (best heard at the apex and left sternal border):
    - Valsalva maneuver or standing increases the murmur (due to decrease in the preload).
    - Murmur decreases with hand grip (due to increase in afterload) or squatting (due to increase in the preload).
  - Murmur of mitral insufficiency (holosystolic murmur)

CXR
- Mild cardiac enlargement
- LV and left atrial hypertrophy

ECG
- LVH
- Inverted T-waves in left leads
- Nonspecific T-wave abnormality

Echocardiography
- Shows the pattern of hypertrophy
- Shows the flow gradient across the left and right ventricular outflow tracts
- Diastolic dysfunction

Management
- In symptomatic patients, beta-blocker or calcium channel blocker may decrease the outflow obstruction and improve the symptoms.
- Implantable defibrillator *if*:
  - Aborted cardiac arrest
  - History of ventricular tachycardia
  - Family history of sudden cardiac death
  - Massive hypertrophy (LV wall thickness $\geq$ 30 mm)
- Myomectomy.
- Heart transplant.

MISCELLANEOUS

Sudden Cardiac Death

- Incidence is ~0.6 to 6/100,000 children in the United States.
- 20 to 25% of sudden cardiac deaths occur during sports.
- Causes:
  - Hypertrophic cardiomyopathy (most common cause)
  - Coronary artery abnormalities
  - Marfan syndrome
  - Congenital heart disease
  - Myocarditis
  - Inherited arrhythmias (long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, etc.)
  - WPW syndrome
  - Ischemic heart disease
  - Other cardiomyopathies (dilated, arrhythmogenic RV dysplasia)
  - Commotio cordis

Superior Vena Cava Syndrome

Background

- Occurs in the setting of obstructed systemic venous return from the upper body to the heart
- Results in increased central venous pressures and presents clinically with swelling of the upper extremities, head, or face
- Can be caused by stenosis or occlusion of the lumen internally by clot (hypercoagulable state, thromboses from indwelling lines) or external compression by a mass

Clinical Presentation

- Swelling and edema of the head and upper extremities
- Prominent venous distention in the same distribution
- Chylothorax

Diagnoses

- Doppler ultrasound may show occluded SVC and other systemic veins; may be limited by acoustic windows and location of obstruction.
- Angiography will show occlusion and formation of collaterals; could have intervention in the cardiac catheterization lab for dilation, stenting, and recanalization.

Dyslipidemia

Background

- Dyslipidemia refers to a pathologic imbalance in the levels of low-density lipoprotein (LDL) cholesterol (LDL-C), high-density lipoprotein (HDL) cholesterol, and triglycerides.
- It is recognized as a risk factor for adult cardiovascular disease (CVD).
- Elevated cholesterol levels continue into adulthood.
- Treating childhood dyslipidemia may help prevent or reduce the risk of adult CVD and reduce the atherosclerotic burden later in life.

Screening Target Group (Table 19.1)

- Birth to 2 years: no lipid screening.
- For age 2–8 years: Obtain fasting lipid profile (FLP) only if there's family history (+) for early CVD, a parent with dyslipidemia, any other risk factors (+), or high-risk conditions.
- For age 9–21 years: Obtain universal lipid screen between age 9–11 and 17–21 years, with nonfasting non-HDL cholesterol (for age 9–19 years < 145; for age 20–21 < 190), or FLP and manage per lipid algorithms as needed.
- Risk stratification and management of children with conditions predisposing to accelerated atherosclerosis and early CVD (Table 19.2):
  - Step 1: Risk stratification by disease process

Table 19.1 Screening target groups for dyslipidemia

Recommendations	Age < 10 years	Age 10–19 years	Age 20–21 years
Target TGs	TGs < 100, LDL-C < 130	TGs < 130, LDL-C < 130	TGs < 150, LDL-C < 160
Manage as per algorithm	TG ≥ 100 < 500,	TG ≥ 130 < 500	High levels—manage as per adult treatment panel (ATP III algorithm)
	LDL-C ≥ 130 ≤ 250	LDL-C ≥ 130 ≤ 250	
Consult lipid specialist	TGs > 500, LDL-C > 250	TGs > 500, LDL-C > 250	

ATP Adenosine triphosphate, *LDL-C* Low-density lipoprotein cholesterol, *TG* Triglyceride

Table 19.2 Risk stratification and management of children with conditions predisposing to accelerated atherosclerosis and early cardiovascular disorders

Risk level	Step 1	Step 2	Step 3	Step 4
High	1. DM I and 2	*CVD risk factors*	*High-risk cutoffs*	Intensive lifestyle management
	2. CKD/end-stage renal disease/post-kidney transplant	1. Family history of early CVD (♂ ≤ 55 years; ♀ ≤ 65 years)	1. BMI ≤ 85th percentile	CHILD 1
				Activity Rx
				Weight loss as needed
	3. Post-heart transplant	2. Fasting lipid profile	2. BP < 90th percentile for age, sex, and height percentile	Condition-specific management
	4. Kawasaki disease with current coronary artery aneurysms	3. Smoking history		
		4. BP (3 separate occasions) for age/sex/height (percentile)	3. LDL-C < 120, TG < 90	
			Non-HDL-C < 120	
		5. Height, weight, BMI	4. FG < 100, HBA1c < 7%	
Moderate	1. Kawasaki disease with regressed coronary aneurysms	6. Diet, physical activity/exercise history	*Moderate-risk cutoffs*	Intensive lifestyle management
			1. BMI < 90th percentile	CHILD 1
			2. BP ≤ 95th percentile for age, sex, and height percentile	Activity Rx
	2. Chronic inflammatory disease			Weight loss as needed
	3. HIV		3. LDL-C < 130, TG < 130	
	4. Nephrotic syndrome			
			Non-HDL-C < 140	
			4. FG < 100, HbA1c < 7%	

ATP Adenosine triphosphate, *BMI* Body mass index, *BP* Blood pressure, *CHILD 1* Cardiovascular Health Integrated Lifestyle Diet from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, *CKD* Chronic kidney disease, *CVD* Cardiovascular disorder, *DM* Diabetes mellitus, *FG* Fibrinogen, *HbA* Glycated hemoglobin, *HDL-C* High-density lipoprotein cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *Rx* prescription, *TG* Triglyceride

  - Step 2: Access CVD risk factors (≥ 2 risk factors move to high risk)
  - Step 3: Risk-specific cutoff points and treatment goals
  - Step 4: Lifestyle change
  - Step 5: Drug therapy

Management

- Drug treatment:
  - LDL > 190 mg/dL if there's no risk factor despite the diet therapy
  - LDL > 160 mg/dL with positive family history or one high-risk factor or two moderate-risk factors
  - LDL > 130 mg/dL with two high-risk factors, one high- and two moderate-risk factors, or clinical CVD
- Statins:
  - Are the recommended initial medication therapy for dyslipidemia in children and adolescents
  - Adverse effects of statins

  - Hepatic transaminase level elevation
  - Creatine kinase elevation and rarely episodes of rhabdomyolysis

PEARLS AND PITFALLS

- Exertional chest pain or chest pain associated with palpitations, syncope, abnormal physical exam, or family history of significant cardiac disease should be further evaluated.
- Syncope is usually benign in pediatrics, but exertional syncope is unusual and can be a sign of a life-threatening condition.
- Ductal-dependent lesions may not present until the PDA begins to close.
- Left-to-right shunt lesions may not present until the PVR drops and there is increased shunting.
- Timing of presentation of left-to-right shunt lesions depends on the rapidity of the drop in PVR as well as the size of the defect.
- Clinical cyanosis and oxygen saturation are dependent on hemoglobin, as it takes 5–10 g of desaturated hemoglobin to clinically appear cyanotic.
- If the patient with a complete AV canal defect does not develop pulmonary overcirculation, it is concerning for elevated PVR.
- Kawasaki disease is the most common cause of acquired heart disease in children of developed countries and usually occurs in children under 5 years of age. KD should be treated with high-dose IVIG as soon as the diagnosis is made. If left untreated, KD leads to coronary artery aneurysms in 25% of cases.
- Myocarditis is most often due to a viral infection, with enteroviruses (such as coxsackie B virus) commonly associated with viral myocarditis.
- In neonates and infants, heart failure commonly presents as failure to thrive, poor feeding, respiratory distress, and irritability. In older children, heart failure commonly presents with exercise intolerance, gastrointestinal complaints, and respiratory symptoms.
- Hypertrophic cardiomyopathy is the most common cardiac cause of sudden death in adolescents and young adults.

Acknowledgement The authors gratefully acknowledge the contributions of Joseph Mahgerefteh, MD, and Daphne T. Hsu, MD, both providers in Pediatric Cardiology, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, New York, to the first edition of this chapter, many of which have been incorporated into this edition as well.

References

1. Artman M, Mahony L, Teitel DF, editors. Neonatal cardiology. 3rd ed. New York: McGraw Hill Education/Medical; 2017.
2. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation. 2015;131(20):1806–18.
3. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Epidemiology and Prevention, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. 2017;135(17):e927–99.

Suggested Reading

Abdurrahman L, Bockoven JR, Pickoff AS, Ralston MA, Ross JE. Pediatric cardiology update: office-based practice of pediatric cardiology for the primary care provider. Curr Probl Pediatr Adolesc Health Care. 2003;33(10):318–47.

Blake JM. A teen with chest pain. Pediatr Clin N Am. 2014;61(1):17–28.

Burke RJ, Chang C. Diagnostic criteria of acute rheumatic fever. Autoimmun Rev. 2014;13(4/5):503–7.

Durani Y, Giordano K, Goudie BW. Myocarditis and pericarditis in children. Pediatr Clin N Am. 2010;57(6):1281–303.

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128(Suppl 5):S213–56.

Frank JE, Jacobe KM. Evaluation and management of heart murmurs in children. Am Fam Physician. 2011;84(7):793–800.

Hsu DT, Pearson GD. Heart failure in children: Part I: history, etiology, and pathophysiology. Circ Heart Fail. 2009;2(1):63–70.

Hsu DT, Pearson GD. Heart failure in children: Part II: diagnosis, treatment, and future directions. Circ Heart Fail. 2009;2(5):490–8.

Liberthson RR. Sudden death from cardiac causes in children and young adults. N Engl J Med. 1996;334(16):1039–44.

Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA. 1996;276(3):199–204.

Menashe V. Heart murmurs. Pediatr Rev. 2007;28(4):e19–22.

Newburger JW, Takahashi M, Gerber MA, Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis and Kawasaki disease, council on cardiovascular disease in the young, American Heart Association. Circulation. 2004;110:2747.

Pilcher TA, Saarel EV. Teenage fainter (dizziness, syncope, postural orthostatic tachycardia syndrome). Pediatr Clin N Am. 2014;61(1):29–43.

Section on Cardiology and Cardiac Surgery. Pediatric sudden cardiac arrest. Pediatrics. 2012;129(4):e1094–102.

Silka MJ. Sudden death due to cardiovascular disease during childhood. Pediatr Ann. 1991;20(7):360–7.

Pulmonology

20

Tanya Martínez-Fernández, Yadira Rivera-Sánchez, and Preeti Sharma

DIAGNOSTIC TESTING FOR RESPIRATORY CONDITIONS

Pulmonary Function Testing (PFT)

Definition of lung volumes and capacities:

- 4 volumes:
  - IRV inspiratory reserve volume
  - TV tidal volume
  - ERV expiratory reserve volume
  - RV residual volume: Volume at maximal expiration
- Capacities are sums of volumes
  - TLC total lung capacity (all four volumes) – volume at maximal inspiration
  - IC inspiratory capacity: (TV + IRV)
  - FRC functional residual capacity (RV + ERV) – resting volume at the end of normal expiration
  - VC vital capacity: (RV + ERV + TV = TLC – RV)

Spirometry

- Provides objective measurements that can be tracked over time
- Forced maneuver breathing from full inspiration (TLC) to RV capturing VC
- Displays volume exhaled and flow rates
  - FVC—volume after full-forced exhalation
  - FEV1—volume exhaled during first sec
  - FEV1/FVC ratio—low with obstruction
  - FEF 25–75—average flows between 25% and 75% of the maneuver
- Interpreted to show obstruction (low flow), restriction (low volume), or mixed process (Fig. 20.1)
  - Obstruction: N ↓ FVC, ↓ FEV1, ↓ FEV1/FVC, ↓ FEF 25–75
  - Restriction: ↓ FVC, ↓ FEV1, N FEV1/FVC, ↓ FEF 25–75
- Consider further testing if spirometry is normal, but positive for asthma-type symptoms:
  - Measurement of spirometry pre and post bronchodilator can be used to evaluate for airway reactivity
    - Increase in FEV1 after bronchodilator (significant if > 12% change)
  - Bronchial challenge testing to measure bronchoconstriction
  - Inhalation challenge or exercise challenge (e.g., methacholine, histamine, cold air, exercise)

Lung Volumes

- Useful in evaluation of restrictive lung disease (low TLC)

T. Martínez-Fernández (✉) · Y. Rivera-Sánchez · P. Sharma
Division Respiratory Medicine, Department of Pediatrics, University of Texas Southwestern Medical Center/Children's Medical Center Dallas, Dallas, TX, USA
e-mail: tanya.martinez@utsouthwestern.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_20

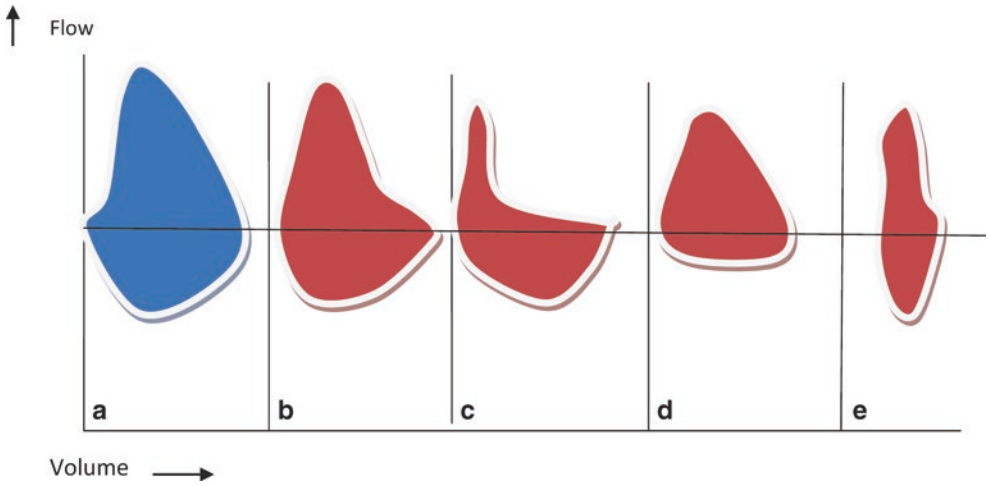


Fig. 20.1 Flow volume loop configurations in normal and different pulmonary disorders. Loop above line is expiratory loop; loop below line is inspiratory. (**a**) Normal; (**b**) early small airway obstruction; (**c**) chronic obstructive disease; (**d**) variable extrathoracic large airway obstruction, e.g., vocal cord pathologies; (**e**) restrictive diseases

- Measurement of RV impossible with spirometry
  - Evaluated by
    - Plethysmography (body box)—most accurate
    - Nitrogen washout, underestimates volume, if obstructive process present

Diffusion capacity measured with use of carbon monoxide gas

- Measure of gas transfer across alveolar-capillary barrier
  - May be decreased in interstitial lung disease, after lung resection

Pulse Oximetry

- Noninvasive, continuous, and rapid measure of peripheral oxygen saturation (SpO2)
- SpO2 estimates percentage of hemoglobin bound by oxygen
- Oxyhemoglobin curve dissociation curve = relation between partial pressure oxygen (pO2) and hemoglobin saturation (Fig. 20.2)
  - In hypoxia, pO2 is on steep part of curve = small pO2 changes, but large SpO2 changes
  - Acidosis, hyperthermia, increase in CO2 shifts curve to the right (lower SpO2 for same pO2)

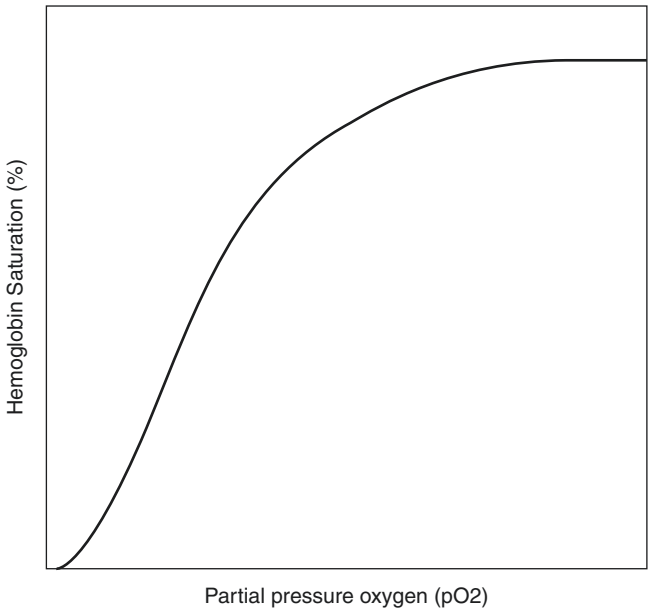


Fig. 20.2 Oxyhemoglobin saturation curve

- Limitations of pulse oximetry
  - Inaccurate readings with poor perfusion, severe anemia, motion artifact, shifts in oxyhemoglobin dissociation curve (e.g., acidosis), deep pigmentation of the skin, dark nail polish
  - Presence of methemoglobinemia and carboxyhemoglobin not recognized by most oximeters and may overestimate SpO2
  - Co-oximeter used to measure effect of dyshemoglobinemias

Blood Gas Analysis

- Gold standard for blood gas analysis is an arterial blood gas (ABG) sample.
- ABG interpretation (see Table 20.1 for ABG values associated with various conditions)
- Upper airway obstruction
  - Early increase in pCO2 and proportionate decrease in pO2. Initially responds well to supplemental oxygen
- Intrapulmonary airway obstruction
  - Mild: Decrease in pCO2, normal to decreased pO2
  - Moderate: Normal pCO2, decrease pO2 moving toward failure
  - Severe: Increase pCO2 and decrease pO2
  - Supplemental oxygen will support patient, but imperative to monitor carbon dioxide as well
- R-L shunt
  - Early decrease in pO2
  - Normal or low pCO2, high pCO2 with development of fatigue
  - Testing with 100% oxygen helps to define: Response to supplemental oxygen is fair to poor, depending on degree of shunt

Limitations of capillary blood gases (CBG)

- Arterialized CBG obtained by warming of a well-perfused heel or earlobe
- CBG is more easily attainable than arterial sample
- Values are comparable to arterial pH and pCO2, but pO2 measurement in CBG is less reliable
- Inaccuracy of blood gas measurements increased if sample processing is delayed, white blood cell (WBC) metabolism continues to consume oxygen and results in acidosis

Chest Imaging

Suggested modalities for various issues

Table 20.1 Arterial blood gases: values associated with various conditions

Acid-base abnormality	pH	pCO2	HCO3	Possible causes
Normal range	7.35–7.45	35–45	21–27	
Respiratory acidosis				Hypoventilation, neuromuscular disorders, severe asthma exacerbation, airway obstruction, intrinsic lung disease, pneumonia
Acute	↓	↑	N	
Compensated	N↓	↑	↑	
Respiratory alkalosis				Pain, hyperventilation, pulmonary embolism, high altitude
Acute	↑	↓	N	
Compensated	N↑	↓	↓	
Metabolic acidosis				Methanol, diabetic ketoacidosis, inborn error of metabolism, lactic acidosis, salicylates, diarrhea, shock
Acute	↓	N	↓	
Compensated	N↓	↓	↓	
Metabolic alkalosis				Vomiting, diuretics, primary aldosteronism
Acute	↑	N	↑	
Compensated	N↑	↑	↑	

N Normal

- **Plain chest radiograph (CXR)**
  - Upright views: Atelectasis, pneumonia, pneumothorax
  - Inspiratory and expiratory or bilateral decubitus views for suspected foreign body may be able to see asymmetric hyperinflation inside with foreign body due to check valve effect
    - Most foreign bodies not seen, as they are radiolucent
    - In bilateral decubitus views, dependent side should have lower volume (like expiratory view) than upright side
  - Decubitus views: Pleural fluid, pneumothorax
- **Fluoroscopy:** Tracheomalacia, diaphragmatic movement
- **Upper gastrointestinal (UGI) series:** Vascular ring, tracheoesophageal fistula
- **Video swallow study:** Aspiration
- **Ultrasound:** Pleural effusion, complicated pneumonia, diaphragm
- **Computed tomography (CT) scan:**
  - Best at providing images of lung anatomy, airway tree, parenchyma, and vascular structures
  - High resolution: Better to evaluate parenchyma like in bronchiectasis or interstitial lung disease
  - Contrast: Used to evaluate for lymphadenopathy, masses, vascular abnormalities, arteriovenous malformations, pulmonary embolism
- **Positron emission tomography (PET) scan:** Anterior, middle mediastinal masses, lymphoma
- **Ventilation-perfusion scan:** Pulmonary embolism
- **Magnetic resonance imaging (MRI):** Vascular lesions, mediastinal and chest wall masses

GENERAL SIGNS AND SYMPTOMS

Stridor/Wheezing

Background

- Wheezing
  - A musical, high-pitched whistling sound produced by airflow turbulence
  - One of the most common symptoms in asthma (see amplified discussion)
- Stridor
  - High-pitched, harsh sound often audible without the stethoscope
  - Results from rapid, turbulent airflow through a partially obstructed airway
- Inspiratory versus expiratory
  - *In*spiratory—*Ex*trathoracic swelling or obstruction will lead to airway collapse on inspiration. Example: Laryngomalacia
  - *Ex*piratory—*In*trathoracic swelling or obstruction will lead to airway collapse on expiration. Example: Tracheomalacia
  - *Biphasic stridor*—Indicates fixed airflow obstruction, subglottic space obstruction

Differential Diagnosis of Acute Stridor

- **Croup or laryngotracheobronchitis** (see amplified discussion)
- **Foreign body aspiration** (see amplified discussion)
  - Most common between 1 and 3 years of age
  - Sudden onset with cough, stridor, or wheezing
- **Bacterial tracheitis** (see amplified discussion)

- **Spasmodic croup or acute spasmodic laryngitis**
  - Children 6 months to 5 years
  - No viral etiology but symptoms similar to viral croup
  - May be triggered by gastrointestinal (GI) reflux
- **Retropharyngeal abscess**
  - Preschool age group
  - Abrupt onset of high fevers, difficulty swallowing, refusal to feed, sore throat, hyperextension of the neck or torticollis, and respiratory distress
- **Peritonsillar abscess**
  - Preadolescents and adolescents
  - Severe throat pain, trismus, muffled voice, trouble swallowing or speaking
- **Allergic reaction or anaphylaxis**
  - Associated with itchiness or hives
  - History of allergy

Differential Diagnosis of Chronic Stridor

Laryngomalacia

- Most common cause of stridor in infants
- Accounts for up to 75% of all causes of stridor

Clinical presentation

- Onset shortly after birth, minimal respiratory distress, positional effects, and marked reduction of noise when infant is at rest
- May present with apnea and feeding difficulties
- Stridor improves in prone position with head elevated and worsens in supine position
- Associated with normal voice quality and pitch

Diagnosis

- Diagnosis cannot be established on the basis of standard radiograph of the neck
- Flexible laryngoscopy can confirm the diagnosis but may miss tracheal abnormalities that can be identified with bronchoscopy
- If moderate to severe obstruction, difficulty with feeding and breathing, or unable to gain weight, flexible or rigid bronchoscopy to rule out other associated airway anomalies

Management

- Usually benign and self-limiting and improves as the child reaches 1–2 years of age
- Careful observation and growth monitoring for most patients
- Surgical correction may be considered in severe cases
- Resolution of symptoms for most patients without therapy in early childhood

Choanal Atresia

- 50% associated with congenital anomalies (i.e., CHARGE association, mnemonic for ***C***oloboma, ***H***eart defects, ***C***hoanal atresia, ***R***etarded growth and development, ***G***enital abnormalities, and ***E***ar anomalies)
- Bilateral—medical emergency during neonatal period, intermittent respiratory distress relieved by crying
- Unilateral—chronic mucoid nasal discharge on affected side in older infants/young children
- Diagnosis: Inability to pass a 6F catheter into oropharynx through nose
- Management: Surgical

Vocal Cord Paralysis (VCP)

- Second most common cause of stridor in infants
- May result from local trauma
- Left side VCP may result from trauma to the recurrent laryngeal nerve at birth or surgical trauma
- Unilateral—congenital or secondary to birth or surgical trauma such as cardiothoracic surgery

- Bilateral—associated with central nervous system abnormalities such as Arnold-Chiari malformation, tumors, or increased intracranial pressure

Clinical presentation

- Unilateral VCP—hoarse voice, weak cry, and biphasic stridor that is louder when awake. Improves when lying with the affected side down
- Bilateral VCP—high-pitched biphasic stridor that may progress to severe respiratory distress. Rarely associated with abnormal vocalization
- Bilateral VCP is associated with increased risk of recurrent aspiration
- VCP may be an early sign of brain stem or spinal cord compression

Imaging

- MRI of the upper spinal cord and brain stem may be required in evaluating patients with unexplained bilateral VCP

Management

- Presence of aspiration and the degree of airway obstruction—primary indicators of need for therapy in patients with VCP
- Continuous positive pressure may provide temporary relief of symptoms of VCP
- Decompression surgery is required to relieve VCP secondary to Arnold-Chiari malformation
- Traumatic VCP should improve in 6 months and, if not, unlikely to improve thereafter

Laryngeal Web

- Strong association with velocardiofacial syndrome (chromosome 22q11.2 deletion)
- Posterior glottic webs are acquired from prolonged intubation
- Laryngeal webs may be associated with anterior subglottic stenosis
- Weak cry and biphasic stridor

Management

- Surgery can be curative if significant obstruction occurs
- Emergency tracheostomy is required to relieve obstruction caused by a complete laryngeal web

Subglottic Stenosis (SGS)

- SGS may be congenital (rare and usually associated with other genetic syndromes or conditions) or post-traumatic (due to airway instrumentation or more commonly, intubation)
  - Even brief periods of intubation may result in chronic SGS
- Airway inflammation secondary to trauma may lead to acquired SGS
- The cricoid cartilage, being a complete ring, is predisposed to traumatic injury and stenosis

Clinical presentation

- History of recurrent croup, a protracted croup illness, previous intubation or airway instrumentation
- Biphasic stridor
- Retractions, flaring, high-pitched stridor, and diminished air entry are associated with significant SGS
- Hypoxemia or carbon dioxide retention in a child with SGS indicates a severe obstruction leading to marked hypoventilation

Diagnosis

- Spirometry will demonstrate flattened inspiratory loops
- Endoscopy will demonstrate narrowing of the subglottic space
- No correlation between the radiographic appearance of SGS and actual degree of narrowing on direct visualization

Management

- If subglottic space only allows an endotracheal tube (ETT) two sizes smaller than expected, consider surgical intervention
- A cricoid split procedure may provide an alternative to tracheostomy in infants with SGS

Subglottic Hemangioma

- Rare cause of upper airway obstruction in children

Clinical presentation

- Considered in the differential diagnosis of chronic upper airway obstruction
- 50% accompanied by cutaneous hemangiomas of head and neck
- Inspiratory or biphasic stridor that worsens as hemangiomas enlarge
- Likely to shrink with age and usually do not require therapy

Diagnosis

- Upper airway endoscopy—asymmetric compressible bluish mass in the subglottic space

Management

- Treatment options include steroids, laser, intralesional steroid injections, and open surgical excision
- Propranolol from months to years by center with expertise
- Tracheostomy in severe obstruction

Laryngotracheoesophageal Cleft

- Associated with tracheoesophageal fistulas
- Rare cause of recurrent aspiration
- Neonates with severe clefts may present with respiratory distress
- Defect involves the anterior wall of the upper esophagus and the posterior aspect of the larynx, with the defect lying in the interarytenoid space

Clinical presentation

- Recurrent aspiration and cyanosis with feeding are the most common clinical presentation

Diagnosis

- Direct laryngoscopy rather than transnasal fiber-optic endoscopy is the diagnostic method of choice

Management

- Type 1—Conservative management with swallow therapy and thickening of feedings
- Types 2–4—Surgical intervention and swallow therapy

Macroglossia

- Macroglossia predisposes patients to obstructive sleep apnea (OSA)
- Lateral-view radiograph to evaluate anatomic relationship between tongue and airway
- Prone positioning may help in the acute management of airway obstruction due to macroglossia
- Airway obstruction may improve with age

Cough

Background

- Cough sensors present in upper and lower airway mucosa, paranasal sinuses, upper GI tract, external auditory canal
- Nocturnal cough is rare in normal children

Clinical presentation

- Differential is wide, so narrow possible diagnoses with history and physical:
  - Age, exposures, family history of asthma, allergies, or lung disease
  - Type of cough
    - Wet, dry, frequency, diurnal, nocturnal, length of cough, seasonality, quality, presence of hemoptysis
    - Sputum production (bronchitis, cystic fibrosis [CF], primary ciliary dyskinesia [PCD], bronchiectasis)
    - Quality
      - Brassy (tracheal irritation, tracheomalacia)
      - Barky (croup)
      - Honking (habit cough)
      - Staccato (chlamydia, mycoplasma)
      - Paroxysmal/whoop (pertussis, CF, foreign body)

  - Association to feedings and exercise (aspiration, exercise-induced asthma)
  - Associated with persistent rhinitis: allergies, PCD
  - Recurrent pneumonia—immunodeficiency
  - If not present during sleep in school age/adolescent, consider habit cough
  - Nighttime cough: asthma, sinusitis
  - Response to medications
  - Useful physical findings: stridor, wheezing, clubbing, poor growth, eczema, tachypnea, focal auscultatory findings, chest wall abnormalities
- Acute cough usually resolves in 1–3 weeks in 90% of children
- Subacute cough lasts 3–8 weeks and chronic cough > 8 weeks

Differential diagnosis

Considerations by length of cough:

- *Acute:* Allergies, foreign body, upper respiratory tract infections
- *Subacute:* Postinfectious cough, viral, pertussis
- *Chronic cough:*
  - All age groups: Gastroesophageal reflux (GER), exposures (tobacco smoke, pollution)
  - Other considerations by age:
    - Infants: Aspiration, congenital airway abnormalities, CF (even if neonatal screen is normal), neonatal infection, chlamydia, congenital heart disease (CHD)
    - Toddlers/preschoolers: Upper respiratory infection (URI), asthma, foreign body, postinfectious cough, pertussis, mycoplasma, immunodeficiencies, bronchiectasis, CF
    - School age/adolescents: Asthma, upper airway cough syndrome, smoking, tuberculosis (TB), bronchiectasis, habit cough

Evaluation of chronic cough

Look for clues and pointers and tailor evaluation according to most likely diagnoses:

- CXR
- Pulmonary function (spirometry)
- Sputum culture
- Allergy testing
- Swallow study
- Sweat test
- Immune function testing, including complete blood count (CBC) with differential, immunoglobulins
- Purified protein derivative (PPD) test
- Consider chest CT if cough is productive
- Echocardiogram
- Refer to specialists for further evaluations, e.g., laryngoscopy, bronchoscopy, echocardiogram

Management

- Recurrent respiratory tract infections/postinfectious cough: Symptomatic therapy
- Upper airway cough syndrome: Antihistamines, nasal steroids
- Dry cough/wheezing: Trial bronchodilators with environmental modifications. If positive response, consider trial with inhaled corticosteroids (ICS)
- GER: Antacids
- Psychogenic cough: Behavioral modifications
- Further management based on diagnostic findings: Refer to specialists for complicated diagnoses

Tachypnea

- Definition by age (breaths/min):
  - Birth to 30 days > 60
  - 2 to 12 months > 50
  - 1 to 5 years old > 40
  - Older than 5 > 20
  - Subtract 10 if the child is febrile

Exercise Intolerance

- The reference standard is the maximal oxygen consumption (VO2 max)
- Pulmonary conditions
  - Most common: Exercise-induced asthma (EIA) and CF
- Less common: Interstitial lung diseases
- Cardiovascular conditions
  - Congestive heart failure and CHD (most common CHD = tetralogy of Fallot)
- Muscular conditions, especially those associated with neuromuscular weakness
  - Duchenne muscular dystrophy
- Hematologic disorders
  - Iron deficiency anemia
  - Sickle cell disease
- Vocal cord dysfunction
  - Paradoxical motion of vocal cords
    - More common in adolescent females
    - May mimic EIA—Need to consider if not responding to EIA treatment
- Sedentariness—Leads to deconditioning, muscle weakness, and obesity

Respiratory Failure

- Type 1 respiratory failure characterized by low blood oxygen levels (hypoxemia, low pO2, normal or decreased pCO2, and alveolar-arterial oxygen gradient (pA-aO2) is increased)
  - Causes: V/Q mismatch, decreased minute volume, diffusion impairment or shunt
- Type 2 respiratory failure affects both oxygen and carbon dioxide levels
  - Low pO2, high pCO2, normal pA-aO2
  - Causes: Reduced breathing effort, increased airways resistance, neuromuscular disease
- Treating the underlying cause is paramount. In severe cases, intubation and mechanical ventilation are required
- If related to respiratory depression is related to narcotics, reversal can be of benefit

Apnea

- Defined by reduced or cessation in respiratory airflow

Three main types

- ***Central***
  - Cessation of airflow secondary to reduction or lack of excitatory signals from central nervous system (brain stem) to respiratory muscles
  - No chest wall effort
  - Prolonged episodes (> 20 s) are more clinically significant and usually associated with cyanosis and/or bradycardia
  - Shorter episodes can be seen in periodic breathing, which is common in premature infants and decreases with age/maturation
- ***Obstructive***
  - Airway (usually upper airway) obstruction/collapse leading to partial or complete obstruction of airflow in spite of chest wall effort
- ***Mixed***
  - Combination of both central and obstructive components
  - Usually central component followed by obstructive

Differential diagnosis of central apnea

- Neonates/infants:
  - Can present with central or mixed apnea
  - Most common cause: Apnea of prematurity or apnea of infancy
    - Associated with immature respiratory centers, laryngeal reflex, and, when mixed, underdeveloped upper airway musculature
    - Usually resolves by 48–53 weeks postconceptional age
    - Can be treated with respiratory stimulants (e.g., caffeine) or continuous positive airway pressure (CPAP)
    - Further evaluation warranted in younger infants (< 2 months) and severe presentations requiring resuscitation

  - Other causes of apnea during infancy usually more severe and include:
    - Infection (e.g., sepsis, pneumonia, meningitis, pertussis, bronchiolitis, botulism)
    - Head trauma, intraventricular hemorrhage, seizure, medications
    - GER, necrotizing enterocolitis
    - Metabolic derangements such as hypoglycemia and acidosis, inborn errors of metabolism
    - Hyper- or hypothermia
    - Heart failure
    - Anemia
    - Congenital central hypoventilation syndrome
- Older children
  - Causes: Cerebral hemorrhage or infarction, brain tumor, seizures, hypoxic injury, spinal cord injury, drugs, medications

Evaluation

- Guided by history (see amplified discussion for ALTE/BRUE)
- If severe presentation, young infant or older child, consider:
  - CBC, serum glucose, electrolytes
  - Sepsis workup
  - Electrocardiogram (ECG)
  - Neuroimaging, electroencephalogram if clinically indicated
  - Consult pertinent specialists
  - OSA (see amplified discussion for OSA)

Cyanosis

Background

- Bluish tint of the skin, either centrally or peripherally, related to respiratory causes, central nervous system causes, or hematologic causes
- Pulmonary causes are a result of poor oxygen delivery
- Cardiac causes include CHD and heart failure
- Hematologic causes include methemoglobinemia and polycythemia
- Can be caused by high altitude and hypothermia

Evaluation

- Assessment of respiratory status—wheezing, distress
- Cardiac assessment to include echo, and if concern for intrapulmonary shunt, consider contrast (bubble) echo
- ABG
- Methemoglobin assessment

Chronic Hypoxia

Causes

- Pulmonary venous desaturation
  - Lung disease with diffusion impairment (interstitial lung disease)
  - Intrapulmonary right-to-left shunting (pulmonary arteriovenous malformations)
- Extrapulmonary/intracardiac right-to-left shunting
  - Cyanotic CHD (tetralogy of Fallot, pulmonary atresia)
  - Pulmonary hypertension can present with intracardiac right-to-left shunting
- Hemoglobin disorders with decreased oxygen affinity
  - Methemoglobinemia (see expanded discussion)

Diagnosis

- Hyperoxia test
  - Give 100% oxygen and obtain a preductal blood gas (i.e., right upper extremity)
  - Normal PaO2 > 500 mmHg
  - Pulmonary disease PaO2 > 150 mmHg, but < 500 mmHg
  - Right-to-left shunting PaO2 < 150 mm Hg
- CXR to evaluate for pulmonary pathology
- CBC—If chronic, will show polycythemia

Methemoglobinemia

Background

- Methemoglobin (MetHb) cannot carry oxygen to tissues
- Methemoglobin occurs with oxidation of ferrous (Fe2+) to ferric (Fe3+) hemoglobin
- Methemoglobinemia can be acquired or inherited
  - Acquired
    - Most common after exposure to exogenous oxidizing agent like nitrites
      - Intestinal bacteria can convert nitrates in well water and pureed leafy vegetables to nitrites
    - Dehydration
  - Inherited
    - Deficiency cytochrome-b5 reductase
    - Hemoglobin M disease

Clinical Presentation

- Presents as cyanosis with MetHb levels > 15%
- Cyanosis with normal pulse oximetry, no respiratory or cardiac findings on physical exam

Evaluation

- Pulse oximetry—May be normal, but does not increase with use of oxygen
- Blood gas—Chocolate-colored blood
- Co-oximetry

Management

- Oxygen
- Severe cases: Methylene blue, N-acetylcysteine, exchange transfusion

Clubbing of Digits or Hypertrophic Pulmonary Osteodystrophy

Causes

- The most common cause is cyanotic heart disease
- The most common pulmonary causes are CF and bronchiectasis (usually more advanced disease)
- Biliary cirrhosis
- Infective endocarditis
- Normal variant as a familial trait

Diagnosis

- Obliteration of the angle between the proximal nail and soft tissue of the digit (Schamroth sign)
- Normal anatomy shows a diamond-shaped space when placing the distal phalangeal joints in mirrorlike fashion

Hemoptysis

Background

- Hemoptysis (coughing blood) is uncommon but can be a serious manifestation of pulmonary disease in children
- Pulmonary vasculature composed of two-pressure system:
  - Bleeding from low-pressure pulmonary vessels (e.g., diffuse hemorrhage) leads to small-volume hemoptysis, while bleeding from systemic pressure bronchial vessels (e.g., bronchiectasis) tends to be profuse

Clinical presentation

- Differentiating from hematemesis (vomiting blood) and epistaxis (nasal bleeding) can be tricky
- Most common reason for symptom usually not true hemoptysis but bleeding from upper airway (e.g., nasal bleeding)
- Diffuse hemorrhage is frequently slow and may present only with anemia and fatigue

Differential Diagnosis

- Most common etiology of true hemoptysis is inflammation or infection
- More common
  - Upper airway and GI bleeding
  - Infection such as bronchitis, pneumonia, lung abscess, TB, fungal infections
  - Foreign body
  - Cystic fibrosis, bronchiectasis

- Less common
  - Airway trauma
  - Tracheostomy
  - Cardiac (CHD, pulmonary hypertension, pulmonary embolism)
- Rare
  - Airway tumor (e.g., carcinoid)
  - Arteriovenous fistula
  - Bleeding disorder
  - Idiopathic pulmonary hemosiderosis
  - Pulmonary renal syndromes (usually in older children)
    - Granulomatosis with polyangiitis, Goodpasture syndrome, systemic lupus erythematosus, microscopic polyangiitis, Henoch-Schönlein purpura
  - Factitious hemoptysis

Evaluation

- History and physical exam not usually helpful; other guided studies frequently useful in the investigation
  - Imaging including CXR or chest CT with contrast to localize lesion or find evidence of pulmonary hemorrhage
  - Helpful labs: CBC for anemia; erythrocyte sedimentation rate (ERS), kidney function, urinalysis for renal involvement or inflammatory disease
  - Bronchoscopy can identify area of active bleeding and should include upper airway evaluation. Bronchoalveolar lavage for evidence of infection or hemosiderin-laden macrophages (presence indicates previous bleeding)
  - Echocardiogram for cardiac disease

Management

- Massive blood loss requires acute resuscitation with volume, blood products, and supportive care with oxygen and mechanical ventilation
- Evaluation by subspecialists (ear/nose/throat (ENT), pulmonologist, gastroenterology, rheumatology), depending on suspected cause

RESPIRATORY CONDITIONS OF THE UPPER AIRWAY

See discussion on stridor for general considerations

Viral Croup (Laryngotracheobronchitis)

Background

- Most common cause is parainfluenza
- Causes subglottic narrowing
- Common between 3 months and 3 years
- Spasmodic croup similar without viral prodrome or other identifiable cause
- Cricoid cartilage has a complete ring and is the narrowest part of the airway in infants
  - Edema at this level will lead to further narrowing, increased airway resistance, and possible airway compromise

Clinical presentation

- Barking or brassy cough
- URI with or without fever, which may be high (39–40 °C)
- Respiratory distress with retractions with hypoxia and hypercapnia in severe upper airway obstruction
- Child may prefer to sit or be held upright
- Mild—no stridor at rest
- Moderate—stridor at rest but no agitation
- Severe—stridor and agitation
- Recurrent croup: Consider underlying anatomic airway abnormality, GER, or atopy

Diagnosis

- Clinical diagnosis
- In typical cases**,** CXR is not required
  - CXR findings—steeple sign on frontal view is a common finding but may be absent

Management

- Reassurance, observation, and hydration

- Dexamethasone 0.6 mg/kg beneficial in mild croup (may decrease need for hospitalization)
- Oxygen and racemic epinephrine in moderate or severe cases
- Racemic epinephrine does not lead to rebound worsening of obstruction, but patient may worsen when drug effects subside. A 2-h observation is important. Worsening of obstruction is unlikely to occur if patient does well after 4 h.
- Racemic epinephrine should be used cautiously in patients with left ventricular outlet obstruction
- Low-density gas such as helium-oxygen (heliox) may be effective in children with severe croup
  - Turbulent flow through large airways is density-dependent.
  - By decreasing gas density, airflow resistance can be decreased.
- Admit for severe distress, hypoxia, and inability to feed/drink or if requiring 2 or more racemic epinephrine treatments
- Endotracheal intubation recommended before patient is restless and cyanotic
- Endotracheal intubation using an ETT one size smaller than predicted tube size (based on age and weight) is the preferred method of establishing an artificial airway in patients with viral croup
- Intubation more likely for bacterial tracheitis and epiglottitis and rare in croup
- If intubation needed, consider measles or influenza A

Prognosis

- Course of viral croup in infants younger than 1 year of age is prolonged
- Symptoms often improve during the day with recurrence of symptoms in the early hours of the morning

Epiglottitis

Background

- Most common pathogen *Haemophilus influenzae*
- Rare in children due to *H. influenzae* vaccination, which leads to individual and herd immunity
- More common in the elderly and immune-compromised children than in the general population
- Uncommon pathogens that can cause epiglottitis: Herpes viruses and fungi
- Pathology involves the epiglotis and other supraglottic structures, but the subglottic space and trachea are usually spared

Clinical presentation

- Rapid onset of illness (hours) with high fever, sore throat, drooling with difficulty swallowing, and difficulty breathing
- Patient sitting up and leaning forward position to enhance airflow
- Stridor is not a prominent feature
- Radiograph lateral neck view: Thumb sign

Management

- Patients with acute epiglottitis should undergo endotracheal intubation to ensure an adequate airway until inflammation subsides
- In severe cases, avoid unnecessary studies until airway is secured
- A skilled provider needs to remain with a patient with epiglottitis until the airway is visualized and secured

Bacterial Tracheitis

Background

- Most common organisms are *Staphylococcus aureus*, *Moraxella catarrhalis,* and *Streptococcus*

- Mean age is 4 years (range 4 weeks to 13 years, typically about 2 years)

Clinical presentation

- Brassy and barky cough, but the patient has high fever and appears very toxic with respiratory distress and stridor
- Patient may lay flat and does not have drooling or dysphagia associated with epiglottitis
- Rapid progression and purulent secretions may mandate early endotracheal intubation
- Does not respond to racemic epinephrine or corticosteroids

Diagnosis

- CXR not needed but may show the classic findings of pseudomembrane detachment in the trachea
- High fever, purulent airway secretions, absence of findings of epiglottitis

Management

- Intubation, especially for younger patients; 50–60% do not require intubation
- Humidification and careful suctioning of the ETT are important
- Antistaphylococcal treatment (i.e., nafcillin or vancomycin)
- Prognosis is good
- Complications can include ARDS, toxic shock, septic shock, pulmonary edema, and subglottic stenosis

RESPIRATORY CONDITIONS OF THE LOWER AIRWAY AND PARENCHYMA

Congenital Airway and Pulmonary Malformations

Pulmonary Sequestration

Background

- *Extralobar:* More common in males; 65% in the left lung, covered by pleura, fed by systemic artery, and drained via systemic vein. May be associated with diaphragmatic hernia and colonic duplication
- *Intralobar:* Typical in the lower lobe, systemic arterial supply, variable venous drainage, and airway connections

Clinical presentation

- Dullness on percussion, decreased breath sounds over the lesion, continuous murmur may be heard on the back, and crackles if infected

Evaluation

- Fetal ultrasound or ultrasound following birth may detect pulmonary mass
- CT scan with contrast confirms diagnosis

Management

- Surgical removal because retained sequestrations have a small possibility of becoming malignant
- Consultations: Pulmonology and surgery

Bronchogenic Cyst

Background

- Arise from abnormal budding of the tracheal diverticulum
- Patient may become symptomatic if the cyst enlarges or becomes infected
- May be asymptomatic and found incidentally

Clinical presentation

- Fever, chest pain, and productive cough are the most common presenting symptoms
- Dysphagia, if causing pressure on the surrounding structures
- CXR can show the cyst, but CT or MRI demonstrates anatomy (usually medial mediastinum)

Management

- Surgical removal

Vascular Ring/Sling

Background

- Congenital anomalies of the large vessels (such as aortic arch)

- May involve airway and/or esophagus
- Variable severity and timing of presentation but, if significant, usually presents during infancy

Clinical presentation
- May cause stridor or wheezing, cough, apnea, failure to thrive, and/or dysphagia
- Imaging:
  - Echocardiogram, CT, and MRI help define anatomy. Can be associated with tracheomalacia secondary to airway compression
  - Esophagogram may indirectly diagnose by demonstrating compression of abnormal vessel upon esophagus

Management
- Surgical intervention

Tracheal Stenosis

Background
- Narrowing of tracheal lumen frequently associated with complete tracheal rings
- Can vary from short- to long-segment stenosis
- Condition is rare

Clinical presentation
- Varies depending on degree of obstruction
- If severe, presents during neonatal period or infancy with respiratory distress, cyanosis, stridor, cough, and dysphagia

Diagnosis
- Direct visualization via rigid bronchoscope
- CT scan could be used to reconstruct via "virtual bronchoscopy"
- Echocardiogram to evaluate associated CHD

Management
- Surgical intervention
- Refer to pediatric ENT or airway surgical specialist

Congenital Pulmonary Adenomatoid Malformation

Background
- More prevalent in the left lower lobe
- 5 subtypes
  - Most are Type 1 (70%): Large (> 5 mm) single or multiple cysts
  - Type 3 (10%): Microcystic, solid, and associated with other anomalies. Worse prognosis

Clinical presentation
- Asymptomatic to respiratory distress depending on extent

Evaluation
- Can be identified by prenatal ultrasound
- CT scan is diagnostic

Management
- Resection if respiratory distress, markedly symptomatic
- If asymptomatic, can observe, but eventually most are surgically removed
  - Even if asymptomatic, there is increased future risk for infections and small risk for malignancy

Congenital Lobar Emphysema

Background
- Congenital bronchial obstruction leads to air trapping and distention of involved lung
- Rare
- Prevalence: Left upper lobe > right middle lobe/right lower lobe

Clinical presentation
- Usual presentation in infancy with respiratory distress, tachypnea, hypoxemia

Diagnosis
- CXR

  - Initially may present in neonate with opacification due to fluid
  - Subsequently, there is hyperinflation with shift to contralateral side
- Confirmation with CT scan

Management

- Surgical resection/lobectomy

FOREIGN BODY (FB) ASPIRATION

Background

- Nuts, particularly peanuts, make up one-third of cases
- Round, globular FBs (hot dog, grapes, nuts, hard candies) are the most frequently found, causing a complete airway obstruction
- Most common in age < 3 years

Clinical presentation

- Initial event: Violent, paroxysmal coughing, choking, gagging, possible airway obstruction if the FB is large
- Asymptomatic interval: FB becomes lodged, reflexes fatigue, immediate irritation subsides. This stage is most dangerous and accounts for delayed diagnosis
  - In this stage, FB might be missed, as physician is reassured by the absence of symptoms
- A positive history must never be ignored, and negative history can be misleading
- Coughing or choking episode accompanied by wheezing is highly suggestive of FB in the airway.
- Must question about nuts, small toys, other small items
- 58% lodge in the right bronchus

Diagnosis

- CXR is negative in 10–30% of cases
- If there is suspicion for FB, patient should undergo inspiratory and expiratory CXRs; in the uncooperative patient, consider doing bilateral decubitus films
- A lack of radiographic findings does not exclude an airway FB; many objects are organic and likely to be radiolucent
- Positive radiographic findings include hyperinflation, atelectasis, or infiltrate
- Soft tissue film of the neck can be of benefit to detect objects in the upper airway
- Patients with tracheostomy are at a higher risk

Management

- Ideal treatment is prompt removal with rigid bronchoscopy
- Can defer bronchoscopy until proper hydration and emptying of the stomach

Complications

- Retained foreign body can lead to hemoptysis, lung abscess, and ultimately bronchiectasis

PULMONARY HEMOSIDEROSIS

Background

- Repeated episodes of intra-alveolar bleeding that leads to abnormal accumulation of iron (hemosiderin) in the alveolar macrophages
- Subsequent development of pulmonary fibrosis and severe anemia

Causes and associated conditions

- Idiopathic pulmonary hemosiderosis (IPH)
- Secondary pulmonary hemosiderosis
  - Cardiovascular:
    - Congestive heart failure
    - Pulmonary hypertension
    - Mitral valve stenosis
  - Inflammatory/autoimmune
    - Goodpasture syndrome
    - Rheumatoid arthritis
    - Wegener granulomatosis
    - Henoch-Schönlein purpura
  - Allergic
  - Heiner syndrome (cow's milk hypersensitivity)

Clinical presentation

- Iron deficiency anemia
- Hemoptysis (helpful if occurs, but infrequent)
- Alveolar infiltrate
- Presence of hemosiderin; it takes 48–72 h for macrophages to convert erythrocyte to hemosiderin
- Widely variable from asymptomatic with infiltrates and anemia to shock and sudden death
- After episode of hemorrhage, the patient will present with wheezing, cough, dyspnea, bronchospasm, and alteration of blood gases

Diagnosis

- Best guided by consulting pulmonologist
- Recurrent "pneumonia", fever, cough, CXR abnormalities
- Hypochromic microcytic anemia
- Elevation of plasma bilirubin
- Infiltrates are typically bilateral and may spare the apices, often with hyperaeration
- IgE, cow's milk antibody levels, stool specimen for heme
- Urinalysis for nephritis
- Antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and anti-glomerular basement membrane (GBM)
- Lung biopsy if diffuse alveolar hemorrhage (DAH)

Management

- Corticosteroid is the treatment of choice for IPH
- Treatment is highly dependent on the underlying cause

ACUTE BRONCHIOLITIS

Background

- Viral bronchiolitis is the most common lower respiratory tract infection in those under 2 years of age
- Respiratory syncytial virus (RSV) is responsible for more than 50% of acute bronchiolitis
- Other common causes are human metapneumovirus, parainfluenza, adenovirus, influenza, rhinovirus, and mycoplasma

Risk Factors

- Maternal asthma
- Maternal smoking
- Persistent rhinitis
- Eczema at < 1 year of age

Clinical presentation

- Nasal congestion, rhinorrhea, and cough
- Tachypnea or elevated respiratory rate is the earliest and most sensitive vital sign change
- Nasal flaring, grunting (in infants), and suprasternal, intercostal, and subcostal retractions are evidence of increased respiratory effort
- Nasal suctioning and repositioning may allow for a more accurate assessment of lower respiratory tract involvement
- Common: Crackles, wheezing, and referred upper airway sounds upon auscultation
- Apnea may be more prominent than wheezing in infants < 2 months or former preterm infants
- Symptoms can range from mild tachypnea to frank respiratory failure
- Clinical course is expected to worsen, with peak symptoms noted around days 3–4 of illness ("day of illness")
- "Day of illness" is an important variable for providing anticipatory guidance for outpatient management and in making decisions regarding admission and discharge of patients

Diagnosis

- Clinical symptoms lead to diagnosis; subsequent evaluation is important in determining treatment
- Initially must assess respiratory rate and oxygen saturation because work of breathing, tachypnea, and hypoxia are most clinically significant in determining severity
- CXR warranted for infants in respiratory distress
- CXR commonly demonstrates hyperinflation, patchy atelectasis, and infiltrates

- In infants under 30 days old, the risk for serious bacterial infection (SBI) warrants full evaluation for SBI and administration of empiric antibiotics
- Recognize that infants older than 30 days with bronchiolitis are at a lower risk for SBIs, thus allowing for decreased invasive testing and observation without administering antibiotics to patients who have classic presentations

Management

- Mainstay of treatment is supportive: Oxygen for hypoxia, hydration, nasal suctioning, and positioning to elevate chest to 30°
- When feeding adequately and work of breathing improves, oxygen can be discontinued if saturations are 90–92% for most of the time
- Infants with respiratory distress and desaturation or dehydration should be hospitalized
- The American Academy of Pediatrics does NOT recommend the use of bronchodilators or systemic steroids in the routine treatment of bronchiolitis
- However, those with recurrent wheezing may respond to bronchodilator therapy
- Corticosteroid medications, inhaled or administered systemically, should not be routinely used in the treatment of bronchiolitis
- If bronchodilator makes the wheezing worse or increases work of breathing, consider pulmonary consultation for trachea or bronchomalacia
- Sweat chloride testing for patients with recurrent wheezing and who are resistant to treatment is recommended
- Ribavirin should not be used routinely in the treatment of bronchiolitis

Prevention

- Palivizumab (Synagis®) 15 mg/kg intramuscular (IM) for premature and high-risk infants as monthly IM monoclonal antibody injection
- Handwashing is best measure to prevent nosocomial infection

BRONCHOPULMONARY DYSPLASIA (BPD)

Background

- Definition has changed since initial description in the 1960s
- "Old" BPD in late premature infants treated with high peak inspiratory pressures and high oxygen concentrations leading to necrotizing bronchiolitis, pulmonary hypertension, alveolar overinflation, atelectasis, cystic disease, and pulmonary fibrosis
- "New" BPD definition revised in 2000 after use of CPAP, gentler ventilation, antenatal steroids, and surfactant instituted as standard
  - *Immature lung* resulting in alveolar arrest and dysmorphic pulmonary vasculature; *lung injury* from oxygen therapy, positive-pressure ventilation, infection, inflammation, and fluid overload; and *inadequate lung injury repair* with ongoing inflammation
  - Other risk factors: lower birthweight, gestational age (< 32 weeks), chorioamnionitis, and *Ureaplasma* colonization

Clinical Presentation

- Need for oxygen, which can progress to respiratory failure leading to increased or progressive need for ventilatory support
- Grading of "new" BPD based on ongoing need for oxygen in premature infants who required oxygen at 28 days
  - On reassessment at 36 weeks postmenstrual age:
    - Mild: On room air
    - Moderate: FIO2 < 30%
    - Severe: FIO2 > 30% or on positive-pressure ventilation
- CXR can present with areas of opacification, atelectasis, hyper-expansion, and pulmonary edema
- Sequelae of BPD and associated conditions include:
  - Tachypnea, retractions

  - Suboptimal growth, increased caloric requirements
  - Dysphagia and GER can lead to aspiration
  - Neurodevelopmental delays with cerebral palsy being the most common presentation
  - Heart failure secondary to pulmonary hypertension, ventricular hypertrophy, pulmonary overcirculation from right-to-left shunting

Management

- Prevention: Good prenatal care, prevention of prematurity
- Postnatal management leading to reduced incidence of BPD:
  - Use of gentle ventilation, permissive hypercapnia, noninvasive forms of airway pressure/ventilation
  - Assure growth and adequate nutrition
  - Vitamin A supplementation in extremely low birthweight infants shown to reduce incidence of BPD
  - Screen for and treat for pulmonary hypertension
  - Use of systemic steroids postnatally decreases risk of BPD and improves extubation success. However, **routine use is contraindicated** due to increase in long-term risk of neurodevelopmental impairment
- Management once BPD diagnosed:
  - Multidisciplinary follow-up of neurodevelopmental, cardiovascular, and nutritional sequelae
  - Bronchodilators, inhaled steroids, diuretics are frequently used
  - Insufficient data related to long-term outcomes
  - Short course of steroids for acute exacerbations
  - Prevent infections; prophylaxis with palivizumab decreases frequency of RSV-related hospitalizations

ASTHMA

Background

- Heterogeneous disease characterized by chronic inflammation of the airways
- US prevalence of childhood asthma ranges from 10% to 15%
- Wheezing observed in about 3% of infants before 3 years of age
- Several asthma phenotypes have been described based on onset of symptoms and natural course of the disease process:
  - Transient
    - Early onset at < 1 year old
    - Decreased lung function at birth
    - Resolved symptoms by mid-childhood
    - No further reductions in pulmonary function
  - Nonatopic
    - Early onset at < 3 years
    - Variable clinical course
  - Late onset
    - Onset > 3 years
    - Variable clinical course
  - Persistent
    - Early onset < 3 years
    - Abnormal lung function by 3 years
    - Most patients are atopic
- Asthma symptoms are more common in boys before puberty, but more severe in girls after puberty
- The **asthma predictive index** was developed to help predict which children would be likely to develop persistent asthma symptoms
  - Its negative predictive value is better than its positive predictive value
  - Positive if:
    - 1 or more major risk factors: Parental history of asthma, atopic dermatitis, sensitization to aeroallergen

OR

- 2 or more minor risk factors: Sensitization to food, more than 4% eosinophilia, wheezing apart from upper respiratory tract infections

Pathophysiology

- Inflammation plays a key role in asthma pathophysiology
- Important contributors to the inflammatory response include:
  - Cell types including lymphocytes, eosinophils, mast cells, neutrophils, macrophages, smooth muscle cells, and epithelial cells
  - Inflammatory mediators such as IL-5, IL-4, and IL-13
- IgE plays an important role in activation and maintenance of allergic disease
  - Early-phase reaction or Type I IgE-mediated reactions occur within minutes of an allergen-related trigger
    - Cells (such as mast cells) release preformed inflammatory mediators that can lead to vasodilation, edema, bronchoconstriction, and increased airway mucus secretion
    - Early airway obstruction occurs, in addition, there is activation of leukocytes, which in turn leads to late-phase IgE-mediated reactions
  - A late-phase IgE-mediated reaction follows 2–12 h later
    - Characterized by persistent obstruction and mucus hypersecretion
    - The late reaction is the consequence of inflammatory mediators
- Respiratory infections
  - Viral respiratory infections are the most common trigger of exacerbations in children (especially those < 10 years) and have been associated with future development of asthma
  - Bronchiolitis associated with RSV and rhinovirus in early childhood increases risk of developing asthma

Table 20.2 Differential diagnosis for asthma

Red flags	Possible diagnosis
Sudden onset of symptoms, witnessed choking, localized wheezing	Foreign body aspiration
Coughing and choking when eating or drinking	Dysphagia with aspiration
Sneezing, cough, nasal congestion	Chronic upper airway cough syndrome
Poor growth and low BMI	Cystic fibrosis, immunodeficiency
Chronic rhinorrhea, recurrent sinusitis, early-onset respiratory symptoms	Cystic fibrosis, primary ciliary dyskinesia
Acute-onset dyspnea and/or stridor in teens	Vocal cord dysfunction
Chronic wet productive cough, recurrent infections	Bronchiectasis
Recurrent pneumonia	Immunodeficiency, anatomical abnormality
Chronic wet cough, difficulties feeding, early onset, noisy breathing	Vascular ring, tracheoesophageal fistula, tracheomalacia
Heart murmur, poor weight gain, cyanosis with feedings	Congenital heart disease
Prematurity, prolonged mechanical ventilation or supplemental oxygen	Bronchopulmonary dysplasia

Assessment

- There is no diagnostic test for asthma
- Diagnosis is based on constellation of clinical symptoms including presence of airflow limitation that is at least partially reversible
- Exclusion of alternative diagnoses (Table 20.2)
- Assess for associated comorbidities, including obesity, GER, rhinitis/sinusitis, depression, anxiety, sleep-disordered breathing, and allergic bronchopulmonary aspergillosis
- **Typical symptoms:**
  - Wheezing, chest tightness, shortness of breath, cough
  - Symptoms are usually worse at night and early morning
  - The more symptoms, the more likely the diagnosis
  - If cough only symptom or chronic sputum production reported, broaden your differential

- **Common triggers:**
  - Respiratory infections (especially viral infections)
  - Exercise
  - Inhaled allergens (e.g., pollen, pet exposure, dust mites, cockroaches, mold)
  - Irritants (tobacco smoke, air pollution)
  - Medications (e.g., nonsteroidal anti-inflammatory medications, beta-blockers)
  - Changes in weather
- **Physical findings and objective data:**
  - Wheezing on exam, especially on forced exhalation; signs of atopy such as allergic shiners, rhinitis, or eczema
  - PFT
    - Spirometry measurements before and after bronchodilator recommended in the assessment of patients ≥ 5 years/o
      - Look for obstruction on spirometry
      - Use bronchodilator response to assess reversibility
      - Decline in lung function (FEV1 and FEV1/FVC ratio) can usually be seen in those with symptoms starting < 3 years and is noted by 6 years
  - Exercise challenge can be used to evaluate for exercise-induced asthma
    - Baseline spirometry obtained prior to treadmill challenge
    - Spirometry obtained after exercise to document drop in pulmonary function
  - CXR
    - May show hyperinflation, peribronchial wall thickening, atelectasis
    - Most helpful to evaluate for differential causes of symptoms
  - Allergy testing
    - Skin testing or serum testing may help in identifying sensitization to inhaled perennial allergens

Asthma classification

- Severity is best assessed prior to initial controller therapy (Table 20.3)
- Assess components of severity: impairment and risk

Table 20.3 Asthma classification

Severity	Daytime symptoms/ SABA use Nighttime symptoms	Activity limitation Pulmonary function
Intermittent		
0–4 years	≤ 2 days/week 0 nights/month	None
5–11 years	≤ 2 days/week ≤ 2 nights/month	None FEV1 > 80%; FEV1/FVC > 85%
12–19 years	≤ 2 days/week ≤ 2 nights/month	None FEV1 > 80%; FEV1/FVC > 85%
Mild persistent		
0–4 years	3–6 days/week 1–2 nights/month	Minor limitation
5–11 years	3–6 days/week 3–4 nights/month	Minor limitation FEV1 > 80%; FEV1/FVC > 80%
12–19 years	3–6 days/week 3–4 nights/month	Minor limitation FEV1 > 80%; FEV1/FVC > 85%
Moderate persistent		
0–4 years	Daily 3–4 nights/month	Some limitation
5–11 years	Daily > 1 night/week	Some limitation FEV1 60–80%; FEV1/FVC 75–80%
12–19 years	Daily > 1 night/week	Some limitation FEV1 60–80%; FEV1/FVC 80–85%
Severe persistent		
0–4 years	Daily > 1 night/week	Extremely limited
5–11 years	Throughout the day Often	Extremely limited FEV1 < 60%; FEV1/FVC < 75%
12–19 years	Throughout the day Often	Extremely limited FEV1 < 60%; FEV1/FVC < 80%

SABA short-acting beta-2 agonist, *FEV1* forced expiration volume in 1 s, *FVC* forced vital capacity

  - **Impairment:** Relates to the frequency and intensity of symptoms, how the disease affects day-to-day function
  - **Risk** estimates likelihood of exacerbations or having reduced lung function

Exercise-Induced Asthma (EIA)

- Clinical presentation of EIA

  - Shortness of breath, coughing, wheezing, chest tightness, or pain associated with physical activity. Can present in isolation or associated with symptoms of poorly controlled asthma
  - Symptoms present during or minutes after exertion, peak after 5–10 min of exercise, and improve within 20–30 min
  - Usually self-limited but may result in a severe asthma attack
- Management of EIA
  - Warm-up period 15 min prior to exercise and wearing scarf/mask may reduce symptoms
  - In 80% of patients, short-acting beta-agonists (SABAs) before exercise prevent symptoms for about 2–3 h
  - Montelukast can lead to decrease in bronchospasm in about 50% of patients, but onset of action is several hours after administration

Management of asthma

Assessment and monitoring:

- After initial diagnosis: Review response to therapy, reassess severity and control, adjust therapy to reduce impairment and risk
- Periodic reassessment recommended due to variable nature of asthma
- Annual increase in asthma exacerbations seen in September
- Reassess patients every 2–6 weeks initially to gain disease control and then every 1–6 months
- Assess frequency of daytime symptoms, nighttime symptoms, and reliever use over the past month
- Can use asthma control tools such as the Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ) as part of assessment
- Evaluate technique and compliance with controller therapy
- PFT at initial assessment, after treatment and stabilization of symptoms, during periods of uncontrolled symptoms, and at least every 1–2 years
- Increased risk of exacerbation *if 1 or more*:
  - Uncontrolled asthma symptoms, increased use of SABA, inadequate dose or use of ICS, < 60% FEV1, psychological and/or socioeconomic barriers, comorbidities, eosinophilia, exposure to known triggers, history of pediatric intensive care unit or intubation, ≥ 1 severe exacerbation in the last year
- Consider step-down in therapy if asthma under good control for at least 3 months

Education:

- Self-management education (patient and families) key in individual asthma control and improve outcomes
- Provide asthma action plan that provides guidance in daily management as well as plan of care for worsening symptoms

Control environmental factors and comorbidities:

- Assess for allergen exposures either by skin testing or serum testing and correlate with medical and exposure history
- Patients should reduce exposure to allergens, irritants, and pollution to which they are sensitized or have a reaction
- Assess for and control comorbidities associated with increased risk for poor control: Obesity, allergic rhinitis/sinusitis, allergic bronchopulmonary aspergillosis, OSA, depression, and other psychosocial factors.

Medications:

- Initial treatment based on severity category (Table 20.4)
- On reassessment of asthma control, adjust therapy regardless of initial severity classification.

Beta-2 agonists

- Relieve airway constriction by binding to receptors on airway smooth muscle
- Frequent use can signal poor asthma control

Table 20.4 Asthma: Initial controller therapy

≥ 6 years	Preferred initial therapy	≤ 5 years	Preferred initial therapy
Intermittent asthma symptoms	**Step 1** SABA as needed	Infrequent viral wheezing and no symptoms in between episodes	**Step 1** SABA as needed Consider intermittent ICS
Persistent symptoms or high-risk factor for exacerbations	**Step 2** Low-dose ICS	Uncontrolled asthma symptoms, > 3 exacerbations/y or consider trial in those with frequent wheezing (every 6–8 weeks)	**Step 2** Daily low-dose ICS
Asthma symptoms/SABA use > 2X/week	**Step 2** Low-dose ICS Consider LRTA	Uncontrolled asthma on low-dose ICS	**Step 3** Double low-dose ICS
Asthma symptoms most days or waking > 1X/week	**Step 3** Medium-/high-dose ICS or if ≥ 12 years, low-dose ICS/LABA	Uncontrolled asthma on double low dose	**Step 4** Refer to specialist Add LTRA Add intermittent ICS or increased ICS frequency
Severe initial presentation (uncontrolled asthma or acute exacerbation)	**Step 4** Short OCS course AND High-dose ICS or if ≥ 12 years, moderate dose ICS/LABA		
Uncontrolled asthma after initial therapy	Step up therapy or use adjunct therapies **Step 3**: Can add LTRA to low-dose ICS **Step 4**: Can add ipratropium (if > 12 years) to ICS or add LTRA to high-dose ICS **Step 5**: Refer to specialist for add-on therapy (e.g., tiotropium, anti-IgE, anti-IL-5, low-dose OCS)		

Adapted with modifications from Global Initiative for Asthma Report [1]
SABA short-acting beta-2 agonist, *ICS* inhaled corticosteroid, *LRTA* leukotriene receptor antagonist, *LABA* long-acting beta-2 agonist, *OCS* oral corticosteroid

- Short-acting beta-2 agonists (SABA)
  - Onset of action is within 15 min, but of relatively short duration (3–4 h)
- Long-acting beta-2 agonists (LABA)
  - Effects can last at least 12 h
  - Used in combination with ICS
- Adverse effects
  - Agitation, irritability, tremors, tachycardia, insomnia, arrhythmias; higher doses used during acute asthma exacerbations can lead to hypokalemia or hypoglycemia

Inhaled corticosteroids

- Most potent and effective medication for long-term control of asthma
- Decrease airway inflammation and bronchial hyperresponsiveness, relieve asthma symptoms, and improve lung function
- Patients should rinse and spit out after inhalation
- Adverse effects
  - Oral thrush, oral absorption, and higher-dose ICS use may lead to decrease in growth velocity and adrenal suppression

Leukotriene receptor antagonists

- Block leukotriene, which acts as a potent mediator leading to bronchoconstriction, vascular permeability, and increased mucus production and activates inflammatory cells
- Usually an add-on therapy and not preferred treatment option in mild persistent asthma
- Adverse effects
  - Generally, well tolerated, but associated with upper respiratory tract infection, fever, headache, sore throat, behavior/mood-related changes

Acute asthma exacerbations

- Patients present with acute or subacute worsening from baseline symptoms and/or pulmonary function
- Brief initial assessment should concentrate on time of onset and possible triggers, severity compared to previous exacerbations, recent use of asthma medications, and associated cardiorespiratory process
- Severe exacerbation presentation: shortness of breath, inability to speak in full sentences, sitting hunched, agitated, accessory muscle use, tachypnea and tachycardia, pulsus paradoxus > 20 mmHg, SpO2 < 92% (after an hour of therapy is a good predictor for hospitalization needs), PEF < 40% baseline
- Life-threatening exacerbations can present with silent chest, drowsiness, or confusion
- CXR not recommended routinely, but patient can present with atelectasis, which needs to be clinically differentiated from pneumonia
- Therapy for acute exacerbations:
  - Oxygen as needed to keep SpO2 > 90%
  - Three SABA treatments spaced every 20–30 min
  - Adding high doses of ipratropium bromide leads to decreased rate of hospitalization
  - Systemic corticosteroids to patients with moderate to severe exacerbations or with poor initial response to SABA

PNEUMONIA

Background

- Lower respiratory tract infection with fever and respiratory symptoms with parenchymal involvement on exam or by CXR findings
- *Streptococcus pneumoniae* is the most common bacterial cause in children older than 1 week of age
- Viruses account for 14–35% of cases
- Complicated pneumonia with empyema and necrosis
- Community-associated methicillin-resistant *Staphylococcus aureus*

Most common causes of pneumonia by age group

- Neonates (0–3 m)
  - Group B strep and Gram-negative bacteria
  - Early and late onset
  - Early onset—first 3 days of life with respiratory distress
- Three weeks to 3 months
  - Chlamydia trachomatis
    - Interstitial infiltrate on CXR
  - RSV and parainfluenza
    - Bronchiolitis or pneumonia
  - *Streptococcus pneumoniae*
    - Major cause of pneumonia through childhood
  - Bordetella pertussis
    - Tracheobronchitis with severe paroxysm, usually no fever
- Three months to 5 years
  - Most common etiology—viruses (RSV, parainfluenza, human metapneumovirus, influenza, and rhinovirus)
  - Strep pneumonia—most treatable pathogen
  - Mycoplasma pneumoniae
    - Increased incidence in children approaching school age
- Five years to adolescence

  - Most common cause
    - Atypical organisms such as *Mycoplasma* and *Chlamydophila pneumoniae*
      - *Mycoplasma*—leading cause of pneumonia in school-age children and young adults

Most common causes of pneumonia by geographic location

- Histoplasmosis
  - Ohio and Mississippi River Valleys and Caribbean
- Coccidioidomycosis
  - California, Arizona, and New Mexico
- Blastomycosis
  - Ohio, Mississippi River Valleys; Great Lakes states
- *Legionella*
  - Infected water worldwide
- Avian influenza
  - Southeast Asia

Pneumonia via animal vectors

- Tularemia
  - Rabbits and ticks
- Psittacosis
  - Birds and parakeets
- Q fever
  - Sheep, cows, and goats

Pneumonia with associated exanthems

- Varicella
  - Human to human airborne droplets
- Measles
  - Human to human droplets

Clinical presentation

- Nonspecific signs and symptoms
- Cough and fever—hallmark symptoms
- Tachypnea is the most sensitive and specific sign of pneumonia
- Most children with cough and fever do not have pneumonia
- Tachypnea, retractions, wheezing, nasal flaring, grunting, apnea, and abdominal pain may be presenting or associated symptoms
- Grunting may be a sign of impending respiratory failure in younger patients/infants
- Findings on exam may be dullness to percussion, crackles, decreased breath sounds, and bronchial breaths
- In the absence of fever, tachypnea, increased work of breathing, or auscultatory abnormalities, bacterial pneumonia is unlikely

Diagnosis

- Clinical diagnosis as above
- Rapid influenza test may help to identify the cause of fever and to reduce unnecessary use of antibiotics
- CBC, chemistry, or serology will not help in identifying etiology or aid in management
- Blood culture rarely helpful (only 10% of the time organism is recovered)
- ESR and C-reactive protein (CRP) may be elevated but are not specific
- Tuberculin test if there are TB risk factors or TB is being considered
- CXR (Fig. 20.3)

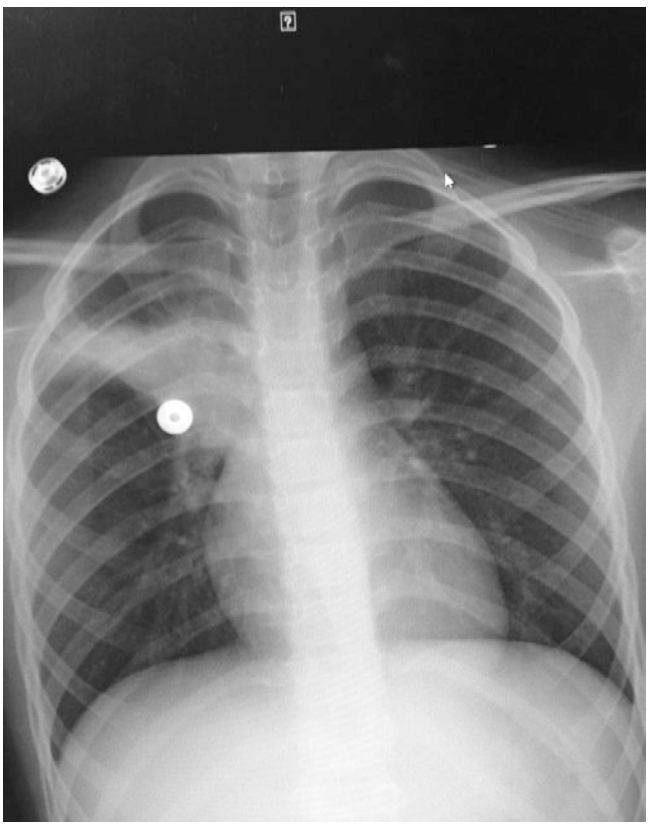


Fig. 20.3 A 9-year-old female presents with cough and fever. Chest radiograph shows right upper lobe infiltrate.

- A CXR will not change clinical management for patients being treated as outpatient
- Afebrile children do not need a CXR
- CXR always lags behind clinical response. No need to obtain to confirm response to antibiotics
- Obtain a CXR if:
  - Complicated pneumonia is being considered
  - Clinical deterioration
  - Prolonged fever with no obvious source of infection
  - Abdominal pain with normal appendix

Management

- National guideline for antibiotic initiation with community-acquired pneumonia:
  - High-dose amoxicillin (80–90 mg/kg/day) for uncomplicated cases being treated as outpatient
  - Augmentin or cefuroxime as outpatient, if resistant
  - School age or > 5 years of age azithromycin to cover for *Mycoplasma*
- Indication for hospitalization: Suspected sepsis, severe dehydration, toxic appearance, hypoxemia (SpO2 < 90%), unresponsive to outpatient therapy, inability to drink
  - Intravenous fluids and O2, if needed, and antibiotics
  - Consider blood culture, CXR, chemistry profiles, and CBC
  - If inpatient: Cefuroxime, ceftriaxone, or cefotaxime are the antibiotics of choice
  - Adolescents: Fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin) may be used for atypical pneumonia
  - If *Staphylococcus* is considered, add clindamycin or vancomycin
  - Uncomplicated pneumonia responds to antibiotics in 48–96 h
  - If no response or persistent pneumonia
    - Repeat CXR
    - Consider empyema, bacterial resistance, and nonbacterial pneumonia (FB, CF, pulmonary sequestration, bronchiolitis obliterans, aspiration, and hypersensitivity pneumonitis)

BRONCHIECTASIS

Background

- Destruction of the airway wall (bronchi and bronchioles) leads to loss of integrity of the muscular and elastic layers of the bronchial wall, results leading to dilated and collapsible airway

Clinical presentation

- Productive cough is most common symptom
- Dyspnea, rhinosinusitis, and hemoptysis are less common
- Crackles, wheezing, and rhonchi are often heard; digital clubbing may be present

Differential diagnosis

- CF is the most common cause of bronchiectasis in pediatric patients in the USA.
- Impaired mucociliary clearance (CF and ciliary dyskinesia)
- Infections (*Mycobacterium tuberculosis*, *Pseudomonas*, adenovirus)
- Immunodeficiency syndromes
- Immune-mediated (connective tissue diseases), allergic bronchopulmonary aspergillosis (ABPA), inflammatory bowel disease (IBD)
- Airway injury (chronic aspiration, inhalation of toxic fumes, hot gases)
- Congenital or connective tissue abnormalities (yellow nail, Marfan syndrome, alpha-1 antitrypsin deficiency, airway cartilage deficiency, tracheobronchomegaly, Young syndrome)
- Obstructed airways (retained FB, intraluminal masses, extraluminal compression)

Evaluation

- PFT may show obstruction, restriction, or both, depending on etiology and severity
- CXR may reveal airway dilation, increased pulmonary markings with "tram tracking" (thickening of the bronchial walls), and areas of atelectasis
- High-resolution CT scan is the gold standard and reveals detailed anatomy of the bronchial tree
- There is a lack of airway tapering with luminal dilation, bronchial wall thickening, honeycombing, and mucous plugging

Management and prognosis

- Determining the primary cause is of critical importance and is best done with direction from pediatric pulmonologist
- Evaluation may include swallow study, sweat chloride testing, and bronchoscopy
- Mucus clearance should be enhanced with hypertonic saline nebulization, inhaled mucolytics, and chest physiotherapy
- ICS can reduce airflow obstruction
- Chronic macrolide therapy has been found to be as beneficial as anti-inflammatory drugs
- Culture should be obtained
- Aggressive treatment of *Pseudomonas* and *Staphylococcal* infections is indicated, but antimicrobial therapy should be targeted to specific pathogens
- If bronchiectasis is localized and severe, lobectomy is a last resort in cases without systemic etiology

CYSTIC FIBROSIS

Background

- Autosomal recessive inheritance pattern due to a mutation on the long arm of chromosome 7
- Highest incidence in Caucasians, highly prevalent in Latinos and African Americans. Less frequently seen in Asians and Native Americans
- CF transmembrane regulator (CFTR) dysfunction/absence leads to:
  - Excessive reabsorption of sodium and deficient chloride secretion
  - Passive movement of water is decreased, and airway secretions are dehydrated with very low surface liquid layer
  - Cilia become compressed, inhibiting ciliary clearance and cough clearance
  - Bacteria thrive, and the immune function at the airway surface is also abnormal
  - Repeated bacterial infection leads to airway damage and bronchiectasis in the lung
    - CFTR dysfunction leads to dysfunction in other organ systems:
      - Organ systems primarily involved: respiratory, GI, genitourinary, and integumentary (sweat glands)
- There are > 1700 mutations in the CFTR protein
- Different classes of mutations result in different levels of CFTR function/production, thus variable clinical presentation
- The most prevalent mutation is F508 deletion (F508del), associated with both pulmonary disease and pancreatic insufficiency
  - 85% of the US population have one copy

Clinical presentation

- ***Pulmonary manifestations***
  - Cough is most common and consistent symptom. Often productive but can also be dry
  - Increased anteroposterior (AP) diameter of the chest due to hyperinflation associated with airway obstruction
  - Hyperresonance, diffuse or localized crackles
  - Nasal obstruction, nasal polyps, recurrent sinusitis
  - Clubbing
  - In advanced disease: Cyanosis, exercise intolerance, shortness of breath, growth failure, respiratory failure, and death

  - Common bacterial pathogens include *Staphylococcus aureus and Pseudomonas aeruginosa*
  - Multidrug-resistant organisms are becoming more common (MRSA*, Stenotrophomonas maltophilia, and Burkholderia cepacia* complex).
- ***Gastrointestinal manifestations***
  - *Meconium ileus* is seen in up to 20% of newborns with CF
  - Characterized by abdominal distention, emesis, and failure to pass meconium in the first 24–48 h
  - Abdominal radiograph (KUB) shows air fluid level with ground glass-appearing material in the central abdomen
  - Gastrografin enema diagnostic and therapeutic
  - Can give hyperosmolar contrast as well
  - May need to consider surgery if medical management fails
  - **Pancreatic-insufficient** (PI) patients will progress to complete or almost complete disruption of pancreatic acini and replacement with fibrous tissue. Lack of endogenous digestive enzymes causes fat malabsorption
    - Symptoms: Frequent, loose, foul smelling, and greasy stools, flatus, and poor weight gain
    - PI also associated with fat-soluble vitamins (ADEK) deficiency
      - Deficiencies can cause night blindness, decreased bone density, and neurologic dysfunction (neuropathy, dementia)
- ***Genitourinary manifestations***
  - Pubertal development is often delayed, particularly if nutrition is poor
  - Females have decreased fertility related to thick cervical mucus
  - Many females with CF carry pregnancies to term, without detriment to lung function
  - > 95% of males are infertile due to absence or atretic vas deferens
- ***Integumentary manifestations***
  - Excessive salt loss in sweat predisposes children to hyponatremia, particularly when hot or exercising
  - Hypochloremic alkalosis and dehydration, especially in hot environments, can be deadly in infants

Complications

- ***Distal intestinal obstruction syndrome (DIOS)***
  - More commonly seen with poor enzyme adherence, also in those with a history of meconium ileus
  - Fecal material accumulates in the terminal portion of the ileum and cecum
  - Osmotic agents such as polyethylene glycol (MiraLAX®) are helpful
  - Can also give enemas and other stool softeners as an adjunct
  - If severe or complete obstruction, can require Gastrografin enema to relieve obstruction
- ***Rectal prolapse***
  - Due to combination of intestinal disease and poor supporting musculature from poor nutrition
  - Evidence of recurrent rectal prolapse in otherwise healthy children is an indication for sweat chloride testing to assess for CF
- ***Nasal polyps***
  - Most prevalent in teens and young adults
  - Local steroids and nasal rinses can be of benefit for symptom control
  - If there are nasal obstructive symptoms such as chronic rhinorrhea, snoring, and sinus pain or pressure, surgical intervention is warranted
  - Even with surgical resection, polyps are likely to return
- ***CF-related liver disease***
  - Found in 2–3% of cases
  - More common in those with severe mutations with little CFTR function
  - Mainstay of treatment is to prevent ongoing liver damage and associated complications of portal hypertension and cirrhosis

- ***CF-related diabetes***
  - Most common comorbidity
  - Affects 20% of adolescents and up to 40% of adults
  - Shares features of both Type I and Type II diabetes but is a distinct entity
  - Primarily caused by insulin insufficiency, but fluctuating insulin levels also play a part
  - Often clinically silent, screen with oral glucose tolerance test (OGTT) annually after age 10 years

Diagnosis

- ***Newborn screening:***
  - US states use different methods of testing
  - In most states, initial testing uses immunoreactive trypsinogen testing and, if elevated, limited DNA testing
  - Confirmatory sweat testing is recommended
  - Newborn screening can miss positive cases, especially pancreatic sufficient or those with less common mutations. CF must be a consideration if there are clinical features
- ***Sweat chloride*** is abnormal if > 40 in infant less than 6 months, and > 60 in those older than 6 months
  - Pilocarpine iontophoresis is used to stimulate sweating
  - Positive results should be confirmed with genetic testing
  - Negative results with high clinical suspicion should also have genetic testing
  - False-positive sweat chloride can occur:
    - If testing is completed on skin affected by eczema or contaminated with lotion
    - Hypothyroidism
    - Skin disorders
    - Untreated adrenal insufficiency
    - Nephrogenic diabetes insipidus
    - Hypoparathyroidism
    - Severe malnutrition
- ***DNA testing*** can confirm and, when sequencing is sent, will identify > 95%
- ***Pancreatic function testing***
  - Pancreatic fecal elastase preferred
  - Can assess fecal fat but much less accurate

Management per CF Foundation Guidelines

- ***Centers of care:*** Care is managed in a network of multidisciplinary centers.
- ***Visits:*** Infants seen monthly for follow-up until age 1 and then quarterly
- ***Imaging:***
  - CXR done annually, generally demonstrating mucous plugging and central and upper lobe bronchiectasis
  - May need CXR to evaluate more closely for bronchiectasis
- ***PFT*** via spirometry assessed quarterly starting at age 5 years
  - Initially obstructive process, and then with increasing lung damage, a restrictive process is noted
- ***Microbiology***
  - Sputum cultures to be assessed a minimum 3 times per year
  - First common bacteria noted is *Staphylococcus aureus*
  - *Pseudomonas* is next commonly seen and treated to eradicate due to potential for colonization and hastening lung damage
  - Also, commonly seen: MRSA, *Stenotrophomonas maltophilia*
  - Low prevalence but primarily seen in CF: *Burkholderia cepacia*

Primary goals of management

- Maintain lung function as close to normal as possible.
- Mainstay therapies include *hydration of airway surface layer* with hypertonic saline, *liquefying mucus* with use of dornase alfa, and *clearance of airways* using various ACTs
- Prevent infections by limiting exposure to other CF patients and other reservoirs of

infection (freshwater lakes, humidifiers, hot tubs)
- Treat infections when present with directed antimicrobial therapy
- Ensure adequate nutrition through high-calorie diet, appropriate enzyme supplementation, and close monitoring of growth

Managing complications
- Mild acute exacerbation treatment
  - Increased inhaled bronchodilator therapies and mucolytics
  - Increased ACTs
  - Usually oral antimicrobials
- Moderate and severe pulmonary exacerbations
  - Usually require hospital admission for IV antibiotics
  - Aggressive respiratory therapies
  - May require additional nutritional intervention to maintain adequate growth during illness

Standard therapies for treatment in CF
- Pancreatic enzyme replacement orally
- Multivitamins (particularly fat-soluble vitamins)
- Bronchodilators
- Hydrating agents (7% hypertonic saline)
- Mucolytics (dornase alfa)
- Antibiotics (inhaled, oral, or IV)
- ACT/chest physiotherapy (CPT)
  - Oscillating chest compression vest
  - PEP (positive expiratory pressure) devices
  - Autogenic drainage
  - Directed coughing, huff coughing
- Anti-inflammatory agents
  - Azithromycin
- Insulin for CF-related diabetes
- CFTR modulator drugs to improve ion transport
  - Ivacaftor; ivacaftor/lumacaftor; ivacaftor/tezacaftor
- Lung transplant indicated for severe and end-stage lung disease
- Surgical intervention required
  - Meconium ileus
  - Intussusception
  - Gastrostomy tube placement
  - Rectal prolapse

CF care across the life span
- Transition to adult care is a requirement of all accredited CF centers
  - There is often formal preparation for patients 18–21 transitioning to adult care
- Median survival is currently 37 years
- Infants now born with CF and who are cared for in an accredited CF center will likely survive beyond age 50

PRIMARY CILIARY DYSKINESIA

Background
- Autosomal recessive disorder with extensive genetic heterogeneity
- Characterized by dysmotile, immotile, or absent cilia
- The ciliary defects lead to abnormal mucociliary clearance

Clinical presentation
- Symptoms in organs where ciliary motility is important for normal function
  - Neonatal respiratory distress or neonatal pneumonia (frequently misdiagnosed as transient tachypnea)
  - Recurrent pneumonias and bronchiectasis
  - Recurrent wheezing frequently diagnosed as asthma
  - Chronic persistent rhinosinusitis
  - Nasal polyps and recurrent otitis media; recurrent otitis media may begin in neonates
  - Men are infertile and women have decreased fertility

Diagnostic evaluation
- Gold standard: Cilia from nose or trachea by brushings or mucosal biopsy for evaluation of

ciliary abnormalities on electron microscopy (absent, abnormal dynein arms, radial spokes, doublet arrangements)
- Genetic testing—need two mutations in a single gene for diagnosis. Problematic due to heterogeneity, and inability to identify two mutations does not rule out diagnosis
- CT scan
  - Sinuses: Paranasal sinuses involvement
  - Chest: Bronchiectasis

Management
- ACT, antibiotics for infections documented on culture with sensitivities, ENT evaluation for surgery if needed

EXTRAPULMONARY RESPIRATORY CONDITIONS

Pleural Effusion

Background
- > 10 mL fluid in the thoracic cavity
- Due to excessive filtration or defective absorption
- Normal fluid balance
  - 0.1–0.2 mL/kg of sterile colorless fluid
  - Ninety percent filters from arterial capillaries, reabsorbed at venous capillaries
  - About 10% returned via lymphatic
  - Normal pleural fluid (0.3 mL/kg)
- Etiologies
  - Pneumonia is the most common
  - Neonatal period: Chylous effusion most common
  - Others: Malignancy, renal disease, trauma, congestive heart failure, and systemic diseases

Clinical presentation
- Suspect in any child with worsening pneumonia
- Respiratory distress, tachypnea, cough, chest pain with pleural inflammation
- Decreased to absent breath sounds, pleural rub with smaller collection of fluid
- Egophony
- Dullness to percussion
- Midline shift

Diagnosis and management
- Transudate: Clear or straw colored; low protein and lactate dehydrogenase (LDH)
- Exudate: Straw colored or cloudy
  - Pleural fluid/serum protein ≥ 0.5
  - Pleural fluid/serum LDH ≥ 0.6
  - Pleural fluid LDH > 2/3 of the upper limit of normal for serum LDH
- Appearance:
  - Purulent fluid—infection
  - Thin white milky fluid—chyle
  - Blood—trauma or malignancy
- CXR—opacification of thorax, blunted costophrenic angles (Fig. 20.4)
  - Decubitus views helpful if fluid is free-flowing

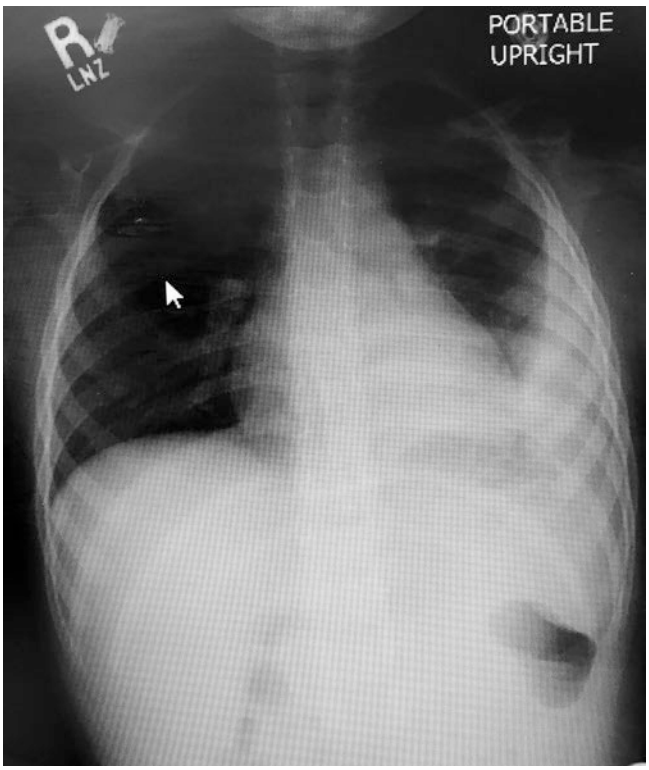


Fig. 20.4 Chest radiograph of a 2-year-old child with left pleural effusion

- Ultrasound helpful to evaluate for loculations
- CT scan for complicated effusions/empyema to define pulmonary and fluid characteristics
- Thoracentesis
  - Routine thoracentesis not recommended
  - Perform thoracentesis to relieve dyspnea for large effusions, worsening symptoms, sepsis, or a lack of improvement in symptoms despite administration of broad-spectrum antibiotics for diagnostic purposes
- Oxygen for hypoxemia
- Consultation with experts as needed

Pneumothorax

Causes

- **Primary spontaneous pneumothorax**
  - Occurs without trauma or underlying cause
  - More frequently in tall, thin males, likely related to subpleural blebs
  - Family history is positive in many patients
  - Usually occurs at rest, but can be precipitated by air travel in an unpressurized cabin, weight lifting, and Valsalva maneuver
- **Secondary pneumothorax**
  - Related to an underlying lung issue (asthma, CF, necrotizing pneumonia, interstitial lung disease)
  - Trauma (blunt trauma)
  - Loud music (air pressure)
  - Catamenial pneumothorax (unusual condition associated with menses due to passage of intra-abdominal air through a diaphragmatic defect)

Clinical presentation

- Onset is abrupt, and the severity depends on degree of lung collapse
- In simple pneumothorax, the lung collapses up to 30%
- In a tension pneumothorax, patient will be hypoxemic, dyspneic, and possibly cyanotic
- Point of maximal impulse shifts due to displacement of intrathoracic organs to the opposite side

Diagnosis

- CXR
  - Upright, if possible
  - Expiratory films accentuate the contrast between lung markings and the clear area of the pneumothorax
- Recurrence rate is high after primary spontaneous pneumothorax

Management

- Small pneumothorax $< 5\%$ may resolve spontaneously
- If $> 5\%$ of pneumothorax or collapse, or if recurrent or under tension, a chest tube for drainage is necessary
- Pneumothoraces complicating CF frequently recur, and definitive treatment may be justified with the first episode
- One means of definitive therapy is sclerosing with doxycycline (chemical pleurodesis)
- Video-assisted thoracic surgery is preferred therapy for blebectomy, pleural stripping, pleural brushing, and instillation of sclerosing agents over open thoracotomy
- Extensive pleural adhesion and aggressive pleural stripping may interfere with lung transplant potential in the future, an issue that must be discussed with the family

Pneumomediastinum

Background

- Can be traumatic or spontaneous
- Spontaneous pneumomediastinum occurs when air leaks through small alveolar rupture to the surrounding bronchovascular sheath
- Less commonly, occurs with air escaping from the upper respiratory tract, intrathoracic airways, or esophageal rupture
- Triggers: (Most common) asthma exacerbation and lower respiratory infection; (less common) Valsalva/strenuous lifting and vomiting

Clinical presentation

- Chest pain, dyspnea, cough, neck pain, dysphagia, odynophagia

Management

- Usually resolves by itself

THORACIC DEFORMITIES

Background

- Thoracic deformities affect rib cage, spine, and respiratory muscles
- Abnormalities can result in restrictive disease due to reduced compliance of chest wall and increased workload/fatigue of respiratory muscles

Pectus Excavatum (Funnel Chest) (Fig. 20.5)

Background

- 1/400 births, more common in males, rare in African Americans
- Can be isolated, familial, or associated with connective tissue diseases (e.g., Marfan or Ehlers-Danlos syndrome), neuromuscular disease (e.g., spinal muscular atrophy)
- Incidence: > 90% of congenital wall anomalies

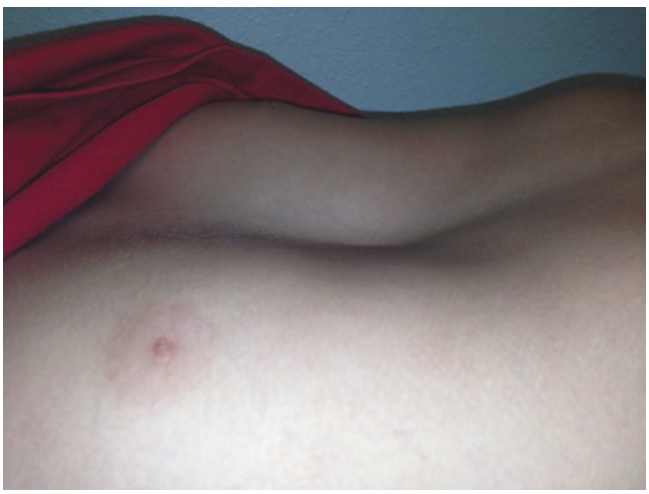


Fig. 20.5 Pectus excavatum. A 12-year-old healthy boy with funnel-shaped chest

Clinical presentation

- Often noted at birth, may be not associated with any symptoms
- Range from asymptomatic to increasing symptoms in more severe cases
  - Exercise intolerance
  - Fatigue
  - Chest pain
  - Palpitations
  - Recurrent chest infections
  - Wheezing
  - Stridor
  - Cough
  - Tall and thin
- Children may experience significant psychological stress because of cosmetic appearance

Evaluation

- CXR; increased AP diameter
- CT for Haller index (HI); if significant, should be repaired
  - HI = lateral internal rib cage dimension/AP internal sternum to vertebrae dimension
  - Normal value HI: 2.5
  - Surgical repair if HI > 3.25 and/or cardiopulmonary involvement
- ECG commonly abnormal; right axis deviation
- Echo may demonstrate cardiac compression and mitral valve prolapse

Management

- Based on severity of deformity and physiologic compromise
- Mild: Observation and physical therapy to maintain posture
- Corrective surgery if significant physiologic compromise (Nuss or Ravitch procedure)

Pectus Carinatum (Pigeon Chest)

Background

- Anterior displacement of midsternum and adjacent costal cartilage
- Rare: 1/1500 of chest wall deformities
- Associated with mild to moderate scoliosis, mitral valve prolapse, and coarctation of aorta

Clinical presentation

- Rarely causes limitations
- Physical appearance most common complaint
- HI less than two is significant

Management

- Surgery for cosmetic and psychological stress

Scoliosis

Background

- Cobb angle = angle from most tilted vertebrae above and below the apex of the curve
- Scoliosis defined as lateral curvature of the spine with Cobb angle > 10°
- Curvatures > 50° more likely to be progressive
- Extreme curvatures can lead to respiratory compromise due to restrictive chest wall disease

Management

- Observe for progression
- Bracing
- Spinal fusion for curves > 40°–45°

PULMONARY HYPERTENSION

Background

- Mean pulmonary artery pressure of 25 mm Hg or more at rest
- Can be caused by left heart disease, lung disease (including BPD), thromboembolic disease, autoimmune disease, variety of other disease or idiopathic

Clinical presentation

- Exertional dyspnea, progressive fatigue in older child
- Infants less specific: Poor appetite, failure to thrive, diaphoresis, tachypnea, tachycardia, and irritability
- Syncope, presyncope, and chest pain are features of more advanced disease; hemoptysis late and sometimes fatal symptom

Management

- Outcome in pediatrics has improved
- Should be seen by specialist (cardiology or pulmonology)
- Patients may require a combination of therapies, and some patients require surgery (septostomy)

Cor pulmonale

- Right ventricular (RV) hypertrophy leading to RV failure caused by increased afterload caused by pulmonary hypertension
- Can be caused by chronic lung disease, bronchopulmonary dysplasia, cystic fibrosis, arterial hypertension, neuromuscular disease

OBSTRUCTIVE SLEEP APNEA (OSA)

Background

- OSA and primary snoring are part of a spectrum of sleep-disordered breathing
  - **Primary snoring** = Incidence 12–20%; no discrete obstructive events or gas exchange abnormalities
  - **OSA** = Prevalence 2–4% in healthy children; obstructive apnea and hypopneas often seen with arousals, disturbed sleep, and gas exchange abnormalities
- The disorder can occur at any age but is most common in the preschool age group (2–6 years) and adolescents
- A higher prevalence has been reported in African American and obese children

Risk factors and associated conditions

- Adenotonsillar hypertrophy
- Obesity
- Craniofacial abnormalities (such as midface hypoplasia and micrognathia)
- Hypotonia (e.g., Down syndrome)
- Neuromuscular disease
- Cerebral palsy

Clinical presentation

- All children should be screened for snoring
- Signs and symptoms that may signal OSA
  - Snoring
  - Gasping during sleep
  - Enuresis (especially if secondary)
  - Restless sleeper
  - Unusual positioning during sleep (hyperextended neck, sleeping propped up)
  - Cyanosis
  - Sweating during sleep
  - Morning headaches
  - Daytime sleepiness in older children
  - ADHD-like symptoms, including hyperactivity and/or inattention, difficulty concentrating
  - Adenoidal facies as well as signs of atopy or nasal congestion
  - Chronic mouth breathing with chronic nasal congestion
  - Tonsillar hypertrophy
  - Obesity
  - Failure to thrive
  - Unexplained hypertension

Management

- History and physical exam cannot distinguish between primary snoring and OSA
- Polysomnography diagnostic test of choice
- Complex, high-risk patients (e.g., craniofacial disorders, genetic syndromes, neuromuscular disorders, severe OSA) should be referred to specialist
- Patients with neuromuscular disease may desaturate during sleep but appear well awake
  - Overnight saturation monitoring may be a helpful screening tool for sleep-disordered breathing in these patients
- Adenotonsillectomy is first-line therapy and curative in about 80% of children with OSA
- Noninvasive positive airway pressure is an option for poor surgical candidates or those with residual OSA after surgery
- High-risk patients should be monitored as inpatients postoperatively
- Patients should be re-evaluated postoperative to determine if additional treatment is required

ACUTE LIFE-THREATENING EVENT (ALTE)/BRIEF RESOLVED UNEXPLAINED EVENT (BRUE)

Background

- Common associations with ALTE
  - GER disorder most common association for awake ALTE
    - Prevalence of GER in infants with ALTE as high as 70%
    - Highly symptomatic infants may benefit from therapy with antacids, positional changes, and thickened feedings
  - Neurologic
    - Seizures second most common association
    - High index of suspicion of child abuse important
    - Up to 10% presenting ALTE associated with child abuse
  - Viral respiratory infections
    - RSV most commonly associated ALTE
    - More common in < 2 months, lower birthweight, history of prematurity
- BRUE now preferred term to more subjective ALTE, but terms frequently used interchangeably
- BRUE
  - < 1 year of age
  - Sudden, brief, and resolved episode with ≥ 1 of the following:
    - Cyanosis or pallor
    - Absent, decreased, or irregular breathing
    - Change in tone

- Altered responsiveness
- Unexplained after adequate history and physical

- Presence of BRUE does not predict SIDS

Management

- Low-risk BRUE: Patients > 2 months, older preterm infant (> 32 weeks and postconceptual age > 45 weeks), event < 1 min, no previous events, no need CPR, negative history and exam
  - Management of low-risk BRUE
    - No need for admission
    - Workup considered even in low-risk BRUE
      - Pertussis testing as infants may present with few symptoms
      - Pulse oximetry monitoring in the emergency department
      - ECG due to severe outcome associated with channelopathies
  - Has good negative predictive value
  - Observation, further testing, and treatment as supported by history and exam

SUDDEN INFANT DEATH SYNDROME (SIDS)

- Factors associated with triple risk model of SIDS:
  - Critical period in development
    - Risk peaks at 2–4 months with most deaths having occurred by 6 months
    - Male predominance
  - Infant vulnerability
    - Brain stem dysfunction
    - Genetic predisposition
    - Defects in arousal
    - Prematurity, low birthweight
    - Poor prenatal care
  - Environmental factors
    - Prone sleep position
    - Tobacco smoke exposure
    - Soft bedding
    - Co-sleeping
    - Overheating
    - Young maternal age
- Increased risk in siblings, but risk of second child death < 1%
- National recommendation on SIDS prevention
  - "Back to sleep": Supine position. "Tummy to play": Awake and monitored
    - Marked decline in SIDS rate following mass education of this public policy
  - Firm mattress
  - Cool ambient air
  - No soft object or loose bedding
  - No co-sleeping
  - Encourage breastfeeding
  - No smoking
  - Sleep in parents' room for 1st year, but on separate surfaces
  - Pacifiers
    - Use pacifier once breastfeeding has been established
    - Offer pacifier at bedtime or nap time

PEARLS AND PITFALLS

Diagnostic Testing for Respiratory Conditions

Interpretation of spirometry

- Obstruction: N ↓ FVC, ↓ FEV1, ↓ FEV1/FVC, ↓ FEF 25–75
- Restriction: ↓ FVC, ↓ FEV1, N FEV1/FVC, ↓ FEF 25–75

Blood gas analysis

- Arterial blood gas analysis (see Table 20.1)
- In capillary blood gases, values are comparable to arterial pH and pCO2, but pO2 measurement in CBG is less reliable.

Chest imaging

- Imaging in suspected FB:
  - Get inspiratory and expiratory or bilateral decubitus views. May be able to see asym-

metric hyperinflation in side with foreign body.
  - Most foreign bodies are not seen, as they are radiolucent.

General Signs and Symptoms

Stridor/wheezing

- **In**spiratory—**Ex**trathoracic swelling or obstruction will lead to airway collapse on inspiration. Example: Laryngomalacia
- **Ex**piratory—**In**trathoracic swelling or obstruction will lead to airway collapse on expiration. Example: Tracheomalacia
- **Biphasic stridor—indicates fixed airflow obstruction—subglottic space obstruction**
- **Laryngomalacia:** Most common cause of stridor in infants, accounts for up to 75% of all causes of stridor
- **Choanal atresia:** Infant/newborn in respiratory distress with inability to pass a 6F catheter into oropharynx through nose
- **Left vocal cord paralysis:** Associated with trauma to the recurrent laryngeal nerve at birth or surgical trauma
- **Subglottic hemangioma:** 50% accompanied by cutaneous hemangiomas of head and neck. Inspiratory or biphasic stridor, which worsens as hemangiomas enlarge
- **Viral croup:** Course of viral croup in infants younger than 1 year of age is prolonged. Symptoms often improve during the day with recurrence of symptoms in the early hours of the morning.
- **Epiglottitis:** Stridor is not a prominent feature.

Cough

- Nocturnal cough is rare in normal children
- Associations: Brassy (tracheal irritation, tracheomalacia); barky (croup); honking (habit cough); staccato (chlamydia, mycoplasma); paroxysmal/whoop (pertussis, CF, FB)

Exercise intolerance

- Vocal cord dysfunction: More common in adolescent females. May mimic EIA—need to consider if not responding to EIA treatment

Hemoptysis

- Differentiating from hematemesis (vomiting blood) and epistaxis (nasal bleeding) can be tricky.
- Most common reason for symptom usually not true hemoptysis, but bleeding from upper airway (e.g., nasal bleeding)

Congenital airway and pulmonary malformations

- With symptoms and presenting during infancy, most will require surgical intervention.

Acute bronchiolitis

- Most common lower respiratory tract infection in < 2 years
- Etiology: RSV > 50%
- Apnea may be more prominent than wheezing in infants < 2 months or former preterm infants.
- Peak symptomatology at days 3–4 of illness ("day of illness")
- "Day of illness": Important variable for providing anticipatory guidance in outpatient management and making decisions regarding admission/discharge
- Routine use of bronchodilators or systemic steroids in management NOT recommended

Asthma

- Asthma symptoms are more common in boys before puberty, but more severe in girls after puberty.
- **Early-phase reaction or Type I IgE-mediated reactions** occur within minutes of an allergen-related trigger.

- **A late-phase IgE-mediated reaction** follows 2–12 h later.
- Viral respiratory infections (such as RSV and rhinovirus) have been associated with future development of asthma and are the most common trigger of exacerbations in young children.
- All that wheezes is not asthma! Think about the differential if diagnosis not clear.
- If cough is the only symptom or chronic sputum production is reported, broaden your differential.
- ICS are the most potent and effective medication for long-term control of asthma.
- EIA: In 80% patients, SABA before exercise prevents symptoms for about 2–3 h.
- Acute asthma exacerbation: SpO2 < 92% after an hour of therapy is a good predictor for hospitalization need.

Pneumonia

- *Streptococcus pneumoniae* is the most common bacterial cause in children older than 1 week of age.
- Viruses account for 14–35% of cases.
- For school-age children needing inpatient therapy: Cefuroxime, ceftriaxone, and cefotaxime are the antibiotics of choice.

Bronchiectasis/cystic fibrosis

- CF is the most common cause of bronchiectasis in pediatric patients in the USA.
- CFTR dysfunction/absence leads to thick secretions, impaired mucociliary clearance, recurrent inflammation, and infection, leading to development of bronchiectasis.
- All US states have newborn screening, but results are not 100% sensitive.
- Diagnostic tests include sweat testing and DNA testing.
- Patients should be managed by a multidisciplinary team at a CF care center.
- Pneumothorax/pneumomediastinum
  - Pneumothorax > 5% hemithorax will require chest tube drainage, but pneumomediastinum usually resolves spontaneously.

Thoracic cage deformities

- Pectus excavatum: > 90% of congenital wall anomalies
- Scoliosis: Curvatures > 50° more likely to be progressive. Extreme curvatures can lead to respiratory compromise due to restrictive chest wall disease.

OSA

- Higher prevalence in African Americans and obese children
- Polysomnography diagnostic test of choice
- Adenotonsillectomy is first-line therapy and curative in about 80% of children with OSA.

SIDS

- Peaks at 2–4 months of age, male predominance
- "Back to sleep" supine position for sleep led to marked decline in SIDS rate

Acknowledgment The authors gratefully acknowledge the contributions of Karen Hardy, MD, Division of Pulmonary Medicine, Department of Pediatrics, Stanford Children's Health Specialty Services, Emeryville, California, to the first edition of this chapter, many of which have been incorporated into this edition as well.

References

1. Global Initiative for Asthma (2018). Global strategy for asthma management and prevention. www.ginasthma.org. Accessed 3 Sept 2018.

Suggested Reading

Alario AJ, McCarthy PL, Markowitz R, Kornguth P, Rosenfield N, Leventhal JM. Usefulness of chest radiographs in children with acute lower respiratory tract disease. J Pediatr. 1987;111(2):187–93.

Al-Qadi MO. Disorders of the chest wall: clinical manifestations. Clin Chest Med. 2018;39(2):361–75.

American Academy of Pediatrics Subcommitee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. Pediatrics. 2006;118(4):1774–93.

Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev. 2013;(30, 4)

Baptist E, Kwak J. A 7-month old girl with cyanotic spells. Pediatr Rev. 2015;36(10):e35–8.

Bhargava S. Diagnosis and management of common sleep problems in children. Pediatr Rev. 2011;32(3):91–8.

Butterfield R. Primary ciliary dyskinesia. Pediatr Rev. 2017;38(3):e10–2.

Caceres M, Ali SZ, Braud R, Weiman D, Garrett HE Jr. Spontaneous pneumomediastinum: a comparative study and review of the literature. Ann Thorac Surg. 2008;86(3):962–6.

Cashen K, Petersen TL. Pleural effusions and pneumothoraces. Pediatr Rev. 2017;38(4):170–81.

Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):260S–83S.

Cherry JD. Clinical practice. Croup N Engl Med. 2008;358(4):384–91.

Cotton RT, Reilly JS. Stridor and airway obstruction. In: Bluestone C, Stool S, Kenna M, editors. Pediatric otolaryngology. 3rd ed. Philadelphia: WB Saunders; 1995. p. 1275–86.

Crotty E, Brody AS. Imaging of the respiratory system. In: Taussig LM, Landau LI, editors. Pediatric respiratory medicine. 2nd ed. Philadelphia: Mosby; 2008. p. 135.

DiFranza JR, Aligne CA, Weitzman M. Prenatal and post-natal environmental tobacco smoke exposure and children. Pediatrics. 2004;113(4 Suppl):1007–15.

Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. Nature. 2008;454(7203):445–54.

Global Initiative for Asthma (2018). Global strategy for asthma management and prevention. www.ginasthma.org. Accessed 3 Sept 2018.

Godfrey S. Pulmonary hemorrhage/hemoptysis in children. Pediatr Pulmonol. 2004;37(6):476–84.

Haddad GG, Green TP. Diagnosis approach to respiratory disorders. In: Kliegman RM, Behrman RE, Jenson HB, Stanson BF, editors. Nelson textbook of pediatrics. 18th ed. Philadelphia: Saunders Elsevier; 2007. p. 1731–2.

Hedges JR, Baker WE, Lanoix R, Field DL. Use of monitoring devices for assessing ventilation and oxygenation. In: Roberts JR, Hedges JR, editors. Clinical procedures in emergency medicine. 4th ed. Philadelphia: Saunders; 2004. p. 32–6.

Hinds D, Cooper M, Daftary A. Case 1: persistent tachypnea in an infant. Pediatr Rev. 2017;30(7):330–2.

Hofferberth SC, Watters K, Rahbar R, Fynn-Thompson F. Management of congenital tracheal stenosis. Pediatrics. 2015;136(3):e660–9.

Holinger LD. Evaluation of stridor and wheezing. In: Holinger LD, editor. Pediatric laryngology & bronchoesophagology. New York: Lippincott Raven; 1997. p. 28–41.

Kair LR, Leonard DT, Anderson JM. Bronchopulmonary dysplasia. Pediatr Rev. 2012;33(6):255–63.

Kobelska-Dubiel N, Klincewicz B, Cichy W. Liver disease in cystic fibrosis. Prz Gastroenterol. 2014;9(3):136–41.

Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. Chest. 2004;126(3):915–25.

LeGrys VA, Yankaskas JR, Quittell LM, Marshall BC, Mogayzel PJ Jr, Cystic Fibrosis Foundation. Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. J Pediatr. 2007;151(1):85–9.

Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, American Academy of Pediatrics. Diagnosis and management of childhood obstructive sleep apnea syndrome. Clin Pract Guidel Pediatr. 2012;130(3):576–84.

Matiz A, Roman EA. Apnea. Pediatr Rev. 2003;24(1):32–4.

Mayer OH, Allen J. Chest wall and spinal deformities. In: Light MJ, editor. Pediatric pulmonol-

ogy. 1st ed. Itasca, IL: American Academy of Pediatrics; 2011. p. 309–45.

McBride W. Congenital lesions of the lung. NeoReviews. Itasca, IL: 2016;17(5):3263–70.

Mindell JA, Owens JA. A clinical guide to pediatric sleep: diagnosis and management of sleep problems. Philadelphia: Lippincott Williams & Wilkins; 2003.

Mueller G, Eigen H. Pulmonary function testing in pediatric practice. Pediatr Rev. 1994;15(10):403–11.

National Heart, Lung, and Blood Institute. National asthma education program Expert Panel Report 3 (EPR-3). Guidelines for the diagnosis and management of asthma. Bethesda: National Institutes of Health; 2007. (NIH Publication No. 08-5846)

Nevin MA. Pulmonary hemosiderosis. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011. p. 1498–500.

Rajagopal H, Karnik R, Sahulee R. Pediatric hypertension. Pediatr Rev. 2016;37(3):129–31.

Ren CL, Esther CR Jr, Debley JS, Sockrider M, Yilmaz O, Amin N, ATS Ad Hoc Committee on Infants with Recurrent or Persistent Wheezing, et al. Official American Thoracic Society clinical practice guidelines: diagnostic evaluation of infants with recurrent or persistent wheezing. Am J Respir Crit Care Med. 2016a;194(3):356–73.

Ren CL, Esther CR Jr, Debley JS, Sockrider M, Yimaz O, Bazzy-Asaad A, et al. Official American Thoracic Society clinical practice guidelines: diagnostic evaluation of infants with recurrent or persistent wheezing. Am J Respir Crit Care Med. 2016b;194(3):356–73.

Rosenberg J. Scoliosis. Pediatr Rev. 2011;32(9):397–8.

Sahn SA, Heffner JE. Spontaneous pneumothorax. N Engl J Med. 2000;342(12):868–74. Review.

Schechter M, O'Sullivan B. Cystic fibrosis. In: Light MJ, editor. Pediatric pulmonology. 1st ed. Itasca, IL: American Academy of Pediatrics; 2011. p. 717–43.

Sharma G, Conrad C. Croup, epiglottitis and bacterial tracheitis. In: Light MJ, editor. Pediatric pulmonology. 1st ed. Itasca, IL: American Academy of Pediatrics; 2011. p. 348–63.

Shields MD, Bush A, Everard ML, McKenzie S, Primhak R, British Thoracic Society Cough Guideline Group. BTS guidelines: recommendations for the assessment and management of cough in children. Thorax. 2008;63(Suppl 3):iii1–iii15.

Stillwell P. Bronchiectasis. In: Light MJ, editor. Pediatric pulmonology. 1st ed. Itasca, IL: American Academy of Pediatrics; 2011. p. 346–75.

Tieder JS, Bonkowsky JL, Etzel RA, Franklin WH, Gremse DA, Herman B, Subcommittee on Apparent Life Threatening Events, et al. Brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants. Pediatrics. 2016;137(5):e20160590.

Weinberger M. Bronchiolitis. In: Light MJ, editor. Pediatric pulmonology. 1st ed. Itasca, IL: American Academy of Pediatrics; 2011. p. 377–90.

Nutrition

21

Susan S. Baker

Abbreviations

AI Adequate intake: the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group of healthy people that are assumed to be adequate—used when there is not enough data to determine an RDA

DRI Dietary reference intake

USDA United States Department of Agriculture

UL Tolerable upper intake level: the highest average daily intake that is unlikely to pose a risk of adverse health effects for almost all individuals in the general population

RDA Recommended dietary allowance: the average daily level of intake of a nutrient sufficient to meet the nutrient requirements of 97–99% of healthy people

GENERAL

- Digestive enzymes, including disaccharidases, peptidases, and acid secretion, are present and functional by approximately 24 weeks of gestation.
- Pancreatic exocrine function and bile acid pool are reduced in the first year of life compared to those in older children and result in a reduced coefficient of fat absorption (% of absorbed fat from the diet).
- After about 1 year of age, pancreatic exocrine function and bile acid pool approach adult characteristics.

Nutrition Requirements

Nutrients can be thought of as essential, nonessential, and conditionally essential:

- Essential—nutrients that cannot be synthesized from precursors and hence must be provided in the diet.
- Nonessential—nutrients that can be synthesized by the body; thus, an extracorporeal source is not required.
- Conditionally essential—nutrients that are synthesized within the body or that have limited synthesis under special physiologic conditions.

The nutrients discussed in the following are all considered essential.

MINERALS

Minerals are inorganic substances that are not made by living things. Minerals are found naturally in soil and water and are absorbed by plants, which are then eaten by people and other animals. Examples of minerals are iron, calcium, and potas-

S. S. Baker (✉)
Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA
e-mail: ssbaker@Buffalo.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_21

sium. The USDA lists 14 essential minerals (excluded in the following are manganese and molybdenum).

Calcium

- 99% found in teeth and bone
- 1% in extracellular fluid, blood, muscle, and other tissues
- Functions in as follows:
  - Blood clotting
  - Mediating vascular contraction and vasodilatation
  - Muscle contraction
  - Nerve transmission
  - Glandular secretions
- Sources:
  - Best sources are dairy, canned fish with bones (salmon, sardines), and fortified cereals.
- Deficiency caused by inadequate intake or malabsorption:
  - Reduced bone mass and bone fragility
  - Often seen in children with developmental disorders and malabsorption
  - Hypocalcemia
  - Neuromuscular hyperexcitability, positive Chvostek and Trousseau signs, carpal-pedal spasm

Chloride

- Chloride, along with sodium, maintains extracellular fluid volume, pH, and plasma osmolality.
- In addition, chloride in the form of hydrochloric acid is an important component of gastric juice.
- Added salt (sodium chloride) is the main dietary source in the USA but is unnecessary to maintain health.
- Good food sources include as follows:
  - Dairy, celery, olives, seaweed, tomatoes:
- May need additional salt in very hot climates, during unaccustomed strenuous physical activity, during diarrhea, if an ileostomy is present, especially in young children, and if suffering from cystic fibrosis

Chromium

- Functions in carbohydrate and fat metabolism and to potentiate the action of insulin.
- Deficiency is rare; described in 3 patients on total parenteral nutrition (TPN) with no chromium content.
- Food sources include as follows:
  - Broccoli, fruits and fruit juice, meats, garlic, basil, whole grains

Copper

- Functions as a component of metalloenzymes that act as oxidases:
  - Reduce molecular oxygen
  - Activate histamine during allergic reactions
  - Regulate serotonin degradation
  - Oxidize ferrous iron
  - Important for bone formation and collagen and connective tissue formation
- Food sources include as follows:
  - Chocolate and cocoa, crustaceans and shellfish, lentils, nuts and seeds, organ meats, and whole grains
- Deficiency is rare but can occur in special conditions:
  - Infants recovering from malnutrition with chronic diarrhea fed cow milk
  - Patients on unsupplemented TPN
  - Young children fed on a milk-only diet
- Menkes kinky hair syndrome:
  - X-linked recessive mutation in the *ATP7A* gene.
  - Gene codes for the copper-transporting polypeptide that regulates copper levels.

  - Characterized by sparse, kinky hair, failure to thrive (FTT), developmental delays, seizures, intellectual disability, and hypotonia.
  - Treatment with copper supplementation does not fully reverse the disease but is the only available treatment.
  - A milder form is called occipital horn syndrome or cutis laxa.
- Wilson disease (Chap. 22 Gastroenterology):
  - Autosomal recessive disease (mutation in the *ATP7B* gene).
  - Characterized by high levels of intracellular copper.
  - Most significantly affected organs are the liver, heart, and nerves.
  - Kayser-Fleischer rings are pathognomonic.

Fluoride

- Functions to prevent the initiation and progression of dental caries—effect is topical.
- Stimulates new bone formation.
- Toxicity results in mottled teeth.
- If water is fluoridated, recommended concentration is 0.7–1.2 mg/L.

Iodine

- Essential component of thyroid hormones T3 and T4, which regulate protein synthesis and enzymatic activity, especially in the developing brain.
- Congenital deficiency is called cretinism (see Chap. 12 Endocrinology).
- Deficiency affects the muscle, heart, pituitary, and kidney:
  - Decreased blood thyroid hormones
  - Hypothyroidism (see Chap. 12 Endocrinology).
- Iodine deficiency is not as common because of salt fortification with iodine.
- Assess with serum thyroid hormone levels; urine iodine.
- Deficiencies of vitamin A, selenium, or iron exacerbate effects of iodine deficiency.
- Food sources include as follows:
  - Dairy, iodized salt, potatoes, seafood, seaweed, meats, bread, and cereals
  - Some foods contain goitrogens, substances that interfere with thyroid hormone production or utilization. They are not clinically significant unless there is coexisting iodine deficiency.

Iron

- Main functions are electron transfer and binding of ligands.
- The major classes of iron-containing proteins are as follows:
  - Heme proteins (hemoglobin, myoglobin, and cytochromes)
  - Iron sulfur enzymes (flavoproteins, heme flavoproteins), iron storage
  - Transport proteins (transferrin, lactoferrin, ferritin, and hemosiderin)
- Functions:
  - Energy production
  - Growth and development
  - Immune function
  - Red blood cell formation
  - Reproduction
  - Wound healing
- Deficiency:
  - Long-term impaired mental and psychomotor development
  - Fatigue
  - Pallor
  - Anemia
  - Reduced capacity for play/work
- Assess iron status with soluble transferrin receptor.
- Ferritin is an acute-phase reactant and does not correlate with functional iron.
- Food sources include as follows:
  - Meats, seafood, enriched/fortified breads and cereals, dark-green vegetables, beans and peas

- Exclusively breastfed infants need iron supplementation at 4 months, as human milk has insufficient iron to meet requirements.
- Increased needs for pregnant women and young children.

Magnesium

- Functions as a cofactor for more than 300 enzyme systems that generate energy both aerobically and anaerobically for glycolysis indirectly as part of the Mg-ATP complex or directly as an enzyme activator.
- Required for mitochondrial oxidative phosphorylation.
- Food sources include as follows:
  - Leafy green vegetables, beans and peas, dairy, whole grains, nuts and pumpkin seeds
- Deficiency can be manifested as hypocalcemia, neuromuscular hyperexcitability, positive Chvostek and Trousseau sign, and carpal-pedal spasm.

Potassium

- Major intracellular cation required for normal cell function. Important in acid-base balance.
- Food sources include as follows:
  - Bananas, beet greens, juices, dairy, oranges, potatoes, prunes, spinach, tomatoes
- Severe deficiency is characterized by hypokalemia and results in cardiac arrhythmias, muscle weakness, hypercalciuria, and glucose intolerance.
- Moderate deficiency occurs without hypokalemia and is characterized by increased blood pressure and salt sensitivity, increased risk of kidney stones, and increased bone turnover.

Selenium

- Functions as a selenoprotein, several of which are oxidant defense enzymes:
  - Regulation of thyroid hormone action
  - Regulation of the redox status of vitamin C and other molecules, important for immune function and reproduction
- Food sources include as follows:
  - Eggs, whole grains, meats, nuts and seeds, garlic, and seafood
- Only deficiency disease is Keshan disease; cardiomyopathy is seen in certain areas of China.

Sodium

- Sodium, along with chloride, maintains extracellular fluid volume, pH, and plasma osmolality. It maintains acid-base balance, blood pressure regulation, fluid balance, muscle contraction, and nervous system function.
- Added salt (sodium chloride) is the main dietary source in the USA but is unnecessary to maintain health.
- Good food sources include as follows:
  - Dairy, especially cheeses, celery, olives, seaweed, tomatoes, breads, meats
- May need additional salt in very hot climates, during unaccustomed strenuous physical activity, during diarrhea, if an ileostomy is present, especially in young children, and if suffering from cystic fibrosis.

Zinc

- Functions as a component of enzymes in the maintenance of structural integrity of proteins and in the regulation of gene expression.
- Necessary for normal growth and development, immune function, nervous system function, protein formation, reproduction, taste, smell, and wound healing.
- Food sources include as follows:
  - Meats, beans and peas, dairy, fortified cereals, seafood, whole grains, and nuts
- Zinc deficiency, first described in Iranian male dwarfs, can occur with diarrhea caused by infectious, inflammatory bowel disease, allergic gastroenteritis, etc.:

- Deficiency symptoms can be subtle and hard to define:
  - Growth retardation
  - Alopecia
  - Diarrhea
  - Delayed sexual maturation
  - Impotence
  - Eye and skin lesions
  - Impaired appetite
- Supplement with 1 mg/kg/day as an oral solution of zinc acetate (30 mg in 5 mL) if suspecting deficiency.
- Use serum zinc levels to assess as clinically available, but serum zinc levels are not an accurate estimate of nutritional zinc status.
- Acrodermatitis enteropathica is a fatal autosomal recessive disease if untreated that affects the uptake of zinc through the bowel:
  - Characterized by periorificial inflammation of tips of fingers and toes, hair loss, and diarrhea.
  - It is treated with zinc supplementation.

VITAMINS (TABLES 21.1 AND 21.2)

- Vitamins are organic molecules that cannot be synthesized by the body and are required in small amounts for normal function.

Table 21.1 Water-soluble vitamins

Vitamin	Deficiency	Toxicity	Assess status
B1, Thiamine[a]	Beriberi Wet—high output cardiac failure Dry—nervous tissue Wernicke encephalopathy Korsakoff syndrome Infantile—affects infants of malnourished mothers	None known; water-soluble vitamin and excreted in the urine	Red blood cell transketolase level or urinary thiamine level
B2, Riboflavin	Very rare in the USA and usually associated with other deficiencies If severe and prolonged, cataracts and anemia Vegans at risk of developing deficiency	None known; water-soluble vitamin and excreted in the urine	Serum riboflavin level
B3, Niacin	Pellagra—"3 Ds": dermatitis (sun-exposed areas) , diarrhea, dementia	Flushing, especially when used as a medication for lowering cholesterol	Serum niacin level
B6	Microcytic anemia, dermatitis, cheilosis, glossitis, depression, and confusion. Can be associated with renal disease	None reported	Serum level of pyridoxine 5′phosphate (PLP)
Folic acid	Associated with increased risk of neural tube defects in infants from deficient mothers. Supplement all women who can become pregnant	Can mask neurological signs of B12 deficiency. Perhaps accelerate progression of preneoplastic lesions	Erythrocyte folate level
Vitamin B12	Megaloblastic anemia, fatigue, weakness, constipation, weight loss, numbness and tingling, depression, dementia, confusion, soreness of mouth, difficulty maintaining balance	None reported	Measure B12 level
Vitamin C	Scurvy—inflammation and swelling of gums, can lose teeth, petechiae, bleeding, and malaise	Low toxicity. Can see diarrhea, nausea, and abdominal cramps likely due to osmotic effect of unabsorbed vitamin C supplements	Serum level

[a]B vitamins and folate deficiency rare in the USA, as grains are fortified

Table 21.2 Fat-soluble vitamins (summary)

Vitamin	Deficiency	Toxicity	Assess status
A	Earliest sign is night blindness; xerophthalmia is most common and is often associated with Bitot spots. Top cause of blindness in developing world. Increased severity and risk of infections	Pseudotumor cerebri, dizziness, nausea, headaches, skin irritation, joint pain, coma, and death Provitamin A carotenoids are not associated with adverse effects	Measure serum level
D	Rickets, failure of bone mineralization; osteomalacia in adults. Exclusively breastfed infants need to be supplemented, as prolonged breastfeeding without supplements is associated with rickets	Hypercalcemia leading to vascular and tissue calcification, anorexia, weight loss, polyuria, arrhythmias	Serum 25-hydroxycholecalciferol levels
E	May be seen in prematurely born infants and with fat malabsorption. For those with abetalipoproteinemia and AVED, very high doses are needed	Hemorrhage	Serum level
K	Bleeding. Important in newborns, liver disease, anticoagulant therapy. Perhaps osteoporosis	None described	Serum prothrombin, INR, Individual factors when indicated

AVED ataxia and selective vitamin E deficiency

- Vitamins can be supplied in food, as a supplement, and—in the case of vitamin D—from ultraviolet (UV) light.
- Toxicity is seen with the fat-soluble vitamins A, D, and E.

The following are considered essential vitamins by the US Food and Drug Administration (FDA).

Biotin

- Functions as a coenzyme in bicarbonate-dependent carboxylation for 4 enzymes, 3 of which are mitochondrial:
- Deficiency:
  - Dermatitis.
  - Conjunctivitis.
  - Alopecia.
  - Central nervous system abnormalities.
  - Deficiency can be induced by consuming raw egg white over long periods of time.
  - Congenital deficiency occurs in the autosomal recessive metabolic disorder; biotinidase deficiency, in which biotin is not released from proteins in the diet (also see Chap. 5 Metabolic Disorders).
- Supplementation with biotin can reverse the progression if congenital biotinidase deficiency is recognized early.
- Food sources include as follows:
  - Eggs (cooked), meats, liver, salmon, fruits, cruciferous vegetables, whole grains, and avocados

Folate/Folic Acid

- Functions as a coenzyme in single-carbon transfers in the synthesis of DNA, purine synthesis, generation of folate, and amino acid interconversions.
- Closely related to vitamin B12.
- Deficiency:
  - Low serum folate level
  - Megaloblastic anemia
  - Neutrophil hypersegmentation
- Risk of neural tube defects (NTD) associated with low folate in the periconception time. Any woman capable of becoming pregnant is at risk.
- Food sources include as follows:
  - Enriched grains, beans and peas, green leafy vegetables, avocado, asparagus, orange

Niacin (Also Called Nicotinamide, Nicotinic Acid)

- Functions:
  - Biological redox reactions as nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP)
  - Cholesterol production
  - Conversion of food into energy
  - Digestion and nervous system function
- Deficiency:
  - Pellagra, classic manifestation of severe deficiency characterized by dermatitis, a hyperpigmented rash in sun-exposed areas of skin, diarrhea, and dementia ("the 3 Ds"); rarely seen in the USA except in alcoholics, common in parts of Africa and China
- Food sources include as follows:
  - Beans, meats, enriched grains and their products, nuts, seafood
- Used to lower cholesterol. Side effect of high doses is flushing.
- Liver can synthesize 1 mg of niacin from 60 mg tryptophan provided there is adequate riboflavin, B6, and iron.

Riboflavin (Also Sometimes Called Vitamin B2)

- Riboflavin is bright yellow and gives urine a bright-orange color if consumed in quantity.
- Functions:
  - Fat metabolism
  - Hormone production
  - Nervous system function
- Deficiency often occurs in conjunction with other B vitamin deficiencies:
  - Sore throat.
  - Glossitis.
  - Conjunctivitis.
  - Seborrheic dermatitis.
  - Normochromic, normocytic anemia.
  - Cheilosis, angular stomatitis, and angular blepharitis.
  - Brown-Vialetto-Van Laere syndrome—rare neurological disorder caused by mutations of the *SLC52A3* gene, which encodes the intestinal riboflavin transporter and is associated with deafness, bulbar palsy, and respiratory difficulties. Riboflavin supplements can be life-saving.
- Food sources include as follows:
  - Eggs, enriched grains, meats, dairy, seafood, green leafy vegetables, and mushrooms

Thiamin (Also Sometimes Called Vitamin B1 and Aneurin)

- The first B vitamin identified.
- Functions as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids.
- Assess thiamine status with erythrocyte transketolase activity, serum thiamine level, or thiamine in urine.
- Beriberi—rare in the USA:
  - Wet beriberi:
    - High-output cardiac failure
  - Dry beriberi (Wernicke-Korsakoff syndrome):
    - Polyneuritis, ataxia, altered mental status, nystagmus, and confabulation; generally seen in alcoholics in the USA
  - Acute infantile beriberi occurs in infants of thiamine-deficient mothers who are exclusively breastfed:
    - Hypotension, tachycardia, lactic acidosis, and a high infant mortality (Shoshin beriberi).
    - Intravenous thiamine reverses the disease and is diagnostic; rare in the USA and seen in India when breastfeeding mother's diet is highly restricted.
- Food sources include as follows:
  - Beans and peas, enriched grains, unpolished rice, meats, nuts, sunflower seeds

Vitamin B6 (Pyridoxine and Related Compounds)

- Functions as a coenzyme in the metabolism of the following:
  - Amino acids—protein metabolism
  - Glycogen—carbohydrate metabolism
  - Sphingoid bases—fat metabolism
- Deficiency is rare and if present usually occurs with other B vitamin deficiencies:
  - Seborrheic dermatitis
  - Microcytic anemia
  - Epileptiform convulsions
  - Depression
  - Confusion
- Food sources include as follows:
  - Chickpeas, noncitric fruits, fish, and potatoes

Vitamin B12 (Also Called Biologically Active Cobalamins)

- Functions as a cofactor for 2 enzymes, methionine synthase (transfers a methyl group from methyltetrahydrofolate to homocysteine) and L-methylmalonyl-CoA mutase (converts L-methylmalonyl-CoA to succinyl-CoA).
- Metabolically closely related to folate.
- Deficiency manifested as follows:
  - Megaloblastic anemia
  - Neutrophil hypersegmentation
  - Tingling and numbness in extremities, worse in the lower limbs
  - Vibratory, position sense, and motor disturbances
  - Cognitive problems from memory loss to frank dementia
- Neurological disturbances occur at later stages of deficiency; rare in children.
- Pernicious anemia is the end stage of an autoimmune disorder in which parietal cell autoantibodies prevent the synthesis of intrinsic factor, necessary for B12 absorption in the ileum; rare in children. Treatment is with B12 injections. Some use high-dose oral or nasal spray.
- Food sources include as follows:
  - Dairy, eggs, fortified grains and cereals, meats, seafood
- Supplement those consuming a vegan diet.

Vitamin A

- Fat-soluble retinoids including retinol, retinal and retinyl esters, carotenes, and beta-carotenes.
- Functions:
  - Vision
  - Integrity of epithelial and mucous tissue
  - Growth and development
  - Reproduction
  - Immune regulation
- Supplementation with vitamin A reduces mortality in measles, acute pneumonia, and infantile diarrhea in vitamin-insufficient populations.
- Deficiency characterized by as follows:
  - Progressive loss of vision.
  - Night blindness is one of first signs of deficiency.
  - Xerophthalmia (dry eyes).
  - Keratomalacia—ulceration of the cornea.
  - Bitot spots, buildup of keratin in the conjunctiva, on either or both sides of the pupil, are pathognomonic of vitamin A deficiency.
- Best food sources are as follows:
  - Liver, cod liver oil often used to treat deficiency in the developing world
- Hypervitaminosis:
  - Pseudotumor cerebri.
  - Hypercalcemia.
  - Hepatitis.
  - Poor weight gain.
  - Bone pain/swelling among other symptoms.
  - Treatment is to stop intake of vitamin A.

- Carotenoids found in yellow vegetables do not cause hypervitaminosis A but can cause yellowing of the skin.

Vitamin C (Refers to Ascorbic and Dehydroascorbic Acid)

- Water-soluble vitamin.
- Functions as an antioxidant by providing reducing equivalents for biochemical reactions, often for reactions requiring a reduced iron or copper metalloenzyme; needed for the synthesis of collagen, L-carnitine, proteins, and some neurotransmitters.
- Deficiency:
  - Scurvy (abnormal collagen) characterized by the following:
    - Weakness, tiredness
    - Brown skin spots
    - Decreased red blood cells
    - Gingival disease
    - Bleeding from mucous membranes
    - Changes to hair
    - Poor wound healing
- Food sources include as follows:
  - Citrus fruits, tomatoes and their juice, peppers, broccoli

Vitamin D (Fat-Soluble Vitamin, Also Called Calciferol)

- Functions to maintain normal serum calcium and phosphorus levels.
- Deficiency:
  - Rickets, inadequate skeletal mineralization, characterized by widening of the end of long bones, rachitic rosary (rib beading), bowing of the legs, craniotabes, and—in adults—osteomalacia
- UV light is important in the synthesis of vitamin D in the skin. Sunlight, however, is a risk of skin cancer.
- Naturally present in few foods:
  - Available in fortified dairy, eggs, some beverages, liver from any mammal, and supplements
- All breastfed infants should be supplemented with vitamin D, 400 IU, starting at birth and continuing until they consume 1 quart of formula daily.
- Vitamin D insufficiency/deficiency is often seen in children and should be corrected:
  - Deficiency = serum level of 25-hydroxyvitamin D < 20 ng/mL
  - Insufficiency = serum level of 25-hydroxyvitamin D 20–29 ng/mL
  - Sufficiency = 30–100 ng/mL
- Correct vitamin D deficiency or insufficiency with 2000 IU PO daily or 50,000 IU PO weekly for 6 weeks.
- Hypervitaminosis D is characterized by the following:
  - Vomiting
  - Decreased appetite
  - Irritability
  - Constipation
  - Metastatic calcification of soft tissue

Vitamin E

- A fat-soluble vitamin that includes α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol.
- Likely functions as an antioxidant that prevents propagation of lipid peroxidation, but unlike other vitamins, a specific purpose in a required metabolic function has not been defined.
- Deficiency is rare, but has been associated with the following:
  - Spinocerebellar ataxia
  - Myopathies
  - Dysarthria
  - Absence of deep tendon reflexes
  - Loss of vibratory sense
  - Hemolytic anemia
  - Retinopathy
  - Impaired immune response

- Deficiency has been described in prematurely born infants. Treatment is vitamin E supplementation.
- Patients with abetalipoproteinemia require high doses to prevent poor nerve tissue function, muscle weakness, and retinal degeneration leading to blindness.
- Ataxia with isolated vitamin E deficiency (AVED), caused by a mutation in the *TTPA* gene, is a rare congenital disorder that requires high doses to prevent nerve damage and inability to walk.
- Food sources include as follows:
  - Fortified cereals and juices, green leafy vegetables, nuts and seeds, vegetable oils, peanuts

Vitamin K

- A fat-soluble vitamin that includes phylloquinones and menaquinones.
- Functions as a coenzyme during the synthesis of the biologically active form of proteins involved in blood coagulation and bone metabolism:
  - Plasma prothrombin (coagulation factor II)
  - Plasma procoagulants (factors VII, IX, and X)
  - Likely inhibits arterial calcification
- Deficiency is characterized by vitamin K-responsive hypoprothrombinemia, prolonged PT, INR, and bleeding:
  - Vitamin K is poorly transported across the placenta, so newborn infants are at risk of deficiency and should be treated with a single dose of 0.5–1.0 mg IM vitamin K at birth.
  - Deficiency occurs in cholestatic liver disease and may cause bleeding in this circumstance.
- Food sources are as follows:
  - Mostly green vegetables—vitamin K is an electron acceptor in photosynthesis

MACRONUTRIENTS

Macronutrients are considered a type of food (e.g., fat, protein, carbohydrate) required in large amounts in the human diet:

Energy

- Calories or energy required to sustain the body's functions including respiration, circulation, physical work, and maintenance of core body temperature; available from foods and released by oxidation yielding chemical energy.
- Estimation of caloric requirement has become complicated, as there is now a recommendation to include activity in the estimation and there is no RDA for energy.
- Estimates that can be used clinically (**not** RDA):
  - Preterm infants: 90–120 kcal/kg/day; important to follow growth
  - Infants: 100 kcal/kg/day
  - Children 1–8 years: about 85 kcal/kg/day
  - Children 9–13 years:
    - Boys 50 kcal/kg/day
    - Girls 40 kcal/kg/day
  - Children 14–18 years:
    - Boys 37 kcal/kg/day
    - Girls 30 kcal/kg/day

Fat

- Fats are essential nutrients that are a fuel source and aid in the absorption of fat-soluble vitamins and carotenoids.
- They function in cell signaling and alter expression of specific genes.
- There is no recommended dietary intake because there are insufficient data.
- 98% of dietary fat is triacylglycerol:
  - Essential fatty acids:
    - Linoleic (n-6):
      - Thought to be "pro-inflammatory."

        - Deficiency is dermatitis.
        - Food source is fatty fish.
      - Linolenic acid (n-3):
        - Thought to be "anti-inflammatory."
        - Deficiency is dermatitis.
        - Food source is fatty fish.
      - Trans-fatty acids:
        - Not essential and provide no known benefit for human health; should not be eaten
- Recommendations for fat intake:
  - 2 to 3 years of age: total fat 30–35% of calories.
  - 4 to 18 years of age: total fat 25–35% of calories.
  - Most fats should come from polyunsaturated and monounsaturated fatty acids (fish, nuts, vegetable oils).

Protein

- Protein is the major functional and structural component of the body:
  - Consists of amino acid chains
  - Complex physical structure
  - Considered as indispensable (body cannot make), dispensable (body can make), or conditionally indispensable (body cannot make sometimes or has increased requirement in certain circumstances—e.g., arginine, glycine, tyrosine)
  - Requirements based on age:
    - Birth to 6 months—human milk, estimated at about 1.5 g/kg/day, is highly variable.
    - 7–12 months: 1.2 g/kg/day.
    - 1–3 years: 1.05 g/kg/day.
    - 4–13 years: 0.95 g/kg/day.
    - 14–18 years: 0.85 g/kg/day.

Carbohydrates

- Carbohydrates provide energy, especially for the brain:
  - Monosaccharides are 1 sugar, e.g., glucose.
  - Disaccharides are 2 sugars linked together, e.g., lactose.
  - Oligosaccharides are 3 to 10 sugars linked together, e.g., raffinose and stachyose.
  - Polysaccharides contain more than 10 sugars linked, e.g., starch or glycogen.
  - Added sugar are sugars and syrups added to foods during processing or preparation:
    - Baked goods like cookies, cakes, pies
    - Beverages like fruit drinks, sodas
    - Dairy like yogurt with fruit syrup
    - Candy
  - Examples of types of added sugar:
    - White sugar
    - Brown sugar
    - Raw sugar
    - Corn syrup and corn syrup solids
    - High-fructose corn syrup
    - Malt syrup
    - Maple syrup

BREASTFEEDING (TABLE 21.3)

- Breastfeeding is recommended as the preferred feeding for all infants.
- Human milk is dynamic; nutrient concentrations vary overtime (months and within a single day, within a single feed, and among women).
- No cow's milk before 1 year of age because of GI blood loss. Use infant formula if needing supplementation.

Colostrum

- Colostrum secreted for the first 7 days after birth; volume varies from 2 to 20 mL per feeding.
- Consists of mammary duct contents, immunologically active cells.
- Yellow color caused by carotenoids.
- High levels of vitamin E and protein.

Table 21.3 Difference between colostrum and mature breast milk[a]

Constituent (per liter)	Colostrum	Mature breast milk
Appearance	Creamy, yellow	Thin, white
Volume (mL/24 hour)[b]	~100	750–1050
Energy (Kcal)	571 ± 80	650–700
Total protein (g)	14–65	9–13
Nitrogen (g)—food	3.0	1.9
protein	3.8	3.5
Casein (g)	11–15	5–6
Whey (g)	2.0	0.5–1.0
IgA (g)	0.12	0.2
IgM (g)	3.5	1–3
Lactoferrin (g)	0.1–0.2	0.1
Lysozyme (g)		
Total carbohydrate (g)	26–76	50–83
Lactose (g)	20–30	67–70
Oligosaccharides (g)	22–24	5–15
Glucose (g)	0.2–1.0	0.2–0.3
Total fat (g)	10–27	28–49
Triglycerides (g)	14.5–19.5	34–47
Fatty acids (g)	13–17	30–42
Cholesterol (g)	0.2–0.3	0.1–0.2
Vitamins	5.35	1.8–3.0
Total carotenoids	1510	750
(umol)	19	140
A (ug)	300	400
B1 (ug)	–	120–150
B2 (ug)	–	0.5–1.0
B6 (ug)	750	1600
B12 (ug)	1830	2460
Nicotinic acid (ug)	0.6	6
Pantothenic acid (ug)	0.5	1.4
Biotin (ug)	0.1–0.3	0.33
Folic acid (ug)	15	2.5
D (ug)	59	50
E (ug)	2–5	2–3
C (ug)		
K (ug)		

[a]Human milk is highly variable in content from woman to woman, day to day, fore- vs. hind milk
[b]Volume is highly variable

- Low fat content.
- Contains immunoglobulins, especially immunologically active secretory IgA, which decrease overtime:
  - IgA offers protection of the intestinal epithelial barrier by binding bacteria, toxins, and other macromolecules so they cannot bind to intestinal cells; inhibits pro-inflammatory responses to oral agents.
  - Provides protection against enteric and other diseases in naturally immunized mothers.

Transition Milk

- Gradual change from colostrum to mature milk.
- Protein, immunoglobulin, and fat-soluble vitamin content decreases; lactose, water-soluble vitamins, fat, and total caloric content increases.
- 90% of women whose milk contained 20 g or more of fat/feeding on the seventh day of lactation successfully breastfed for at least 3 months. 80% of women with 5–10 g fat/feeding are not breastfeeding at 3 months.

Mature Breast Milk

- Transition milk produced from about 7 to 10 days after birth:
  - Gradual change from colostrum to mature milk.
  - Protein, immunoglobulin, and fat-soluble vitamin content decreases; lactose, water-soluble vitamins, fat, and total caloric content increases.
- Mature milk produced 7–10 days after birth recommended as exclusive food for infants until 4–6 months:
  - Reliable source of all nutrients for healthy term infants except the following while exclusively breastfeeding for the first 4–6 months:
    - Vitamin D—supplement with 400 IU daily.
    - Iron—supplement with 1 mg elemental iron/kg/day, starting at 4 months.
    - B12 for babies of vegan mothers.

  - Contains protective factors in addition to immunoglobulins, including as follows:
    - Oligosaccharides
    - Lactoferrin
    - Lactoperoxidase
    - Lysozyme
    - Soluble CD14
    - Defensins
    - Live cells: activated neutrophils, macrophages, and lymphocytes
    - Cytokines
    - Opsonins
  - Contains growth factors:
    - Epidermal growth factor
    - Factors that affect neonatal intestinal development
    - Erythropoietin
    - Insulin
    - Insulin-like growth factors I and II
    - Lactoferrin
    - Nerve growth factor
    - Transforming growth factor-α
- Contraindications to breastfeeding:
  - Women infected with HIV or T-cell lymphotropic virus in the developed world
  - Active pulmonary tuberculosis and not completed 2 weeks of treatment
  - Infants with inborn errors of metabolism, such as galactosemia
- Medications and breastfeeding:
  - Many are safe (up-to-date information: US National Library of Medicine, Drugs and Lactation Database (LactMed), https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm).
- Contraindicated medications during breastfeeding:
  - Antithyroid medications
  - Radioactive drugs
  - Most chemotherapy drugs
  - Metronidazole
  - Diazepam
  - Sulfonamides
  - Tetracycline
- Chemical contamination:
  - Many women have detectable levels of chemical agents in breast milk.
  - The CDC recommends continued breastfeeding despite the presence of chemical toxins in milk.
- Impediments to breastfeeding:
  - Work
  - Public attitudes
  - Lack of family/peer support
  - Lack of access to clean rooms to express while at work
  - Stress
  - Mastitis
  - Lack of understanding that first week of nursing can be painful to nipples, a condition that passes
- Normal feeding pattern in breastfeeding:
  - Feeding is dependent on infant cues progressing from hands moving toward the mouth, sucking on fists and fingers, fussiness, agitation, flailing of extremities, and finally loud, persistent crying. The sequence can last 45 min, including nuzzling.
  - In the first 1–2 weeks, infants are fed 8–12 times in 24 h.
  - From about 2–4 weeks, frequency is about 7 to 9 times in 24 h.
  - Both breasts are offered at each feeding.
  - Time to complete a feed varies with mother-infant dyad from about 10–15 min.
- Stools vary overtime:
  - Meconium is cleared within 3–4 days of life.
  - After day 4, most infants have 3 or more stools a day
  - Some breastfed infants may stool infrequently—once every 7–10 days. As long as healthy and growing, it is not a concern.
  - Stools are pale yellow after about the fifth day of life, but can be green and frothy.
- Colitis (blood in stools)—most likely cause in healthy child is protein intolerance:
  - Can stop breastfeeding and use a hydrolyzed infant formula

– Preferable to continue breastfeeding and remove dairy products from mother's diet; supplement her with calcium.

FORMULA FEEDING (TABLE 21.4)

Formula Feeding for Term Infants

- No cow's milk before 1 year of age, associated with GI blood loss.
- Feed formula only until 1 year of age.
- Formula types are grouped according to protein, fat, or carbohydrate content.

Protein

- Cow milk based:
  - Standard iron-fortified formula of choice when not breastfeeding or breastfeeding stopped before 1 year.
  - No vitamin or mineral supplementation is necessary.
- Soy protein based:
  - Support growth and development equivalent to that of breast milk or cow milk-based formula.
  - Recommended for galactosemia, hereditary lactose intolerance, documented IgE-associated cow milk allergy, parents who want a vegetarian diet for children.
  - **Not** recommended for the following:
    - Preterm infants with birth weights < 1800 g
    - Infants with cow milk protein-induced enterocolitis or enteropathy
    - Prevention of colic
    - Prevention of allergy
    - Infants who have sucrose-isomaltose deficiency
- Hydrolyzed cow milk:
  - Developed for infants who cannot digest or are intolerant of intact cow milk protein.
  - Protein is first heat treated and then enzymatically treated to give peptide chains.

Table 21.4 Difference between breast milk and formula

Constituent/L	Mature human milk[a]	Formula
Energy (kcal)	650–700	680
Total protein (g)	8–21	14
Casein:whey (approximate)	3:7	Variable
Fat (g)	28–49	36
Carbohydrates	+	+ or lactose free available
Lactose		
Vitamins	Inadequate	Adequate
Vitamin D		
Minerals	Inadequate	Adequate
Iron	Inadequate	Adequate
Zinc		
DHA/ARA	✓	✓
Oligosaccharides	✓	
Enzymes	✓	
Amylase	✓	
Lipase	✓	
Protease	✓	
Antiproteases	✓	
Arylsulfatase	✓	
Catalase	✓	
Lysozyme	✓	
Histaminase	✓	
Peroxidases	✓	
Ribonuclease	✓	
Platelet activating acetyl hydrolase factor	✓	
Growth factors/hormones	✓	
Erythropoietin	✓	
Insulin	✓	
Insulin-like growth factors I and II	✓	
Lactoferrin	✓	
Nerve growth factor	✓	
Relaxin	✓	
Transforming growth factor α	✓	
Anti-infective/ immunological	✓	
Opsonins	✓	
Enzymes	✓	
Immunoglobulins	✓	
Cytokines	✓	
Live cells	✓	

[a]Human milk is highly variable in volume and content from woman to woman, day to day and fore- vs. hind milk. There are a plethora of infant formulas that are constantly being designed, changed, and marketed. This table provides information on a "typical" term infant formula.

  - Lactose free; contains sucrose, tapioca starch, corn syrup solids, cornstarch as carbohydrates.
  - Contains varying amounts of medium-chain triglycerides (MCTs), polyunsaturated vegetable oil to supply essential fatty acids
  - Indications:
    - Cow milk protein-induced enterocolitis
    - Malabsorption due to GI or hepatobiliary diseases such as cystic fibrosis, short gut, biliary atresia, cholestasis, or prolonged diarrhea
- Chemically defined:
  - Single amino acids are formulated specifically for infants with extreme protein hypersensitivity whose symptoms persist on hydrolyzed formulas.

Carbohydrate

- Lactose, major carbohydrate in human milk and in most cow milk formula:
  - Lactose is a disaccharide hydrolyzed in the small intestine to produce galactose and glucose.
  - Some reaches the colon where it is fermented, producing acid that helps to maintain an environment that fosters acidophilic bacteria that suppress the growth of pathogenic organisms.
  - Soy, hydrolyzed protein, and chemically defined formulas do not contain lactose.
  - Other carbohydrates included in some formulas:
    - Prebiotics—diverse group of complex nondigested carbohydrates fermented by gut bacteria and thought to promote growth of advantageous bacteria
    - Some examples: oligosaccharides, fructooligosaccharides, inulin

Fat

- Formulas can include medium-chain triglycerides (6–12-carbon length), long-chain triglycerides, vegetable oil blends, egg, and sometimes fish oils; lecithin-emulsifying agent.
- Rarely contain lipids from dairy source in USA.

Stooling Pattern in Formula-Fed Infants

- Meconium passes by 3–4 days.
- Stooling is about once a day after meconium passage.
- Hydrolyzed formula-fed infants can stool up to 12 times a day.

Colitis in Formula-Fed Infants or Blood in Stool

- Most likely cause is milk protein intolerance.
- Change formula to hydrolyzed protein and reassess. If blood in stools resolves, continue hydrolyzed formula for the first year.
- In the unlikely event blood in stool does not resolve, use a chemically defined formula; reassess. If blood resolves, continue chemically defined formula for the first year.
- If blood does not resolve, refer to GI to assess for very early-onset inflammatory bowel disease (VEO-IBD)
- For term infants who are failing to thrive on infant formulas, after establishing there is no medical reason, formula can be concentrated to 26 kcal/oz. by increments of 2 kcal/oz. over the usual 20 kcal/oz.

INTRODUCTION OF SOLIDS

- Exclusive breastfeeding recommended for about 4–6 months. After addition of solids (complementary foods), breastfeeding should continue for as long as the mother and infant wish.
- For breastfed infants, complementary foods are introduced at 4–6 months because human milk becomes limiting in calories, iron, and zinc.
- Thus, it is best to start with meats or iron-fortified cereals.

- For formula-fed infants, introduce complementary foods at 4–6 months.
- Delaying the introduction of solid foods beyond 4–6 months of age may increase the risk of allergy.
- The texture of complementary foods should be advanced based on the oral motor skills of the infant.
- Introduce only one new food at a time every 3–5 days.
- No salt or sugar to be added to the infant's diet.
- Delay introduction of cow milk or other animal milks until 12 months of age to prevent GI blood loss.

Home-Prepared Baby Foods (www.foodsafety.gov)

- Foods can safely be prepared from whole foods with the following precautions:
  - Best to begin with fresh foods. If using processed fruits and vegetables, use products without added sugar or salt.
  - No unpasteurized dairy products.
  - No honey.
  - No juice in the first year.
  - Wash hands and equipment.
  - Use separate cutting boards for meat, poultry, and fish, i.e., do not cut fresh vegetables on a cutting board used for meats/fish.
  - Wash fruits and vegetables, even if they will be peeled.
  - Cook meats, poultry, and fish well—meat to internal temperature of 160°, fish to at least 145°, white meat poultry to 165°.
  - OK to freeze for about 1 month.

Toddlers

- Generally defined as children from 12 to 36 months of age.
- Most studies show a consistency of toddler intake supporting the observation that if they are presented with a good-quality diet, they will self-regulate their intake.
- Snacking is important—about 24% of consumed calories.
- Toddlers require about 3 meals and 2 to 3 snacks a day:
  - Diet in transition.
  - About 1000–1400 kcal/day.
  - Whole (full fat—3% fat) milk until age 2 years; then change to low-fat or fat-free milk.
- At risk of iron deficiency, especially if breastfed and not supplemented with iron in the first year of life.
- Frequently exhibit food "neophobia"—reluctance to try new foods; offer new foods at least 10 times.
- May exhibit "food jags"—will only eat a certain food or limited variety of foods for a period of time; generally passes with time.
- Caution parents about small, hard foods, as they present a choking hazard.
- Many prepared foods for toddlers are high in salt and added sugars—help parents read labels and make good choices.

Children

- Develop healthy behaviors around eating.
- Avoid food fights—parents never win.
- Avoid foods with added sugars and salt for meals and snacks.
- Calories depend on size and activity level, in general about 1200–1400 kcal/day.
- Provide fresh fruits and vegetables; if canned or frozen, choose those without added sugar and salt.
- Make half of the meal plate fruits and/or vegetables.
- Lean meat, nuts, eggs as protein source.
- Serve whole-grain breads and cereals.
- Reduce refined grains in the diet.
- Avoid frying: broil, grill, or steam.
- Limit fast food and junk food.
- Offer water or milk instead of sugary fruit drinks and sodas.

Adolescents

- Healthy diet:
  - Includes the following:

    - A variety of vegetables from all subgroups—dark green, red, orange, legumes, starch
    - Whole fruits
    - At least half of grains as whole grains
    - Fat-free or low-fat dairy products
    - Protein from seafood, lean meats, eggs, beans and peas, nuts, seeds, soy products
    - Oils
    - Less than 10% of calories from saturated fats
    - Less than 2300 mg sodium
    - Less than 10% of calories from added sugars
    - No, or as little as possible, trans-fats
  - Caloric requirement depends on size and activity and especially high for those engaging in aerobic sports (1500–3000 kcal/day).
  - Girls at risk of iron deficiency.
- Exercise.
- Sleep 7–9 hours a night.

PREMATURE INFANTS

- No DRI or RDA for premature infants, but consensus recommendations exist that depend on weight and whether enteral or parenteral feeding is prescribed.
- Goal is to mimic fetal growth rate, but rarely achieved in the neonatal ICU.

Parenteral Nutrition (Total Parenteral Nutrition or TPN)

- Fluid:
  - > 1000 g birth weight—60–80 mL/kg/day for the first day; then increase by 20 mL/kg/day to a maximum of 120–140 mL/kg/day.
  - < 1000 birth weight—higher rates.
- Proteins:
  - Provide minimum of 2–3 g/kg/day amino acids.
- Glucose:
  - Use 12.5% solution to avoid venous irritation.
- Fat:
  - Plan for lipid to provide 25–40% of calories.
  - Use 20% fat emulsion.
  - Infants require a minimum of 0.5 g/kg/day fat to protect against essential fatty acid deficiency.
- Minerals:
  - Metabolic bone disease is common.
  - Calcium to phosphorus ratio 2:1 for optimal utilization.
  - Lower pH of TPN solution, more soluble calcium and phosphorus:
    - Can add cysteine to lower pH and permit more calcium and phosphorus to solubilize—talk with pharmacist.
    - If using TPN for 2 weeks or less, the only trace element needed is zinc.
- Vitamins—use commercially available preterm vitamin mixture.

Complications of TPN

- Growth failure caused by inadequate calories or an imbalance of nutrients.
- Hyperglycemia—check rate of glucose administration; reduce rate of administration; consider insulin.
- Hyperlipidemia—triglycerides to 250–300 mg/dl are acceptable. Reduce lipid infusion.
- Sepsis caused by line contamination—careful handling of the line.
- Liver toxicity—reduce reliance on TPN as much as possible; if possible, some enteral feeds.
- Consider intravenous fat blends designed for infants such as Omegaven or Smoflipid.
- Aluminum toxicity—reduce TPN as much as possible, as this is a contaminant that is difficult to avoid.

Enteral Feeding

- Human milk is enteral feeding of choice for premature infants but is nutritionally inadequate.

- Use human milk fortifiers that provide additional protein, minerals, and vitamins.
- Human milk is associated with decreased enterocolitis and perhaps improved neurological development.

Premature Formula

- Use commercially prepared preterm infant formulas that are designed to meet the needs of the preterm infant and usually contain as follows:
  - Energy: Requirement is estimated at 90–120 kcal/kg/day; follow growth; weight gain should be about 15 g/kg/day.
  - Protein: Provide minimum of 3–4 g/kg/day amino acids. Soy-based are formulas not recommended.
  - Carbohydrate: Content of most preterm formulas provides 10–14 g/kg/day or 40–50% of calories.
  - Fat: Formulas for premature infants have a fat blend:
    - Medium-chain triglycerides (MCTs)
    - Vegetable oils rich in polyunsaturated long-chain triglycerides
    - Meets essential fatty acid requirement of at least 3% of energy as linoleic acid
  - Minerals—preterm infants have increased needs:
    - Metabolic bone disease is common.
    - Goal for calcium: 60–80 mg/kg/day.
    - Goal for phosphorus: 39–67 mg/kg/day.
- Mix as 22 or 24 kcal/oz.
- Higher vitamins and then regular formulas, supplementation not generally required.

After Discharge of a Preterm Infant

- Close follow-up to assure adequate growth.
- Discharge can be at 1500 g.
- Very-low-birth weight infants at risk of significant nutritional deficits.
- Human milk preferred.
- Requires supplementation with a fortifier for a minimum of 12 weeks.

NUTRITION SUPPORT

Necessary when children cannot or will not consume adequate nutrients to support normal growth and development and to replete malnourished states. Nutrition support can be supplements, tube feedings, or intravenous.

Start with Careful Nutrition Assessment and Repeat as Indicated, Usually Weekly Initially

- Diet history
- Anthropometrics:
  - Weight
  - Height
  - Body mass index (BMI)
  - Mid-arm circumference (estimate of lean body mass)
  - Triceps skinfold (estimate of fat mass)
- Laboratory:
  - Complete blood count (CBC)
  - Electrolytes
  - Minerals, especially phosphorus and magnesium
  - Proteins, albumin
  - Vitamins
  - Dual-energy X-ray absorptiometry (DXA) for bone mineral status

Supplements

- Use if child is willing to consume a supplement.
- Many available over the counter and/or with a prescription.
- Some examples:
  - PediaSure
  - Ensure
- Prescribe a medical food (FDA oversight). Medical foods are specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone:
  - Used to treat inborn errors of metabolism

- Used as supplements for some diseases associated with malnutrition, such as inflammatory bowel disease
- Used in malabsorption, allergy

Enteral Tube Feeds

- **Nasogastric (NG) tube feeding:**
  - Indications:
    - Cannot or will not consume adequate nutrition to support normal growth and development and reverse malnutrition if present
    - Short-term support and/or rehabilitation
  - Complications:
    - Misplaced tube (into lung), perforate esophagus
    - Aspiration
    - Delivery of inadequate nutrients (underestimate needs)
    - Delivery of excessive nutrients (overestimate needs)
- **Percutaneous endoscopic gastrostomy (PEG) tube feeding:**
  - Indications:
    - Long-term nutrition support
    - Placement, endoscopic or laparoscopic
  - Complications:
    - Tethered colon
    - Bleeding
    - Infection
    - Buried bumper
    - Delivery of inadequate nutrients (underestimate needs)
    - Delivery of excessive nutrients (overestimate needs)
- **Bolus vs. continuous feeds:**
  - When possible, bolus feeds are preferred:
    - Normal cycling of fed and unfed state
    - Allows for cycling of hunger and satiety hormone cholecystokinin
    - Easier for family to provide
  - Continuous feeds:
    - Cannot tolerate bolus feeds

Parenteral Nutrition (PN)

- Indications:
  - If the GI tract is partially functional, use enteral feeds in addition to PN.
  - Use only when not possible to meet nutritional requirements via the GI tract.
  - Use when the GI tract is dysfunctional and anticipate prolonged course.
  - Must be hemodynamically stable.
  - Correct all electrolyte and mineral abnormalities before starting PN.
  - PN cannot be used to correct electrolyte and mineral abnormalities.
  - Do not use for short-term nutrition support:
    - Premature infants (see section on premature infants)
    - 1–3 days infants
    - 4–5 days children and adolescents
    - 7–10 days young adults
- Complications:
  - Inherently nonphysiologic:
    - Nutrients delivered directly into the systemic circulation
    - Bypasses modulating effect of the GI tract and liver
  - Abnormal or imbalance in supplied nutrients
  - Line sepsis
  - Line occlusion
  - Hyper-/hypoglycemia
  - Hyperlipidemia
  - Prescription to fluctuate with disease state, interventions, etc.
- Peripheral:
  - Solution 900 mOsm/L or less.
  - Need frequent replacement.
  - Use for days or weeks only.
  - Use in conjunction with enteral feeds.
  - Easy insertion.
- Central:
  - Several choices for lines:
    - Tunneled cuffed catheter:
      - Placed surgically

        - Lower infection rate
        - Appropriate for long-term PN
      - Peripherally inserted central catheter (PICC):
        - Appropriate for support for several months
        - Easily placed
        - Careful to estimate insertion length accurately
        - Confirm position radiographically
      - Implanted ports:
        - Long-term PN
        - Surgically placed
        - Accessed via a needle into the port
- Prescription of nutrients—based on nutritional assessment above, specific disease, and the DRI for age:
  - Get help from a dietitian and pharmacist.
  - Most hospitals have standard formulas that can be used.
  - Determine energy requirement.
  - Determine protein needs.
  - Determine fat.
  - Provide electrolytes, minerals, trace elements, and vitamins.

NUTRITIONAL DISORDERS

Protein energy malnutrition (PEM) is a deficiency or imbalance in intake of energy and/or nutrients—common.

Undernutrition

In addition to protein energy deficits, often associated with vitamin A, vitamin D, thiamine, and zinc deficiency:

- Stunted growth, low height for age:
  - Associated with chronic malnutrition
  - Decreased fat and lean body mass
  - Decreased activity, apathetic
  - Delayed motor and mental development
- Underweight, low weight for height, wasting
  - Indicates recent and severe weight loss, may be associated with an infection
  - Increase in total body water as fat mass is lost
- Kwashiorkor (edematous malnutrition):
  - Appearance:
  - Irritable
  - Subcutaneous tissue present
  - Dermatosis—hyperpigmentation with peeling skin
  - Hypopigmented hair
  - Hepatomegaly caused by fat deposition (fatty liver)
  - Edema
  - Hypoproteinemia
  - Hypotension, bradycardia, thermolabile
  - Susceptible to infection
  - Intravascular volume depletion (in spite of peripheral edema)
  - Deficiency in protein
  - Hypoglycemia
- Marasmus (wasting malnutrition):
  - Appearance:
  - “Wizened old man”
  - Emaciated and weak appearance
  - Irritable
  - Thin, dry skin
  - Severe loss of subcutaneous tissue
  - Thin, sparse hair
  - Deficiency in calories and energy primarily
  - Adaptive to food restriction
  - Severe wasting of all tissues
  - Normal serum albumin
  - No edema
  - Hypoglycemia
  - Hypotension, bradycardia, thermolabile
- Marasmic kwashiorkor:
  - Elements of both kwashiorkor and marasmus

Vegetarian Diets

Can generally support normal growth and development, but require extra careful attention to nutrition:

- Semi-vegetarian—occasionally consume meat, fish, or chicken.
- Pescatarian—consume fish and shellfish and no meat.
- Lacto-ovo-vegetarian—consume eggs, milk and milk products, and no meat.
- Macrobiotic—consume whole grains, fruits, vegetables, beans, seaweed, and white meat or white fish.
- Vegan—consume no animal products of any sort:
  - Requires care that all nutritional needs are met.
  - Multivitamin with minerals is helpful to prevent specific deficiencies for which they are at risk.
  - At risk, especially, of inadequate consumption of the following:
    - Inadequate energy
    - Omega-3 fatty acids
    - Protein
    - Iron
    - Zinc
    - Calcium
    - Vitamin D
    - Vitamin B12

Protein-Losing Enteropathy

- Severe protein loss from the GI tract resulting in hypoalbuminemia and often fat-soluble vitamin deficiencies.
- Assess with fecal alpha-1-antitrypsin.
- Some common causes:
  - Gastritis such as Ménétrier disease, lymphocytic gastritis, *Helicobacter pylori* gastritis
  - Milk protein allergy
  - Celiac disease
  - Inflammation of the bowel due to inflammatory bowel disease or infections
  - Intestinal lymphangiectasia, primary (congenital) or secondary (cardiac disease or increased retroperitoneal lymph nodes)
  - Post-Fontan procedure
  - Giardiasis
  - Malignancy
  - Cirrhosis
- Treatment:
  - Nutritional—low long chain fat, high-protein, and high medium-chain triglyceride (MCT)-containing diet.
  - Identify primary cause and treat.

Lactose Intolerance (See Also Chap. 22 Gastroenterology)

Milk protein allergy is not lactose intolerance:

- Lactose intolerance is caused by a decrease in the disaccharidase lactase.
- Milk protein allergy is caused by immunoglobulin response to cow's milk protein:
  - IgE mediated:
    - Can occur at any age.
    - Reaction occurs immediately after ingestion.
    - Skin, oropharyngeal, respiratory, GI tract, and/or cardiovascular signs and symptoms. Symptoms can be mild or life-threatening.
    - Diagnose with IgE antibodies to cow milk (see also Chap. 11 Allergy and Immunology).
  - Non-IgE mediated:
    - Delayed onset, more than 2 h after ingestion.
    - Primarily occurs in infants.
    - Most commonly, infants less than 6 months who have blood in stools.
    - Additional symptoms can be vomiting, diarrhea, failure to thrive, and hypoalbuminemia.

- Diagnosis:
  - History
  - Gold standard: double-blind, placebo-controlled food challenge under clinical supervision; rarely done
  - Open challenge, most common

Failure to Thrive

Failure to thrive (FTT), more recently called faltering growth, often is the result of inadequate nutrition:

- Growth faltering in infants is described as weight gain less than the second percentile for gestational corrected age and decreased velocity of weight gain.
- In children, described as decreased growth velocity.
- Causes:
  - Inadequate intake:
    - Most common reason.
    - Caused by many possible problems: poverty, psychosocial or behavioral problems, beliefs about foods that translate into dietary restrictions, congenital anomalies (cleft lip/palate), intrauterine alcohol exposure, neurological problems affecting oral motor skills, lead poisoning, infections, any disease that may cause decreased appetite and hence inadequate intake.
    - Assess with history, including dietary recall.
    - Rule out organic cause such as a brain tumor, chronic constipation, and neurodevelopmental disorders.
  - Increased requirements:
    - Malabsorption as occurs in cystic fibrosis, celiac disease, pancreatic insufficiency (Shwachman-Diamond syndrome).
    - Chronic infections such as tuberculosis, recurrent urinary infections.
    - Assess with sweat chloride, fecal fat, and fecal elastase—for pancreatic insufficiency, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), CBC with white cell differential, serum IgA, and transglutaminase IgA. Consider thyroid function tests.
    - Stool for calprotectin, blood, white blood cell (WBC), giardia antigen.
  - Increased losses:
    - Brain tumor, allergy, malignancy.
    - Vomiting, diarrhea (may be caused by increased intake of juices and candies with a high osmotic load).
    - Assess with history, fecal alpha-1-antitrypsin, and fecal calprotectin.

Refeeding Syndrome

- Occurs when undernutrition is being treated—nutritional rehabilitation.
- Dangerous, can be associated with cardiac standstill.
- Highest risk is during the first 1–2 weeks of rehabilitation.
- Abnormalities:
  - Hypophosphatemia, hypokalemia
  - Vitamin (especially thiamin) deficiencies
  - Hemolysis, rhabdomyolysis
- Management:
  - Correct electrolyte abnormalities.
    - NOTE: All serum values can be normal prior to starting nutritional rehabilitation; this is not necessarily reassuring.
    - Repeat electrolytes, phosphorus, and magnesium as macronutrient supplementation begins.
  - For nutrition, "start low and go slow"; initially provide approximately resting energy expenditure; avoid rapid increases in caloric intake. Nutrition can be PO, enteral, or intravenous.
  - Monitor serum phosphorus, electrolytes, vitamins, and minerals.

  - Provide supplemental phosphorus, potassium, and magnesium as indicated by serum values.
  - Supplement with vitamins and minerals.

SPECIFIC CONDITIONS REQUIRING NUTRITIONAL SUPPORT

In every situation, malnutrition is a comorbidity leading to increased morbidity and mortality. Malnutrition occurs because of decreased appetite in chronic disease and increased requirements. Careful attention to growth, energy, and protein intake as well as vitamin, mineral, and trace element status is important.

Cystic Fibrosis (Also See Chaps. 20 and 21 Pulmonology and GI)

- Recommendation: vitamin A, D, E, and K supplementation and high-protein and high-energy (aim for 150% of DRI) intake

Viral Gastroenteritis

- Oral rehydration solution is the treatment of choice for children with dehydration caused by acute viral gastroenteritis.
- Early refeeding is associated with a shorter duration of diarrhea. Studies have not shown an increase in vomiting or diarrhea following early refeeding.
- The banana, rice, applesauce, and toast (BRAT) diet has not been studied and is not currently recommended.
- Lactose reduction has shown some benefit in reducing the duration of diarrhea in hospitalized patients; however, there are no data to support lactose reduction in children in the outpatient setting.

Chronic Liver Disease

- Do not restrict food; do not restrict protein:
  - At risk of protein energy malnutrition
  - At risk of specific deficiencies:
    - Thiamine
    - B12
    - Folic acid
    - Fat-soluble vitamins, A, D, E, K
    - Zinc
    - Selenium
    - Magnesium
- Monitor:
  - Electrolytes
  - Albumin
  - Fat-soluble vitamins
  - Prothrombin time, INR
- Supplement:
  - Calories—may require enteral feedings.
  - Protein (do not limit protein).
  - Vitamins and minerals.
  - Give one dose of 5 mg vitamin K IM if prolonged PT or INR.
  - Use enteral feeding if cannot consume adequate nutrition by mouth.

Heart Failure

Heart failure is caused by structural or functional disorders, of which there are many:

- At risk of the following:
  - Protein energy malnutrition
  - Acidosis—correct
  - Iron deficiency with or without anemia
- Monitor:
  - Weight
  - CBC
  - Electrolytes
  - Minerals
  - Albumin
  - Vitamins, especially B vitamins
- Supplement:

  - Increased caloric needs (120 kcal/kg/day) to achieve optimal growth—consider tube feeds.
  - Vitamins.
  - Minerals.
  - Electrolytes as needed.

Renal Disease

- At risk of the following:
  - Protein energy malnutrition
  - Vitamin and mineral deficiencies, especially vitamin D
  - Hyperphosphatemia, hyperkalemia
  - Iron deficiency anemia
  - Osteopenia
- Nutritional treatment:
  - Protein (100–140% of DRI) and energy to achieve growth; use supplements if necessary; if cannot meet energy requirements PO, consider tube feeding.
  - Supplement with multivitamins, minerals, and trace elements.
  - Low-potassium and low-phosphorus diet.
  - Limit sodium to DRI.
  - Total calcium intake 100–200% of DRI.
  - Iron to correct iron deficiency anemia.

Burns

- At risk of the following:
  - Increased energy and protein requirements:
    - Metabolic rate increases proportionally with burn size = increased energy expenditure.
    - Massive protein and lipid catabolism.
    - Total body protein loss.
    - Muscle wasting.
    - Peripheral insulin resistance.
    - Increased body temperature.
    - Synthesis of acute-phase proteins.
    - Infection of burned area—sepsis.
- Nutritional treatment:
  - NG or nasojejunal tube feeding if there's gastroparesis, tube for enteral nutrition support on entering ICU.
  - Avoid parenteral nutrition as much as possible, but if necessary, supply centrally.

Malignancies

- There are many different types of cancers; nutritional risk varies with type, treatment, and host factors:
  - Lower risk:
    - Standard-risk leukemia
    - Early-stage tumors
  - Higher risk:
    - Solid tumors, especially of the head and neck
    - Advanced stage of malignancy
    - Relapsed disease
  - Obesity risk posttreatment
- Common themes:
  - Decreased appetite, mucositis—decreased intake
  - Surgery, malabsorption, diarrhea, vomiting—increased nutrient requirements
  - Chemotherapy—decreased appetite, mucositis, renal compromise, vomiting, diarrhea
  - Radiation—decreased appetite, mucositis, renal compromise, vomiting, diarrhea
- Nutritional support:
  - Low threshold for enteral feedings.
  - Parenteral nutrition only if absolutely necessary.
  - Supplement with vitamins, minerals, and trace elements.
- Monitor:
  - Anthropometrics, weight, mid-arm muscle circumference for estimation of lean body mass unless MRI/DXA is available for estimation of body composition
  - Electrolytes, vitamins, minerals, and trace elements, including zinc, especially if diarrhea is present

Allergies

Nutrition must prevent reactions to foods and support optimal growth and development:

- At risk of inadequate intake of low-quality foods:
  - Depends on the kinds and number of food allergens—many protein-rich foods are common allergens (cow milk, fish, soy, egg).
  - Depends on the palatability of the elimination diet.
  - Depends on the acceptability of the diet to the child.
- Supplement:
  - Multivitamin with minerals and trace elements
  - Additional protein and calories with commercial supplements if diet is highly restricted
  - Tube feed if the child refuses diet

Neurological Impairment

- At risk:
  - Children with cerebral palsy who cannot easily feed themselves, chew, or swallow.
  - Gastroesophageal reflux caused by poor muscle tone, positioning in wheelchair.
  - Constipation caused by poor muscle tone, inability to go to the toilet.
  - Children with minimal movement are at risk of obesity:
    - Enteral feeding products that supply adequate fluids and DRI for vitamins and minerals and can have an excess of calories for non- or minimally mobile children.
    - If there's decrease in enteral feeding product to reduce caloric intake, there's a need to provide additional water, vitamins, minerals, and trace elements.
- Supplement:
  - If unable to feed, needs gastrostomy tube
  - If able to feed, may need pureed foods

Family and Cultural Practices

- Food fads vary overtime, rarely grounded in good nutrition.
- When talking with families, focus on the DRI and USDA dietary guidelines.
- Supplements from nutrition stores, "nutraceuticals," are not regulated by federal law:
  - Contents of package can vary or not be present at all.
  - Package can contain non-identified harmful contaminants.
  - When recommending supplement, use only those with the United States Pharmacopeia (USP) designation that demonstrates they meet these standards.

PEARLS AND PITFALLS

- Breastfeeding is not contraindicated in cases of mastitis, skin candidiasis, atopic dermatitis, gadolinium contrast for imaging studies, hepatitis B, or hepatitis C.
- Zinc homeostasis is via the GI tract. Consider zinc deficiency for children who have prolonged bout of diarrhea.
- The first sign of vitamin A deficiency is night blindness.
- When nutrition support is needed, use parenteral nutrition as a last resort or only when the GI tract has failed.
- It may be necessary to present a new food 10 or more times before a toddler will accept it. Caution mothers not to take the first few refusals as nonacceptance.
- For breastfed infants with blood in stools, continue breastfeeding, remove dairy from mother's diet, supplement her with calcium, and reassess before breastfeeding is stopped.

Suggested Reading

American Academy of Pediatrics Committee on Nutrition. In: Kleinman RE, Greer FR, editors. Pediatric nutrition. 7th ed. Elk Grove: American Academy of Pediatrics; 2014.

Dietary reference intakes tables and application. http://nationalacademies.org/hmd/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx. Washington DC: National Academies of Sciences, Engineering, and Medicine. Health and Medicine Division. (n.d.) Last updated 16 Jan 2018. Accessed 26 Nov 2018.

Duggan C, Watkins JB, Koletzko B, Walker WA, editors. Nutrition in pediatrics: basic science, clinical applications. 5th ed. Shelton: People's Publishing House; 2016.

Stipanuk MH, Caudill MA. Biochemical, physiological and molecular aspects of human nutrition. 4th ed. St. Louis: Elsevier/Saunders; 2019.

Gastroenterology

22

Robert D. Baker

ABDOMINAL PAIN

Age-Appropriate Differential Diagnosis of Acute Abdominal Pain (Tables 22.1, 22.2, 22.3, 22.4, and 22.5)

- Acute abdominal pain can originate outside the abdomen
  - Lower lobe pneumonia
  - Pharyngitis
  - Urinary tract infection
- Most abdominal pain that comes to medical attention is short in duration and not life-threatening
- Constipation is a frequent cause of acute abdominal pain, but a child with constipation may have additional reasons for pain
- Only 2% of episodes of acute abdominal pain require surgery
- Age of onset, concomitant signs and symptoms, history, and physical exam lead to the correct disposition
- Laboratory tests and imaging are often helpful, even if normal

Functional Abdominal Pain (Rome IV Criteria)

- Rome criteria are developed as an international effort to diagnose and treat functional gastrointestinal (GI) disorders based on scientific data. The criteria are determined by a panel of experts and disseminated by the Rome

Table 22.1 Cause of acute abdominal pain in neonates (0–2 months)

	Serious	Less serious
Common	NEC Adhesions	Colic
Uncommon	Volvulus Testicular torsion	Dietary protein allergy

Table 22.2 Causes of acute abdominal pain in infants (2 months to 2 years)

	Serious	Less serious
Common	Foreign body ingestion Trauma	Constipation Gastroenteritis Viral illness Dietary protein allergy Urinary tract infection
Uncommon	Adhesions Hemolytic uremic syndrome Hirschsprung disease Intussusception Incarcerated hernia Sickle cell crisis Tumor	Hepatitis

R. D. Baker (✉)
Department of Pediatrics, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Amherst, NY, USA
e-mail: rbaker2@buffalo.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_22

Table 22.3 Causes of acute abdominal pain in preschool children (2–5 years)

	Serious	Less serious
Common	Appendicitis Foreign body ingestion Intussusception Trauma	Constipation Viral illness Gastroenteritis Pharyngitis Urinary tract infection Pneumonia
Uncommon	Adhesions Hemolytic uremic syndrome Intra-abdominal abscess Diabetic ketoacidosis Ovarian torsion Sickle cell crisis Tumor	Henoch-Schönlein purpura Hepatitis

Table 22.4 Causes of acute abdominal pain in children (6–11 years)

	Serious	Less serious
Common	Adhesions Appendicitis Diabetic ketoacidosis Inflammatory bowel disease Trauma	Constipation Viral illness Gastroenteritis Pharyngitis Urinary tract infection Dysmenorrhea Pneumonia
Uncommon	Hemolytic uremic syndrome Perforated ulcer Primary bacterial peritonitis Hemolytic uremic syndrome Intra-abdominal abscess Myocarditis/ pericarditis Pancreatitis Ovarian/testicular torsion Sickle cell crisis Tumor	Abdominal migraine Cholecystitis Henoch-Schönlein purpura Hepatitis Familial Mediterranean fever

Foundation (non-profit), Raleigh, NC (https://theromefoundation.org/). In the following outline, Rome IV criteria are referenced and denoted in parentheses.

Table 22.5 Causes of acute abdominal pain in adolescents (12–18 years)

	Serious	Less serious
Common	Adhesions Appendicitis Diabetic ketoacidosis Inflammatory bowel disease Hemolytic uremic syndrome Pelvic inflammatory disease Trauma	Constipation Viral illness Gastroenteritis Pharyngitis Urinary tract infection Pneumonia Ruptured ovarian cyst
Uncommon	Hemolytic uremic syndrome Perforated ulcer Primary bacterial peritonitis Intra-abdominal abscess Myocarditis/ pericarditis Pancreatitis Sickle cell crisis Ovarian/testicular torsion Ectopic pregnancy Tumor	Abdominal migraine Cholecystitis Henoch-Schönlein purpura Hepatitis Familial Mediterranean fever Urolithiasis

Functional Dyspepsia (H2a)

- Postprandial fullness, early satiety, epigastric pain, or burning not associated with defecation, no other medical reason for symptoms
- Postprandial distress syndrome: Postprandial nausea, excessive belching, and upper abdominal bloating
- Epigastric pain syndrome: Epigastric pain or burning that interferes with normal activity

Irritable Bowel Syndrome (IBS) (H2b)

- Abdominal pain at least 4 days a month for at least 2 months
  - Related to defecation: Change in frequency, change in form
  - Diarrhea dominant, constipation dominant, and mixed types. There is also an unspecified type

Diagnosis of IBS

- Careful history and physical exam may be sufficient to make diagnosis. Can be simple constipation
- Fecal calprotectin differentiates IBS from GI inflammation
- Caution should be taken not to overlook infection (including *Helicobacter pylori* and *Giardia intestinalis*)
- Celiac disease (even with constipation), malabsorption (lactose intolerance) and inflammatory bowel disease (IBD) can mimic IBS

Treatment of IBS

- Educate parents and child that irritable bowel syndrome is a chronic illness that cannot be cured
- Reassure them that it is not a life-threatening condition and does not lead to physical impairment
- Behavioral treatment with focus on coping skills
- Dietary fiber supplementation and stool softeners for constipation
- Few drug treatment trials in children—caution with any medication in children
- Antispasmodics may help in moderate to severe cases, e.g., peppermint oil and dicyclomine

Abdominal Migraine (H2c)

- Paroxysmal episodes of severe abdominal pain
- Lasting 1 h or more
- Usually mid-abdominal
- Episodes separated by weeks to months
- Stereotypic pattern specific for individual
- Symptoms (not explained by other medical conditions) including anorexia, nausea, vomiting, headache, photophobia, and pallor

Treatment

- After the episode is over, future episodes may be prevented with cyproheptadine

Cyclic Vomiting (Abdominal Migraine)

Background

- Episodes of vomiting interspersed with well interval
- Idiopathic cyclic vomiting may be migraine equivalent

Clinical presentation

- Prodromes: Pallor, intolerance to noise/light, nausea, lethargy, headache, or fever
- Precipitants: Excitement, infection, stress, and others
- Average 12 episodes per year
- Each episode may last 1–3 days with 4 or more emesis per hour

Diagnosis

- Diagnosis of exclusion: Lab based on history and physical examination, endoscopy, contrast upper GI, brain MRI, and metabolic studies

Treatment

- Hydration and ondansetron
- Sumatriptan can abort episodes of cyclic vomiting in children and adults

Prevention

- Cyproheptadine or amitriptyline

Functional Abdominal Pain: Not Otherwise Specified (H2d)

- Usually a teenager
- Epigastric discomfort, early satiety, bloating, nausea, belching
- Associated with meals
- No relationship to defecation
- Pathophysiology not understood
- Episodic or continuous abdominal pain at least 4 times a month
- Not associated with physiologic events (eating, menses)

- Not sufficient criteria for IBS
- Not explained by other medical conditions

Treatment

- Reassurance, empathy, and education
- Cognitive behavioral therapy (CBT) and hypnotherapy have been shown to be effective for abdominal pain
- Pharmacologic treatment is mainly empiric, e.g., prokinetic agents

Chronic, Recurrent Abdominal Pain

Clinical manifestations of chronic recurrent abdominal pain and management

- Most children with chronic abdominal pain will have "functional GI disease." Work-up should be minimal.

Potential alarm features that may trigger further investigations (Table 22.6) [1]

Helpful laboratory tests:

- Complete blood count (CBC), differential, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total protein, albumin, glucose, celiac panel, thyroid panel

Table 22.6 Warning signs and symptoms of an organic cause for chronic abdominal pain

Recurrent vomiting	Chronic diarrhea
Perianal disease	Dysphagia
Oral lesions	Skin rashes
Persistent localized pain	Decrease in linear growth
Unexplained weight loss	Blood in stool
Fever, if not explained	Abdominal mass
Enlarged liver or spleen	Abdominal guarding
Family history of inflammatory bowel disease	Family history of celiac disease
Arthritis	Urinary symptoms
Delayed puberty	Dysmenorrhea, amenorrhea

From Hymans et al. [1], with permission

Helpful stool tests:

- Stool for occult blood, fecal calprotectin, fecal pancreatic elastase, *G. intestinalis* antigen, *H. pylori* antigen

Helpful imaging:

- Ultrasound (gallbladder disease, ovarian cysts, dilated biliary system, pancreatic disease)
  - Ultrasound will be positive less than 1% of the time
- Plain film of abdomen for constipation (radiologist dependent) dilated loops
- Upper GI series for malrotation, upper GI obstruction
- Computed tomography (CT) scan for bowel wall thickening, abscesses, partial obstruction
- Magnetic resonance enterography (MRE) similar to CT with less radiation exposure

Age-appropriate differential diagnosis of recurrent abdominal pain

- 2–5 years: Constipation, carbohydrate intolerance, gastroesophageal reflux
- 6–10 years: School phobia, indigestion and stomach irritation from dietary indiscretion, nonsteroidal anti-inflammatory drugs (NSAIDs), acid and spicy foods, carbonated beverages
- 11–21 years: School phobia, indigestion and stomach irritation from dietary indiscretion, NSAIDS, acid and spicy foods, carbonated beverages, hepatitis

Referred Abdominal Pain

- Referred abdominal pain is pain experienced at a distance from the source of the pain
- Children less than 5 years of age are poor at localizing pain
- They frequently indicate the periumbilical area for pain, abdominal and sometimes extra-abdominal

- Older children are more precise in localizing pain
- Visceral pain comes from the intra-abdominal organs. Nerve fibers from these organs respond to distention, but not cutting, tearing, or inflammation. Pain from visceral organs is poorly localized
  - Pain from the stomach, duodenum, liver, and pancreas is perceived to be epigastric
  - Pain from the small bowel, most of the colon, and appendix is felt in the mid-abdomen
  - Pain from the lower colon and genitourinary tract is localized in the suprapubic area
- Somatic pain comes from the peritoneum and the abdominal wall. Excitation of somatic fibers transmit tearing, cutting, and inflammatory sensations. Localization is more precise than visceral pain, but referred pain occurs, especially to dermatomes corresponding to somatic nerve excitation
  - Irritation of the diaphragm results in shoulder pain
  - Pleural irritation can be perceived as abdominal pain
  - Pain from kidney stones is felt in the groin area

Acute Appendicitis

Background

- Most common abdominal surgical emergency in childhood, but rare before 5 years of age
- MANTRELS (mnemonic)
  - Migrating
  - Anorexia
  - Nausea/vomiting
  - Tender in right lower quadrant (RLQ)
  - Rebound
  - Elevated temperature
  - Leukocytosis
  - Shift to left

Clinical presentation

- Rapidly progressing from diffuse abdominal discomfort to point tenderness with peritoneal signs in 12 h
- Localized abdominal tenderness is the single most reliable finding in the diagnosis of appendicitis
- Guarding: gentle finger percussion is a better test for peritoneal irritation
- Rovsing sign
  - RLQ pain with palpation of the left lower quadrant (LLQ); referred rebound tenderness when palpating the LLQ
- Obturator sign
  - RLQ pain with internal and external rotation of the flexed right hip
- Psoas sign
  - RLQ pain with extension of the right hip or with flexion of the right hip against resistance
- Dunphy sign
  - Sharp pain in the RLQ elicited by a voluntary cough
- Markle sign
  - Pain elicited in a certain area of the abdomen when the standing patient drops from standing on toes to the heels with a jarring landing

Laboratory

- White blood cell (WBC) count elevated but can be normal within the first 24 h, but with a left shift
- Left shift plus abnormal elevated CRP is 94% specific

Imaging studies

- Point of service ultrasound has become the diagnostic modality of choice
- Ultrasound diagnostic criteria:
  - Wall thickness > 6 mm
  - Lack of compressibility
  - Luminal distention

Appropriate diagnostic evaluation when appendicitis is suspected

- *Nil* per os (NPO), intravenous (IV) hydration, pain medication
- Antibiotics before surgery, e.g., cefoxitin, piperacillin/tazobactam, or imipenem/cilastatin
- CBC with differential and platelet count, chemistries, CRP, and ESR
- Ultrasound; if equivocal—CT scan
- Surgical consult
- If simple appendicitis—surgery
- If not clearly acute appendicitis—observe—reevaluate
- If walled-off perforation or abscess, antibiotics plus-minus drainage. Either no surgery or delayed surgery
- If "free perforation" or generalized peritonitis—immediate surgery

Malrotation

Background

- Failure of normal rotation and fixation of GI tract during organogenesis resulting in the cecum being in the right upper quadrant (RUQ) and free to fold and unfold
- The small bowel is on the right side of the abdomen, so the root of the mesentery is narrow
- Ladd's bands extend from the cecum to the abdominal wall, crossing the duodenum
- Rotation abnormalities may be as frequent as 1 in 100 live births. Many go undetected or are picked up incidentally

Clinical features

- Intermittent abdominal pain
- Intermittent bilious or non-bilious vomiting

Diagnosis

- Upper GI series radiograph showing abnormal position of the cecum, abnormal position of the ligament of Treitz, and/or partial obstruction of the duodenum

Management

- Because of the danger of midgut volvulus, even asymptomatic malrotations should be surgically "fixed" with Ladd's procedure

Volvulus

Background

- Midgut volvulus is a surgical emergency because twisting around the mesenteric root can result in occlusion of the superior mesenteric artery and subsequent ischemia of bowel from the distal duodenum to the mid-transverse colon
- If resection of the GI tract from the distal duodenum to the mid-transverse colon is necessary, the child will be left with extremely short gut
- 45% is a result of malrotation. Remainder is idiopathic, due to adhesions or Meckel diverticulum
- Intestinal malrotation is often associated with other congenital anomalies including heterotaxy syndrome, omphalocele, gastroschisis, congenital diaphragmatic hernia, esophageal atresia, renal anomalies, and cardiac anomalies.
- Heterotaxy syndrome: failure of normal embryological rotation results in abnormally positioned organs in the chest and abdomen

Clinical presentation

- Symptoms are nonspecific and malady is rapidly progressive
- Abdominal pain
- Bilious vomiting (ominous presentation suggestive of bowel obstruction)
- Abdominal distention

Investigations

- Labs are nonspecific
- Radiograph usually proximal dilation and distal paucity of gas
- Plain film may not show classic picture
- Upper GI series is 96% sensitive; shows "corkscrew sign"

Management

- Urgent surgical consultation
- Fluid resuscitation, evacuation of the stomach, and proceed to surgery quickly
- Other types of volvulus
  - Stomach, organo-axial, and mesentero-axial
  - Sigmoid, "coffee bean" on plain film

Intussusception

Background

- Invagination of proximal segment of bowel into distal segment
- Occurs at any age but most common 6–36 months
- Usually ileocolic but can have other lead points
- Outside this age group, suspect unusual etiology, e.g.:
  - Meckel diverticulum
  - Enlarged mesenteric lymph node
  - Benign or malignant tumors of the mesentery or of the intestine, including lymphoma, polyps, ganglioneuroma, hamartomas associated with Peutz-Jeghers syndrome
  - Mesenteric or duplication cysts
  - Submucosal hematomas, which can occur in patients with Henoch-Schönlein purpura (HSP) and coagulation dyscrasias
  - Ectopic pancreatic and gastric rests

Clinical presentation

- Classic triad
  - Severe intermittent abdominal pain
  - Sausage-shaped abdominal mass
  - Currant jelly stools (late presentation suggest vascular compromise)
- Vomiting (can be bilious)
- Lethargy (out of proportion of abdominal pain)

Diagnosis

- Early diagnosis via ultrasound (close to 100% accurate) means that triad seldom encountered anymore

Management

- Air enema (most often reduced with air enema); infrequently, surgery
- If air enema fails, a surgery must be performed to reduce intussusception

Acute Pancreatitis

Clinical and laboratory features associated pancreatitis

- Abdominal pain (older child), bloating (younger child)
- Amylase and/or lipase 3 times the upper limit
  - Amylase can be from salivary glands, gonads, or from intestinal obstruction; while lipase is more specific to the pancreas
- Ultrasound for stones and ducts, CT for complications, necrosis, hemorrhage, pseudocyst
- Endoscopic retrograde cholangiopancreatography (ERCP) for stone removal
- ERCP and magnetic resonance cholangiopancreatography (MRCP) to delineate anatomy

Management

- Pain control
- Nutrition enteral feeds
- Fluid therapy (if adequate kidney function, give at least 2 times maintenance fluids)
- In most cases, no total parenteral nutrition (TPN), no antibiotics

Recurrent Pancreatitis

- No underlying etiology found in one-third of cases

- Toxic-metabolic: Medications, hypercalcemia, hyperlipidemia, post graft-versus-host disease, chronic renal failure, organic compounds
- Genetic: PRSS1 (protease serine 1) mutation, CFTR, SPINK1 (serine peptidase inhibitor kazal type 1), CPA1 (carboxypeptidase A1) mutation, CTRC (chymotrypsin C) mutation
- Autoimmune: Isolated and syndromic (IgG4)
- Anatomic: Pancreas divisum, annular pancreas
  - These anatomic anomalies are disputed as causes of pancreatitis
- After severe acute pancreatitis

Cholelithiasis

Risk factors associated with the development of cholelithiasis

- Predisposing factors: Hemolytic disease, obesity-related, metabolic syndrome, prematurity, necrotizing enterocolitis, congenital heart disease, cystic fibrosis, TPN-related, ethnicity (Amerindian) , ileal disease, and ileal resection
- Gene: *Lith1, Lith2* cholesterol formation. *APOBEC-1* when downregulated associated gallstones. FXR (farnesoid X receptor) related to gallstone formation. Mutation in *ABCB4* described in adults with stones
- Other genes: *ABCG5, ABDG8, CYP7A1, CCK1R*, and more
- Black pigmented stones associated with hemolytic disease. Brown pigmented stones associated with infection. Cholesterol stones are found in obesity and TPN.

Diagnosis and treatment

- Diagnosis via imaging: Radiography, ultrasound, CT scan
- Gallstones in infants do not necessarily require treatment. 50% resolve spontaneously
- If complications are likely (hemolytic disease) or are likely to be severe (cystic fibrosis), elective cholecystectomy indicated
- Symptomatic stones are most often treated with surgery. Dissolution and lithotripsy are used less often

Cholecystitis

Background

- Inflammation of the gallbladder secondary to obstruction—gallstones (usual), edema, external compression

Clinical presentation

- RUQ pain, sometimes radiating to back and accompanied by vomiting
- Murphy's sign—pain on palpation in RUQ. Can be elicited with ultrasound transducer
  - Classic description of Murphy's sign includes having the patient exhale and then palpating deeply below the right ribcage, in the mid clavicular line; when the patient inhales, the gallbladder moves down against the examiner's fingers, causing pain and interruption of inhaled breath. The same procedure on the left side of the abdomen will not produce the same effect.
- Fever and jaundice present in 25–30%. More common in young children
- Pain increases usually over a week, but mild discomfort may have been present for years

Imaging studies

- Ultrasonography
  - Can show the presence of stones and a thickened gallbladder wall with possible gallbladder dilation
  - The ultrasonographer can produce a positive Murphy's sign with the transducer
- Hepatobiliary scintigraphy
  - If the gallbladder cannot be visualized

Laboratory

- Elevated liver enzymes, especially GGT and alkaline phosphatase
- The WBC count and direct bilirubin are usually elevated

- The amylase value can be elevated, making it harder to know if the problem is cholecystitis or pancreatitis

Treatment

- Bowel rest, intravenous pain control, and IV fluids
- If fever is present or the child looks ill or unstable, antibiotics are needed for enteric bacteria
- The timing of curative cholecystectomy is best determined by the surgeon

Complications

- Perforation of the gallbladder, with peritonitis or abscess formation

Choledocholithiasis (Common Bile Duct Stone)

- Stone obstructing the biliary duct system
- Jaundice with or without pain
- Progresses to symptoms similar to cholecystitis, RUQ pain, fever, vomiting
- Pancreatitis may be present if stone blocks the pancreatic duct
- Leukocytosis, elevated AST, ALT. Elevated alkaline phosphatase and GGT. Elevated amylase and lipase if pancreas involved
- Dilated biliary ductal system bile: Ultrasound, MRCP, or ERCP

Diagnosis and treatment

- Diagnosis via imaging
  - Ultrasound, MRCP, ERCP
  - ERCP allows stone retrieval, stent placement, and sphincterotomy—not always possible in a small child

Cholangitis (Rare in Pediatrics)

- Post Kasai portoenterostomy
  - *Roux-en-Y* loop allows pathway for bacteria to enter cholangioles
  - Difficult to diagnosis
    - In face of fever, increased liver tests—treat empirically with IV broad-spectrum antibiotics
- Primary sclerosing cholangitis—extraintestinal complication of IBD
  - No accepted treatment—recurs post liver transplant
  - Some have advocated long-term treatment with vancomycin
  - Crossover variety with autoimmune hepatitis

Acalculous Cholecystitis

- Typically occurs during a significant systemic illness such as sepsis
- Illness requiring a stay in the intensive care unit

VOMITING

- Vomiting is the result of a complicated reflex in response to a number of stimuli
  - The forceful expulsion of gastric contents through the oral cavity
- Must differentiate from regurgitation, which is not forceful
  - Clinically, sometimes difficult to make this distinction
- The emetic reflex has 3 phases. Phases can occur in sequence or independently of each other:
  - Prodromal period called nausea
  - Retching
  - Vomiting
- Emetic reflex has afferent limb, central integration, efferent limb
- Initiated by pain, inflammation, toxins, motion, pregnancy, radiation exposure, postoperative conditions, unpleasant emotions, etc.
- Serotonin receptor antagonists in the prevention and treatment of vomiting

  - Vomiting is initiated through release of 5-HT (serotonin) in small intestine, binding to 5-HT3 receptors that initiate signals in the afferent vagal nerve that activates the vomiting reflex
  - 5-HT3 antagonists (ondansetron and others) block this pathway
- Other important neurotransmitter receptor sites exist (muscarinic, M1: dopamine, D2; histamine, H1; neurokinin, NK1; and substance P)
- Vomiting can be initiated via many mechanisms and systems
  - GI, neurologic, renal, urogenital, psychiatric
  - Associated with infections, allergies, anatomic abnormalities
  - Acute and chronic
  - Motion and emotions
- Vomiting and infection
  - Acute infection of the stomach, small bowel and colon. Usually viral, but also due to bacteria, fungi, and others
  - Viral: Rotavirus, calicivirus, (HuCV) norovirus, sapovirus, Snow Mountain virus, hepatitis E virus, enteric adenovirus, astrovirus, and others
  - Bacteria: *Shigella, Salmonella, Yersinia, Campylobacter, Vibrio,* diarrheagenic *Escherichia coli, Clostridium*, and others
    - Clinical symptoms are nausea, vomiting, diarrhea, and abdominal pain
    - Organisms infecting the stomach and upper GI tract associated with more nausea and vomiting and less diarrhea, while with colon involvement diarrhea predominates
    - Even among organisms of the upper GI tract there is a varying degree of vomiting (norovirus was originally called "winter vomiting sickness")

Age-appropriate differential diagnosis of vomiting (Table 22.7) [2]

- Neonate and young infant
  - Gastroesophageal reflux disease (not true vomiting, rather, regurgitation)

Table 22.7 Causes of vomiting in children

Infant	Child	Adolescent
Common		
Gastroenteritis	Gastroenteritis	Gastroenteritis
Gastroesophageal reflux	Systemic infection	GERD
Overfeeding	Gastritis	Systemic infection
Malrotation/volvulus, pyloric stenosis, intussusception)	Toxic ingestion	Toxic ingestion
	Pertussis syndrome	Gastritis
Pertussis syndrome	Medications	Sinusitis
Otitis media	Reflux (GERD)	Inflammatory bowel disease
Meningitis	Otitis media	Appendicitis
Pyelonephritis	Meningitis	Migraine
	Pneumonia	Pregnancy
	Malrotation/volvulus	Ipecac abuse, bulimia
	Intussusception	Concussion
	Inguinal hernia	
Rare		
Hydrocephalus/shunt malfunction	Hepatitis	Hepatitis
Brain tumor	Pancreatitis	Pancreatitis
Subdural hematoma	Brain tumor	Brain tumor
Hirschsprung disease	Cyclic vomiting	Cyclic vomiting
Paralytic ileus	Duodenal hematoma	Inguinal hernia
Metabolic	Metabolic	Superior mesenteric artery syndrome
Adrenal hyperplasia		Surgical adhesions
Addison disease		Biliary colic
Renal tubular acidosis		Renal colic
Ureteropelvic junction obstruction		Diabetes ketoacidosis

Adapted from Nelson et al. [2], with permission
GERD Gastroesophageal reflux disease

  - Food protein-induced enteropathy (FPIES)
  - Hypertrophic pyloric stenosis
  - Intestinal obstruction: Malrotation, volvulus, atresias, Hirschsprung disease
  - Inborn errors of metabolism
- Bilious vomiting in a newborn infant
  - Bilious vomiting in a neonate is usually an ominous symptom suggesting an obstruction distal to the second portion of the duodenum
  - Diagnosis is via imaging, plain film, ultrasound, and upper GI series
  - Stomach should be evacuated, infant stabilized, and plans for urgent surgery
- Projectile vomiting in a newborn infant
  - True projectile vomiting is suggestive of an upper small bowel obstruction. Be careful, parents can describe forceful regurgitation as projectile
  - Hypertrophic pyloric stenosis will be the most common cause
  - Uncommon causes: Foveolar hyperplasia, pyloric webs, pyloric atresia, antral web, antral atresia, adrenal insufficiency
  - Pyloric web can present as a "windsock" abnormality
  - Diagnosis is by physical exam (visible peristalsis), ultrasound (mass, mucosal thickening), upper GI series, and endoscopy
  - Treatment: Evacuate the stomach, stabilize, correct electrolytes, surgery. Dilation via endoscopy sometimes possible, especially in foveolar hyperplasia
- Older infant and child
  - Gastroenteritis
  - Infections
  - Intussusception
  - Anaphylaxis
  - Adrenal crisis
  - Increased intracranial pressure
  - Cyclic vomiting
  - Migraine
  - Eosinophilic esophagitis or gastroenteritis
  - Child abuse
- Adolescent
  - Functional dyspepsia
  - Functional nausea and vomiting
  - Appendicitis
  - IBD
  - Pregnancy
  - Bulimia, psychogenic vomiting
  - Rumination syndrome
  - Cannabinoid hyperemesis syndrome

ESOPHAGUS

Gastroesophageal Reflux in an Infant

- Infantile reflux is common (about 60% of infants)
- Non-forceful expulsion of gastric contents
- Can last up to 18 months of age
- Treat conservatively unless associated with complications:
  - Weight loss or poor weight gain
  - Aspiration, especially with pneumonia
  - Extreme irritability

Conservative treatment

- Small, frequent feeds (may need extra calories because of loss due to reflux)

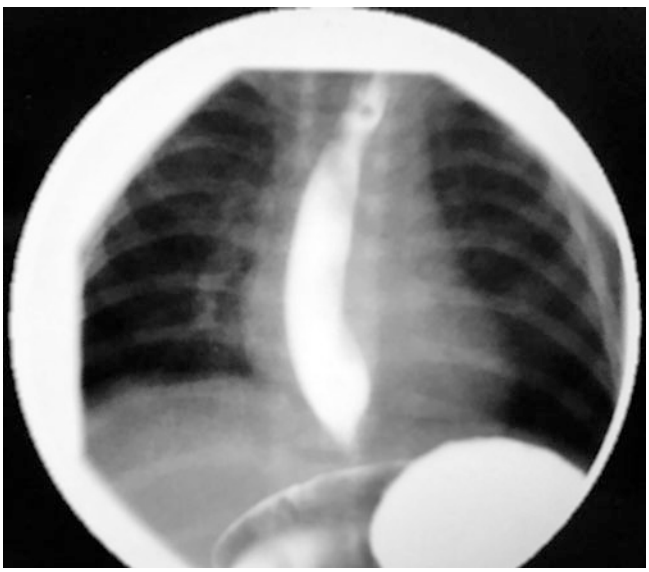


Fig. 22.1 Barium swallow image showing severe reflux

- Upright after meals for at least 15 min; burp well
- Elevate the head of the crib, position on back
- Trial of thickened formula or human milk (one teaspoon rice cereal per ounce of fluid). If helpful, continue. If not, stop
- For formula-fed infants, time-limited trial of hypoallergenic formula (no more than 7 days)

Medical treatment
- Continue conservative treatment
- Trial of H2RA acid suppression (ranitidine and others)
- If not responding, consider further work-up

Further work-up (Fig. 22.1)
- Upper GI radiograph to look for partial obstruction
- pH probe/impedance off medication to quantify reflux, on medication to assess efficacy of acid suppression
- Gastric emptying scan (scintigraphy)
  - Can assess gastric emptying—not very reliable and not reproducible
  - The scan may identify esophageal reflux and aspirations
  - The major diagnostic role is in the assessment of pulmonary aspiration
  - Patients should be rescanned after 24 h in order to assess delayed pulmonary soilage by refluxed gastric contents

Further treatment
- If still not responding, especially not gaining weight, transpyloric tube feedings
- Surgery as a last resort (fundoplication)

Eosinophilic Esophagitis (EE)

- Non-immunoglobulin E (IgE) immune-mediated inflammatory process causing intense (> 15 eosinophils per high-powered field) infiltration of the esophageal mucosa
- Thought to be food antigen related

Clinical presentation
- Vomiting in the younger child
- Food impaction in adolescents
- Esophageal strictures can occur

Management
- 75% respond to milk elimination
- Almost 100% respond to amino acid formula
- Can be treated with swallowed, poorly absorbed steroids
- Relapse when the intervention is stopped

Caustic Esophageal Injuries

Background
- Ingestion of caustic agents
- More predominant in males
- Age between 1 and 3 years is more common
- **Alkaline** agents cause severe injuries rapidly after ingestion and more damage to:
  - Oropharynx
  - Hypopharynx
  - Esophagus (45%)
- **Acid** agents cause more damage to the stomach after ingestion

Clinical presentation
- Dysphagia
- Drooling
- Abdominal pain
- Hematemesis
- Respiratory distress

Management
- Avoid neutralizing agents, e.g., vinegar or sodium bicarbonate
- Endoscopy is indicated after 6 h to document full extent of injuries
- Endoscopy should not be later than 4 days post-ingestion to minimize perforation

Complication
- Esophageal stricture

Rumination (Rome IV Rumination Criteria [H1c])

Clinical diagnosis

- Repeated regurgitation with re-chewing or expulsion of food that begins right after a meal and does not occur during sleep
- Not preceded by retching
- Cannot be explained by conditions, and an eating disorder has been excluded
- Symptoms must be present for minimum of 2 months
- Rumination can occur at any age, but frequently in teenage girls
- Contraction of abdominal muscles with relaxation of the lower esophageal sphincter (LES)
- Characteristic high pressure "r-wave" on motility studies

Associated medical conditions

- Intellectual disability
- Bulimia
- Psychological stress or psychological trauma

Management

- Multidisciplinary approach
- Primary focus on behavioral therapy and biofeedback
- Tricyclic antidepressants and nutritional support may be necessary

Bezoars

Background

- Accumulation of exogenous matter in the stomach and intestine
- Trichobezoar, hair; phytobezoar, plants, animal material, and chewing gums; lactobezoar, milk solids

Clinical presentation

- Gastric outlet obstruction complete or partial
- Anorexia, vomiting, weight loss, severe halitosis, abdominal pain, and distension

Diagnosis

- Plain film, ultrasound, or CT scan can confirm the diagnosis

Management

- Endoscopic removal
- Surgery if endoscopy is not successful
- Lactobezoar usually resolve when feeding withheld for 24–48 h

Foreign Body in the Esophagus and Stomach

Background

- Majority of cases between 6 months and 3 years
- Coins and small toys are most common
- Upper esophageal sphincter (UES) cricopharyngeus is the most common site, and the next is the LES

Clinical presentation

- 30% of cases are asymptomatic
- Any history of ingestion should be taken seriously and investigated even with no symptoms
- Initial bout of choking, gagging, and coughing may be followed by salivation, dysphagia, and refusal to eat
- Vomiting
- Pain in the neck, throat, or sternal notch regions
- Stridor, wheezing, cyanosis, or dyspnea if the foreign body impinges on the larynx
- Cervical swelling, erythema, and subcutaneous crepitations suggest perforation

Diagnosis

- Plain film anteroposterior and lateral neck, chest and abdomen (wood, glass, plastic, bone, and aluminum may be radiolucent)

Timing of endoscopy in foreign body ingestions (Table 22.8) [3]

- Coin in the esophagus
  - Most coins pass into the stomach and through the GI tract without incident

Table 22.8 Timing of endoscopy in foreign body ingestion

Type	Location	Symptoms	Timing
Button battery	Esophagus	Yes or no	Emergency
	Gastric/SB	Yes	Emergency
		No	Urgent (if age < 5 and BB ≥ 20 mm)
			Elective (if not moving)
Magnets	Esophagus	Yes	Emergency (if not handling secretions)
		No	Urgent
	Gastric/SB	Yes	Emergency
		No	Urgent
Sharp object	Esophagus	Yes	Emergency (if not handling secretions)
		No	Urgent
	Gastric/SB	Yes	Emergency (if signs of perforation, with surgery)
		No	Urgent
Food impaction	Esophagus	Yes	Emergency (if not handling secretions)
		No	Urgent
Coin	Esophagus	Yes	Emergency (if not handling secretions)
		No	Urgent
	Gastric/SB	Yes	Urgent
		No	Elective
Long object (> 4 cm)	Esophagus	Yes or no	Urgent
	Gastric/SB	Yes or no	Urgent
Absorptive object	Esophagus	Yes	Emergency (if not handling secretions)
		No	Urgent
	Gastric/SB	Yes or no	Urgent

From Kramer et al. [3], with permission
BB Button battery, *SB* Small bowel. Emergency = Move to endoscopy as quickly as possible, < 2 h Urgent = Endoscopy within 24 h after appropriate *nil* per os (NPO) period. Elective = Endoscopy after appropriate NPO period at next available time

  - Symptomatic patients require intervention
  - Asymptomatic patients can be observed for 12–24 h
  - Once in the stomach, coins usually pass without intervention (Fig. 22.2)
  - Can be monitored by checking the stool for passage and with weekly radiographs, if indicated
  - If the coin does not pass through the stomach by 4 weeks or if the patient is symptomatic, removal by endoscopy should be considered
- Button battery in esophagus is an emergency
  - Tissue injury can occur within 2 h of ingestion. Remove endoscopically immediately
- Button battery in the stomach
  - Button batteries that are larger than 2 cm in diameter, are causing symptoms, or are present for more than 48 h should be removed endoscopically

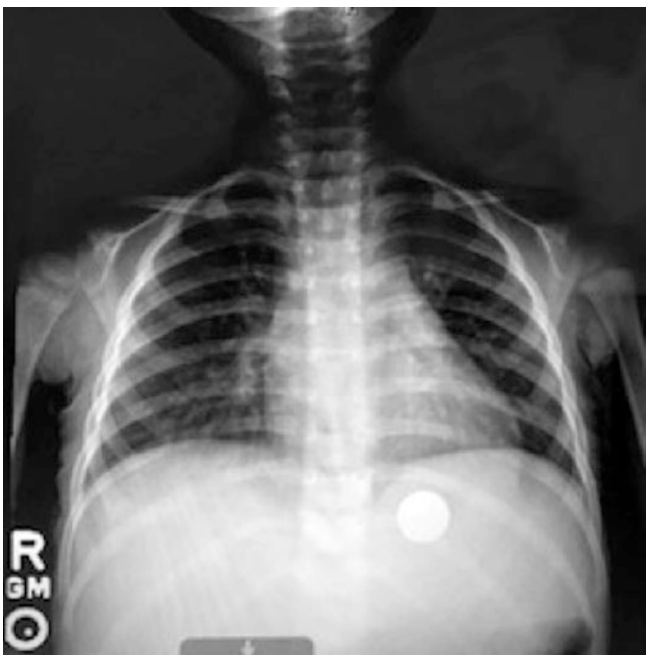


Fig. 22.2 Radiograph showing a coin in stomach. It passed without intervention within 72 h

  - If they pass into the duodenum, most pass in fewer than 72 h and do not require additional intervention
- Multiple high strength magnets pose a risk of tissue necrosis in intestines
  - Remove before they enter the small bowel
- Food impaction usually associated with esophageal dysmotility
  - Eosinophilic esophagitis

Reflux Esophagitis

- Chronic, recurrent epigastric pain, heartburn (in adolescents), regurgitation, belching, vomiting; brought on by eating, especially acid food
- Chronic cough and wheezing
- Inflammation of esophagus and lower esophageal sphincter causing dysfunction of LES
- Empiric treatment with lifestyle changes: Small frequent meals, avoid acid foods, avoid foods that induce reflux (caffeine, chocolate, carbonated beverages), elevate the head of bed
- Empiric treatment with acid suppression
- Diagnosis by upper endoscopy with biopsies—differentiate from eosinophilic esophagitis

Esophageal Stenosis

- 3 types: Webs (thin), fibromuscular (thicker), cartilaginous (distal, more extensive)
- Frequently presents at 6 months of age when solid foods introduced
- Consider achalasia and gastroesophageal reflux disease
- Can be associated with other anomalies: Tracheoesophageal fistula, cardiac defects, intestinal atresias, chromosomal abnormalities

Esophageal Atresia and Tracheoesophageal Fistula (TEF)

- Common: 1 in 4000 live births
- Five types:
  - Esophageal atresia with distal tracheoesophageal fistula (most common, 86%)
  - Isolated esophageal atresia (8%)
  - H-type tracheoesophageal fistula (4%)
  - Esophageal atresia with proximal and distal tracheoesophageal fistulas (1%)
  - Esophageal atresia with proximal tracheoesophageal fistula (1%)
- Associated anomalies
  - VACTERL: Vertebral, anorectal, cardiac, tracheal, esophageal, renal, and limb anomalies
  - Trisomy 13, 18, and 21
  - CHARGE syndrome: Coloboma, choanal atresia, decreased smell, swallowing and feeding difficulties, hearing loss and balance problems
  - Schisis association: Neural tube defect, cleft lip/palate, omphalocele, and diaphragmatic hernia
- Survival and prognosis often dependent on associated anomalies

PEPTIC ULCER DISEASES

Acid-peptic disorder refers to acid-related disease of the esophagus, stomach, and duodenum

Gastritis and Peptic Ulcers

Peptic ulcers are rare in children, but can be encountered in extreme cases

Causes

- The common causes of peptic ulcers include *H. pylori*
- NSAIDs, e.g., ibuprofen
- Stress-related gastric injury
- Less common causes include ingestion of corrosive substances, hypersecretory states (Zollinger-Ellison syndrome), IBD, systemic mastocytosis, chronic renal failure, and hyperparathyroidism

Clinical presentation

- Poor growth indicates the presence of chronic disease or poor nutrition
- There are no focal findings specific for acid peptic disease
- Dental caries and eroded enamel may indicate frequent vomiting or reflux
- Pale conjunctiva, tachycardia, or flow murmur may indicate anemia associated with chronic disease or blood loss
- Halitosis with regurgitation or dysphagia may indicate achalasia
- Epigastric tenderness
- Wheezing or bronchospasm can be associated with chronic reflux

Diagnosis

- Upper endoscopy with biopsies
- "Test and treat" strategy for pediatric *H. pylori* infection is not recommended
- Testing for *H. pylori* should be performed in children with gastric or duodenal ulcers. If *H. pylori* infection is identified, then treatment should be advised, and eradication be confirmed
- Wait at least 2 weeks after stopping proton pump inhibitor and 4 weeks after stopping antibiotics before testing for *H. pylori*

Treatment

- *H. pylori* eradication, empiric acid suppression, NSAID avoidance, lifestyle changes
- *H. pylori* eradication:
  - PPI+amoxicillin+clarithromycin
  - PPI+amoxicillin for 5 days then PPI+clarithromycin +metronidazole for 5 days
  - Other treatment regimens depending on resistance and treatment failure

Duodenitis

- Chronic abdominal pain, nausea, vomiting
- Causes similar to gastritis, plus celiac disease, Crohn's disease
- Treatment: *H. pylori* eradication, empiric acid suppression, NSAID avoidance, lifestyle changes. Gluten-free diet for celiac disease, immune suppression for Crohn's disease
- Diagnosis by upper endoscopy with biopsies

Zollinger-Ellison Syndrome (ZES) (Rare)

- Caused by gastrin-secreting tumor
- Usually in pancreas, but can be in other areas
- Very high serum gastrin levels

Presentation

- Multiple ulcers, usually in the stomach, but other GI locations
- Diarrhea, weight loss, GI bleed

Treatment

- High-dose proton pump inhibitor
- Surgical resection if possible

GASTROINTESTINAL ATRESIA, STENOSIS, AND OBSTRUCTION

Atresia is congenital absence or closure of tubular structure. Obstruction is "luminal discontinuity" of any portion of the GI tract. Stenosis is partial obstruction.

Infantile Hypertrophic Pyloric Stenosis (HPS)

Background

- Male to female ratio 4:1
- 3–12 weeks of age, more common in firstborn
- Hypertrophy of the pyloric sphincter muscle causing progressively increasing gastric outlet obstruction
- Early exposure to erythromycin has been linked to increase in HPS

Clinical presentation

- Visible peristalsis, palpable pyloric mass ("olive"), hungry, dehydrated, decreased urination
- Non-bilious, projectile vomiting containing HCL
- Hypochloremic, hypokalemic metabolic alkalosis
- Carbon dioxide retention

Diagnosis—suggestive symptoms and physical exam

- Ultrasound is definitive—pyloric muscle wall should be less than 3 mm
- Ultrasound diagnostic criteria for pyloric stenosis:
  - Pyloric thickness > 4 mm
  - Pyloric length > 14 mm
- Upper GI series—classic "string" sign. Can look for other causes of obstruction

Treatment

- Stabilize—evacuate stomach, IV fluid resuscitation, correct electrolytes
- Surgery—pyloromyotomy. Atropine works but hospital stay prolonged

Adrenal insufficiency can present like HPS

- But hyponatremia, hyperkalemic acidosis, and hypotension

Superior Mesenteric Artery Syndrome (Cast Syndrome) (Wilkie Syndrome)

- Partial to complete obstruction of the duodenum where it passes between the superior mesenteric artery (SMA) and the aorta
  - Aortic-SMA angle is < 25°
  - Seen in the contexts of severe weight loss, anorexia, surgery (especially surgery for scoliosis)

Symptoms—vomiting, gastric distention
Treatment—condition resolves with weight gain

- Eat in supine position
- Enteral tube feeding if possible
- TPN

Duodenal Atresia

- 1 in 6000 live births in the USA. Two-thirds thought to be due to failure of recanalization, while the remainder due to annular pancreas, pre-duodenal portal vein, Ladd's bands
- Associated anomalies: Down syndrome, malrotation, congenital heart disease
- Outcome frequently depends on associated abnormalities
- Prenatal ultrasound shows polyhydramnios 30–60% of the time. Sometimes fluid-filled fetal stomach and proximal duodenum
- Postnatal vomiting usually bilious, but not always
- No abdominal distension
- "Double bubble" on radiograph because of stomach distension and proximal small bowel distension. Gasless distal GI tract
- Correction is planned surgery—stabilization, empty stomach, and proximal duodenum;

look for complicating features. During surgery check for additional GI atresias

Jejunal Atresia

Animal models show that vascular incidents that cause ischemia result in necrosis and subsequent atresia

Atresia types

- **Type I:** Intraluminal web with continuity of muscular layers
- **Type II:** Complete atresia with fibrous cord connecting segments
- **Type IIIa:** Complete atresia with V-shaped defect in the associated mesentery
- **Type IIIb:** Extensive mesenteric defect with distal small bowel spiraling around vasculature forming "apple-peel"
- **Type IV:** Multiple atresias along a segment of bowel
- Usually atresias are accompanied by "microcolon," but this finding is nonspecific

Colonic Atresias

- Follow similar pattern but must be clearly distinguished from Hirschsprung disease

FUNCTIONAL CONSTIPATION (ROME IV, H3A)

Definition

- Must have at least 2 of the following:
  - Less than 2 defecations per week
  - At least one accident per week after toilet training is complete
  - History of stool retention
  - Painful bowel movements
  - Fecal mass in rectum
  - Large diameter stool—obstruct the toilet
  - Other symptoms: Irritable, decreased appetite
- Definition for children 4 or older same as before but must exclude IBS
- Constipation is very common, as many as 40% of all children

Constipation and withholding

- When a child does not recognize or respond to the urge to defecate, stool is retained in the rectum, the urge to defecate subsides, and the rectal wall stretches to accommodate the fecal load
- Repeated withholding or avoidance of defecation leads to larger stool load in the rectum, causing further stretching and potential thinning of the rectal wall
- The retained stool becomes larger, harder, drier, and more difficult to pass the next time the urge arises

Clinical presentation

- Abdominal pain (pain can be severe enough to mimic an acute abdomen)
- Rectal bleeding and anal fissure
- Abdominal distension, tenderness to palpation, and presence of fecal mass
- External anal inspection can assess for anal atresia and displacement and may identify anal fissures, skin tags, or external hemorrhoids. Digital rectal examination (DRE) is not always necessary to make the diagnosis in classic cases
  - Palpation of a firm or large rectal stool mass on rectal examination often confirms clinical suspicions; abnormalities in sphincteric tone may indicate anal stenosis
  - Empty rectal vault with expulsion of stool on finger withdrawal is a classic but infrequently seen finding in Hirschsprung disease

Abdominal radiograph (KUB)

- Abdominal radiograph is not required to make the diagnosis in classic cases of functional constipation

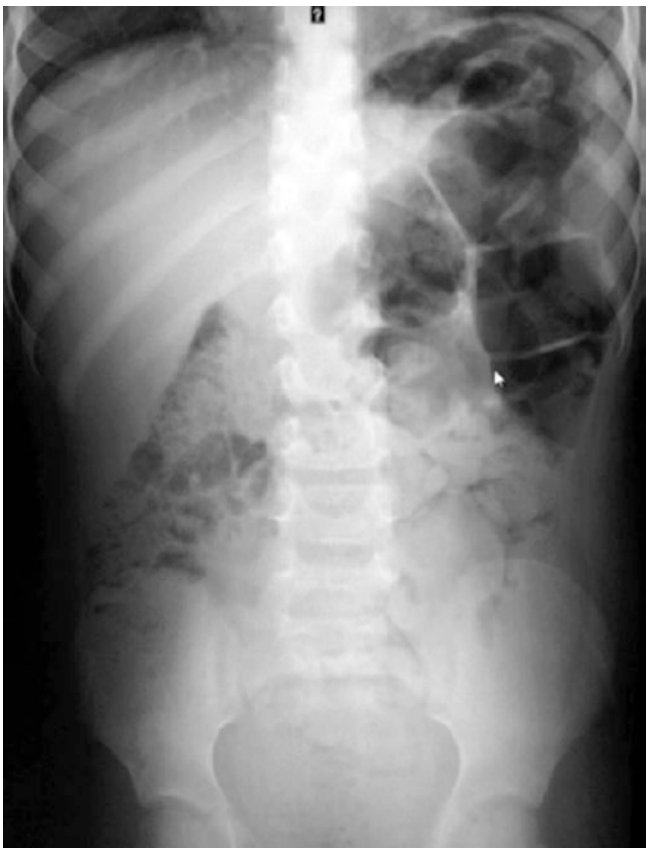


Fig. 22.3 5-year-old with encopresis for 2 years and fecal impaction. The radiograph shows large amount of stool in colon and rectum

- Fecal burden and impaction usually seen on KUB (Fig. 22.3)

Treatment

- Demystification—explain what is happening and why
  - Incontinence is "constipation with overflow" and is involuntary
  - Younger child likely to "withhold" rather than "attempt to expel"
- Cleanout
  - High-dose osmotic laxatives to rid the colon of formed stool, e.g., polyethylene glycol (PEG 3350), lactulose, and magnesium products such as magnesium hydroxide and magnesium citrate
  - Daily dose osmotic laxative to maintain regular defecations
  - Toilet sitting to establish bowel habits
  - Maintaining adequate hydration is a safe recommendation

Nonfunctional Causes of Constipation (Compared to functional constipation, these are much less common)

- Anatomic
  - Imperforate anus
  - Anal stenosis
  - Abnormal musculature, prune belly, gastroschisis, Down syndrome
- Dysmotility
  - Hirschsprung disease
  - Hypothyroidism (hypopituitarism)
  - Diabetes mellitus
  - Colonic inertia
  - Anal achalasia
  - Visceral myopathies
- Drug-, toxin-induced
  - Heavy metals (lead)
  - Opiates
  - Chemotherapy
  - Antidepressants
  - Vitamin D intoxication
- Associated with other diseases
  - Celiac disease
  - Cystic fibrosis
  - Multiple endocrine neoplasia 2B
- Spinal cord anomalies
  - Tethered cord
  - Trauma

Encopresis

- Encopresis is the repeated passage of feces into inappropriate places (usually the underpants)
- It is also called fecal incontinence

Pathophysiology

- Prolonged and repetitive stool withholding and avoidance of defecation lead to large amounts of retained stool in the rectum
- The large fecal mass becomes impacted and extremely difficult to evacuate. Peristaltic movement of the colon pushes semiformed and liquid stool lower in the colon, resulting

in leakage around the large mass of stool into the child's underpants

Management
- Disimpaction with osmotic laxatives
- Maintenance therapy with osmotic laxative on daily basis
- Behavioral modification
- Education

Anal Fissure

- Split in the squamous epithelium distal to the dentate line (mucocutaneous junction)
- *Acute fissure*—blood on the surface of the stool, toilet paper, or dripping from the anus
  - Usually caused by constipation
  - Treatment—osmotic laxatives and *sitz* baths
  - If not in midline or difficult to heal, think of underlying disease
    - Immune deficiency
    - Crohn's disease
- *Chronic anal fissure*—indurated edges, not always in midline
  - Immune deficiency, Crohn's disease
  - Trauma
  - Infection—venereal disease, skin tuberculosis
  - May still be merely chronic constipation
  - Treatment—stool softeners, *sitz* baths; treat any underlying condition

Hirschsprung Disease (HD)

- Aganglionosis of rectum and distal sigmoid but can include varying lengths of the colon and rarely the entire GI tract (total intestinal aganglionosis)
- Failure of the neural crest cells to populate the myenteric plexus
- Never any skip areas; extends from rectum caudad
- 1 in 5000 live births; 4:1 male to female ratio

Cause
- *RET* proto-oncogene considered the major cause of HD

Associations
- Trisomy 21
- Waardenburg-Shah syndrome
- Ondine's curse—congenital central hypoventilation syndrome
- Multiple endocrine neoplasia
- Neurofibromatosis
- Neuroblastoma

Diagnosis (Table 22.9)
- Early constipation—no passage of meconium within 24 h of birth is suggestive
- Deep rectal biopsy
- Un-prepped contrast enema
- Motility only in older child—cooperation required

Treatment
- Surgical excision of aganglionic segment with reconstruction using normal proximal bowel results in satisfactory function in the majority of cases

Hirschsprung Disease-Associated Enterocolitis
- Severe diarrheal illness
- Probably infectious
- Can occur even after correction
- Less common after 2 years of age

Table 22.9 Differences between functional constipation and Hirschsprung disease

Functional constipation	Hirschsprung disease
Passage of meconium in the first 24 h	Delayed passage of meconium > 24 h
Full rectal vault	Empty rectal vault
Large stool caliber	Pencil-thin stool
Normal ganglion cells in the myenteric and submucosal plexus	Absent ganglion cells in the myenteric and submucosal plexus of rectum and distal sigmoid
Encopresis may be present	Not associated with encopresis

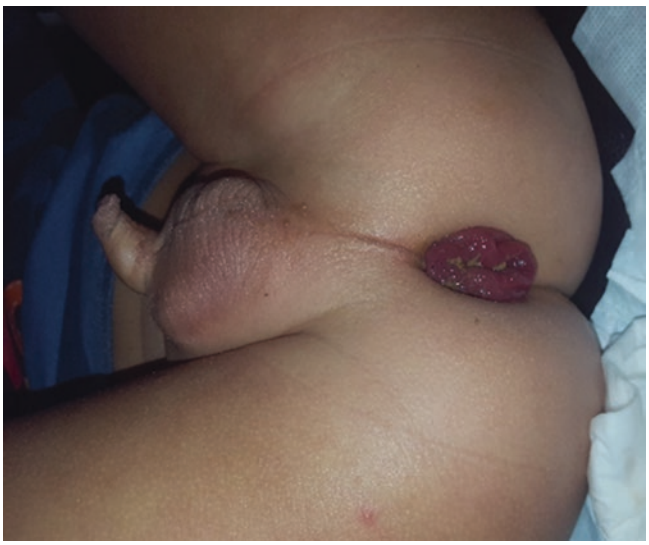


Fig. 22.4 A toddler with rectal prolapse due to chronic constipation

Rectal Prolapse

Protrusion of one or more layers or the rectum (Fig. 22.4)

- Common in children less than 4 years
- Predisposing factors
  - Straining with constipation or toilet training
  - Diarrhea
  - Intestinal parasites—check stool for ova and parasites
  - Malnutrition with muscle wasting
  - Cystic fibrosis—test for CF
- Unusual causes
  - Juvenile polyps
  - Solitary rectal ulcer
  - Ehlers-Danlos syndrome
- Procidential—prolapse of all layers
  - Usually requires manual reduction

Treatment

- Usually self-resolving
- Avoid straining—supported toilet sitting
- Stool softeners if indicated
- Injection sclerotherapy and rectopexy are last resorts

INFLAMMATORY BOWEL DISEASE (IBD)

Chronic unchecked inflammation

- Genetic component
- Immune and microbial components
- Involves the GI tract but extraintestinal manifestations are common
- Incidence peaks between 15 and 30 years of age
  - Very-early-onset IBD (VEOIBD) less than 5 years may have uncommon immune deficiency—refer to immunologist

Histologic features of IBD (Fig. 22.5)

Ulcerative Colitis (UC)

- Affects the colon
- Inflammation of the mucosal layer
- No skip areas from distal colon (usually spares rectum) to ileocecal valve (sometimes "backwash" ileitis found)

Crohn's Disease (CD)

- CD includes Crohn's enteritis and Crohn's colitis
- Can involve any portion of the GI tract from oral cavity to anus
- Transmural inflammation can lead to perforation and/or abscess formation
- Can affect nutritional status and growth

Indeterminate Colitis (ID)

- Features do not clearly categorize it as CD or UC
- Most cases will eventually be recognized as CD

Crohn's disease compared to features of ulcerative colitis (Table 22.10)

Diagnosis of IBD

- Index of suspicion
  - Teenager with chronic abdominal pain, diarrhea, blood in stool, unexplained anemia, weight loss or poor weight gain, retarded growth, retarded pubertal development
  - Family history of IBD

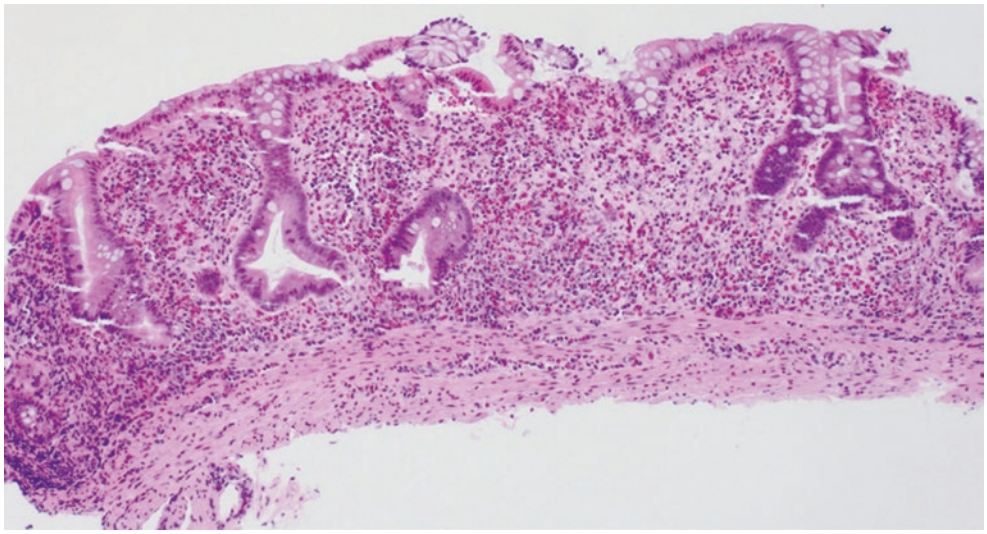


Fig. 22.5 Histologic features of inflammatory bowel disease showing crypt atrophy and basal plasmacytosis

Table 22.10 Distinguishing features of Crohn's disease and ulcerative colitis

Feature	Crohn's disease	Ulcerative colitis
Serositis	+	–
Thickened bowel wall	+	– Except with carcinoma
Stricture	+	– Except with carcinoma
Mucosal edema	+	– (Usually)
Ulcers	+ (In one line)	+
Fat wrapping	+	–
Fistula	+	–
Distribution	Focal	Diffuse
Rectal involvement	–	+
Granuloma	+	–
Fissuring ulcers	+	–
Transmural inflammation	+	–
Submucosal edema	+	–
Submucosal inflammation	+	–
Neuronal hyperplasia	+	–
Thick muscularis mucosa	+ (Patchy)	+ (Diffuse)
Pyloric gland metaplasia	+	–
Mucosal inflammation	+ (Focal)	+ (Diffuse)
Architectural distortion	+ (Focal)	+ (Diffuse)
Paneth cell metaplasia	– (Usually, no)	+

Screening studies:

- CBC differential, platelet count
- ESR, CRP, stool calprotectin
- Chemistries including total protein and albumin
- Stool for occult blood and stool cultures
- Serologic tests: Anti-*Saccharomyces cerevisiae* antibodies (ASCA), outer membrane protein C (OmpC) for CD, perinuclear antineutrophil cytoplasmic antibodies (pANCA) for UC, and others (use only as adjunctive information)
- Imaging: Abdominal radiograph, upper GI series with small bowel follow-through, CT of abdomen with IV and PO contrast, and MRI with IV and PO contrast (MRE); upper GI and barium enema largely replaced by more advanced imaging

Definitive diagnosis

- Colonoscopy with terminal ileal intubation
- Simultaneous upper endoscopy adds information even if negative
- If suspicion is high and esophagogastroduodenoscopy (EGD) and colon are negative, consider capsule endoscopy or double balloon endoscopy

Treatment of IBD

- Initially UC, CD, and ID treated similarly with immune suppression
  - Steroids to induce remission, then wean

- Immunomodulators: 6-mercaptopurine and methotrexate
- Biologics: Infliximab, adalimumab, and others
- CD can be initially treated with enteral nutrition
- Surgery
- In severe UC, colectomy with J-pouch is an option
- In CD abscesses, strictures, perforation may require surgery

Gluten-Sensitive Enteropathy (Celiac Disease)

- Inflammatory disease of small intestine
- Immune regulated
- Sensitivity to dietary gluten
- Genetic predisposition required—*HLA*-DQ2/DQ8 required
- Occurs in 1 in 100 to 1 in 200 individuals in general population
- Grains containing gluten:
  - Wheat, barley, and rye
  - Oats do not contain gluten, but may be contaminated during processing
  - Buckwheat is gluten-free

Signs and symptoms (otherwise not explained)

- Failure to thrive
- Persistent diarrhea
- Chronic constipation (paradoxical)
- Recurrent abdominal pain
- Vomiting
- Short stature
- Pubertal delay
- Iron deficiency
- Dermatitis herpetiformis rash
- Abnormal liver tests
- Chronic fatigue

At-risk individuals

- First-degree relatives
- Autoimmune thyroiditis
- Type 1 diabetes
- Down syndrome
- IgA deficiency
- Turner syndrome
- Williams syndrome
- Juvenile chronic arthritis

Serologic screening tests done on a gluten-containing diet (at least 3 g/day for 6 weeks)

- Tissue transglutaminase (tTG)
  - tTG-IgA is highly sensitive and specific and cost-effective, less sensitive under 2 years of age
  - tTG-IgG not as sensitive or specific, but useful in IgA deficient individuals
- Anti-endomysial antibody (EMA)—as good as tTG-IgA but more expensive and operator dependent
- Deamidated gliadin peptide (DGP)—useful in young children less than 2 years of age

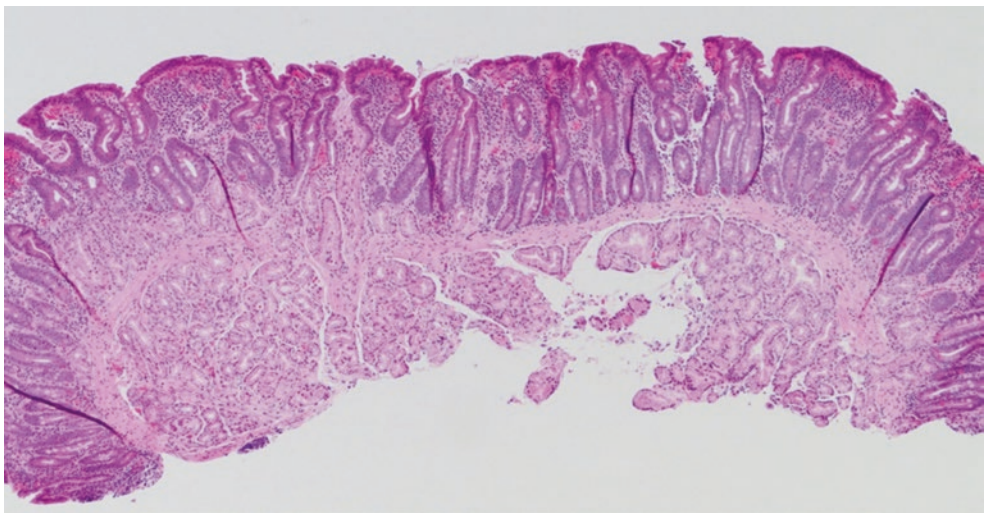


Fig. 22.6 Histologic features of celiac disease with marked villous blunting and crypt hyperplasia, an increase in intraepithelial lymphocytes

Definitive diagnosis

- Upper endoscopy with small bowel and stomach biopsies recommended
  - Lifelong, life-altering diagnosis dictates maximum certainty
  - Staging—Marsh classification

Histologic features of celiac disease (Fig. 22.6)

Treatment and outcomes

- Lifelong gluten-free diet
  - Resolution of symptoms in most individuals
  - Serologic markers normalize usually within weeks but can be up to a year
  - Small bowel mucosa returns to normal
  - Risk of GI neoplasm reduced, but not to baseline
- Long-term (yearly) follow-up recommended
  - Dietary adherence
  - Growth and development
  - Bone health

Cystic Fibrosis (CF)

GI/Hepatobiliary Manifestations

- Caused by mutation in cystic fibrosis transmembrane conductance regulator protein (CFTR)
- Over 2000 mutations listed in database—F508del is the most common
- Mutation causes abnormally tenacious mucus and secretions affecting lungs, pancreas, hepatobiliary tract, GI tract, and sweat glands

Diagnosis of CF most often with newborn screen (available in all 50 states in the USA)

- Measures immunoreactive trypsinogen (IRT) but must be confirmed by sweat test or gene testing

Pancreatic Insufficiency (PI)

- Occurs in approximately 85% of CF patients and is somewhat gene mutation specific
- Prevalence increases with age
- Decreased enzyme and bicarbonate production
  - Fat and fat-soluble vitamin malabsorption
  - Decreased enzyme activation

Diagnosis of PI

- Stimulation of the pancreas with IV secretin/cholecystokinin and collection of pancreatic secretion via duodenal tube (endoscope) is most accurate way of assessing function but infrequently done because of invasive nature of test
- 72-hour fecal fat collection—amount of fat in stool is compared to amount of fat in diet, 85% absorption in infants, 93% in older children and adults—not often done because laborious and unpleasant
- Test of choice: Fecal elastase measures pancreatic elastase in stool—not affected by exogenously administered enzymes but cannot be used to assess adequacy of enzyme replacement

Pancreatic enzyme replacement

- Exogenous enzymes administered with all meals and snacks
- Fat-soluble vitamins need to be monitored and supplemented

CF-Related Diabetes Mellitus (CFRD)

- As damage progresses to pancreatic tissue, there is a decrease in:
  - Glucagon-producing alpha cells
  - Insulin-producing beta cells
- Prevalence increases with age, 75% overall, 50% of adults, 20% of adolescents
- Occurs only in pancreatic insufficient (PI) individuals
  - Worsening lung function and nutritional status associated with development of CFRD

Pancreatitis

- 20% of pancreatic sufficient (PS) CF individuals will experience bouts of pancreatitis

- Treatment is IV fluids, enteral nutrition, analgesia, plus/minus enzymes
- Repeated bouts can lead to pancreatic "burnout"

Gastrointestinal Issues

- Decreased motility due to decrease in GI secretions and thick mucus layer
- Meconium ileus
  - Partial or complete obstruction at birth
  - Relieved by hyperosmolar enemas 50–90% of the time
  - Sometimes complicated by perforation, peritonitis, volvulus, atresia
  - Surgery
- Distal intestinal obstruction syndrome (DIOS) (previously called meconium ileus equivalent)—impaction of fecal material at distal ileum, cecum, and proximal colon
  - Occurs at any age
  - Most often treated with polyethylene glycol lavage
  - N-Acetylcysteine enemas rarely used because of success with lavage
- Nutrition—intake frequently inadequate in CF
  - Increased work of breathing
  - Decreased appetite
  - Residual malabsorption
  - Good nutrition without fat restriction important, but obesity should be avoided
  - Dietary advice should be individualized
- Rectal prolapse

Hepatobiliary Complications

- Virtually all CF patients will have some liver diseases
  - Prevalence increases with age, 20% of adults have clinically significant liver disease

Manifestations

- Neonatal cholestasis
- Hepatomegaly
- Raised levels of liver enzymes
- Hepatic steatosis
- Focal biliary cirrhosis
- Multilobular cirrhosis with portal hypertension
- Esophageal varices and bleeding
- Liver failure requiring transplantation

Treatment

- Avoid liver toxic medications and substances
- Immunize against hepatitis A and B
- Optimize nutrition
- Plus/minus ursodeoxycholic acid (CF Foundation recommends its use; others have suggested that it is not helpful)
- Treat esophageal varices with endoscopic banding
- Liver transplant when necessary

Shwachman-Diamond Syndrome (SDS)

Characteristics

- Pancreatic insufficiency
  - Fatty infiltration of pancreas affecting acinar cells; requires enzyme replacement
  - Can be visualized on CT
  - Improves with age—some no longer requiring enzyme replacement
- Bone marrow dysfunction
  - Persistent neutropenia—frequent infections requiring prophylactic antibiotics; human granulocyte stimulating factor—bone marrow transplant
  - Red cells and platelets may be affected
- Skeletal abnormalities 50% of individuals
  - Long-bone dysostosis
  - Metaphyseal chondrodysplasia
  - Thoracic cage abnormalities 30% of individuals

Pancreatic Insufficiency Differential Diagnosis

- Cystic fibrosis
- Shwachman-Diamond syndrome
- Johanson-Blizzard syndrome
  - Deafness
  - Imperforate anus

  - Urogenital malformations
  - Dental anomalies
- Pearson syndrome
  - Refractory sideroblastic anemia
- Jeune syndrome
  - Anomalies of upper thoracic bones leading to respiratory compromise

Primary Intestinal Lymphangiectasia

Background
- Obstruction of lymphatic drainage of the intestine
- Diffused or local dilation of enteric lymphatics
  - Leads to protein-losing enteropathy

Associated condition
- Turner syndrome
- Noonan syndrome
- Klippel-Trenaunay syndrome
- Weber syndrome
- Heart failure

Clinical presentation
- Varies in severity from asymptomatic to life-threatening
- Protein-losing enteropathy is the main cause of the clinical manifestations of this disease

Diagnosis
- Presence of alpha-1 antitrypsin in stool
- Direct measurement of alpha-1 antitrypsin clearance from plasma

Management
- Replace long-chain fat with medium-chain triglycerides in diet or formula and treatment of the cause

Short Bowel Syndrome

Background
- Loss > 50% of small intestine with or without portion of large intestine can result in generalized malabsorption
- Child's small intestine 200–250 cm, adult's 300–800 cm
- Infant with 15 cm small bowel with ileocecal valve of 20 cm or more without ileocecal valve can eventually wean from TPN
- Trophic feeds will increase pancreatobiliary flow and decrease TPN toxicity

Long-term complications of short bowel
- Renal stones secondary to steatorrhea Ca, binds to fat and not to oxalate, excess oxalates reabsorbed, and excreted in urine
- Bloody diarrhea secondary colitis as a result of enteral feeding (this may improve with hypoallergenic diet)
- Constipation
- Failure to thrive

Bacterial Overgrowth Syndrome

Background
- Overgrowth of aerobic and anaerobic bacteria in the small bowel
- The normal small intestine has relatively few bacteria residing inside

Mechanism of development of diarrhea
- Bile acids are deconjugated and fatty acids hydroxylated by bacteria
- These processes lead to an osmotic diarrhea

Conditions may result in bacterial overgrowth
- Short bowel syndrome
- Pseudo-obstruction
- Bowel strictures
- Malnutrition
- Previous GI surgery

Clinical presentation
- Diarrhea
- Bloating
- Abdominal distension
- Abdominal pain or discomfort
- Fatigue
- Weakness or lethargy
- Ataxia

Diagnosis
- History
- Breath hydrogen with lactulose testing
- Neurologic findings
- Metabolic acidosis (low HCO3)
- Elevated D-lactic acid

Treatment complications
- Malabsorption
- Fat-soluble vitamin loss

Therapy
- Broad-spectrum antibiotics cover Gram-negative and anaerobic bacteria, e.g., metronidazole or with nonabsorbable rifaximin

Surgical management
- Depends upon the underlying cause

DIARRHEA

- Usually self-limited; recovery in a few days
- Most children with or without dehydration can continue to eat
- Reason for diarrhea
  - Viral
  - Bacterial
  - Parasitic
  - Antibiotic associated
  - Osmotic
  - Inflammation
  - Starvation

Clinical presentation
- Diarrhea, non-blood or bloody
- Nausea and vomiting may be present
- Dehydration symptoms:
  - Increased thirst, irritability, or lethargy
  - Dry or parched mucous membrane
  - Sunken fontanel
  - Reduced skin turgor
  - Prolonged capillary refill
  - Reduced urine output
  - Tachycardia, normal or low blood pressure

Management of acute diarrhea with dehydration
- Oral or nasogastric hydration with oral rehydration solution (ORS) for mild to moderate dehydration
- Regular diet
- Avoid juices and soft drinks, e.g., apple juice, Sprite, 7-Up, or Gatorade
- Fluid therapy for a patient with acute gastroenteritis unresponsive to oral rehydration
- Several advances in formulation of ORS have improved efficacy
- Oral hydration technique:
  - Patients with mild to moderate dehydration should receive 50–100 mL/kg of ORS over 2–4 h to correct fluid deficit
  - In addition, ongoing fluid losses from vomiting or diarrhea should be replaced
  - For children with significant vomiting, ORS should initially be administered in 5-mL aliquots every 1–2 min
  - Administration of fluid with a teaspoon, syringe, or dropper may facilitate initial fluid resuscitation
  - Fluid volumes can be increased as tolerated
  - Repletion for ongoing fluid losses may be estimated at 5–10 mL/kg (5 mL/kg for each emesis and 10 mL/kg for each diarrheal episode)
- Between 5% and 15% of children with acute diarrhea continue to be have clinical signs of dehydration 4 h after starting ORS
  - Fluid treatment for severe dehydration
  - Nasogastric, nasojejunal, intravenous, intraosseous fluids
  - ORS, normal saline, lactated Ringer's solution
  - Normal saline and albumin boluses have worse outcome than no-bolus therapy

Important tips for management of diarrhea
- Vitamin A deficiency increases the risk of dying from diarrhea, measles, malaria by 10–24%

- Zinc deficiency increases the risk of mortality from diarrhea, pneumonia, and malaria
- Persistent diarrhea lasts at least 14 days; nutritional supplementation is very important
- Ondansetron is an effective and less toxic antiemetic (if diarrhea associated with persistent vomiting) and may limit dehydration and hospitalizations

Extraintestinal manifestations and clues to causative agent

- Reactive arthritis: *Salmonella, Shigella, Yersinia, Campylobacter, Cryptosporidium, Clostridium difficile*
- Guillain-Barré syndrome: *Campylobacter*
- Glomerulonephritis: *Shigella, Campylobacter, Yersinia*
- Appendicitis-like presentation: *Yersinia*
- IgA nephropathy: C*ampylobacter*
- Erythema nodosum: *Yersinia, Campylobacter, Salmonella*
- Hemolytic uremic syndrome (HUS): *Shigella dysenteriae* 1*, E. coli* O157: H7
- Hemolytic anemia: *Campylobacter, Yersinia*

Antibiotics and drug of choice in treatment of diarrhea

- Most cases of diarrhea are self-limited, and no antibiotic treatment is needed, and in some cases, antibiotics are contraindicated
- *Shigella*
  - Ciprofloxacin, trimethoprim-sulfamethoxazole, and azithromycin
  - Third-generation cephalosporin is appropriate empiric therapy in the setting of acute illness
- *Salmonella*
  - Antibiotics are indicated in infants < 3 months, patients with systemic diseases, malignancy, or immunocompromised
  - Third-generation cephalosporin, e.g., cefotaxime
- *C. difficile*
  - Metronidazole oral or IV is the first line, may use again if relapse; this just means reinfection and is not a resistance
  - If no response, the second line is vancomycin (oral)
- *Entameba histolytica*
  - Metronidazole followed by iodoquinol or paromomycin
- *Campylobacter jejuni*
  - Erythromycin or azithromycin

Chronic Diarrhea

- Malabsorptive
  - Carbohydrate—see "Disaccharide Intolerance"
  - Toddler's diarrhea—chronic diarrhea of unknown etiology in a toddler who is otherwise doing well
    - Thought to be due to excessive fructose/sorbitol
    - Treatment—eliminate juice but maintain normal diet
  - Fat malabsorption—greasy, bulky, foul-smelling stool
    - Diagnosis—72-h fecal fat collection with calculation of percent fat absorption
    - Cholestasis—biliary atresia, primary sclerosing cholangitis
    - Pancreatic insufficiency
    - Bile salt malabsorption—ileal disease and/or resection
- Postinfectious enteritis—in minority of cases of infectious diarrhea, persistent mucosal damage leads to persistent diarrhea
  - Mechanism is not understood but is not disaccharidase deficiency
  - Postinfectious enteritis has become much less common since recommendations to "feed through" diarrhea have been implemented

Chronic Inflammatory Diarrhea

- Collagenous colitis (microscopic colitis)
  - Submucosal collagenous bands on colonic biopsy
  - Lymphocytic/eosinophilic infiltrates on colonic biopsy
  - Oral budesonide may induce remission

- Eosinophilic gastroenteritis
  - Dense infiltrate of eosinophils in intestinal biopsy, with or without peripheral eosinophilia
  - Diagnosis of exclusion—all other reasons for intestinal eosinophilia must be ruled out
- Allergic colitis (protein-induced colitis)
  - Non-IgE allergy to food protein (commonly cow protein and/or soy protein in formula or breast milk) induces proctitis
  - Streaks of blood and mucus in stool
  - Usually responds to hypoallergenic formula or mother's elimination diet
  - Resolves by 12–18 months of age
- Food protein-induced enterocolitis syndrome (FPIES)—uncommon
  - Vomiting
  - Non-bloody diarrhea
  - Failure to thrive
- Celiac disease
- IBD

VIPoma

- Watery diarrhea—hypokalemia—acidosis syndrome
- Excessive secretion of vasoactive intestinal peptide (VIP)

Congenital Diarrhea

- Microvillus inclusion disease—rare severe secretory diarrhea starting from neonatal period to a few months of age
  - Myosin motor protein type Vb mutation in some families
  - Severe dehydration and metabolic acidosis require IV/oral correction
- Tufting enteropathy—presents similarly to microvillus inclusion disease
  - "Tufts" of epithelial membrane partly separated from villus tip
  - Variable villus atrophy
- Autoimmune enteropathy—diarrhea in early infancy
  - Villus atrophy, crypt hyperplasia, inflammatory infiltrate
  - Can be associated with IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome and mutation in *FOXP3* gene
- Congenital chloride diarrhea—defect in Cl^-/$HCO3^-$ exchanger in the intestine (Table 22.11)
  - Stool chloride exceeds stool Na^+ plus K^+ when hydrated
  - May be history of polyhydramnios and/or dilated loops of fetal intestine
  - Treatment—replace chloride and maintain hydration
- Congenital sodium diarrhea—rare defect in Na^+/H^+ exchanger
  - Decrease Na^+ absorption and increased stool Na^+
  - Metabolic acidosis and hyponatremia
  - Replace Na^+ and maintain hydration

Table 22.11 Difference between congenital chloride and sodium diarrhea

Type of congenital secretory diarrhea	Clinical features
Congenital chloride diarrhea	Low PH diarrhea (acid)
	Metabolic alkalosis
$Cl^-/HCO3^-$ transport defect	Hypochloremia
	High chloride in stool
Congenital sodium diarrhea	High pH diarrhea (alkaline)
	Metabolic acidosis
Na^+/H^+ transport defect	Hyponatremia
	High Na in stool

Disaccharide Intolerance

Lactose intolerance

- Primary alactasia—rare congenital, complete lack of lactase enzyme
- Primary hypolactasia—common genetic lack of lactase persistence allele, associated with decreased lactase with age
  - The amount of lactose that can be tolerated is extremely variable from one individual to another and is not entirely based on the activity of the residual lactase
  - Lack of lactase persistence allele has geographic and ethnic variability
- Secondary hypolactasia—temporary decrease in lactase due to intestinal injury, severe gastroenteritis, celiac disease, Crohn's disease, etc.

Management of lactose intolerance, taking into consideration the mechanisms causing the disorder

- Primary alactasia—lifelong avoidance of milk and dairy products. Use of Lactaid treated products can be attempted
- Primary hypolactasia—small to moderate amounts of lactose-containing foods may be tolerated. Lactase-treated products may be used
- Secondary hypolactasia—if lactose intolerance is due to acute infectious gastroenteritis, no treatment may be required or decrease dairy products for a short time. If injury is more long-lasting (celiac disease, Crohn's disease) low-lactose diet combined with lactase-treated dairy may be required. When gastrointestinal injury has resolved, dairy products can be resumed

GASTROINTESTINAL BLEEDING

- Occult bleeding—detected by testing for blood in stool
  - Source can be upper/lower GI tract or extra-GI in origin (e.g., nosebleed)
- Melena is black, tarry stool suggestive of bleeding from the proximal GI tract
  - Black stool can be due to medication and foods—test for blood
- Hematochezia bright red blood per rectum suggestive of lower GI bleed or very brisk upper GI bleed
- Hematemesis is vomiting blood—can be dark (coffee grounds) or red

Upper GI Bleeding

Hematemesis: Check Gastroccult—Is It Really Blood?

- Suggests bleeding is proximal to ligament of Treitz
- Dark/coffee grounds: Has been exposed to stomach acid
- Red blood: Upper stomach, esophagus, extra-GI, or brisk bleed
- Esophageal erosion
- Mallory-Weiss gastropathy
  - Forceful vomiting/retching forces cardia of stomach through diaphragmatic opening, resulting in tearing of mucosa
  - Treat the cause of vomiting—short course of acid suppression
- Gastritis
  - *H. pylori*—triple therapy—2 antibiotics and acid suppression
- Ulcer, gastric, and duodenal—most due to *H. pylori* infections
  - Cobblestone appearance of antral mucosa on endoscopy
- Extra-GI
  - Nosebleed
  - Hemoptysis
- Esophageal varices

Esophageal Varices

Background

- Cavernous or portal vein thrombosis is the most common type
- Umbilical vein thrombosis in neonates

Causes

- Portal hypertension
- Mediastinal tumor
- Superior vena cava (SVC) thrombosis
- Chronic liver disease resulting in portal hypertension

Clinical presentation

- Hematemesis
- Splenomegaly

Diagnosis

- Upper endoscopy (Fig. 22.7)

Management

- Treatment of the cause
- Band ligation
- Sclerotherapy

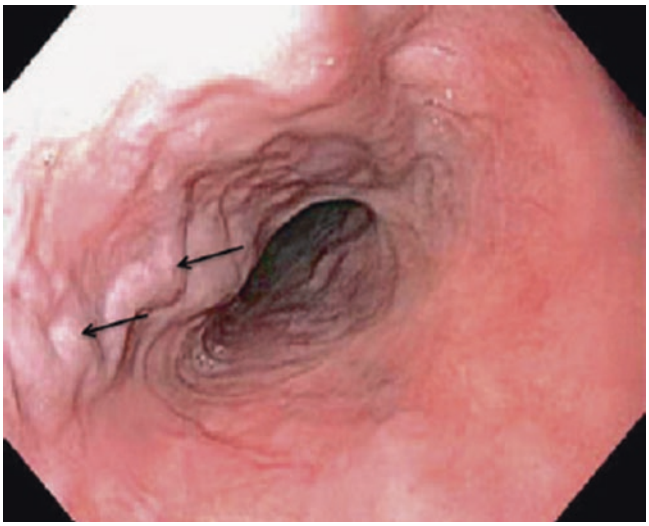


Fig. 22.7 Endoscopic picture of esophageal varices (*arrows*). (Courtesy of Sherif Elhanafi, MD, Department of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona)

Lower GI Bleeding

- Infant
  - Swallowed maternal blood—Apt test
  - Anorectal fissure—examination
  - Necrotizing enterocolitis—imaging for pneumatosis intestinalis
  - Malrotation/midgut volvulus imaging, upper GI series
  - Hirschsprung-associated enterocolitis—antibiotics and fluid resuscitation, then unprepped contrast enema
  - Coagulopathy (e.g., vitamin K deficiency), coagulation studies (prothrombin time [PT], partial thromboplastin time [PTT)] and international normalized ratio [INR]. Gastric or duodenal ulcer with brisk bleed—upper endoscopy
  - Duplication cyst—imaging
- Infant and toddler
  - Anal fissure
  - Milk- or soy-induced colitis—remove suspected allergens from child's diet
  - Intussusception—ultrasound imaging
  - Meckel diverticulum
  - Duplication cyst
  - Coagulopathy
  - Eosinophilic gastroenteritis
  - Very-early-onset IBD
- Preschool
  - Infection colitis
    - *Salmonella, Shigella, E. coli, Yersinia, Campylobacter, C. difficile*
  - Hemolytic uremic syndrome—*E. coli* O157: H7
  - Henoch-Schönlein purpura—IgA vasculitis
  - Juvenile polyps
  - Solitary rectal ulcer
- School age and adolescent
  - IBD

Meckel Diverticulum

Background

- Congenital anomaly: Remnant of the yolk sac that remains attached to the intestine and develops lining epithelium similar to that of the stomach
- Rule of two: 2% of population, 2:1 male to female ratio, 2 ft from ileocecal valve, 2 in. long, 2% of individuals develop complications, usually before the age of 2
- May occur in the first decade of life
- Ulceration of adjacent ileal mucosa from acid of ectopic stomach mucosa can cause intermittent painless bleeding

Clinical presentation

- Significant painless rectal bleeding is Meckel diverticulum until proven otherwise
- Stool is brick- or currant jelly-colored, bleeding can be less dramatic melanotic stools
- Anemia and hypovolemia (the bleeding is usually self-limited due to contraction of splanchnic vessels)
- Obstruction because Meckel diverticulum may act as a leading point for intussusceptions
- Meckel diverticulitis with a presentation similar to appendicitis

Diagnosis

- The most sensitive test is Meckel diverticulum scan, 99m technetium pertechnetate
- The uptake can be enhanced by cimetidine, glucagon, and gastrin

Treatment

- Surgical

POLYPS

Single Hamartomatous Polyp (Juvenile Polyp) (Fig. 22.8)

- Common
- 0.5–5.0 cm in diameter
- Painless, bright red rectal bleeding
- Sometimes seen protruding from rectum or in diaper after auto-amputation
- There can be up to 5 polyps
- 70% in rectosigmoid area but can be in proximal colon
  - No malignant potential
- Should be removed with pan-colonoscopy and polypectomy
  - Rule out polyposis syndrome
  - Can perform repeat polypectomy

Intestinal Polyposis Syndromes

- Multiple hamartomatous polyps with increased malignant potential
- Autosomal dominant
- Includes 4 separate types:
  - Juvenile polyposis syndrome (JPS)
  - Peutz-Jeghers syndrome (P-JS)
  - Cowden syndrome (CS)—a *PTEN* mutation
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS)—a *PTEN* mutation

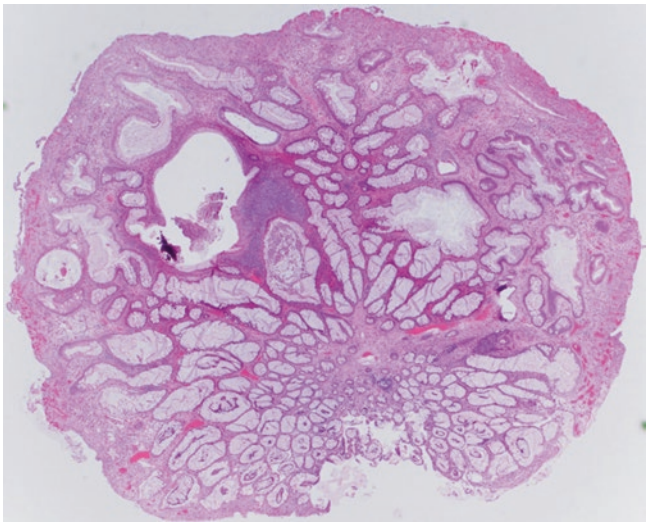


Fig. 22.8 Histologic features of a juvenile polyp showing spherical, eroded and granular surface, stromal compartment expanded, low crypt density, and flattened reactive epithelium

- Indications for genetic testing:
  - Children with 5 or more juvenile polyps
  - Any number of adenomatous intestinal polyps

Juvenile Polyposis Syndrome (JPS)

- Sometimes associated with mutation in *SMAD4* gene—presents in 3 forms:
  - Juvenile polyposis of infancy with rectal prolapse, diarrhea, bleeding, and protein-losing enteropathy—death before 2 years despite colectomy
  - Juvenile polyposis coli—only the colon involved
  - Generalized juvenile polyposis syndrome occurs throughout the GI tract and can affect nutrition and growth

Peutz-Jeghers Syndrome (P-JS)

- Rare—autosomal dominant
- Mucocutaneous freckling

- Hamartomatous polyps throughout the GI tract, mainly small bowel
- 90% will have mutation in *STK11* tumor suppressor gene
- Start screening for malignancy at 8 years of age with capsule endoscopy; if negative, restart at 18, every 3 years
- Midgut polypectomy via laparoscopy, intraoperative endoscopy, or double balloon endoscopy—requires an expert

Cowden Syndrome (CS): Rarely Presents in Childhood

- Small hamartomatous polyps distal to the hepatic flexure
- Associated anomalies: Macrocephaly, papillomatous papules, keratosis

Bannayan-Riley-Ruvalcaba Syndrome (BRRS)

- Polyps mainly in ileum and colon
- Associated anomalies: Macrocephaly, developmental delays, boney malformation of hands and feet, pectus excavatum, scoliosis, genital pigmentation, hemangiomatosis
- Mutation in PTEN tumor suppressor gene

Familial Adenomatous Polyposis (FAP)

- More common than other polyposis syndromes: 3 in 10,000 live births
- Cancer risk—if polyps not detected and treated, all will develop colorectal cancer
- Hundreds to thousands of adenomatous polyps can develop in colon—gastric fundic polyps can comprise 50% of total but do not require treatment
- Associated conditions: Increased risk of hepatoblastoma in childhood, increased risk of malignancy of ampulla of Vater and duodenal tumors in adults, increased risk of extra-GI tumors.
- Congenital hypertrophy of the retinal pigment epithelium (CHRPE) may be a tip-off to the diagnosis of FAP
- Surveillance
  - Whether familial gene mutation is known or not, yearly screening starting at age 10 years
  - When greater than 100 adenomas found or adenomas greater than 5 mm, perform colectomy with ileorectal anastomosis or ileo pouch anal anastomosis
  - Still need annual sigmoidoscopy
- Risk of desmoid—increased risk with FAP
  - Non-metastasizing, locally expanding tumor of the abdominal wall or within the abdomen
  - No effective treatment
  - Surgery carries high mortality rate

LIVER

Jaundice

- Yellow-green coloration of skin, conjunctivae due to increased bilirubin
- Indirect bilirubin (unconjugated)—breakdown product of red blood cells before liver conjugation
  - High indirect bilirubin is usually due to hemolysis
  - Newborn hyperbilirubinemia is due to increased indirect bilirubin
  - Usually hematologic problem and not a GI problem
- Direct bilirubin (conjugated) breakdown product of red blood cells that has been conjugated by the liver to make it water soluble
  - Increased direct bilirubin greater than 15% of total is due to liver disease

Neonatal Cholestasis

- Accumulation of substances that should be excreted in the bile (essentially equivalent to direct hyperbilirubinemia)
- Biliary atresia, idiopathic neonatal hepatitis, and alpha-1-antitrypsin deficiency account for over 80% of cases
- Causes of neonatal indirect hyperbilirubinemia
  - Anatomic
  - Infectious
  - Metabolic
  - Genetic
  - Toxic
  - Miscellaneous

Biliary Atresia

- The result of an idiopathic inflammatory process damaging intra- and extrahepatic ducts. End result of fibrosis and oblation of biliary tract, cirrhosis, and liver failure
- Syndromic forms associated with other anomalies: Polysplenism, asplenism, portal vein malformations, malrotation, duodenal and esophageal atresia, polycystic kidneys, renal agenesis
- Non-syndromic form without other anomalies more frequent
- Clustering in time and place points to an environmental/infectious etiology, but none has been identified

Clinical features

- Jaundice (predominantly direct hyperbilirubinemia) and acholic stools—child born at term and does well for 1st month
- Splenomegaly, hepatomegaly
- Later ascites, wasting, and failure to thrive

Table 22.12 Diagnostic screening tests for infants with direct hyperbilirubinemia

Name of test
Abdominal ultrasound
Adenovirus
Alpha-1-antitrypsin phenotype
Alpha-1-antitrypsin level
Blood for organic acids
Cytomegalovirus (IgM) urine
Epstein-Barr virus titers
Ferritin
Galactose-1-uridyl transferase
Gamma-glutamyl transferase
Hepatitis B virus by PCR
Hepatitis C virus by PCR
Herpes (IgM)
HIDA scan (pretreated with phenobarbital)
Lactate
Parvovirus
Percutaneous liver biopsy
Pyruvate
Rubella (IgM)
Serologic test for syphilis (IgM and IgG)
Serum alkaline phosphatase
Serum iron and total iron binding capacity
Skull radiograph
Sweat test or stool elastase
Thyroid screen
Toxoplasmosis (IgM)
Urine for amino acids
Urine for bile acid analysis
Urine for organic acids

N.B. Start phenobarbital treatment immediately
Rule out potentially treatable viral infections first
IgM Immunoglobulin M, *PCR* Polymerase chain reaction, *HIDA* Hepatobiliary iminodiacetic acid, *IgG* Immunoglobulin G

Diagnosis (Table 22.12)

- Ultrasound may show a small or absent gallbladder
- Hepatobiliary iminodiacetic acid (HIDA) scan shows absent excretion—but this is not specific
- Liver biopsy early shows bile duct proliferation and bile canalicular stasis. Later increased fibrosis and bile duct drop out

Surgery

- Kasai procedure—hepatoportoenterostomy
- Intraoperative cholangiogram may precede surgical procedure
- Attempt to establish bile duct drainage. More successful if done early, i.e., before 8 weeks of age
- Results are variable—improvement seen in weeks or years
- A bridge to liver transplant—can be 1 year to 20 years of age—usually about 3 years
- Primary transplant can be an option—size limits to organs available

Wilson Disease

- Hepatolenticular degeneration—autosomal recessive copper storage disease due to a defect in incorporation of copper into ceruloplasmin → buildup of copper in body tissues
- Defect in *ATP7B* gene—no defect in ceruloplasmin gene, but rapid excretion of ceruloplasmin because of lack of copper incorporation (aceruloplasminemia)
- Presents in the second to fourth decade but has been diagnosed in the elderly

Hepatic presentation

- Acute hepatitis, acute liver failure, chronic hepatitis, steatohepatitis, portal hypertension, cirrhosis, elevations of serum aminotransferase, gallstones, hepatocellular carcinoma

Neuropsychiatric presentation

- Tremors, coordination defects, dystonia, ataxic gate, fixed grin, headaches, seizures, dementia, neurosis anxiety, depression, bipolar, antisocial behavior

Other less common presentations

- Renal (damage due to copper buildup)
- Hematologic (intravascular hemolysis)
- Cardiac, skeletal abnormalities (bone demineralization due renal tubular dysfunction)
- Hormonal imbalance

Diagnosis

- Ceruloplasmin less than 20 mg/dL
- Hepatic copper greater than 250 μg/g dry weight
- Urine copper greater than 100 μg/24 h
- Presence of Kayser-Fleischer rings
- Genotyping identification of 2 disease-causing mutations in *ATP7B*

Treatment

- Copper chelators—D-penicillamine and trientine used in initial therapy and maintenance
- Zinc acetate—inhibits copper absorption—useful for maintenance and during pregnancy
- Treatment is lifelong

Gilbert Syndrome

Background

- Common—heterogeneous group—all have an at least 50% reduction in *UGT1A1* gene coding for UDP-glucuronosyltransferase enzyme, the enzyme responsible for conjugating bilirubin. Complete absence of this enzyme causes severe Crigler-Najjar syndrome (Table 22.13)

Presentation

- Causes mild unconjugated hyperbilirubinemia, up to 4 mg/dL and minimally elevated transaminases
- Picked up after puberty, routine screening, or conjunctival icterus
- May cause mild fatigue

Diagnosis

- Can be presumptive in the right setting, but rule out Wilson disease
- In the Caucasian, homozygous finding of extra TA repeat in TATA box, (TA)7-TAA necessary for Gilbert syndrome

Table 22.13 Differences between Gilbert syndrome and Crigler-Najjar syndrome types I and type II (milder)

Gilbert syndrome	Crigler-Najjar syndrome type II	Crigler-Najjar syndrome type I
Defect in bilirubin UDP-GT	Partial activity of UDP-GT	Complete absence of UDP-GT
Mild elevation of indirect bilirubin < 5 mg/dL	Indirect bilirubin levels ranging from 7 to 20 mg/dL	Serum indirect bilirubin levels ranging from 20 to 50 mg/dL
Asymptomatic Jaundice	Asymptomatic Jaundice	Jaundice develops in the first few days of life kernicterus
Fasting, febrile illness, exercise can exacerbate jaundice	–	Hypotonia, deafness, oculomotor palsy, lethargy, and, ultimately, death
No treatment	No treatment	Phototherapy Liver transplantation

UDP-GT Uridine diphosphate-glucuronosyltransferase

Implications

- Essentially no life-altering or life-shortening complications
- May decrease metabolism of irinotecan (a chemotherapeutic agent)

Alagille Syndrome

- Autosomal dominant disorder with mutation in *JAG1* gene or the *NOTCH2* gene. Liver histology can be confused with biliary atresia

Clinical features

- Paucity of intrahepatic ducts *plus at least 3* of the following:
  - Cholestasis
  - Cardiac disease (often peripheral pulmonic stenosis)
  - Skeletal malformations ("butterfly" vertebrae)
  - Ocular anomalies (posterior embryotoxon)
  - Alagille's facies—prominent forehead, deep-set eyes, mild hypertelorism, pointed chin, bulbous nose tip (dysmorphologists correctly identified Alagille's facies 79% of the time—casting doubt on specificity)

Outcomes

- Severity of disease varies from life-threatening to asymptomatic
- About half will require liver transplant
- Complex heart disease and vascular anomalies account for further complications and mortality
- About a 75% 10-year survival

Hepatitis A Virus (HAV)

Background and epidemiology

- HAV is the most common cause of viral hepatitis worldwide
- No known animal reservoir
- Mode of transmission is fecal-oral route
- Risk factors include international travel to areas with poor hygiene, personal contacts, and foodborne outbreaks
- Incubation period is 15–50 days
- *Highest period of communicability* is 1 week before and after the onset of symptoms
- CD8 + T cells are responsible for the destruction of infected liver cells

Clinical presentation

- In children younger than 5 years may be asymptomatic or with just few symptoms
- Older children and adults may develop symptoms of acute infection which may last 2 weeks to several months
- Symptoms include malaise, anorexia, fever, nausea, vomiting, and eventually jaundice
- Most cases generally resolve without sequelae within a few weeks

Diagnosis

- *Anti-hepatitis A virus immunoglobulin M* (IgM) in a single serum sample is a good test for current or recent infection (< 6 months)

Prevention

- HAV vaccine at 12 months and booster dose at least 6 months after the initial dose
- Prevention of HAV infection can be promoted by enforcing good hygiene in child care centers, with conscientious hand washing after changing diapers and before handling food
- If traveling is imminent to endemic areas (< 2 weeks) or the patient is immunocompromised, immunoglobulin (IG) can be administered simultaneously with vaccine
- One dose of vaccine given at least 2 weeks before departure is sufficient for travelers to endemic areas. Give booster after return 6 months after first dose
- Postexposure prophylaxis:
  - Administer HAV vaccine ASAP and within 2 weeks of exposure
  - If cannot be vaccinated or immunocompromised, give IVIG ASAP and within 2 weeks of exposure

Treatment

- Supportive
- Avoid acetaminophen, it can exacerbate damage to liver cells

Prognosis

- HAV does not carry the risk of chronic infection
- Immunity after infection is lifelong

Hepatitis B Virus (HBV)

Background and epidemiology

- The infection has an incubation period of 3 months
- HBV is commonly transmitted via body fluids such as blood, semen, and vaginal secretions
- HBV does not spread by breastfeeding, kissing, hugging, sharing utensils
- Perinatal transmission occurs during delivery such that without prophylaxis, 70–90% of exposed infants are infected

Clinical presentation

- Acute self-limited hepatitis:
  - Increase in serum transaminases and resolution of the infection within 6 months
  - Nausea
  - Fever
  - Abdominal pain
  - Jaundice, fatigue
  - General malaise
  - Papular acrodermatitis (Gianotti-Crosti syndrome) that also manifests with EBV infection
- Fulminant hepatitis:
  - Acute hepatitis associated with a change in mental status due to hepatic encephalopathy
- Chronic hepatitis:
  - Younger age at time of infection determines if chronic infection develops. Risk for chronic infection is:
    - 90% of infants
    - 25–50% in children ages 1–5
    - 5–10% in older children and adolescents
  - Generally, is asymptomatic in childhood, having minimal or no effect on growth and development, with normal or minimally elevated serum ALT
  - Chronic infection increases risk for hepatocellular carcinoma

Hepatitis B viral serology and liver functions tests

Serologic marker for hepatitis B infection (Table 22.14) [4]

- *HBsAg* is the first serologic marker to appear and found in infected persons; its rise correlates with the acute symptoms
- *Anti-HBc* is the single *most valuable serologic* marker of acute HBV infection, because it appears as early as HBsAg and continues later in the course of the disease when HBsAg disappeared
- *Anti-HBs* marks serologic recovery and protection and marks vaccine immunity

Table 22.14 Serologic markers for hepatitis B infection

Marker	Definition	Detection	Meaning
HBsAg	Hepatitis B surface antigen	RIA/EIA	Active HBV infection
Anti-HBs	Antibody to HBsAg	RIA/EIA	Resolving or past infection Protective immunity Immunity from vaccination
HBeAg	Nucleocapsid derived Ag	RIA/EIA	Active infection, active viral replication
Anti-HBe	Antibody to HBeAg	RIA/EIA	Cessation of replication or replicating precore mutant
HBV-DNA	HBV viral DNA	PCR	Active infection, loss means resolution
HBcAg	Core antigen of HBV		Detected only in liver Sensitive indicator of replication
Anti-HBc-IgM	Antibody to HBcAg	RIA/EIA	Recent infection

Adapted from Wylie et al. [4], with permission
HBV hepatitis B virus, *RIA* radioimmunoassay, *EIA* enzyme immunoassay

- *Both Anti HBs and Anti HBc* are detected in a person with resolved infection
- *HBeAg* is present in person with active acute or chronic infection and marks infectivity
- *Anti-HBe* marks improvement and is the goal of therapy in chronically infected patients
- *Remember*: Alanine transaminase (AST) and aspartate aminotransferase (ALT) can be derived from muscle; you should verify that serum creatine kinase and aldolase values are within the normal range before assuming that the elevated serum AST and ALT values are hepatic in origin
- Tests reflecting cholestasis
  - High-serum concentrations of gamma-glutamyltransferase (GGT)
  - High-serum alkaline phosphatase
  - High conjugated bilirubin
- Test reflecting liver failure
  - High prothrombin time, despite administration of vitamin K
  - *Low-serum albumin* concentrations are the most useful indicators of impaired synthetic liver function
- HBV perinatal infection
  - Nearly all perinatally acquired HBV infection are asymptomatic
  - Maternal screening of all pregnant women for HBV is now standard
  - Prophylaxis for all newborns of HBV-positive women in the first 12 h after birth:
    - Combination of passive (hepatitis B IgG) and active immunization (first dose of the vaccine) followed by the complete HBV vaccine schedule
  - Maternal anti-hepatitis antibody can persist in infant for up to 18 months, which complicates testing
  - Breastfeeding does not increase transmission risk

Treatment

- Treatment is mostly supportive, but FDA-approved therapies exist to prevent progression to cirrhosis, liver failure, and hepatocellular carcinoma
- Interferon therapy is approved, but treatment is long, filled with complications, and does not always work
- Nucleotide analogue tenofovir, approved for children 12 years and older, provides long-term viral suppression. Cure rates not known.
  - Interferon-alpha (Interferon-alpha2b, pegylated interferon alpha-2a)
  - Nucleoside analogs (entecavir, lamivudine, and telbivudine)
  - Nucleotide analogs (tenofovir and adefovir)

Vaccination

- Passive (hepatitis B immunoglobulin [HBIG]) and active (HBsAg) immunization decrease perinatal transmission

- Universal active immunization (three-dose regimen) recommended by World Health Organization—177 countries have followed recommendations
- Vaccination programs have decreased the prevalence of HBV disease and hepatocellular carcinoma

Hepatitis C Virus (HCV)

- RNA (ribonucleic acid) virus of the *Flaviviridae* family—mutates rapidly leading to many genotypes and subtypes with geographic differences in distribution. Also complicates the task of developing a vaccine
- Infection is common in adults—less common in children

Transmission

- Requires "blood to blood." Divide into "percutaneous" and "non-percutaneous"
  - Blood and blood products no longer a source of infection
  - Most common mode of transmission in children is perinatal
  - Second most common is associated with illegal drug use. Tattoos have been suspected but no conclusive answer
  - Perinatal transmission occurs in approximately 5% of HCV-positive pregnancies. 20% of these infants clear the infection spontaneously

Diagnosis

- *HCV infection* is investigated by measuring anti-HCV antibody and is confirmed by the detection of serum HCV RNA by PCR. At least 2 positive tests are needed to diagnosis HCV infection
- *Screening of infants* born to HCV-infected mothers:
  - Measure serum anti-HCV antibody *at 18 months of age* due to persistence of maternal antibodies
  - Anti-HCV antibody detection 97% sensitive and 99% specific but not useful in infants of HCV-positive mothers until *18 months* of age
  - May not pick up early infection
- The HCV RNA by polymerase chain reaction (PCR) test can be either qualitative (used for diagnosis) or quantitative (used to monitor disease activity). "Not detected" does not mean that there is no virus in the sample
- Know that children with chronic hepatitis C infection should undergo periodic screening tests for hepatic complications and the treatment regimens are available

Symptoms and outcomes

- Acute HCV infection in childhood and adolescence is relative asymptomatic
- There are rare examples of "rapid progression," reason unknown
- There have been cases of spontaneous clearance of virus up to age 11 years
- It is likely that liver damage and disease will progress with age. HCV is the most common reason for liver transplant in the USA

Treatment

- Direct acting antivirals (DAA) have been approved for children 12 and over
- DAAs are 100% effective, relatively complication-free
- Delay treatment until a DAA regimen can be implemented. Treatments are expensive and insurers have resisted paying for the treatment. But cost benefit is in favor of treatment
- Therapies are approved for adults - changes a likely as new drugs become available
- Genotypes 1a and 1b:
  - Ledipasvir and sofosbuvir
  - Ombitasvir, dasabuvir, and paritaprevir, with or without ribavirin
  - Grazoprevir, elbasvir

- Genotype 2:
  - Sofosbuvir plus ribavirin or daclatasvir
- Treatment for 12–24 weeks

Autoimmune Hepatitis (AIH)

- Unknown etiology—plasma cell and monocyte infiltrate portal tracts
- Two types—both have female predominance
  - Type I (classic AIH) characterized by the presence of antinuclear antibody (ANA), antismooth-muscle antibody (ASMA), anti-actin, anti-asialoglycoprotein receptor
  - Type II (anti-LKM-1 AIH) anti-liver-kidney microsome antibodies—occurs at a younger age and is more resistant to treatment—more likely to have extrahepatic autoimmune phenomenon (thyroiditis, ulcerative colitis, etc.)

Presentation and diagnosis

- Symptoms range from minimal fatigue, jaundice to severe jaundice, dark urine, elevated aminotransferases, and coagulopathy
- Needs to be distinguished from other causes of hepatitis—hepatitis A virus, HBV, HCV, Wilson disease
- Liver biopsy revealing mononuclear and plasma cell infiltration of the portal tracts is helpful

Treatment and outcome

- Responds to immunosuppression
- Induction of remission—oral prednisone until normalization of aminotransferases—can be prolonged time (6–12 months)
- Maintenance of remission—azathioprine or 6-mercaptopurine
- Pulse with steroids for relapses
- Immunosuppression can be discontinued after at least 3 years of treatment, 1 year of normal aminotransferases, and normal or near-normal biopsy
- Liver transplant in about 8%—frequent recurrence in transplanted liver—mortality about 5%

Hepatomegaly

Background

- Hepatomegaly more than 3.5 cm below the right costal margin in newborn
- Hepatomegaly more than 2 cm below the right costal margin in children

Causes of liver diseases in children and adolescents

- Hepatitis
  - Viral
  - Autoimmune
  - Toxic
  - Drug related
- Wilson disease
- Budd-Chiari syndrome (hepatic vein obstruction)
- Fatty liver disease
- Congestive heart failure
- Storage liver disease
  - Fat
  - Nonalcoholic steatohepatitis (NASH)
  - Rey syndrome
  - Glycogenesis
  - Mucopolysaccharidosis

Evaluation of hepatic dysfunction (initial evaluation)

- CBC
- Reticulocyte count
- Comprehensive metabolic panel
- Fractionated bilirubin
- ESR
- Gamma-glutamyl transpeptidase
- PT

Evaluation for the etiology of liver dysfunction

- Hepatitis serologies A, B, and C
- Alpha-1-antitrypsin
- Alpha-fetoprotein
- Serum ceruloplasmin
- Antinuclear antibodies
- Antismooth muscle antibodies
- Anti-liver/kidney microsomal antibodies
- Sweat chloride
- Serum lipid profile

Portal Hypertension

Background

- Elevation of portal pressure > 10–12 mmHg
- Major cause of morbidity and mortality in children with liver disease
- In children, extrahepatic obstruction due to portal vein thrombosis is the most common cause
- Cavernous transformation (extensive collateral of small blood vessels from paracholedochal and epicholedochal venous system)
- In children with biliary atresia, CF, and other liver diseases, the incidence of intrahepatic obstruction causing portal hypertension is increasing as they survive longer

Clinical presentation

- Bleeding from esophageal varices is the most common presentation
- Cholestasis and liver dysfunction with elevated serum bilirubin and transaminases may occur in portal vein obstruction

Diagnosis

- Ultrasound, CT, or MRI

Management

- Endoscopic treatment of esophageal varices and liver transplantation

PEARLS AND PITFALLS

- Listen to your patient and the family of the patient. They know better than you what is going on. Don't be judgmental.
- Unwitnessed foreign bodies within the airway have the potential to masquerade as more common diseases such as croup and bronchiolitis/asthma.
- Esophageal foreign bodies have the potential to cause significant airway compromise.
- Impaction is often to underlying pathology such as eosinophilic esophagitis, GERD, and known prior strictures.
- Always rule out Wilson disease in any teenager with hepatitis. It is treatable but serious if it is missed.
- Treat constipation vigorously. The "go slow" approach usually does not work.
- Track growth, weight gain, and development. These are the clues that something may be wrong.

References

1. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150(6):1456–68.e2.
2. Nelson R, Sreedharan R, Liacouras CA. Digestive system. In: Kliegman RM, Stanton BF, Schor NF, St. Geme III JW, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier Saunders; 2011. p. 1242.
3. Kramer RE, Lerner DG, Lin T, Manfredi M, Shah M, Stephen TC, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Endoscopy Committee, et al. Management of ingested foreign bodies in children: a clinical report of the NASPGHAN endoscopy committee. J Pediatr Gastroenterol Nutr. 2015;60(4):562–74.

4. Wylie R, Hyams JS, Kay M, editors. Pediatric gastrointestinal and liver disease. 5th ed. Philadelphia: Elsevier; 2016.

Suggested Reading

Green SS. Ingested and aspirated foreign bodies. Pediatr Rev. 2015;36(10):430–6. quiz 437

Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005;40(1):1–19.

Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150(6):1456–68.e2.

Kleinman RE, Goulet O-J, Mieli-Vergani G, Sanderson IR, Sherman PM, Shneider BL, editors. Walker's pediatric gastrointestinal disease. 6th ed. Raleigh: People's Medical Publishing House–USA; 2018.

Sierra D, Wood M, Kolli S, Felipez LM. Pediatric gastritis, gastropathy, and peptic ulcer disease. Pediatr Rev. 2018;39(11):542–9.

Suchy FJ, Sokol RJ, Balistreri WF, editors. Liver disease in children. 4th ed. Cambridge, UK: Cambridge University Press; 2014.

Wylie R, Hyams JS, Kay M, editors. Pediatric gastrointestinal and liver disease. 5th ed. Philadelphia: Elsevier; 2016.

Nephrology

23

Beatrice Goilav

GENERAL

Normal Renal Function

- Glomerular filtration increases progressively from day 1 after birth and continues to increase with growth until the second year of life.
- If corrected for surface area, the glomerular filtration rate (GFR) reaches adult values of 120 cc/min/1.73 m^2 by 2 years of age.

Creatinine Level

- Serum creatinine may be elevated in the first 10 days of life, reflecting the maternal creatinine.
- Infant: 0.2–0.4 mg/dL.
- Child: 0.3–0.7 mg/dL.
- Adolescent: 0.5–1.0 mg/dL.
- Adult male: 0.9–1.3 mg/dL. For adult males, higher values correspond to the higher muscle mass compared to females.
- Adult female: 0.6–1.1 mg/dL.

Proteinuria

Definition

- Dipstick 1 + or 30 mg/dL is considered proteinuria.

Dipstick

- Negative.
- Trace means 10–20 mg/dl.
- 1 + means 30 mg/dl.
- 2 + means 100 mg/dl.
- 3 + means 300 mg/dl.
- 4 + means 1000–1500 mg/dl.

Consider False Positive

- Too concentrated urine, e.g., specific gravity (SG) > 1.015 and protein < 2 +.
- Consider false negative if SG < 1.005 and protein negative.

Diagnosis

- First morning sample immediately in the morning (important to instruct the child to empty the bladder before going to sleep the night before the test in the morning and to minimize upright position and walking).
- Divide urine protein/creatinine ratio (UPr/UCr), if ≤ 0.2 is normal in child > 2 years of age.
- If dipstick > 1 + or UPr/UCr > 0.2 on repeat urine morning sample, the patient should be referred to a nephrologist for evaluation of a renal disease.

B. Goilav (✉)
Pediatric Nephrology, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA
e-mail: bgoilav@montefiore.org

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_23

- Dipstick 3 + or greater suggests nephrotic-range proteinuria.
- On 24 h urine collections, protein < 4 mg/m^2/h is normal, and nephrotic-range proteinuria is greater than 40 mg/m^2/h.

Orthostatic Proteinuria

- Significant proteinuria in upright position and resolved in supine position
- Presence of proteinuria with UPr/UCr greater than 0.2 on random urine specimen but less than 0.2 on first morning specimen
- Benign condition, no further workup or treatment necessary

Transient Proteinuria

- Dipstick is > 1 + with a subsequent negative test.
- Common causes: exercise, fever, intercurrent illness, and stress.

Persistent Proteinuria

- Persistent proteinuria is the signal indicator of renal disease.
- Positive first voided morning specimen > 1 + protein on dipstick or UPr/UCr > 0.2—repeat with 2-week interval and rule out intercurrent illnesses.

Hematuria

Definition

- Presence of five or more red blood cells (RBCs) per high-power (400×) field in 3 consecutive fresh, centrifuged specimens obtained over the span of several weeks.
- Microscopic hematuria = urine grossly appears normal; gross hematuria = blood is visible to the naked eye.
- Confirmation of hematuria is critical, i.e., presence of RBCs in urine sediment.

Causes of False-Positive Urine Dipstick for Hematuria

- Myoglobinuria or hemoglobinuria, negative for RBCs on microscopic evaluation

Causes of Discolored Urine with Negative Urine Dipstick and Urine Microscopic Examination

- Medications, e.g., sulfonamides, nitrofurantoin, and salicylates.
- Food coloring, beets, and blackberries.
- In newborns, a red or pink discoloration in the diaper can be seen when urate crystals precipitate from the urine.

Clinical Approach to a Child with Gross Hematuria

- Confirm the diagnosis by microscopy.

Glomerular Hematuria

- Discolored urine (tea or cola colored), RBC casts, and dysmorphic RBC morphology

Causes

- Postinfectious glomerulonephritis—2 weeks after infection
- Lupus nephritis (LN)—malar rash, joint pain, anemia
- Alport disease—young men with sensorineural hearing loss and ocular abnormalities
- Immunoglobulin A (IgA) nephropathy—gross hematuria with upper respiratory tract infections or acute gastroenteritis (stimulation of IgA production)
- Membranoproliferative glomerulonephritis (MPGN)—intermittent gross hematuria, persistent C3 hypocomplementemia (also triggered by infections)
- Henoch-Schönlein purpura
- Hemolytic uremic syndrome (HUS)—dark urine, hypertension (HTN), oliguria, pallor, anemia, history of schistocytes on peripheral smear, thrombocytopenia, and history of bloody diarrhea

Laboratory

- Complete blood count (CBC), comprehensive metabolic panel (CMP), serum protein, cholesterol, C3, C4, antistreptolysin O (ASO),

anti-deoxyribonuclease (DNase) B, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies, throat culture, and UPr/UCr
- Hepatitis and HIV serologies

Non-glomerular Hematuria

- Normal RBC morphology.
- Presence of clots—urine may be brown due to clot in the bladder.
- May be accompanied by dysuria.

Causes
- Pyelonephritis
- Cystitis
- Hemoglobinopathy, such as sickle cell anemia (trait)
- Nephrocalcinosis
- Kidney stones (most common: calcium (Ca) oxalate stone)
- Hypercalciuria, caused by the following:
  - Idiopathic hypercalciuria caused by conditions resulting in hypercalcemia
  - Hyperparathyroidism
  - Vitamin D intoxications
  - Immobilization
  - Loop diuretics
  - Sarcoidosis
  - Cushing syndrome
  - Corticosteroid therapy
  - Williams syndrome
  - Bartter syndrome
  - Dent disease (X-linked recessive condition of the proximal tubule, characterized by tubular proteinuria, hypercalciuria, and chronic kidney disease)
- Hyperoxaluria (primary [genetic], enteric [malabsorption syndromes], or secondary [high consumption of oxalate-rich foods])
- Tumor
- Polycystic kidney disease (autosomal recessive—in infancy, in utero; autosomal dominant—adults in approximately the fifth decade)
- Trauma
- Meatal stenosis
- Coagulopathy
- Renal vein thrombosis (RVT)

Diagnostic Workup for Extraglomerular Causes
- Urine culture
- Urine calcium (Ca)/Cr ratio (normal is ≤ 0.2 in adults and children > 8 years old, but may be higher in younger children and infants)
- Renal/bladder ultrasound looking for debris or stone
- If for crystalluria, urolithiasis, or nephrocalcinosis: 24 h urine for Ca, creatinine, uric acid, oxalate, cysteine, and citrate levels

Idiopathic Hypercalciuria [1]

Etiology
- May be inherited as an autosomal dominant disorder
- May be caused by conditions resulting in hypercalcemia
- Hyperparathyroidism
- Vitamin D intoxication
- Immobilization
- Loop diuretics
- Sarcoidosis
- Cushing syndrome
- Corticosteroid therapy
- Williams syndrome
- Bartter syndrome
- Dent disease (X-linked nephrolithiasis)

Clinical Presentations
- Recurrent (+/− painful) gross hematuria
- Microscopic hematuria
- Diffuse abdominal pain

Table 23.1 Screening of high blood pressure (BP) and hypertension (HTN) in children and adolescents—American Academy of Pediatrics Clinical Practice Guideline 2017 (Flynn et al. [2])

Age	Normal BP (mmHg)	Elevated BP (mmHg)	Stage 1 HTN (mmHg)	Stage 2 HTN (mmHg)
1– < 13 years	< 90th percentile	≥ 90th percentile to < 95th percentile	≥ 95th percentile to < 95th percentile + 12	≥ 95th percentile + 12
		or	*or*	*or*
		120/80 to < 95th percentile	130/80 to 139/89	≥ 140/90
		(Whichever is lower)	*(Whichever is lower)*	*(Whichever is lower)*
≥ 13 years	< 120/< 80	120/< 80 to 129/< 80	130/80 to 139/89	≥ 140/90

Diagnosis

- 24-hour urine collection to measure urinary calcium concentration (has to be > 4 mg/kg/day).
- Spot urine Ca/Cr ratio > 0.2 suggests hypercalciuria in a child > 8 years old.
- Normal ratio may be as high as 0.8 in infants < 7 months.

Treatment

- If untreated, 15% develop nephrolithiasis.
- Hydrochlorothiazide 1–2 mg/kg/24 h as single morning dose, with dose titration until the 24 h urinary calcium concentration is < 4 mg/kg/day and clinical manifestations resolve.
- Sodium restriction leads to decreased sodium excretion and increased reabsorption of calcium from the urine (lowers calcium concentration in urine).

Hypertension [2]

Definition

- Pediatric HTN is sustained elevation of either the systolic or diastolic blood pressure (BP) at or above the 95th percentile of BP for a child's age, gender, and height percentile or equal or greater than 130/90 mmHg in children aged 13 years and older.
- The age- and height-specific BP percentiles were adjusted to children with normal BMIs and are therefore lower in the new guidelines. (Table 23.1) [2].
- Elevated BP ≥ 90th percentile:
  - The BP threshold has been changed for children aged 13 years and above to match the adult guidelines, which consider every BP > 120/80 mmHg as elevated.
  - Elevated BP has to be confirmed on 3 different occasions in the outpatient setting.
- There is no definition for the diagnosis of HTN in the inpatient setting; therefore, one should refrain from making this diagnosis while the patient is acutely ill.

Proper Technique When Measuring BP

- Correct cuff size to a child's bare arm:
  - Bladder width that is at least 40% of the child's midarm circumference.
  - Bladder length that encircles 80–100% of the midarm circumference.
  - After the child has been sitting for 5 min with both feet on the ground.
  - All BP elevations must be confirmed by manual auscultation

Causes of HTN (List Not All-Inclusive)

- Primary HTN is less common in the pediatric population, but on the rise due to increase in prevalence of obesity and metabolic syndrome among adolescents.
- Secondary causes become more common in younger patients and should always be ruled out, even if the patient is obese.
- Cardiac:
  - Coarctation of the aorta—BP discrepancy between arms and legs; leg BP equal to or lower than arm BP
- Renal:
  - Autosomal recessive polycystic kidney disease in newborns or autosomal domi-

nant polycystic kidney disease in older children and adolescents
  - Congenital renovascular abnormalities
  - Reflux nephropathy
  - Obstructive uropathy
  - Glomerulonephritides
  - HUS
  - Urinary tract infections
  - Chronic pyelonephritis
  - Renal cortical scars
  - Nephrotoxic medications
- Pulmonary:
  - Pulmonary HTN:
    - Bronchopulmonary dysplasia
    - Obstructive sleep apnea
- Neurological:
  - Increased intracranial pressure:
    - Hemorrhage
    - Tumor
  - Pain
- Neoplastic:
  - Wilms tumor
  - Neuroblastoma
- Endocrine:
  - Congenital adrenal hyperplasia
  - Hyperaldosteronism
  - Hyperthyroidism
- Prematurity and low birth weight:
  - Renal artery stenosis
  - Renal vein thrombosis
  - Multiple intrarenal thrombi after removal of the umbilical artery line
- Over-the-counter medications:
  - Decongestants/cold preparations
  - Herbal medications/supplements
- Other medications:
  - Corticosteroids
  - Calcineurin inhibitors (cyclosporine, tacrolimus)
  - Nonsteroidal anti-inflammatory medications
  - Caffeine
  - Oral contraceptive pills
  - Abrupt discontinuation of long-acting antihypertensive medications
  - β-Adrenergic agonists/theophylline
  - Erythropoietin
  - Stimulants for treatment of attention deficit disorder
- Syndromes:
  - Williams syndrome:
    - Supravalvular aortic stenosis
    - Midaortic syndrome
    - Renal artery stenosis
    - Renal anomalies
  - Neurofibromatosis:
    - Renal artery stenosis

Clinical Approach to the Child with HTN

- All children diagnosed with HTN should undergo an evaluation to investigate for secondary causes of HTN.
- Initial evaluation:
  - Focused history and physical examination
  - Urinalysis:
    - Hematuria, proteinuria, or pyuria
  - Blood urea nitrogen (BUN)/creatinine
  - CBC:
    - Anemia secondary to renal disease or chronic condition
  - Electrolytes:
    - Hyper or hyponatremia
    - Hyper or hypokalemia
    - Hypercalcemia
  - Evaluation for metabolic syndrome:
    - Lipid profile
    - Fasting blood glucose
  - Pregnancy test:
    - Preeclampsia
  - Renal and bladder ultrasound with Doppler:
    - Renal masses, e.g., Wilms tumor.
    - Renal scars.
    - Severe hydronephrosis due to ureteropelvic junction obstruction with impaired renal blood flow.
    - Doppler measures resistive indices of blood flow to the kidneys:
      - Any abnormality, especially together with size discrepancy between the kidneys, should prompt further imaging studies, e.g., magnetic resonance angiogram (MRA) or angiogram.

  - Echocardiography:
    - Structural heart disease, e.g., coarctation of the aorta
    - Left ventricular hypertrophy (LVH) secondary to prolonged HTN

Treatment

- If it's secondary HTN, treat underlying condition.
- If it's primary HTN:
- **Lifestyle modification**:
  - Weight loss if overweight.
  - Moderate-to-vigorous aerobic exercise.
  - Increase intake of fresh vegetables, fruits, and low-fat dairy foods.
  - Reduce carbohydrate, fat, and processed sugar intake.
  - Limit or avoid sugar-sweetened, caffeinated beverages.
  - Salt restriction.
  - Smoking cessation, if applicable.
- **Indication for antihypertensive medications**:
  - If it's symptomatic HTN, treat immediately (hypertensive emergency = evidence of end-organ damage—seizure, neurological deficits, myocardial infarction, acute kidney injury (AKI); hypertensive urgency = patient displaying symptoms associated with potential organ damage—headache, blurry vision, chest pain, palpitations, and dizziness).
  - Patients who have not experienced normalization of their BP with the above interventions after 2 months.
  - LVH can develop within 2 months of uncontrolled HTN.
  - Hypertensive retinopathy.
  - Diabetes mellitus (DM).
- **The pharmacologic agents**:
  - Calcium channel blocker.
  - Angiotensin-converting enzyme (ACE) inhibitors (first choice in diabetics, patients with LVH, and patients with known chronic, proteinuric kidney disease).
  - Angiotensin receptor blockers.
  - β-Blockers (not for patients with known asthma or diabetes mellitus [DM]).
  - Diuretics.
  - The lowest dose should be started, titrating to effect until the maximum recommended dose is achieved or until the patient experiences adverse effects.

PERSISTENT PROTEINURIA

Nephrotic Syndrome

Definition

- Proteinuria
- Hypoalbuminemia
- Edema
- Hypercholesterolemia

Background

- More common in males during childhood, equal gender distribution among adolescents.
- Caused in 85% by minimal change disease in children, but in adolescents, most commonly due to focal segmental glomerulosclerosis (FSGS).
- Minimal change disease refers to the pathological picture in which the glomerulus looks normal on light microscopy, but on electron microscopy there is effacement of the podocyte foot processes.
- Common between 2 and 6 years of age.
- In adolescents, nephrotic-range proteinuria in the absence of hypoalbuminemia may be due to FSGS.

Clinical Presentation

- Periorbital and facial edema in the morning, lower extremity edema later in the day.
- Slow progression—facial edema may be attributed to allergies at the beginning, causing some delay in initial diagnosis.
- Overtime, edema becomes generalized, accompanied by ascites and pleural effusions.

- Abdominal pain and diarrhea are common; HTN and hematuria are uncommon.
- HTN at presentation should raise the suspicion of an underlying nephritis with nephrotic-range proteinuria or of FSGS.

Diagnosis

- Urinalysis reveals 4 + proteinuria.
- Microscopic hematuria in 20% of cases.
- Spot urine protein /Cr ratio > 2.
- Urinary protein exceeds > 40 mg/m^2/h.
- Serum creatinine value is usually normal.
- Diminished renal perfusion due to decreased effective blood volume.
- Serum albumin < 2.5 g/dl.
- Serum cholesterol and triglycerides are elevated.
- C3 and C4 are normal, and serologies related to infections or autoimmune diseases are negative.
- Renal biopsy is not indicated unless < 1 year or > 10 years or in any case that is not responsive to steroids, i.e., the urine does not become protein-free within 6 weeks of treatment with high-dose steroids.

Treatment

- Treating the underlying cause:
  - First episode: prednisone 60 mg/m^2/day divided into two doses for 6 consecutive weeks, followed by 6 weeks of alternate-day therapy with 40 mg/m^2/day.
  - Relapse: prednisone 60 mg/m^2/day divided into two doses until the patient's urine is negative for protein on 3 consecutive days, followed by 4 weeks of alternate-day therapy with 40 mg/m^2/day.
  - Confirm negative purified protein derivative (PPD) or Quantiferon test before starting steroid therapy, if patient at high-risk for exposure to TB.
  - If the patient has multiple relapses a year, displays signs of steroid toxicity, or shows steroid dependence, a second-line agent is to be considered (steroid-sparing agent):
    - In younger children, oral cyclophosphamide with 2 mg/kg/day for 3 months should be the second-line agent of choice.
    - In older children and adolescents, calcineurin inhibitors can be beneficial, but relapses occur with discontinuation.
    - Mycophenolate mofetil, shows steroid-sparing effect, but dosing guidelines are not evidence based.
  - The use of steroid-sparing agents in steroid-resistant nephrotic syndrome can be considered, but there is no evidence suggesting significant outcome improvement.
- Supportive treatment:
  - Sodium restriction as long as the patient has nephrotic-range proteinuria.
  - Water restriction, if hyponatremia.
  - Diuretics.
  - Admit, if hypertensive.
  - If fluid restriction and parenteral diuretic are not effective, start intravenous (IV) 25% albumin 1 g/kg/dose (max. dose 50 g) q 8–12 h followed by furosemide 1–2 mg/kg/dose—monitor electrolytes.
  - If the patient is steroid resistant, antiproteinuric agents such as ACE inhibitors or angiotensin receptor blockers should be added to the therapy.

Complications

- Children with nephrotic syndrome are immunocompromised from the disease *per se*, because they lose IgG and important complement cofactors in the urine. Infections are the most common complication; and among those, spontaneous bacterial peritonitis (due to *Streptococcus pneumoniae*, *Escherichia coli*, and group B *Streptococc*i) needs to be suspected in a child who has nephrotic syndrome and abdominal pain. This an indication for admission even in the absence of fever. Ascitic fluid should be aspirated by a pediatric surgeon.

- Once they are in remission, all children with a diagnosis of nephrotic syndrome must receive polyvalent pneumococcal vaccine if not previously immunized.
- Varicella vaccine must be given for varicella-negative children.
- Thromboembolic events occur in 2–5% of cases due to urinary loss of antithrombin III and protein C and S.
- Newborns, infants, and small children with nephrotic syndrome may require thyroid hormone supplementation due to loss of thyroglobulin-binding protein in the urine.

Prognosis

- Children between the ages of 1 and 8 years are usually steroid responsive, defined as complete resolution of proteinuria within 4 weeks of daily high-dose steroids.
- 80 to 90% of patients will respond to steroid therapy within 2 weeks.
- If proteinuria continues after 6 weeks of therapy, a renal biopsy should be considered, because then the child, by definition, has steroid-resistant nephrotic syndrome, even if there is some reduction in proteinuria.
- Patients who relapse as soon as steroids are discontinued or tapered are considered steroid dependent.
- Only 30% of children with nephrotic syndrome have only one episode; relapses are common and usually occur 2 to 3 times per year—any intercurrent illness can trigger a relapse.
- Minimal change disease resolves in > 80% (child outgrows the disease), but children who presented at a younger age or who have frequent relapses may continue relapsing into adulthood.
- Steroid-sensitive nephrotic syndrome can convert to steroid resistant, at which point a renal biopsy is indicated.
- 30% of FSGS cases respond to steroids initially.
- FSGS can progress to end-stage renal disease (ESRD) and can recur in kidney transplants, particularly if the patient presented at young age and progressed rapidly to ESRD—exact causes of recurrence are not known (possible "circulating factor").

FSGS may be due to genetic mutations in genes related to podocyte architecture, but is not protective of recurrence after kidney transplantation, unless it is a known pathogenetic mutation as the underlying cause can still be due to a circulating factor of idiopathic FSGS.

Membranous Nephropathy (MN)

Background

- Most common cause of nephrotic syndrome in adults

Etiology

- Can be a separate idiopathic renal disease or associated with systemic lupus erythematosus (SLE) (WHO class V LN), drugs (penicillamine, gold), toxins, or infections (hepatitis B, malaria, syphilis). In adults, may be due to auto-antibodies to M-type phospholipase A2 receptor (PLA2r).

Clinical Presentation

- Generalized edema due to nephrotic-range proteinuria:
  - 80% have concurrent microscopic hematuria.
- Very rare in children—only 5% of nephrotic syndrome in childhood is due to MN.
- Presence of HTN at presentation is an adverse prognostic factor.

Diagnosis

- Renal biopsy—degree of sclerosis also allows prediction of prognosis.
- C3 is normal unless it is secondary to SLE.
- Diffuse thickening of the glomerular basement membrane (GBM) (due to IgG and C3 deposition) without proliferative changes.

Treatment
- Salt restriction and diuretics.
- ACE inhibition reduces proteinuria.
- If the patient is nephrotic, treat with steroids. If there's no response, escalate to cyclophosphamide and continue with tacrolimus or cyclosporine. It may recur after cessation of therapy

Prognosis
- 2% of children progress to ESRD.

Congenital Nephrotic Syndrome

Background
- Autosomal recessive.
- Genetic mutation in the nephrin gene (*NPHS1)*; nephrin is a protein that is part of the slit diaphragm.
- Also called "Finnish type" due to increased frequency in Finnish population (1:8200 live births).

Clinical Presentation
- Nephrotic syndrome presenting between birth and 3 months of age.
- Edema may appear as late as several weeks after birth, but urine shows nephrotic-range proteinuria at birth.
- > 80% born premature.
- Placenta enlarged, 25% of the baby's birth weight.
- Enlarged kidneys.
- No extrarenal malformations.
- Severe intractable edema.

Diagnosis
- Commercially available genetic testing offers definite diagnosis.
- Differential diagnosis: TORCH and HIV infections can cause secondary nephrotic syndrome and need to be ruled out first.

Complications, Prognosis, and Treatment
- Iron and vitamin D deficiency due to loss of binding proteins (total iron saturation may be falsely resulted as > 100% because transferrin is lost in urine).
- Hypothyroidism (significant and requires early treatment) due to loss of thyroid-binding globulin.
- Frequent infections due to loss of IgG.
- Clots due to loss of antithrombin III.
- Symptomatic treatment requires daily substitution of albumin (needs permanent IV placement early).
- Only bilateral nephrectomy is "curative," and the patient then has to be placed on peritoneal dialysis.

Infantile Nephrotic Syndrome

Background
- Group of nephrotic syndromes.
- 66% have underlying genetic mutation without extrarenal manifestations.

Clinical Presentation
- Steroid-resistant nephrotic syndrome presenting between 4 and 12 months of age.
- Nephrotic syndrome may present alone or as part of a syndrome.

Diagnosis
- Genetic testing offers definitive diagnosis.
- Most common genes affected: *PLCE1* (phospholipase C, epsilon 1), *CD2AP*, *ACTN4* (α-actinin 4), and *TRPC6* (transient receptor potential cation channel 6).
- Pierson syndrome is caused by *LAMB2* mutations and presents with ocular abnormalities (buphthalmos, microcoria).
- Wilms tumor, aniridia, genitourinary abnormalities, and intellectual disability (ID) formerly known as mental retardation (WAGR) syndrome is caused by *PAX6* mutation (important gene during development).

- Biopsy may be nonspecific and shows diffuse mesangial sclerosis.

Prognosis and Treatment
- Progression to ESRD at varying speeds
- No recurrence of disease in kidney transplant

Frasier Syndrome

Background
- Autosomal dominant, but mostly sporadic

Clinical Presentation
- Male pseudohermaphroditism with normal female external genitalia, but streak gonads
- 46, XY
- Onset of proteinuria at age 2–6 years
- Steroid-resistant nephrotic syndrome

Diagnosis
- Renal biopsy shows FSGS.

Prognosis and Treatment
- Increased susceptibility to gonadoblastoma, which requires removal of gonadal streaks
- No increased risk for Wilms tumor
- Slow progression to ESRD in adolescence or early childhood
- No recurrence of disease in kidney transplant

PERSISTENT HEMATURIA/ PROTEINURIA

Acute Postinfectious Glomerulonephritis

Etiology
- Most commonly caused by nephritogenic toxins of group A beta-*hemolytic streptococci*—usually presenting as streptococcal pharyngitis in cold weather and skin pyoderma in warm weather.
- It may also follow *S. pneumoniae*, gram-negative bacteria, bacterial endocarditis, or viral infections, especially influenza.

Clinical Presentation
- Most common in children between 5 and 15 years of age.
- 1 to 2 weeks after streptococcal pharyngitis or 3–6 weeks after streptococcal pyoderma.
- Nephritic presentation; various degrees of edema, HTN, and oliguria.
- Encephalopathy and heart failure may develop.
- Acute phase resolves in 6–8 weeks.
- Proteinuria and HTN should normalize within 4–6 weeks after onset.
- Microscopic hematuria may persist for up to 2 years, and the patient needs to be followed until its resolution.

Diagnosis
- Urinalysis: dysmorphic RBCs, RBC casts, proteinuria, polymorphonuclear leukocytes.
- Mild normochromic anemia.
- Low C3 ± normal; low C3 should return to normal within 6–8 weeks.
- Confirmation of diagnosis with positive throat culture.
- Positive ASO titer if related to streptococcal pharyngitis, but anti-DNase B level positive if related to skin nephritogenic strains (impetigo).
- Indication for renal biopsy: rapidly progressive glomerulonephritis (RPGN), C3 level not normalizing beyond 8 weeks after the acute illness, or persistent microscopic hematuria beyond 2 years' duration.

Management
- Early systemic antibiotics do not eliminate the risk of glomerulonephritis, but family members should be cultured and treated if positive.
- 10-day course of antibiotics is recommended to limit the spread of nephritogenic strains.
- Salt restriction.

- Diuretics.
- Calcium channel blockers and ACE inhibitors for the treatment of HTN.

Prognosis
- 90% recover completely.

Denys-Drash Syndrome

Background
- Mutation in the Wilms tumor 1 gene (*WT1*)

Clinical Presentation
- Male pseudohermaphroditism with ambiguous external genitalia.
- There are three possible clinical/karyotype presentations:
  - 46, XY with nephrotic syndrome, male pseudohermaphroditism with ambiguous external genitalia, and Wilms tumor
  - 46, XY with nephrotic syndrome and ambiguous external genitalia and/or internal genitalia
  - 46, XX with nephrotic syndrome and Wilms tumor
- Onset of proteinuria as early as at birth.
- Steroid-resistant nephrotic syndrome.

Diagnosis
- Renal biopsy shows diffused mesangial sclerosis.

Prognosis and Treatment
- Increased susceptibility to Wilms tumors
- Rapid progression to ESRD by age < 4 years (may even occur in newborn period)
- No recurrence of disease in kidney transplant

IgA Nephropathy (Berger Disease)

Background
- The most common chronic glomerular disease worldwide
- Peak incidence between 10 and 30 years of age, more common in Asians and Caucasians

Clinical Presentation
- Recurrent episodes of gross hematuria, usually associated with concurrent upper respiratory infection (URI) or acute gastroenteritis.
- Differential diagnosis: *Postinfectious glomerulonephritis usually occurs 1–2 weeks after infection*.
- May also present as persistent microscopic hematuria.
- Proteinuria is usually less than 1000 mg/24 h.
- Rare: nephritic/nephrotic manifestation, facial edema, mild-to-moderate HTN, elevated creatinine and BUN level (azotemia).
- Negative serologies for viral infections or autoimmune diseases, including normal complement levels.
- Serum IgA level has no diagnostic value.
- Diagnosis made by renal biopsy—indications for biopsy: persistent proteinuria or microscopic hematuria, elevated serum creatinine.
- Most children do not have progressive kidney disease until adulthood, 15–20 years after onset of the disease.
- Long-term follow-up is very important.

Poor Prognostic Factors
- Persistent HTN
- Abnormal renal function
- Persistent nephrotic-range proteinuria
- Worst prognosis—renal biopsy shows diffused mesangial proliferation, extensive glomerular crescent formation (proliferation of the Bowman's capsule epithelium), glomerulosclerosis, tubulointerstitial changes such as atrophy and fibrosis

Treatment
- BP control.
- Alternate day of corticosteroids if the patient presents with overt nephritic syndrome with nephrotic-range proteinuria.
- ACE inhibitors are effective in reducing proteinuria, a combination of ACE inhibitors and angiotensin receptor blockers (caution: need to check renal function frequently due to synergistic reduction in GFR).

- Fish oil contains anti-inflammatory omega-3 fatty acids and was thought to protect from progression, but not evidence based.
- Tonsillectomy not proven to reduce frequency of hematuria and renal disease progression.

Alport Syndrome

Background

- 85% of cases are X-linked recessive—young men, mutation in the *COL4A5* gene.
- In the past, carriers of the genetic mutation (i.e., the mothers of the male patients) were believed to maintain normal renal function throughout life, but now there is evidence that they also progress to ESRD. Hence, carriers should be followed by a nephrologist as well.

Clinical Presentation

- Single or recurrent gross hematuria may occur with URI (mostly in toddlers, young children), but most commonly persistent microscopic hematuria (more than 2 years' duration).
- Progressive proteinuria is common > 1 g/24 h in the second decade of life.
- Extrarenal manifestations in X-linked recessive form.
- Sensorineural hearing loss begins with high-frequency range deficit.
- Ocular abnormalities: 30–40% of patients, anterior lenticonus (extrusion of the central portion of the lens into the anterior chamber).

Pathogenesis

- Defect in collagen type IV, which is present in the kidney, ear, and ocular lens
- Most commonly X-linked, but autosomal recessive (mutation in the *COL4A3* or *COL4A4* gene) and dominant (mutation in the *COL4A3* or *COL4A4* gene) forms described as well—female gender does not exclude diagnosis of Alport syndrome

Diagnosis

- Careful family history
- Screening of first-degree female relatives (carriers)
- Audiogram, ophthalmologic examination (critical)
- Absence of GBM staining for alpha-3, and alpha-4 of type IV collagen in male hemizygotes
- Abnormal GBM architecture (basket weaving)

Treatment and Prognosis

- Risk of progression to ESRD is highest in males affected by X-linked mode of inheritance and occurs in 75% before age 30 years.
- Treatment is supportive and consists of control of proteinuria.
- Patients do well after kidney transplantation but may develop anti-GBM disease (antibodies directed against normal GBM in the transplanted kidney) in ~15% of cases.

Nail-Patella Syndrome

Background

- Autosomal dominant
- Localized to chromosome 9, *LMX1B* gene

Clinical Presentation

- Hypoplasia or absence of the patella
- Dystrophic nails
- Dysplasia of elbows and presence of iliac horns
- Renal involvement in 30–40%:
  - Microscopic hematuria
  - Mild proteinuria

Diagnosis

- Renal biopsy reveals normal light microscopy and immunofluorescence staining, but on electron microscopy, GBM looks "moth-eaten."

Treatment
- No specific therapy.
- 10% of cases progress to ESRD.

Membranoproliferative Glomerulonephritis (MPGN)

Background
- There are three types; type I is the most common.
- Presence of crescents on biopsy is associated with poor prognosis.

Clinical Presentation
- May present with asymptomatic proteinuria and hematuria, nephrotic syndrome, or an acute nephritic picture with gross hematuria.
- Recurrent gross hematuria with intercurrent illness.
- Renal function may be normal or diminished.
- HTN is common.
- C3 level is persistently decreased in 75% of cases (at the time of presentation, consider differential diagnosis: postinfectious GN).

Diagnosis
- Biopsy.
- Presentation.
- Generalized increase in mesangial cells and matrix; capillary walls appear thickened, containing regions of duplication and splitting (train tracks).
- Complement abnormalities (low C3).

Prognosis and Treatment
- 2 years of alternate-day steroids followed by repeat biopsy.
- ACE inhibition to control proteinuria.
- Some patients recover completely; 50% progress to ESRD.
- C3 level never normalizes.

Poor Prognostic Factor
- Type II histology (see Dense Deposit Disease)

Dense Deposit Disease (MPGN Type II)

Background
- Very rare
- Poorly understood pathogenesis
- More aggressive disease than other types of MPGN
- Possible abnormality in the complement counter-regulatory system (lack of inactivation of the complement system) due to genetic defect, consumption, or inactivating antibodies
- Now also referred to as C3 glomerulonephritis

Clinical Presentation
- Median age: 10 years old.
- Clinically indistinguishable from other types of MPGN.
- 50% present with nephrotic syndrome at onset.
- 30% have HTN at presentation.

Diagnosis
- Biopsy.
- Generalized increase in mesangial cells and matrix; capillary walls appear thickened, containing regions of duplication and splitting (train tracks).
- Complement abnormalities (low C3).

Prognosis and Treatment
- Poor prognosis
- No proven therapy; therefore, only supportive care
- If there's genetic defect in the complement system, plasmapheresis or plasma infusion
- Progression to ESRD in 10 years
- Recurrence of disease in kidney transplant. Also known as immunec-mplex disease. Similar to type I, but deposits are in subepithelial space.

Lupus Nephritis (LN)

Classification

- The International Society of Nephrology (ISN)/Renal Pathology Society (RPS) (formerly WHO) groups LN into 6 classes and distinguishes between acute (A) and chronic (C) lesions:
  I. Minimal disease
  II. Mild mesangial expansion and deposits
  III. Focal and segmental proliferation
  IV. Diffuse proliferation
  V. Membranous
  VI. Fibrosis
- Class IV considered most aggressive, requiring most intense treatment.
- The National Institutes of Health (NIH) scoring system informs about overall level of acuity and chronicity, including the tubulointerstitial compartment.

Clinical Presentation

- Typically, adolescent female with SLE:
  – 20% of SLE begins in childhood, and up to 60% of children with SLE have LN.
  – LN more aggressive in children and patients of black ancestry.
- Renal disease may precede serologies and extrarenal manifestations of SLE.
- Hematuria.
- Proteinuria.
- Reduced renal function (azotemia).
- HTN.
- Extrarenal manifestations: anemia, arthritis, malar rash, serositis, cerebritis, abnormal clotting/bleeding.

Diagnosis

- Serologies: positive ANA, anti-double-strand DNA (dsDNA) antibodies
- Low C3 and C4
- Autoantibodies against multiple self-antigens (ribonucleoproteins)
- Definitive diagnosis on renal biopsy—also needed to guide therapy

Treatment

- Immunosuppression—be aggressive; if biopsy shows class IV LN, pulse methylprednisolone and cyclophosphamide or mycophenolate mofetil
- Management of extrarenal manifestations
- Sunscreen to protect from ultraviolet-induced disease flare

Prognosis

- Presence of anemia, azotemia, and HTN at presentation is considered bad prognostic factor.
- A patient can change LN class, so it is not unusual for patients requiring multiple biopsies throughout the course of the disease—immunosuppression may have to be adjusted according to change in LN class.

Anti-glomerular Basement Disease and Goodpasture Syndrome

Background

- Antibody against specific epitopes of class IV collagen in the glomerular/alveolar basement membrane
- Isolated renal disease = anti-GBM disease
- Pulmonary involvement = Goodpasture syndrome

Clinical Presentation

- Rare in childhood.
- Hemoptysis associated with pulmonary hemorrhage can be life-threatening.
- Acute nephritic syndrome with hematuria, proteinuria, and HTN.
- Progressive renal dysfunction occurs within days to weeks.

Diagnosis

- Serum antibodies to GBM confirm the diagnosis.
- On kidney biopsy, linear deposition of IgG and C3 along the glomerular basement membrane, crescent formation possible.
- Serum C3 is normal.

Prognosis and Treatment

- Recovery of renal function improved with steroids, cyclophosphamide, and plasmapheresis

Familial Thin Basement Membrane Nephropathy

Background

- Isolated, nonprogressive hematuria with thinning of the glomerular basement membrane
- Autosomal dominant
- Differential diagnosis—Alport syndrome, GBM having irregular structure

Clinical Presentation

- Persistent microscopic hematuria.
- RBC casts.
- History may reveal another family member with the same condition.
- No family history of renal failure.
- Proteinuria in up to 30% of adults.

Diagnosis

- Biopsy reveals thin basement membrane on electron microscopy; light microscopy looks normal.
- Urinalysis and microscopy on affected first-degree family members.

Treatment and Prognosis

- No long-term complications, but if significant proteinuria, may require ACE inhibitor

TUBULAR ABNORMALITIES

Renal Tubular Acidosis (RTA)

Background

- Net acid excretion = amount of acid eliminated by the kidneys
- Components of acid elimination:
  - Bicarbonate reclamation
  - Ammonium excretion
  - Titratable acid excretion

Diagnosis

- Normal anion gap (AG) metabolic acidosis.
- AG Na−(Cl+ HCO3) if < 12 means absence of an AG.
- > 20 means no RTA.
- Urine pH distinguishes proximal from distal types.
- pH < 5.5 in the presence of acidosis suggests proximal RTA.
- pH > 6.0 in the presence of acidosis suggests distal RTA.
- Classically, patients present with failure to thrive and repeated episodes of vomiting and dehydration.
- Patients appear ill; if they look well, yet have acidosis, they don't have RTA!
- Workup:
  1. Determine AG.
  2. Measure urinary AG: (UNa + UK)–UCl, which is an indirect measurement of ammonium and determines ability of the kidneys to respond to metabolic acidosis:
     - Approach is based on the fact that unmeasured cations and anions are constant and that ammonium would be the primary cation other than sodium or potassium that would be excreted with chloride.
  3. Normal urine AG: zero or positive, with metabolic acidosis. Urine AG: negative (− 20 to − 50), with RTA. Impaired ammonium (excretion with chloride) results in $Na^+ + K^+ > Cl^-$, so urine AG becomes zero or positive:
     - Careful: Patients with diarrhea may have a non-AG metabolic acidosis due to gastrointestinal (GI) losses of bicarbonate (pancreatic fluid is bicarbonate rich), but have a negative urine AG.

- Approach to patient with hyperchloremic metabolic acidosis:
  1. Measure urinary AG.
  2. If urinary AG negative—acidosis due to GI losses of bicarbonate.
  3. If urinary AG positive—acidosis due to renal bicarbonate loss or impaired urinary acidification.

Proximal RTA Type II

- Threshold of bicarbonate reabsorption in the kidney is the main determinant of the serum bicarbonate concentration.
- Hallmark of type II RTA = lowered threshold for reabsorption of bicarbonate—threshold is usually 14–18 mEq/L and correlates with serum levels seen in these patients.
- Patients require large amounts of bicarbonate (> 6 mEq/kg/day).
- Treatment with bicarbonate will increase urinary pH due to increased excretion.
- Distal acid secretion is intact; hence, urine pH can decrease to < 5.
- Normal calcium excretion, no nephrocalcinosis.

Clinical Symptoms

- Polyuria
- Polydipsia
- Growth failure

Seen in the Following Conditions (Some Examples)

- Idiopathic Fanconi syndrome
- Cystinosis
- Acute tubular necrosis

Distal RTA Type I

- Hallmark = inability to lower urine pH maximally in the face of moderate-to-severe systemic acidosis.
- Urine pH is always > 6.0.
- Primary function of the distal nephron is acid-base homeostasis, which is to excrete acid generated from dietary intake.
- In the growing child, excretion of 1–3 mmol of acid per kg per day is needed.
- Most pathophysiological consequences of distal RTA are due to accumulation of acid—even if the proximal tubule normally reabsorbs bicarbonate, acid continues to accumulate, resulting in increased base deficit.
- Once bicarbonate buffers in the extracellular fluid are depleted, bones serve as buffer (hydroxyapatite is dissolved and hydroxyl ions serve to neutralize acid).
- Results in negative calcium balance and hypercalciuria with nephrocalcinosis and/or nephrolithiasis.
- Clinically distinct forms:
  - Congenital distal RTA:
    - Autosomal dominant
    - Autosomal recessive with hearing loss
    - Autosomal recessive without hearing loss
  - Acquired distal RTA:
    - Immunologic destruction of α-intercalated cells (Sjögren's syndrome, SLE, Graves disease, medications [amphotericin B, lithium, melphalan, foscarnet])

Type IV RTA

- Classic etiology: deficiency of or resistance to effects of aldosterone on renal tubular cells:
  - Term applied to all forms of hyperkalemic RTA, regardless of serum aldosterone concentration.
  - Aldosterone has direct effect on α-intercalated cells to promote proton secretion.
  - Acidosis in type IV RTA is not as severe as in other forms, but the main problem is hyperkalemia.
  - Hyperkalemia can be life-threatening.

- Most common inherited form of aldosterone deficiency is congenital adrenal hyperplasia.
- Aldosterone resistance is caused either by defects in the mineralocorticoid receptor or the epithelial sodium channel (ENaC)—both result in type IV RTA.
- Acquired forms of type IV RTA:
  - Most common—obstruction of the urinary tract (mechanisms not clear)

Bartter Syndrome

- Genetic defect (in this syndrome, multiple gene mutations can result in the same clinical picture)

Clinical Presentation

- History of polyhydramnios.
- Dysmorphic feature.
- Hypokalemic metabolic alkalosis.
- Hypercalciuria.
- High level of renin, aldosterone, and prostaglandin E.
- Normal or low BP.
- Low serum Mg.
- High level of urine Cl (patients with chronic vomiting have low urine Cl).

Treatment

- Prevention of dehydration.
- Correction of hypokalemia.
- Vitamin K supplements.
- Indomethacin can be effective by inhibiting prostaglandin E.

Gitelman Syndrome (Table 23.2)

- Hypokalemic metabolic alkalosis with hypocalciuria and hypomagnesemia

Clinical Presentation

- Recurrent muscle cramps and spasms
- Recurrent episodes of dehydration

Table 23.2 Difference between Bartter and Gitelman syndromes

Features	Bartter syndrome	Gitelman syndrome
Age	Prenatal, neonatal, and early infancy	Late childhood, adolescence, or adulthood
Location of defect	Ascending loop of Henle (mimic effects of loop diuretics)	Distal tubule (mimic effects of thiazides)
Clinical presentation	Polyuria, polydipsia, vomiting, constipation, salt craving, volume depletion	Severe muscle cramps, numbness, fatigue, recurrent episodes of dehydration
Blood pressure	Usually normal or low if dehydrated	Lower than general populations
Growth retardation	More common	Less common
Metabolic effect	Hypokalemic metabolic alkalosis	Hypokalemic metabolic alkalosis
Aldosterone and renin levels	High	Usually normal
Mg level	Low in 30%	Always low
Urine Ca	Normal or high (nephrocalcinosis)	Low
Urine PGE	High	Normal

PGE prostaglandin E

Treatment

- Correction of hypokalemia and hypomagnesemia
- Vitamin K and Mg supplementation

Cystinosis

Background

- First treatable lysosomal storage disease

Etiology

- Autosomal recessive mutation in the *CTNS* gene, which encodes cystinosin = protein that is responsible for transporting cystine out of lysosomes
- Formation of cystine crystals within lysosomes due to the failure to transport cystine out of the lysosomes

- Cystine = 2 molecules of cysteine joined by a disulfide bond
- Accumulation of cystine crystals in lysosomes seen in electron microscopy

Clinical Presentation

- Microscopic hematuria.
- Hypothyroidism.
- Photophobia in young children should raise suspicion—caused by crystal deposition in the cornea (detectable as early as 16 months).
- Low to normal IQ.
- Fanconi syndrome (proximal tubular defect) with metabolic acidosis, phosphaturia, proteinuria, and glucosuria.
- Craving salt (due to proximal tubular loss of sodium).

Diagnosis

- Multiple organs involved: cornea, conjunctiva, liver, spleen, kidneys, intestines, rectal mucosa, pancreas, testes, lymph nodes, bone marrow, macrophages, thyroid, skeletal muscle, and choroid plexus.
- Renal biopsy scan shows crystals in tubular cells—birefringent hexagonal or rectangular crystals, but clinical suspicion required first, because tissue has to be processed in a special way to preserve the crystals.
- Genetic testing offers definitive diagnosis.

Treatment

- Oral cysteamine treatment—difficult to maintain compliance, because medication that smells like rotten eggs and tastes terrible has to be taken four times a day; new formulation somewhat improved due to decreased frequency of administration
- Replacement of renal losses
- Thyroxine
- Recombinant human growth hormone administration
- Dialysis, kidney transplantation

Prognosis

- Without treatment, average age of death is 28.5 years; patients are short, thin, blind, and unable to move, progressively lose vision and ability to speak, and develop dementia.
- With treatment, normal life is expected, but they may still develop ESRD and require transplant—no recurrence of disease in transplanted kidney.

DIABETES INSIPIDUS (DI; SEE CHAPTER 12 ENDOCRINOLOGY FOR CENTRAL-TYPE DI)

Nephrogenic Diabetes Insipidus (NDI)

Background

- Definition: insensitivity of the distal nephron to the antidiuretic effects of the neurohypophysial hormone, arginine vasopressin

Etiology

- Primary form presents with three different inheritance patterns:
  - 90% X-linked recessive—vasopressin 2 receptor mutation
  - Autosomal recessive—aquaporin 2 mutation
  - Autosomal dominant—aquaporin 2 mutation
- Secondary form can be seen due to nephrotoxic drugs, chronic pyelonephritis, obstructive uropathy, sickle cell trait, etc.

Clinical Presentation

- Normal birth weight, no polyhydramnios.
- Urine concentrating defect present at birth, but breastfed infants thrive because breast milk has low renal osmolar load, decreasing risk of dehydration—diagnosis delayed.
- Constipation is a common symptom.
- Failure to thrive if remains unrecognized later, but bone age not delayed.

- May develop intellectual disability if untreated due to central nervous system calcifications after hemorrhage or necrosis.
- Many NDI patients are characterized as hyperactive, distractible, restless, and with short attention span.

Diagnosis
- History of inability to toilet train, frequent daytime accidents due to polyuria.
- Constant thirst—children would rather just drink than eat.
- First morning urine SG is < 1.015 (specimen obtained when the child wakes up in the morning).
- Hypernatremia with polyuria.
- Vasopressin test: vasopressin given intranasally and urine collected before and thereafter—urine osmolality remains < 200 mOsm/L.
- Plasma antidiuretic hormone levels normal or high.
- Renal and bladder ultrasound shows a large bladder with a trabeculated wall, hydroureters, and hydronephrosis.
- Voiding studies show large-capacity hypotonic bladder dysfunction.

Treatment
- Low solute diet—restrict sodium and protein
- Thiazide diuretics (less salt delivered to the distal nephron results in less water loss)
- Indomethacin (decreases GFR; hence, less sodium and water enter the nephron and can be lost)

CYSTIC KIDNEY DISEASES

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

- Infantile polycystic disease
- Mutation in the *PKHD1* gene encoding fibrocystin/polyductin

Incidence
- 1:20,000 live births

Clinical Presentation
- May be associated with oligohydramnios, pulmonary hypoplasia, respiratory distress, and spontaneous pneumothorax in the neonatal period.
- Potter facies and other components of the oligohydramnios complex, low-set ears, micrognathia, flattened nose, limb position defects, and growth deficiency.
- Bilateral flank mass during the neonatal period or early infancy.
- HTN is usually noted within the first few weeks of life.
- Urine output is usually not diminished.
- Transient hyponatremia often with AKI.
- Renal function is usually impaired but may initially be normal in 20–30% of cases.
- Ascending cholangitis.
- Hypersplenism related to portal HTN
- Progressive liver dysfunction

Diagnosis
- Renal ultrasound
- Hyperechogenic kidneys with poor corticomedullary differentiation
- Genetic testing
- Signs of hepatic fibrosis and/or portal HTN

Treatment
- Supportive

Prognosis
- 30% of patients die in the neonatal period from pulmonary hypoplasia.
- If the patient survives the neonatal period, excellent prognosis, but will require kidney +/– liver transplant.
- ESRD is seen in > 50% of cases.
- Dialysis and transplant become the standard of therapy.

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- 85% of patients have the *PKD1* gene encoding polycystin-1.
- 10 to 15% of patients have the *PKD2* gene encoding polycystin-2.
- While autosomal dominant mode of inheritance is the most common, spontaneous mutations are relatively frequent.

Incidence
- 1:500—most common monogenic disease!

Clinical Presentation
- ADPKD presents most commonly in adult life, but cysts can already be seen in utero (no impact on disease progression).
- Gross hematuria, bilateral flank masses, HTN, and urinary tract infection.
- ADPKD is a systemic disease and affects many organs, e.g., liver, pancreas, spleen, and ovaries; intracranial aneurysm appears in clusters within certain families.
- Mitral valve prolapse in 12% of cases.

Diagnosis
- Ultrasound, multiple bilateral macrocysts.
- Absence of family history does not preclude this diagnosis.
- Neonatal ADPKD and ARPKD may be indistinguishable.

Treatment
- Supportive.
- Only aggressive BP control has been proven to slow down disease progression
- Vasopressin-2 receptor inhibitors have shown to slow cyst growth, but no data is available on clinical outcome.

Prognosis
- Progression to ESRD in the fifth to sixth decade.
- Variability of disease within families with the same mutation (poor genotype-phenotype correlation).
- Women with *PKD2* mutation have the most favorable outcome, but still progress.

Nephronophthisis (NPH)

Background
- Most common type (25%) is juvenile nephronophthisis type I (mutation in the *NPHP1* gene).

Clinical Presentation
- Polyuria
- Polydipsia
- Anemia due to erythropoietin deficiency (out of proportion to degree of kidney failure)
- Failure to thrive
- Extrarenal features (Joubert syndrome):
  - Ocular motor apraxia (inability to perform the horizontal eye movement)
  - Retinitis pigmentosa
  - Coloboma of the eye
  - Cerebellar vermis aplasia with broad-based gait

Diagnosis
- Renal ultrasound shows loss of corticomedullary differentiation.
- Renal biopsy shows cystic dilation of medullary collecting tubules.

Prognosis
- ESRD occurs on average by age 13 years.

Laurence-Moon-Bardet-Biedl Syndrome

Background
- Autosomal recessive

Clinical Presentation
- Obesity
- Retinitis pigmentosa

- Hypogonadism
- Polydactyly
- Mental deficiency
- Cystic dysplasia of the kidneys

Treatment
- Supportive

Prognosis
- Progression to ESRD in late adolescence/early adulthood, requiring dialysis/kidney transplantation

Multicystic Dysplastic Kidney Disease

Background
- Not the same as polycystic kidney disease
- Not a monogenic disorder

Clinical Presentation
- Unilateral abdominal mass of the newborn.
- Bilateral multicystic dysplasia results in fetal demise.
- Effectively, the patient has only one functioning kidney.

Diagnosis
- Usually diagnosed on prenatal ultrasound.
- Need to do voiding cystourethrogram (VCUG) to rule out contralateral vesicoureteral reflux, which is commonly encountered (30–50%).
- Expectation is that the dysplastic kidney involutes over time.
- Stable size is acceptable, but if the dysplastic kidney grows, referral to urology for nephrectomy is indicated because the dysplastic kidney contains immature cells, which may undergo malignant transformation.

Treatment
- Serial renal ultrasounds to ensure involution or stable size of the dysplastic kidney
- Parental reassurance that the solitary functioning kidney is compatible with life

Prognosis
- Favorable, normal life expectancy.
- Patient needs to avoid contact sports to prevent injury and trauma to the solitary kidney.

RENAL FAILURE

Acute Kidney Injury (AKI) [3, 4]

Definition
- Sudden decline in renal function
- Increase in BUN and serum creatinine values
- +/− Hyperkalemia
- +/− Metabolic acidosis
- +/− HTN

Prerenal AKI

Definition
- *Hypoperfusion of the kidneys*

Causes (Most Common)
- Hypovolemia due to GI diseases
- Congenital heart disease
- Sepsis

Diagnosis
- Clinical history should reveal causes of volume depletion, such as the following:
  - Dehydration due to vomiting or gastroenteritis
  - Hemorrhage
  - Cardiac failure, or third-space fluid losses

Laboratory Findings
- Decreased urine output.
- Normal urinary sediments.
- Increased urine osmolality (> 400.0 mOsm in the older child and > 350.0 mOsm in the neonate).
- Low urinary sodium (< 10.0 mEq/L [10.0 mmol/L]).
- Low fractional excretion of sodium (< 1% in the older child and < 2.5% in the newborn).

- Increased BUN-to-creatinine ratio.
- Renal ultrasonography and renal scan findings should be normal.

Renal or Intrinsic Renal Failure

Definition

- Parenchymal injury due to vascular spasm, intravascular coagulation, and microvascular injury

The Most Common Causes

- Acute tubular necrosis, e.g., rhabdomyolysis secondary to dehydration
- Interstitial nephritis
- Hemolytic-uremic syndrome, e.g., history of diarrhea
- Glomerulonephritis, e.g., prosthetic valve causing endocarditis, streptococcal pharyngitis
- Nephrotoxic drugs, e.g., cystic fibrosis patient receiving aminoglycosides

Diagnosis

- Clinical history may reveal as follows:
  - Dehydration
  - Hypoxic-ischemic events
  - Toxic ingestion, nonsteroidal anti-inflammatory drugs (NSAIDs), or other nephrotoxic medication uses
  - Signs and symptoms of sepsis, gross hematuria, or trauma
- Decreased urine output can be described as oliguria (< 0.5 mL/kg per hour in a child or < 1 mL/kg per hour in an infant) or as anuria (no urine output).

Laboratory Finding

- RBC casts, granular casts, and RBCs—findings seen in glomerulonephritis.
- Studies should include streptococcal antibodies, hepatitis B and C panels, and complement studies.
- Streptococcal antibodies, including the anti-streptolysin O titer, anti-DNAse B titer, and group A antibody to *Streptococcus pyogenes* titer, should be obtained.
- A low complement C3 value may indicate an underlying diagnosis of SLE and membranoproliferative or poststreptococcal glomerulonephritis.
- For a patient with a high suspicion of glomerulonephritis, a biopsy may be warranted if the patient has, in addition to gross hematuria and proteinuria, rapidly rising BUN and creatinine serum values (= RPGN).
- Low urine osmolality (< 350.0 mOsm).
- Large muddy-brown granular casts.
- High urinary fractional excretion of sodium (> 2% in the older child and > 2.5–3% in the newborn); renal scans can be helpful in diagnosis because they can demonstrate whether the renal cortex is perfused or if there is cortical necrosis with little chance of a return of the renal function back to baseline, as well as the differential function between the left and the right kidney (e.g., one kidney has lost all of its function and the other is compensating).
- If necessary, a renal biopsy is the next step in determining the cause of intrinsic renal failure.

General Indicators for Renal Biopsy

- Rapidly increasing serum creatinine concentration
- To establish a diagnosis of acute vs. chronic glomerulonephritis
- Positive serology for systemic diseases such as MPGN or SLE and azotemia with urinary findings of hematuria or proteinuria
- To demonstrate an active lesion in which immunosuppressive medications, such as steroids, may help to reverse the disease process and recover renal function

Acute Interstitial Nephritis (AIN)

Background

- Tubulointerstitial compartment makes up 80% of the renal parenchyma.
- AIN is a cause of acute kidney injury (AKI) in childhood in up to 7% of cases.

Clinical Presentation

- Nonspecific
- Fatigue due to anemia (erythropoietin is produced in the interstitium)
- Usually unexpected finding of elevated serum BUN and creatinine
- 30 to 40% non-oliguric AKI
- Rarely systemic symptoms of allergic reaction (rash, joint pain), eosinophilia
- Urine sediment usually bland with some WBCs

Diagnosis

- History of medications:
  - Most commonly antibiotics, among which penicillins are most common
  - NSAIDs
  - Any other medications
- Infections
- Autoimmune diseases (SLE, tubulointerstitial nephritis with anterior uveitis [TINU])
- Urine eosinophils (identified by Wright stain) pathognomonic for allergic AIN, but absence does not exclude AIN
- Urinalysis usually quite bland, low SG due to concentrating defect (damage to the tubulointerstitium)
- Biopsy usually not indicated due to clinical constellation making other diagnoses unlikely

Prognosis and Treatment

- Generally, self-resolving, monophasic illness (i.e., once serum creatinine plateaus, it should improve later; if not, then look for other causes of AKI).
- Most patients have mild, vague symptoms, but if the patient feels ill or if serum creatinine rises at significant speed, obtain renal biopsy for exclusion of rapidly progressive GN, followed by short course of high-dose steroids (2 mg/kg, max. 60 mg/d, 5 days, then taper; or methylprednisolone 1 g daily for 3 days).
- Rarely, chronic interstitial nephritis occurs due to chronic drug use or chronic obstructive uropathy; progresses to ESRD.

Acute Tubular Necrosis (ATN)

Background

- Hypoperfusion of the kidneys leading to reversible damage of the proximal tubule

Etiology

- Hemorrhage
- Severe volume depletion
- Sepsis with decreased effective blood volume (third spacing)

Diagnosis

- Oligoanuria
- Elevated serum creatinine and BUN, muddy-brown casts in urine

Treatment

- Normal saline for volume replacement

Management of Renal Failure

- Maintaining renal perfusion
- Fluid and electrolyte balance
- BP control
- Adequate nutrition
- Adjust medications to decrease GFR
- Initiate renal replacement therapy (early dialysis)

Hemolytic Uremic Syndrome (HUS)

Etiology

- Typical HUS = diarrhea-associated HUS:
  - Shiga toxin-producing *E. Coli* 0157:H7 (causative agent in 80% or more in developing countries)
  - *S. pneumoniae*
- Atypical HUS = (genetic) abnormality of complement regulatory pathways:

  - Any organism can trigger the disease.
  - Usually in younger patients.
- Age:
  - More common in children 2–5 years of age

Clinical Presentation for Typical HUS

- Onset preceded by acute gastroenteritis or pneumonia
- Fever
- Vomiting
- Abdominal pain
- Watery diarrhea which then becomes bloody
- Dehydration
- Edema
- Petechiae
- Hepatosplenomegaly
- HTN, pallor, lethargy

Clinical Presentation for Atypical HUS

- Patient may be < 6 months.
- No GI symptoms.
- Insidious onset with lethargy, pallor, and feeding difficulties.
- Severe HTN.
- Possible family history.

Diagnosis

- Triad consisting of the following:
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
  - AKI
- Peripheral smear: schistocytes, burr cells, or helmet cells.
- Hemoglobin level in the 5–9 g/dl range.
- Leukocytosis may exceed 30,000 (associated with worse prognosis for renal recovery).
- Thrombocytopenia in 90% of cases.
- Elevated BUN/creatinine with oligoanuria.
- Microscopic hematuria and proteinuria.
- Prothrombin time (PT) and partial thromboplastin time (PTT) are usually normal.

Treatment

- Supportive.
- Meticulous attention to fluids and electrolytes, control of HTN, and early dialysis.
- Antibiotics are contraindicated for treatment of diarrhea if *E. coli* 0157 is suspected.
- Atypical HUS is caused by a defect in the complement regulatory system and requires blockade of the complement system with an antibody that binds to C5 (eculizumab), thereby inhibiting its activation.

Prognosis

- Disease is monophasic; once the patient recovers, no relapse should occur in typical HUS. Any deviation from this clinical course is suggestive of atypical HUS, and plasmapheresis should be initiated immediately pending genetic testing.
- Patients recovering from typical HUS require long-term follow-up because of complications such as HTN and chronic kidney disease.
- Patients with atypical HUS and confirmed genetic defect in the counter-regulatory complement system require treatment with an inhibitor of the C5 component, which is most likely lifelong. This treatment leads to inability of the patient to clear infections with encapsulated organisms; hence, prior vaccination is imperative.

MISCELLANEOUS

(Nocturnal) Enuresis [5]

Background

- 90 to 95% of children are nearly completely continent during the day, and 80–85% are continent during the night after the age of 6 years for girls and 8 years for boys.
- More common in boys (60%).
- Family history (50%).
- If one parent was enuretic, there's 44% a chance of enuresis in the child; and if both parents

were enuretic, 77%; age at resolution in parents can guide expectations of resolution in child.

Clinical Presentation

- Primary or secondary enuresis
- History of voiding dysfunction manifested as holding urine and often combined with constipation
- Diabetes mellitus and insipidus (urinalysis on the first morning urine sample is helpful—if SG is < 1.015, it is suspicious for DI; presence of glucose requires workup for DM).

Treatment

- Reassurance of parents.
- Exclude any type of voiding dysfunction during the daytime, as this may be the cause of the nocturnal enuresis (prolonged withholding of urine).
- Fluid restriction in the evening is moderately successful.
- Acute treatment should be avoided before the age of 6 years.
- Motivational therapy.
- Conditioning therapy (vibratory alarm) curative in 30–60%.
- Desmopressin:
  - Well tolerated and has very few reported adverse effects.
  - Severe hyponatremia associated with seizures and deaths has been reported and occurs only due to water intake after drug is taken at night.

Renal Vein Thrombosis (RVT)

Etiology

- Neonatal asphyxia, dehydration, shock or sepsis, congenital hypercoagulable states, infant born to a mother with DM

Clinical Presentation

- Sudden onset of gross hematuria and unilateral or bilateral flank masses.
- Also, patient may present with microscopic hematuria, flank pain, HTN, or oliguria.
- Bilateral RVT results in AKI.

Diagnosis

- Hematuria, flank masses in a patient with predisposing clinical factors.
- Ultrasound shows marked enlargement, and Doppler ultrasound will confirm diagnosis.

Treatment

- Supportive, hydration

Sickle Cell Nephropathy

Background

- Consequences related to sickling and anemia = "renal sickle cell crisis"

Clinical Presentation

- Hematuria and renal papillary necrosis:
  - Painless gross hematuria
  - More frequent with sickle cell trait
  - Occurs due to low oxygen tension in the renal papilla causing local sickling and thrombosis within the vasa recta of papilla, leading to progressive destruction of the papilla and secondary deposition of calcium—echogenic papillae on renal ultrasound
- Proteinuria with sickle cell glomerulopathy

Diagnosis

- Renal ultrasound
- History of sickle cell disease or trait
- Urinary concentrating defect = low urine SG in the setting of dehydration

Treatment

- Supportive
- ACE inhibitors in case of proteinuria

Prognosis

- Secondary to chronic anemia; patients with sickle cell disease may develop FSGS with progression to ESRD.

PEARLS AND PITFALLS

- Transient proteinuria in children is common, and attention should be paid to the concentration of the urine sample when interpreting it.
- A first morning urine sample should be obtained first before referral of the patient.
- It is important to distinguish between painful and painless gross hematuria.
- Painful hematuria is more likely to be lower tract than glomerular.
- Painless hematuria may be either glomerular or lower tract hematuria.
- Asymptomatic hematuria persisting for > 2 years warrants referral to a specialist for renal biopsy.
- Kidney stones in children under the age of 12 years warrant genetic workup.
- In 2017, the guidelines for the diagnosis of HTN in children have been changed, including changes in terminology, with "prehypertension" being replaced by "elevated BP"; new normative pediatric BP tables based on non-overweight and non-obese children; and a simplified classification in adolescents ≥ 13 years of age. The overall normal BP limits are now lower in children.
- A urinalysis that contains both protein and blood may be suggestive of nephritis, and further evaluation is warranted.
- Patients with nephritis may present with edema and nephrotic-range proteinuria, but they distinguish themselves from patients with nephrotic syndrome by displaying elevated BP and a rise in serum creatinine from baseline.
- Any child with edema and HTN presenting to the emergency department should be admitted for further workup and observation.
- Clinical and serological markers of lupus nephritis, such as proteinuria, hematuria, HTN, hypocomplementemia, and elevated anti-dsDNA antibody titers, do not correlate with class or severity of renal involvement in SLE.

Acknowledgment Dr. Goilav would like to thank Dr. Casimir Cohen for his invaluable advice in the writing of this chapter.

References and Suggested Reading

1. Bushinsky DA, Coe FS, Moe OW. Nephrolithiasis. In: Brenner BK, editor. Brenner & Rector's the kidney, vol. 2. 8th ed. Philadelphia: Saunders; 2008. p. 1299–349.
2. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, Subcommittee on Screening and Management of High Blood Pressure in Children, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3):e20171904.
3. Andreoli SP. Acute renal failure. Curr Opin Pediatr. 2002;14(2):183–8.
4. Goldstein SL. Pediatric acute kidney injury: it's time for real progress. Pediatr Nephrol. 2006;21(7):891–5.
5. Cooper CS. Voiding dysfunction. eMedicine Drugs Dis Pediatr: Surg. 2017. http://emedicine.medscape.com/article/1016198-overview. Accessed 24 Feb 2019.

Fluids and Electrolytes

24

Benjamin Steinman and Beatrice Goilav

GENERAL

Body Fluid Composition

- Total body water (TBW) is 75% of body weight in term infants
- TBW decreases to 60% of body weight until puberty, then males 60%, females 50% (due to increased adipose tissue)
- TBW is divided into extracellular fluid (ECF) and intracellular fluid (ICF):
  - ICF is 40% of body weight
  - ECF is 20% of body weight. ECF is divided into:
    - Interstitial fluid (15%) and plasma (5%) of body weight, respectively
- (**Tip: 60–40–20** to remember % TBW)
- Example: 20 kg child:
  - TBW = 12 L (60%)
  - ICF = 8 L (40%)
  - ECF = 4 L (20%):
    - Interstitial fluid = 3 L (15%), plasma = 1 L (5%)

Fluid Compartments

Osmolality

- ECF and ICF volumes are maintained due to osmotic equilibrium
- Normal plasma osmolality = 285–295 mOsm/kg. Typically, equivalent to ICF osmolality
- Calculated plasma osmolality = (Na × 2) + Glucose/18 + BUN/2.8
- Note: Urea typically an ineffective osmole except in very high concentrations, e.g., inborn errors of metabolism (IEM) and liver failure
- Calculated osmolality is typically equivalent to measured osmolality
- It is useful to obtain measured osmolality in suspected toxic alcohol ingestion (see **Metabolic Acidosis**)
  - Toxic alcohol ingestion causes increase in osmolar gap > 10 between measured and calculated osmolality
- Osmolality can be affected by hyperglycemia, hyperlipidemia, and hyperproteinemia (see **Hyponatremia**)

Osmotic equilibrium

- Osmotic equilibrium is maintained since cells are permeable to water
- Osmotic equilibrium is further regulated by antidiuretic hormone (ADH):
  - Elevated osmolality causes increased ADH secretion, which leads to increased water

B. Steinman
Department of Pediatrics, The Children's Hospital at SUNY Downstate, SUNY Downstate Medical Center, Brooklyn, NY, USA

B. Goilav (✉)
Pediatric Nephrology, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA
e-mail: bgoilav@montefiore.org

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_24

reabsorption to bring osmolality back to equilibrium
  - ADH is sensitive to osmolality changes of < 1%

Fluid Changes

- The gain or loss of fluid primarily affects ECF in early stages of dehydration
- Fluid changes can be isosmotic, hyperosmotic, or hypoosmotic (Table 24.1)

Isosmotic

- Expansion/contraction of isosmotic fluid to ECF will increase/decrease ECF volume without changes to ICF, e.g.,
  - Expansion: Normal saline infusion
  - Contraction: Secretory diarrhea

Hyperosmotic

- Hyperosmotic expansion will increase osmolality in ECF and will draw water into ECF, expanding ECF and decreasing ICF volume, e.g.:
  - Hypertonic saline, glucose infusion, diabetic ketoacidosis (DKA)

Table 24.1 Fluid compartment changes

Fluid changes	Changes to ECF volume	Changes to ICF volume	Changes to ECF osmolality	Changes to ICF osmolality
Volume expansion				
Hypoosmotic (SIADH, water intoxication)	Increase	Increase	Decrease	Decrease
Hyperosmotic	Increase	Decrease	Increase	Increase
Isosmotic	Increase	No change	No change	No change
Volume contraction				
Hypoosmotic	Decrease	Increase	Decrease	Decrease
Hyperosmotic	Decrease	Decrease	Increase	Increase
Isosmotic	Decrease	No change	No change	No change

ECF extracellular fluid (ECF), *ICF* intracellular fluid, *SIADH* syndrome of inappropriate antidiuretic hormone secretion

- Hyperosmotic contraction will increase osmolality in ECF and decrease volume of both compartments, e.g.:
  - Diabetes insipidus (DI) (dilute urine), excessive sweating

Hypoosmotic

- Hypoosmotic expansion will decrease osmolality in ECF and expand both compartments, e.g.:
  - Water intoxication, syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Hypoosmotic contraction will decrease osmolality in ECF, and water will be drawn into ICF, expanding ICF and decreasing ECF volume, e.g.:
  - Adrenal insufficiency (concentrated urine)
- Third spacing, i.e., changes in interstitial fluid/edema, e.g.:
  - Heart failure, protein-losing enteropathy, liver failure, nephrotic syndrome, and sepsis

SODIUM (NA)

Background

- Requirements: 2–4 mEq of Na^+/100 mL. May be slightly more in term newborn due to natriuresis after 2–3 days of life
- Na^+ is the primary ECF cation and the main determinant of osmolality
- Changes in serum sodium are typically affected by **water** gain or loss, not **sodium** gain or losses. This can be appreciated when determining the causes of hyper- and hyponatremia

Hypernatremia

Definition

- Serum $Na^+ > 150$ mEq/L

Causes

- Water deficit (e.g., decreased feeds, concentrated formula, premature infants, DI)
- Excessive sodium intake (e.g., excess formula, hypertonic saline, hyperaldosteronism)
- Combined sodium and water losses (e.g., diarrhea/vomiting with inadequate intake, phototherapy, burns, fever, diabetes mellitus, diuretics, obstructive uropathy)

Signs and symptoms

- Irritability, weakness, and lethargy. Infants may have a high-pitched cry and tachypnea. Skin will often have a doughy consistency
- Hypernatremic dehydration is initially well tolerated, since fluid shifts from the ICF to the ECF, which maintains intravascular volume. This causes delay in diagnosis; patients look well and the level of dehydration is underestimated
- Hypernatremia can also cause hyperglycemia and hypocalcemia
- Lab findings of prerenal azotemia include:
  - Fractional excretion of sodium (FeNa) < 1% and blood urea nitrogen creatinine (BUN/Cr) ratio > 20:1

Diagnosis (Fig. 24.1)

- Assess volume status
  - **Hypovolemia:** TBW loss > Na^+ loss
    - Renal (diuretics, renal disease)
    - Extrarenal (sweating, diarrhea, burns, phototherapy)
    - Urinary Na^+ will be > 20 mEq/L in renal losses
  - **Euvolemia:** Decrease in TBW, no increase in Na^+
    - Renal losses: DI, hypodipsia
    - Extrarenal: Insensible losses
    - Urinary osmolality will be < 290 mOsm/kg in DI.
  - **Hypervolemia:** Increased Na^+> increased TBW
    - Think salt gain; urinary Na^+ is increased.
      - Primary hyperaldosteronism, Cushing syndrome, hypertonic saline

Treatment (Tables. 24.2 and 24.3)

- Bolus with 0.9% normal saline (NS) if signs of vascular compromise are present
  - Maintenance fluids and electrolytes: See Maintenance Fluid Requirements
- Fluid deficit
  - The fluid deficit in a patient with hypernatremia is composed of two parts:
    - Free water deficit: The additional free water that the patient needs to correct his hypernatremia
      - Free water deficit = [(Serum Na^+/140) − 1] × 0.6 × weight (kg)
    - Solute water deficit: The remaining fluid deficit, which is lost from ECF and ICF with corresponding electrolyte deficits
      - Solute water deficit (aka solute fluid deficit or SFD [L]) = Total water deficit − free water deficit
- Electrolyte deficits
  - Solute Na^+ deficit = SFD (L) × proportion from ECF × 140 mEq/L or replace 8 mEq Na^+/100 mL water lost
  - Solute K^+ deficit = SFD (L) × proportion from ICF × 160 mEq/L or replace 6 mEq K^+/100 mL water lost
- Slowly correct the serum sodium and fluid deficit over 48 h.
- Free water deficit replaced over 48 h (see Complications below)
- Consider replacing free water deficit even more slowly for severe hypernatremia
- Do not correct > 12 mEq/24 h or 0.5 mEq/h
- Do not use Ringer's lactate solution, as it is hypotonic

Complications

- Cerebral hemorrhage occurs if hypernatremia is left untreated due to increased ECF osmolality, which causes fluid to shift from ICF

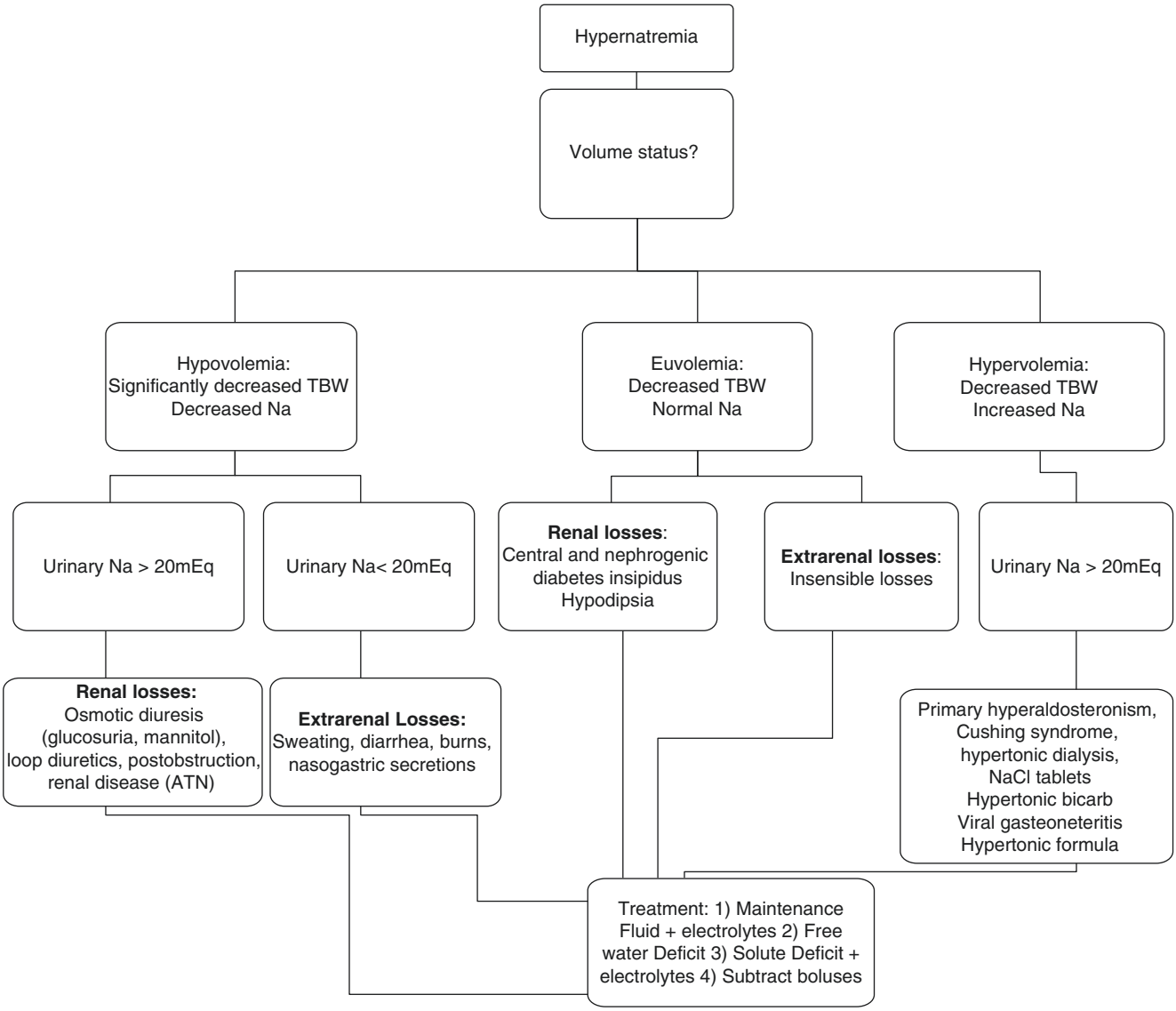


Fig. 24.1 Hypernatremia workup

Table 24.2 Calculation of intravenous rehydration in cases of hypernatremia

	Water requirements	Sodium requirements	Potassium requirements
Maintenance × 48 h	**Maintenance fluid requirements** × 2	3 mEq/100 mL	2 mEq/100 mL
Fluid deficit	1 mL: 1 g of weight lost	–	–
Free water deficit	$[(\text{Serum } Na^+ /140) - 1] \times 0.6 \times \text{weight (kg)}$	–	–
Solute deficit	Fluid deficit – free water deficit	8 mEq/100 mL	6 mEq/100 mL
Bolus	–	–	–
Total	–	–	–

and decreased brain volume. This can lead to tearing of bridging blood vessels

- Seizures can occur, but they are more common during correction
- Rapid correction can cause cerebral cellular swelling and seizures since idiogenic osmoles are produced in the ICF with long-standing hypernatremia. This will cause fluid to shift

Table 24.3 An example of how to calculate and how to order intravenous fluid (IVF) in cases of hypernatremic dehydration

A 20 kg child with Na^+ 160 and 10% dehydration who received 20 cc/kg 0.9% normal saline bolus × 1			
	Water requirements	Sodium requirements	Potassium requirements
Maintenance × 48 h	Maintenance fluid requirements × 2	3000 mL/100 mL = 30	3000 mL/100 mL = 30
	Weight of 20 kg = 3000 mL	30 × 3 mEq = 90 mEq/24 h	30 × 2 mEq = 60 mEq/24 h
		90 × 2 = 180 mEq/48 h	60 × 2 = 120 mEq/48 h
Fluid deficit	20 kg × 0.1 = 2 kg = 2000 mL	–	–
Free water deficit	160/140 = 1.14	–	–
	1.14 − 1 = 0.14		
	0.14 × [0.6 × 20] = 1680 mL		
Solute deficit	2000 –1680 mL = 320 mL	320/100 = 3.2	320/100 = 2.86
		3.2 × 8 = 25.6 mEq	3.2 × 6 = 19.2
Bolus	−400 mL	−61.6 mEq	–
Total	4600 mL	144 mEq	139.2 mEq

Fluid rate: 4600/48 h = 95 mL/h

to ICF during correction. Therefore, correct free water deficit over 48 h

Hyponatremia

Definition

- Na < 130 mEq/L
- If TBW loss is present, losses are entirely from ECF, and shift into ICF can cause overestimation of dehydration. However, patients may also be intravascularly depleted and require fluid resuscitation

Diagnosis (Fig. 24.2)

Etiology

- Diarrhea and diuretics are the most common causes

Check serum osmolality:

- **Isosmolar**, i.e., pseudohyponatremia: hyperlipidemia, hyperproteinemia
  - Total body sodium stores are normal
- **Hyperosmolar**, i.e., dilutional hyponatremia without symptoms of hyponatremia since it is the change in osmolality that produces symptoms, not sodium in and of itself
  - Normal osmolality:
    - Hypertriglyceridemia
    - Hypercholesterolemia
    - Intravenous immunoglobulin (IVIG)
  - Elevated osmolality
    - Hyperglycemia
    - Mannitol infusion
  - To correct for hyperglycemia: Add 1.6 Na^+ for every 100 mg/dL of glucose over 100 mg/dL
- **Hypo-osmolar: Assess volume status**
- Hypovolemic hyponatremia: Na^+ losses > water losses
  - **Extrarenal:** Hypotonic fluid or replacement (e.g., diluting formula) in diarrheal states (the most common cause), vomiting, and dehydration. ADH is also stimulated by volume loss, exacerbating hyponatremia. This form of dehydration is also seen in cystic fibrosis and hypoaldosteronism
  - **Renal:** Diuretics, ACE inhibitors, mineralocorticoid deficiency
  - Urine Na^+ > 20 mEq/L in renal losses
  - Third space losses are isosmotic, but ADH secretion can cause hyponatremia. Can be seen with diuretics
  - Urea is effective osmole in cases where it accumulates (renal failure, IEM). In such instances, patients can have normal osmo-

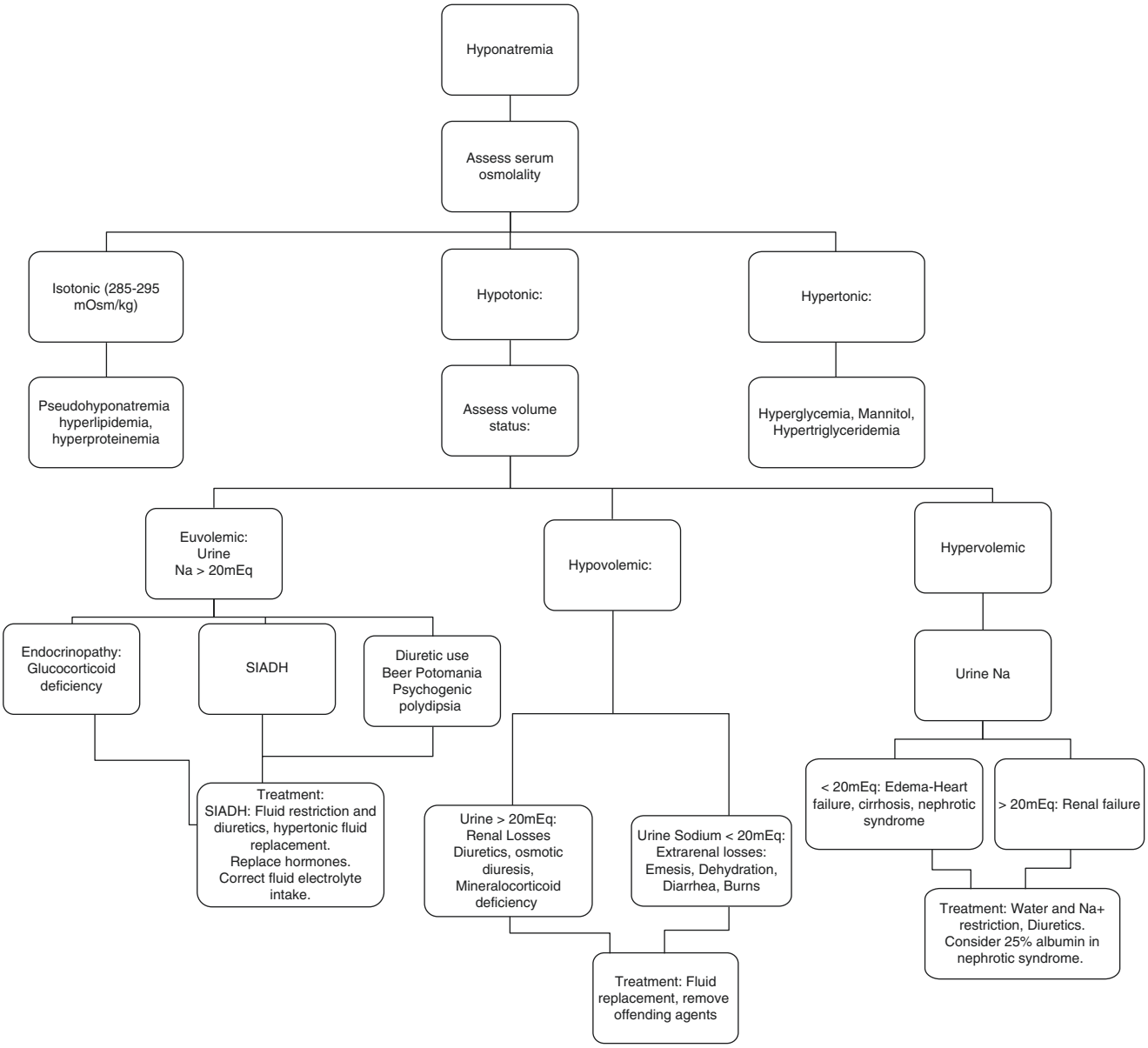


Fig. 24.2 Hyponatremia workup

lality and hyponatremia. Type 2 renal tubular acidosis (RTA) (proximal) has salt and bicarb wasting, along with other lab abnormalities (see RTA in Chap. 23)

- Hypervolemic hyponatremia: Decreased effective intravascular volume and ADH release causes increased water retention
  - Can be seen in congestive heart failure, renal failure, and nephrotic syndrome
  - Patients will be edematous, with possible ascites, and hypertensive
  - Low urine Na^+ is expected
- Euvolemic: Caused by fluid gain > sodium gain
  - Hypothyroidism, beer potomania, psychogenic polydipsia, ACTH deficiency
  - SIADH-retained water increases intravascular volume

Signs and symptoms

- True hyponatremia will be reflected in hypo-osmolality
- Hypo-osmolality in ECF allows for a fluid shift into ICF, which leads to brain cellular swelling and increased ICP/decreased cerebral blood flow. These changes eventually cause seizures, cerebral herniation, and apnea
- Symptoms: Nausea, vomiting, lethargy, altered mental status, seizures, hypothermia, Cheyne–Stokes breathing, rhabdomyolysis. If hyponatremia is chronic, patients may be able to maintain low Na^+ (< 110), as equilibration occurs

Treatment (Tables 24.4 and 24.5)

- If the patient is symptomatic, bolus with 3% saline, correct serum sodium by 4–6 mEq/L (1 mL/kg will raise by 1 mEq)
- If asymptomatic, rapid correction can result in central pontine myelinolysis. This condition evolves over several days and features altered mental status, spastic quadraparesis, and, eventually, death. This usually occurs in chronic hyponatremia
- Calculate maintenance fluid
- Calculate fluid loss 1 g =1 mL. Na^+ deficit is 8 mEq/100 mL of fluid lost
- Then calculate excess Na^+ deficit = [140 − current serum Na^+ (mEq/L)] × 0.6 × total body weight (kg)
- Using the child's baseline weight, maintenance and deficit fluid and electrolytes are calculated and generally replaced over 24 h
- Correct < 0.5 mEq/h. Administer desmopressin if sodium increases too rapidly
- Hypovolemic: Replace intravascular volume with NS, and remove offending agents
- Hypervolemic: Water and Na^+ restriction, diuretics as needed. Consider 25% albumin in nephrotic syndrome if severely hypoalbuminemic
- Euvolemic: Often corrects spontaneously over 3–6 h with cessation of causative activity

Water Intoxication

Etiology

- Occurs with excess water intake (dilutional hyponatremia) and decreased ADH secretion where water intake > kidney excretory ability
- Occurs in infants < 6-months-old with incorrectly mixed formula, athletes replacing sweat losses with water (e.g., marathon runners), forced water intake, iatrogenic IV fluids, beer potomania (water > sodium content)

Features

- See Hyponatremia

Table 24.4 Calculation of intravenous rehydration in cases of hyponatremia

	Fluids	Na^+	K^+
Maintenance fluids	**Maintenance fluid requirements**	3 mEq/100 mL	2 mEq/100 mL
Deficit fluids	1 mL: 1 g of weight lost	8 mEq/100 mL lost	6 mEq/100 mL lost
Additional Na^+ deficit	–	(140 − serum Na^+) × 0.6 × wt (kg)	–
Bolus	–	–	–
Total	Maintenance + deficit − bolus	–	–

Table 24.5 An example of how to calculate and how to order intravenous fluid (IVF) in cases of hyponatremic dehydration

A 20 kg child with Na^+ 130 and 10% dehydration who received 20 cc/kg 0.9% normal saline bolus × 1			
	Water requirements	Sodium requirements	Potassium requirements
Maintenance	Weight of 20 kg = 1500 mL	1500 mL/100 mL = 15	1500 mL/100 mL = 15
		15 × 3 mEq = 45 mEq/24 h	15 × 2 mEq = 30 mEq/24 h
Deficit	20 kg × 0.1 = 2 kg = 2000 mL	2000 mL/100 = 20	2000 mL/100 = 20
		20 × 8 = 160 mEq	20 × 6 = 120 mEq
Additional Na^+ deficit	[140–130] × 20 kg × 0.6 = 120 mEq	120 mEq	–
Bolus	−400 mL	−61.6	–
Total	3100 mL	263 mEq (rounded)	150 mEq

Fluid rate: 3100/24 h = 129 mL/h

DEHYDRATION

See Hypernatremia and Hyponatremia

Isonatremic Dehydration

- Na^+ will be normal. Patients may have elevated BUN/Cr ratio and increased SG in urine > 1.025 in children, > 1.015 in infants
- Decreased bicarbonate if there is diarrhea and vomiting. Anion gap is variable
- Vital sign changes include tachycardia and narrow pulse pressure

Fluid replacement: Stepwise process

1. Patient with hemodynamic instability characterized by severe dehydration, e.g., for increased capillary refill time and low blood pressure (BP), will need initial fluid bolus with isotonic solutions such as NS
2. Maintenance fluids, 3 mEq/100 mL sodium, 2 mEq/100 mL potassium
3. Deficit fluids: Add Na^+ 8 mEq/100 mL of fluid lost, K^+ 6 mEq/100 mL of fluid lost
4. Subtract bolus fluids

Dehydration and Maintenance Fluid Calculations

Maintenance Fluid Requirements

- Holliday–Segar method for maintenance fluid and calorie calculation. **1 mL = 1 kcal:**
  - First, 10 kg—100 cal/kg/24 h
  - Next, 10–20 kg—50 cal/kg/24 h
  - For every kg above 20 kg—20 cal/kg/24 h
  - For every 100 calories metabolized in 24 h, an average healthy child will require 100–120 mL of H_2O, 2–4 mEq of Na^+, and 2–3 mEq of K^+
  - Consists of urine (60% of maintenance fluid), stool (5%), and insensible losses (25–40% depending on age, so ~33%)

Classification of Dehydration by Severity (Table 24.6)

- Calculate fluid deficit (L) as pre-illness wt. (kg) – post-illness wt. (kg)
- Dehydration % = [(pre-illness wt.−post-illness wt.)/pre-illness wt.] × 100
  - Mild dehydration = 5% in infants and 3% in children > 1 year
  - Moderate = 10% in infants and 6% in children > 1 year
  - Severe = 15% in infants and 9% in children > 1 year

Table 24.6 Assessment of dehydration based on clinical signs

	Mild	Moderate	Severe
Skin turgor	Normal	Tenting	None
Skin (touch)	Normal	Dry	Clammy
Buccal mucosa/lips	Dry	Dry	Parched/cracked
Eyes	Normal	Deep set	Sunken
Tears	Present	Reduced	None
Fontanel	Flat	Soft	Sunken
Central nervous system	Consolable	Irritable	Lethargic/obtunded
Pulse rate	Normal	Slightly increased	Increased
Pulse quality	Normal	Weak	Feeble/impalpable
Capillary refill	Normal	~2 s	> 3 s
Urine output	Normal to decreased	Decreased	Anuric
Extremities	Warm	Cool	Cold/mottled/cyanotic

Oral Rehydration for Mild and Moderate Isonatremic Dehydration

- Mild-to-moderate isonatremic dehydration can be treated effectively with oral rehydration solutions
- Replace 50–100 mL/kg body weight over 2–4 h
- Administer 5 mL with teaspoon, syringe, or dropper every 5 min as tolerated
- Ondansetron administration to children with severe vomiting can reduce the need for intravenous therapy and hospital admission
- Nasogastric tube can be used for replacement in cases of severe vomiting or painful oral ulcers (herpangina)

Fluids for oral replacement:

- Oral rehydration solution
- Pedialyte

Inappropriate fluids for replacements

- Water
- Juices
- Sodas

Contraindication of oral rehydration

- Circulatory instability or shock
- Altered mental status
- Intractable vomiting
- Bloody diarrhea or ileus
- Abnormal serum sodium values
- Glucose malabsorption

Calculating Replacement in Isonatremic Dehydration (Table 24.7)

- Deficit calculations and fluid therapy in isonatremic dehydration:
  - With this type of dehydration, there is loss of both fluid (fluid deficit) and electrolyte (solute deficit) in a proportional manner
  - Solute deficit: Total amount of electrolytes lost
  - In illness < 3 days, 80% of the losses are from ECF and 20% from ICF.
  - In illness > 3 days, there is more intracellular dehydration; hence, 60% of the losses are from the ECF compartment and 40% from ICF compartment
  - Solute Na^+ deficit (mEq) = fluid deficit (L) × proportion from ECF based on the duration of illness (0.8 or 0.6) × 140 mEq/L (extracellular sodium concentration)
  - Solute K^+ deficit = fluid deficit (L) × proportion from ICF based on duration of illness (0.2 or 0.4) × 160 mEq/L (intracellular potassium concentration)
  - Replace maintenance and deficit evenly over 24 h.
  - Remember to both supplement with maintenance fluid and electrolyte requirement and to replace ongoing losses

Table 24.7 An example of how to calculate and how to order intravenous fluid (IVF) in cases of isonatremic dehydration

A 20 kg child with Na^+ 135 and 10% dehydration who received normal saline bolus × 1			
	Water requirements	Sodium requirements	Potassium requirements
Maintenance	Weight of 20 kg = 1500 mL	1500 mL/100 mL = 15	1500 mL/100 mL = 15
		15 × 3 mEq = 45 mEq/24 h	15 × 2 mEq = 30 mEq/24 h
Deficit	20 kg × 0.1 = 2 kg = 2000 mL	2000 mL/100 = 20	2000 mL/100 = 20
		20 × 8 = 160	2 × 6 = 120
Bolus	−400 mL	−61.6	–
Total	3100 mL	144 mEq (rounded)	150 mEq

Fluid rate: 3100/24 h =129 mL/h

POTASSIUM (K)

- K < 1% in plasma
- Intracellular and extracellular concentration can be altered by:
  - Medications (e.g., insulin, beta-agonists, beta-blockers)
  - Change in pH: Acidosis and alkalosis
  - Exercise
  - Change in serum osmolality

Hyperkalemia

Definition

- K > 5.5 mEq/L in infants through adulthood
- Allow up to 6.5 mEq/L in term newborns

Regulation

- > 40% is transiently moved intracellularly with increased potassium load. Most is renally excreted
- Aldosterone is the primary hormone involved in potassium excretion

Causes

- Pseudohyperkalemia
  - Hemolysis (heel-stick, tourniquet)
- Excessive intake (rare)
- Transcellular shifts
  - Acidosis
  - Cellular breakdown: Rhabdomyolysis, tumor lysis, hemolysis
  - Medications: Succinylcholine, beta-blockers
  - Exercise, increased serum osmolality (e.g., DKA)
- Decreased excretion (e.g. ACE-I, NSAIDs)
- Renal failure, hypoaldosteronism (e.g., congenital adrenal hyperplasia [CAH]), pseudohypoaldosteronism

Clinical features

- Affects membrane depolarization:
  - Electrocardiogram (EKG): Peaked T waves → ST depression, increased PR interval, flattened P wave → widened QRS → ventricular fibrillation
  - Paresthesia, fasciculations, weakness
- Identify medications, causes of cellular shifts, tumor lysis (elevated PO4, hyperuricemia), hemolysis (anemia, hemoglobinuria), rhabdomyolysis (elevated creatine kinase), and renal insufficiency. Assess acid/base, BUN/Cr for dehydration, and DKA. In infants, consider CAH

Treatment

- Stop implicated medications
- EKG if > 6.5 mEq/L:
  - Ca^{++} gluconate: Stabilize membrane
  - Transcellular shift into ICF: Insulin + glucose (fastest), bicarbonate, beta-agonist (albuterol nebulizer)

  - Removal (slower onset): Loop diuretics, sodium polystyrene sulfonate (Kayexalate). Begin dialysis if severe, as in renal insufficiency and tumor lysis. Hemodialysis is preferred over peritoneal dialysis

Hypokalemia

Definition

- K < 3.0 mEq/L

Etiology

- Pseudohypokalemia (extremely elevated white blood cell count)
- Transcellular shifts
  - Alkalosis, decreased insulin, beta-blockers
  - Occurs during correction of DKA if K^+ is not added
- Extrarenal
  - Vomiting results in hypochloremic hypokalemic alkalosis. Hypokalemia is further exacerbated by increased aldosterone due to volume losses
  - Diarrhea, laxatives
    - Diarrhea—hyperchloremic hypokalemic
      - Acidosis in diarrhea, alkalosis in laxative abuse
- Renal
  - RTA, diuretics
  - Bartter syndrome (+hypercalciuria), Gitelman syndrome (hypomagnesemia)
  - Diuretic: Alkalosis, hypokalemia, high urine chloride, normal BP
- Thyrotoxic periodic paralysis, more common in Asian population
- Liddle syndrome: Gain of function of sodium receptor in distal tubule; features of hyperaldosteronism with hypertension

Clinical features

- EKG: Flattened T wave → ST depression, U wave → ventricular fibrillation, *torsades de pointes*
- Muscle weakness, cramps, paralysis, constipation

Diagnosis

- Urinary K^+, K/Cr ratio (< 1.5 likely gastrointestinal or transcellular, > 1.5 likely renal)
- The transtubular potassium gradient (TTKG) = K urine/K plasma × (plasma osmol/urine osmol) > 4 = urinary losses, < 4 =nonrenal losses

Treatment

- If symptomatic: Oral K^+ preferred, IV K^+ 1 mEq/kg, max 40 mEq/L
  - Use potassium chloride. If acidotic, use potassium acetate or citrate
- Can use potassium-sparing diuretics if there is evidence of renal insufficiency. Replace magnesium if low, since hypomagnesemia can cause hypokalemia

CHLORIDE (CL)

Hypochloremia

Definition

- Cl < 97 mEq/L

Causes

- Loss of body fluids (along with Na^+) from prolonged vomiting, diarrhea, sweating, or high fevers. Seen in CF as hyponatremic hypochloremic metabolic alkalosis
- Medications: Bicarbonate, corticosteroids, diuretics, and laxatives

ACID–BASE

Background

- Normal pH 7.35–7.45, normal HCO_3^- 20–28, normal PCO_2 35–45
- **Tip:** Determine if pH is appropriate for CO2 level: Drop the 7, and compare numbers after decimal point, e.g., CO_2 35 and pH 7.35 is appropriate

Regulation

- Acid–base balance regulated by buffers
  - Bicarbonate the major buffers—$CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$
  - $NH4^+$ is produced to allow for acid excretion in urine

Henderson–Hasselbalch pH = 6.1 + log[HCO_3^-/CO_2], or H = 24 × PCO_2/(HCO_3^-)

- CO_2 regulated by lungs, HCO_3^- regulated by kidneys
- Increased renin–angiotensin–aldosterone system stimulates HCO_3^- reabsorption (e.g., contraction alkalosis)
- Increased parathyroid hormone (PTH), acetazolamide, and proximal RTA decrease HCO_3^- reabsorption
- CNS receptors sense increase or decrease in HCO_3^- and will decrease or increase respiratory rate (increase/decrease CO_2) to maintain physiologic pH, respectively

Acid–base disorder can be simple or mixed: Simple

- Metabolic acidosis/alkalosis with respiratory compensation or respiratory acidosis/alkalosis with metabolic compensation

Mixed

- Bronchopulmonary dysplasia (BPD): Respiratory acidosis and metabolic alkalosis (furosemide)
- Respiratory failure and sepsis: Metabolic acidosis and respiratory acidosis

Table 24.8 Compensatory processes

	Acute	Chronic
Metabolic acidosis	$CO_2 = 1.5 + HCO_3 + 8$ (±2)	–
Metabolic alkalosis	$CO_2 = CO_2$ increases by 7 for every 10 increase of HCO_3–	–
Respiratory acidosis	$HCO_3^- = 24 + (PCO_2 - 40/10)$	$24 + 4 (PCO_2 - 40/10)$
Respiratory alkalosis	$HCO_3^- = 24 - 2 (40 - PCO_2/10)$	$HCO_3^- = 24 - 5 (40 - PCO_2/10)$

- Respiratory compensation occurs within 12–24 h; renal compensation takes days
- Compensation cannot correct to normal pH

Compensatory Processes (Table 24.8)

Hint: **Remember:** 1–2–4–5 in respiratory acidosis/alkalosis

- Respiratory acidosis:
  - Acute: HCO_3^- will increase by 1 for every 10 increase in CO_2
  - Chronic: HCO_3^- will increase by 4 for every 10 increase in CO_2
- Respiratory alkalosis:
  - Acute: HCO_3^- will decrease by 2 for every 10 decrease in CO_2
  - Chronic: HCO_3^- will decrease by 5 for every 10 decrease in CO_2

Acidosis, alkalosis

- Approach acid–base disorders stepwise:
  1. pH: Acidotic/alkalotic? May be normal if mixed acidotic/alkalotic disorder, but CO_2 and HCO_3^- will be abnormal!
  2. CO_2: Elevated or decreased?
  3. Bicarbonate: Elevated or decreased?
  4. Compensation: Appropriate or inappropriate (i.e., mixed disorder) (longer duration of episode if renal compensation occurs)

Metabolic Acidosis

- pH < 7.2 results in decreased cardiac contractility, pulmonary vasoconstriction, decreased

adenosine triphosphate (ATP), altered mental status, and coma
- Associated lab abnormalities:
  - BUN/Cr ratio will be increased in either prerenal azotemia or renal insufficiency
  - DKA: Glycosuria, ketonuria
  - Addison disease: Hypoglycemia, hyperkalemia
  - Diarrhea is the most common cause (HCO_3^- lost in stool)
  - RTA: Distal (type I) hypokalemia, hypercalciuria, failure to thrive, cannot acidify urine (pH > 5.5.)
  - Proximal (type II), usually with Fanconi syndrome: Glycosuria, hypokalemia, phosphaturia, aminoaciduria, uric aciduria (pH < 5.5.)
  - Hyperkalemic (type IV): Decreased concentration or response to aldosterone; CAH

Anion gap
- $Na^+ – (Cl^- + HCO_3^-)$. Normal gap 8–12
  - Gap represents unmeasured anion.
  - Increased, i.e., gain of acid: The H+ is buffered by HCO_3^-, but the anions are increased (e.g., lactate) and chloride is unchanged
  - Normal, i.e., loss of base: Loss of HCO_3^- balanced by increased Cl^- to maintain electroneutrality

Increased anion gap
- Gain of acid: **MUDPILES:** Methanol, Uremia, DKA, Phenformin (metformin) iron, INH, IEM, Lactic acidosis, Ethylene glycol/ethanol, Salicylates
- Methanol, ethylene glycol intoxication: There is typically < 10 mOsm/kg difference between calculated serum osmolality (2Na + BUN/2.8 + glucose/18) and measured serum osmolality. If intoxication is present, there will be > 10 mOsm/kg difference between measured and calculated osmolality

Normal anion gap
- Loss of base: aka hyperchloremic metabolic acidosis. **Causes:** Hyperalimentation, Addison's disease, RTA, Diarrhea, Acetazolamide, Spironolactone, Saline infusion
- RTA versus diarrhea can be differentiated based on the urine anion gap
  - Urine anion gap = $Na^+ + K^+ – Cl^-$. Normal < 10 mEq/L
  - NH_4^+ (i.e., acid loss) is unmeasured cation. NH_4^+ is excreted with chloride to maintain electroneutrality
  - Gap is negative (i.e., increased NH_4^+ excretion, and therefore increased Cl^- excretion) in RTA
  - Gap is normal or zero in diarrhea

Metabolic Alkalosis

- Addition or decreased excretion of base

Causes
- Emesis is the most common cause. (Decreased HCl as well as increased resorption of base since intravascularly depleted)
- Identify cause by determining urinary chloride level
  - Decreased urinary chloride (chloride responsive): Volume depletion. Causes:
    - Emesis (including bulimia)
    - Diuretics (after effects wear off, chloride returns to normal)
    - CF
    - Laxatives
  - Elevated urinary chloride level (chloride resistant): Does not respond to fluid replacement. Causes:
    - If high BP (think elevated aldosterone picture): Renin-secreting tumor, adrenal adenoma, Cushing, Liddle, 11B hydroxylase (aka apparent mineralocorticoid excess), 17-a-hydroxylase
    - Normal BP: Gitelman, Bartter; hypoparathyroidism. Rarely CF

Clinical Features

- Depends on underlying disease
- Chloride responsive, i.e., volume depletion: Lethargy, thirst
- Chloride unresponsive: Hypertension. Cardiac arrhythmias, hypomagnesemia, increased potassium losses, and increased shift into ICF. May have signs and symptoms of hypokalemia. Ionized Ca^{++} decreases due to increased binding to albumin → tetany, seizure

Diagnosis

- Measure urinary chloride, renin, and aldosterone (differentiate adrenal tumor, renovascular disease, and adrenal etiology)

Treatment

- Underlying etiology. Mild, will resolve. Proton pump inhibitors in vomiting, potassium-sparing diuretics. K^+ supplements, arginine will raise K^+, acetazolamide. Chloride responsive: NaCl and KCl. Liddle: Amiloride or triamterene

DISEASE STATES AND SPECIFIC THERAPY

Gastroenteritis

Background

- Formerly a major cause of mortality in underdeveloped countries
- Excessive fluid losses lead to hypovolemia, metabolic acidosis, and shock

Treatment

- Oral (can be used in mild and moderate dehydration)
- Goal is to maintain serum osmolality and decrease diarrheal load
- Oral rehydration solution versus juices or broth:
  - Na^+ reabsorption is impaired in diarrheal states, so cotransport with glucose is required to maintain Na^+ balance
  - Oral rehydration solutions have a serum osmolality between 200 and 310, with approximate equimolar distribution of sodium and glucose. ORS hasten the absorption and improve the diarrhea
  - If glucose/sodium ratio (e.g., fruit juices), or sodium/glucose ratio > 1:1 (broth); excess is eliminated as diarrhea. They may worsen the diarrhea
- Replace diarrheal losses 1 mL/1 mL or replace 10 mL/kg body weight for each diarrheal episode and 2 mL/kg body weight for each episode of emesis
- If severe dehydration, shock, worsening dehydration despite oral therapy, or ileus, use IV fluid therapy and treat as in shock
- Switch to oral therapy when feasible
- Breastfeeding and milk-based formula can be used; avoid high-glucose/low-sodium (e.g., sports drinks)

Oliguria/Acute Renal Failure

Background

- Patients with oliguria/acute renal failure are at risk for fluid overload and electrolyte abnormalities
- Maintenance fluid (see **Maintenance Fluid Requirements**) is equal to total body fluid loss—urine (60% of maintenance fluid), stool (5%), and insensible losses (25–40% depending on age, so ~33%)
- In severe oliguria, the goal is to avoid fluid overload. Replace insensible losses (25–40% of maintenance); administer diuretics as needed and then replace urine mL/mL. Do not supplement potassium until patient is able to void

Hyperosmolar Nonketotic Coma

Background

- Typically occurs in Type 2 DM, since these patients have enough insulin on board to con-

tinue glycolysis and prevent ketone synthesis. Therefore, no acidosis
- Occurs after prolonged urinary losses, more dehydrated than DKA, and a high mortality

Treatment
- Aggressive fluid resuscitation with multiple boluses of NS is the most important component
- Insulin therapy is not as important, as ketosis and acidosis are not major features of this condition. Therefore, ensure adequate fluid resuscitation prior to insulin administration

PEARLS AND PITFALLS

- When possible, always choose enteral rehydration over parenteral rehydration—it is more physiologic and less prone to causing major electrolyte abnormalities.
- When correcting the fluid and electrolyte imbalance of a patient over a period of 48 h, the maintenance needs for that period of time have to be included in the calculations.
- All fluid balance corrections have to be accompanied by regular monitoring of the progress by obtaining a basic metabolic panel or venous blood gas every 4 h in the acute phase (first 12 h) and every 6 h once the trend of the electrolytes shows evidence of correction.
- Weighing patients with dehydration twice a day provides another reliable tool in determining the success of the fluid balance correction.
- Severe dehydration may require a combination of both parenteral and enteral fluids via nasogastric tube, if the patient is not in shock or on pressors.
- A patient with profuse diarrhea will have metabolic acidosis from loss of alkaline pancreatic fluids. A patient cannot be diagnosed with renal tubular acidosis for 2 weeks following a diarrheal illness before the enteral acid–base balance restores.

Suggested Reading

Cross JT, Hannaman RA. MedStudy: pediatrics board review core curriculum. Colorado Springs: MedStudy; 2018. Print.

Kliegman RM, Stanton B, St Geme J, Schor N, Behrman RE. Nelson textbook of pediatrics. 20th ed. Philadelphia: Saunders Elsevier; 2016.

Powers K. Dehydration: isonatremic, hyponatremic, and hypernatremic recognition and management. Pediatr Rev. 2015;36(7):274–85.

Rudolph CD. Rudolph's pediatrics. 22nd ed. New York: McGraw-Hill, Medical Pub. Division; 2003.

Urology

25

Catherine J. Chen and Micah A. Jacobs

URINARY TRACT INFECTION (UTI)

Definitions

- Sterile pyuria: Presence of white cells in the urine in the setting of a negative culture (≥ 3 WBC hpf or positive leukocyte esterase on dipstick)
- Asymptomatic bacteriuria: Urine culture with significant bacterial colony count in an asymptomatic patient
- Uncomplicated UTI: Positive urine culture in a symptomatic patient (frequency, urgency, new urinary incontinence)
- Complicated UTI: Urine culture with significant bacterial colony count and associated urologic abnormalities (hydroureter, hydronephrosis, and vesicoureteral reflux)
- Pyelonephritis: Positive urine culture plus fever

Background

- Most UTIs are bacterial infections of the mucosal surface of the urinary tract
- The infection may occur anywhere from the urethra to the renal parenchyma
- A temperature greater than 38 ° C may help to differentiate acute pyelonephritis from lower tract UTI
- The most common organism causing UTI in children is *Escherichia coli*
- Other bacterial pathogens include *Pseudomonas aeruginosa* (non enteric Gram negative), *Enterococcus faecalis*, *Klebsiella pneumoniae*, and group B *Streptococcus* (predominantly in neonates)
- Most UTIs in sexually active females are caused by *E. coli* or *Staphylococcus saprophyticus*
- Diagnosis of UTI depends on obtaining accurate urine culture findings (Table 25.1)
- No laboratory tests can reliably distinguish cystitis from pyelonephritis

Risk factors

- Constipation is a high-risk factor for recurrent UTI
- Uncircumcised male infants

Table 25.1 General criteria to diagnose a urinary tract infection

Method of urine collection	Interpretation
Bag collection	Not recommended. However, if done, and urine analysis is suggestive of an infection, a catheterized or suprapubic aspiration must be completed. If culture is sent, there is high false-positive rate
Urethral catheterization	Pyuria on urine analysis *and* > 50,000 colony forming units/ml of a uropathogen on culture
Midstream urine analysis	
Suprapubic aspiration	

C. J. Chen · M. A. Jacobs (✉)
Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA
e-mail: micah.jacobs@childrens.com

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_25

- Dysfunctional elimination syndrome (bowel bladder dysfunction, including urinary holding behaviors)
- Indwelling or intermittent catheterization
- Anatomical abnormalities, including vesicoureteral reflux and bladder outlet obstruction

Clinical presentation (by age group)

- Presence of fever and urine infection is highly suggestive of pyelonephritis
- **Newborn (birth–1 month)**
  - Fever
    - May be the only presenting symptom without a clear source of infection
    - Temperature elevations greater than 38.0 °C are indicative of upper UTI
- **1 month–24 months**
  - Fever, hypothermia, vomiting, difficulty feeding, cloudy or malodorous urine, frequency, irritability, hematuria, or failure to thrive
- **Preschool (2–6 years)**
  - Abdominal pain, suprapubic pain, costovertebral angle pain, dysuria, urgency, or incontinence (day- or nighttime) in a previously toilet-trained child
  - Pyelonephritis in young children is more likely to manifest as vague abdominal discomfort rather than as the classic flank pain and tenderness observed in adults

Imaging

- Ultrasonography
  - Renal ultrasonography is the safest and fastest method for detecting congenital renal and urinary tract anomalies such as hydronephrosis
- Cystography
  - Fluoroscopic voiding cystourethrography is the gold standard for diagnosing vesicoureteral reflux
  - Other methods include radionuclide cystogram and contrast-enhanced ultrasound
- Renal scan
  - Dimercaptosuccinic acid (DMSA) scintigraphy currently is the accepted gold standard for diagnosing acute pyelonephritis and renal scarring
  - For the purpose of diagnosing renal scarring, DMSA scintigraphy should be performed 3 months after acute infection to allow resolution of acute reversible lesions

Acute management (review American Academy of Pediatrics [AAP] guidelines)

- Uncomplicated UTI: Trimethoprim-sulfamethoxazole (TMP-SMX) twice a day or appropriate culture-specific antibiotics for 3–7 days
- Acute pyelonephritis: 7–10-day oral regimen if > 3 months and if able to maintain hydration as an outpatient. Recommend urology referral

Management of recurrent UTI

- Referral to urology for further workup for anatomical abnormalities and discussion of prophylaxis antibiotics. Prophylaxis antibiotics are not always indicated. While prophylaxis antibiotics may decrease UTIs, there is increased risk of bacterial resistance in those on prophylaxis antibiotics. There are no studies that demonstrate its efficacy in reducing renal scarring
- Common prophylaxis regimens
  - TMP-SMX: 2 mg/kg as a single daily dose or 5 mg/kg twice a week
  - Nitrofurantoin: 1–2 mg/kg as a single daily dose

Vesicoureteral Reflux (VUR)

Background

- VUR or the retrograde flow of urine from the bladder into the ureter
- Anatomic and functional disorder that can result in substantial morbidity, both from acute infection and from the sequelae of reflux nephropathy

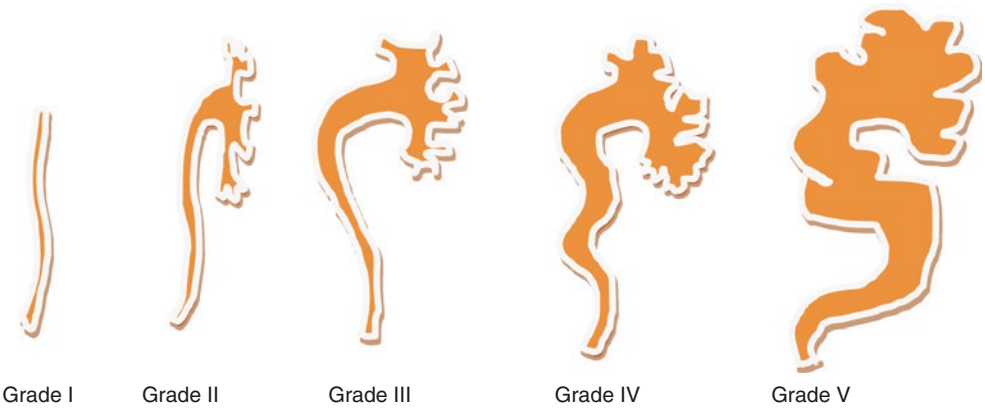


Fig. 25.1 Grades of vesicoureteral reflux (VUR)

International Classification System for VUR (Fig. 25.1)

- Grade I—Reflux into non-dilated ureter
- Grade II—Reflux into renal pelvis and calyces without dilation
- Grade III—Reflux into renal pelvis and calyces with dilation
- Grade IV—Reflux with moderate ureteral tortuosity and dilation of pelvis and calyces
- Grade V—Reflux with gross dilation and tortuosity of ureter, pelvis, and calyces and loss of papillary impressions

Clinical presentation

- Children with VUR may present with hydronephrosis and/or pyelonephritis (febrile UTI)
- Hydronephrosis is often prenatally identified using ultrasonography
- Infants can manifest as failure to thrive with or without fever; other features include vomiting, anorexia, and lethargy
- Older children may report voiding symptoms or abdominal pain

Diagnosis

- Diagnosis is based on imaging studies
- Imaging with ultrasound after the first UTI is indicated in children of any age with febrile UTI
- Children with prenatally identified hydronephrosis (> 7 mm anteroposterior diameter of the renal pelvis) should be evaluated postnatally, with an ultrasound after 48 h of life
- **Voiding cystourethrography (VCUG)**
  - VCUG is the gold standard in the diagnosis of VUR, providing precise anatomic detail and allows grading of the reflux
- **Radionuclide cystography**
  - Lower radiation doses than with VCUG
  - This study provides less anatomical definition but has higher sensitivity in detecting reflux compared to VCUG

Management

- General principles of management in children with known VUR
  - Spontaneous resolution of VUR is common in young children with low-grade reflux
  - Severe reflux is unlikely to resolve spontaneously
  - Sterile reflux, in general, does not result in reflux nephropathy
  - Long-term antibiotic prophylaxis in children has been associated with increased antibiotic resistance
  - Surgery to correct VUR is highly successful
- Constipation is extremely common and may be a much more important etiologic factor than the reflux itself
  - Constipation is a higher risk factor for infection than reflux; it is extremely important that the constipation is addressed

- Time voiding and double voiding may improve symptoms of dysfunctional voiding and reduce the risk of infection in select patients
- Serum chemistries are used to assess for baseline renal function
- A complete blood count (CBC) report can assist in tracking the response to treatment
- Urinalysis helps to determine the presence of proteinuria, which indicates possible renal impairment

Antibiotic prophylaxis

- If used, it is started once a child has completed treatment of the initial UTI
- There are conflicting studies regarding the utility and efficacy of antibiotics in reflux. If used, the duration is based on shared decision-making between the parents and physician
- Discontinue if no VUR is seen on imaging studies
- Antibiotics are usually administered as suspensions once daily, typically in the evening to maximize overnight drug levels in the bladder
- In infants younger than 3 months, the agent of choice is amoxicillin
- For older children, the most common antibiotics used are TMP-SMX and nitrofurantoin

Accepted indications for surgical treatment

- Breakthrough febrile UTIs despite adequate antibiotic prophylaxis
- Severe reflux (grade V or bilateral grade IV) that is unlikely to spontaneously resolve
- Renal scarring on DMSA scan
- Parental choice
- Poor renal growth or function or appearance of new scars

Ureteropelvic Junction Obstruction

Definition

- Ureteropelvic junction (UPJ) obstruction is defined as an obstruction of the flow of urine from the renal pelvis to the proximal ureter
- UPJ obstruction is the most common obstructive lesion

Society of Fetal Ultrasound (SFU) grading of hydronephrosis

- Grade 1: Normal parenchyma with slight splitting of the renal pelvis
- Grade 2: Normal parenchyma with full renal pelvis and dilation of the major calyces
- Grade 3: Normal parenchyma dilation of the minor calyces
- Grade 4: Loss of normal parenchyma

Clinical presentation

- Maternal ultrasound may reveal fetal hydronephrosis
- Palpable renal mass in newborn infants
- Abdominal flank pain
- Febrile UTI
- Hematuria after minimal trauma
- More common on the left side

Diagnosis

- Renal ultrasound
- A VCUG is not always necessary in isolated UPJ obstruction but, to rule out urethral obstruction, should be considered in boys with bilateral hydronephrosis
- A ^{99m}Tc-mercaptoacetyltriglycine (MAG3) renal scan can be used once diagnosis is made to determine renal function and drainage

Management

- Ultrasound 48 h after birth
- Urology referral
- Low-grade hydronephrosis may resolve, but referral is appropriate
- If hydronephrosis is high grade (SFU grade 3 or 4), spontaneous resolution is less likely
- Surgical intervention and timing of intervention for an obstructed UPJ are dependent on imaging findings, history of UTIs, and shared decision-making between the family and physician

Ureterocele

Background

- Ureterocele is a cyst outpouching of the distal ureter into the urinary bladder, typically diag-

nosed after prenatal imaging demonstrating hydronephrosis
- Ureteroceles may be asymptomatic and present with a wide range of clinical signs and symptoms, from recurrent cystitis to bladder outlet obstruction or renal failure

Clinical presentation
- Prenatal imaging
- UTI
- Urosepsis
- Obstructive voiding symptoms
- Urinary retention
- Failure to thrive
- Hematuria
- Cyclic abdominal pain
- Ureteral calculus

Diagnosis
- The first-line imaging study for evaluating the upper and lower urinary tract in children is renal and bladder ultrasonography
- VCUG is essential to evaluate the lower urinary tract for a ureterocele, posterior urethral valve (PUV), ectopic ureter, and vesicoureteral reflux

Management
- Observation alone is rarely a good option in symptomatic ureteroceles
- Antibiotic prophylaxis starts in newborns with prenatal diagnosis of ureterocele
- Indication for surgery depends on the site of the ureterocele, the clinical situation, associated renal anomalies, and the size of the ureterocele

Posterior Urethral Valves (PUV)

Background
- The most common cause of severe obstructive uropathy in male infants
- Posterior urethral dilation, bladder muscle hypertrophy, hydronephrosis, renal dysplasia, and renal failure will depend on the severity of obstruction

Clinical presentation
- PUV should be considered if there is inability to empty bladder or weak urine stream
- If unrecognized during the neonatal period, may present later with failure to thrive, uremia, sepsis, and renal failure
- If less severe, may present with UTI or urinary incontinence at later age

Diagnosis
- Established with VCUG

Treatment
- Transurethral ablation of the valve leaflets by endoscopy

Female Urethral Prolapse

Background
- Urethral prolapse is a circular protrusion of the distal urethra through the external meatus. It is a rarely diagnosed condition that occurs most commonly in prepubertal black females and postmenopausal white women
- Risk factors for urethral prolapse in children include increased intra-abdominal pressure as a result of chronic coughing or constipation

Clinical presentation
- Vaginal bleeding associated with urethral mass is the most common presentation

Management
- Treatment of urethral prolapse ranges from applications of estrogen creams to sitz baths
- Surgery may be indicated in severe, persistent, or symptomatic cases

Prune-Belly Syndrome (Eagle-Barrett Syndrome)

- Deficient abdominal muscles
- Undescended testes
- Urinary tract abnormalities
- Massive dilation of ureters and upper tracts

- Very large bladder oligohydramnios and pulmonary hypoplasia
- Various degrees of renal dysplasia

Urinary Incontinence

Background

- Most children will have control of micturition by age 4–5 years

Causes

- UTI
- Constipation
- Child abuse
- Psychosocial stressor
- Back or sacral anomalies and underlying spinal cord malformation
- Labial adhesions resulting in incontinence from vaginal voiding
- Female epispadias
- Ectopic ureter
- Bladder outlet obstruction

Clinical presentation

- Ectopic ureter: Continuous urinary leakage
- Detrusor instability: Signs of urinary urgency, such as bouncing up and down
- Stress incontinence: Occurs with Valsalva, coughing, or sneezing

Diagnosis

- Depends on history and physical examination
- Urinalysis and urine culture
- Renal ultrasound
- Magnetic resonance imaging (MRI) on the back if spinal cord or vertebral malformation is suspected
- Assessment of constipation

Treatment

- Depends on the etiology of incontinence
  - Ectopic ureter: Surgical
  - Detrusor instability
    - Behavior modification (i.e., timed voiding, address constipation)
    - Medication (i.e., anticholinergics such as oxybutynin, mirabegron)
    - Surgical (Botox injection)
  - Stress incontinence. This is more commonly seen in the adult patient; however, it may be seen in very athletic children (especially girls)
    - Behavior modification (i.e., timed voiding)
    - Pelvic floor strengthening exercises (Kegel exercises)
    - Surgical intervention (i.e., injection of bulking agents, placement of artificial sphincters or slings). Treatment is tailored to each patient and clinical situation

Bladder Exstrophy

- Bladder exstrophy is the externalization of the bladder plate on the anterior abdominal wall
- Bladder should be covered with plastic wrap to keep bladder mucosa moist
- Application of gauze or petroleum gauze should be avoided because significant inflammation will result
- Consult pediatric urologist

Hypospadias

Background

- The most common congenital anomaly of the penis
- The meatus can be in a ventral position from the distal penis to the perineum
- Some mild forms may not need surgical correction
- Associated with chordee, which is more severe in proximal hypospadias cases

Management

- If there is a complete foreskin, circumcision can be performed
- Consult a urologist for surgical decision-making and counseling

Phimosis

Background

- Phimosis occurs when foreskin cannot be retracted
- Most boys will be able to retract their foreskins by age 5 years old; however, some may not be able to until their teen years [1]
- Physiologic phimosis: Seen in all newborn males in normal development of congenital adhesions between the foreskin and glans
- Pathologic phimosis: Nonretractile foreskin secondary to scarring of the prepuce

Treatment

- In causes of pathologic phimosis, corticosteroid cream to foreskin may be tried prior to surgery
- Indications for circumcision include UTI and known anatomical abnormalities such as reflux, balanitis obliterans xerotica (BXO), and balanoposthitis

Paraphimosis

Description

- Paraphimosis is the inability to place the retracted foreskin to its anatomical position
- Foreskin retracted past the coronal sulcus may become edematous, making the replacement of the foreskin over the glans more difficult

Treatment

- Reduction is emergent and may require sedation and anesthesia
- Reduction can be done by compressing the penis to decrease edema, application of sugar or D50 on the edematous foreskin, and pinpricks to the foreskin to allow egress of the edematous fluid. The use of a penile block may be helpful

Balanoposthitis

Definition

- Inflammation and cellulitis of prepuce and/or glans penis

Treatment

- Topical steroids and topical or oral antibiotics
- Eventual circumcision may be indicated, especially if recurrent

Circumcision

AAP Circumcision Policy Statement [2].

- "Existing scientific evidence demonstrates potential medical benefits of newborn male circumcision; however, these data are not sufficient to recommend routine neonatal circumcision."
- "In circumstances in which there are potential benefits and risks, yet the procedure is not essential to the child's current well-being, parents should determine what is in the best interest of the child."
- "To make an informed choice, parents of all male infants should be given accurate and unbiased information and be provided the opportunity to discuss this decision."
- "If a decision for circumcision is made, procedural analgesia should be provided."

Indication of circumcision

- Many families choose to have their male infants circumcised for cultural, religious, or hygienic reasons. Only a few accepted medical indications are recognized: pathologic phimosis, history of paraphimosis, or balanoposthitis

Anatomic contraindication

- Hypospadias with incomplete foreskin
- Epispadias
- Ambiguous genitalia (including bilateral cryptorchidism or micropenis)
- In more severe cases of the following, circumcision may be left to the discretion of the urologist: chordee, penile torsion, penile webbing, and buried penis

Medical contraindications to neonatal circumcision

- Any current illness or medical condition that requires monitoring

- Age less than 12–24 h
- Known bleeding diathesis (e.g., hemophilia or thrombocytopenia)
- Disorders of the skin or connective tissue that would impair normal healing

Instruments usually used for circumcision

- Gomco clamp
- Plastibell device
- Mogen clamp

Complications

- Bleeding
- Infection
- Meatal stenosis
- Penile skin bridges

Education of the parents

- Instruct parents concerning the occurrence of physiologic childhood phimosis, which can last into the school-age years
- Stress the danger of forcibly retracting the foreskin for hygienic purposes
- The adhesions found between the inner prepuce and the glans naturally lyse
- The AAP does not recommend routine neonatal circumcision; however, if circumcision is performed, the AAP recommends the use of procedural analgesia [2]

Micropenis

Definition

- Stretched penile length from pubis to the tip of the penis < 2.5 cm

Causes

- Deficiency of gonadotropin secretion during the last two trimesters
- Testosterone insensitivity
- Kallmann syndrome
- Prader-Willi syndrome
- Panhypopituitarism

Treatment

- Testosterone may be beneficial in selected cases

Testicular Torsion

Background

- Testicular or spermatic cord torsion is an emergency
- It occurs in one in 4000 males < 25 years old
- Most commonly in boys age 12–18
- Most occurs in tunica vaginalis

Clinical presentation (Table 25.2)

- Acute onset of pain
- Nausea and vomiting
- Scrotal edema and redness
- Loss of cremasteric reflex
- High-lying horizontal testis

Diagnosis

- Color-flow Doppler ultrasound; decreased blood flow on the affected side

Management

- Rapid consultation by the urologist in suspected cases

Table 25.2 Differentiation between acute epididymitis and testicular torsion

Testicular torsion	Epididymitis
Inadequate fixation of testis within the scrotum	*E. coli* in young children, gonococcus, or *Chlamydia* after puberty is the most common cause
Sudden onset (hours)	Gradual onset (days)
Usually nausea and vomiting	Usually no nausea and vomiting
No dysuria, no frequency, no fever	May have fever, dysuria, frequency, and urethral discharge
No pyuria	Urinalysis usually reveals pyuria
Absent cremasteric reflex	Normal cremasteric reflex
Scrotum is swollen and testis is exquisitely tender and often difficult to examine	Tenderness and induration occurring first in the epididymal tail and then spreading
High-lying horizontal testis	Normal position testis
Absent or decreased blood flow in the affected testicle on US	Increased blood flow occurs with epididymitis on US
Immediate surgical exploration	Antibiotics, NSAIDS, scrotal support/elevation

- Obtain immediate scrotal ultrasound through the emergency department or urgent care. Do not delay imaging
- Immediate exploration, detorsion, and contralateral testicular fixation are required
- Manual detorsion may be attempted after obtaining a testicular ultrasound
- In the majority of cases, torted testis rotates inward (e.g., the left testis is rotated clockwise)

Prognosis
- Testes can be lost if the surgery was delayed as little as 4 h, and by 24 h, infarction is almost universal

Neonatal Testicular Torsion

Background
- Majority of the case is extravaginal torsion, which is the torsion of entire spermatic cord and testis
- This can be a prenatal event (occurs in utero) or a postnatal event (within the first 30 days of life)

Clinical presentation
- If the torsion occurred as a prenatal event, the testicle is likely nontender; however, it can be tender, depending on proximity of the event to delivery. Scrotum can be discolored
- If the torsion occurred as a postnatal event, there is usually acute tenderness, swelling, and overlying scrotal skin changes compared to previously known normal scrotal physical exam

Management
- Testicular salvage is rarely successful
- Contralateral testis should be fixed as precautionary measure

Testicular Appendage Torsion

Background
- Torsion of testicular appendix, which is a remnant of mesonephric tubule
- Often masquerades as testicular torsion or epididymitis

Clinical presentation
- Acute scrotal pain
- Pain can be mild to severe
- Often there is a palpable tender nodule at the superior or inferior pole of the testicle with blue discoloration (blue dot sign)
- Vertical orientation of the testes is preserved
- The cremasteric reflex is usually intact
- There is normal blood flow to the testicle
- A reactive hydrocele may be seen

Diagnosis
- Doppler ultrasound can differentiate between torsion of appendix and testis
- Testicular appendage torsion appears as a lesion of low echogenicity with a central hypoechogenic area

Treatment
- Usually resolves spontaneously
- NSAIDs

Cryptorchidism

Background
- Most common genital problem of newborn males
- Occurs in one-third of premature boys and in 3–4% of newborn males

Clinical presentation
- Diagnosis is made by physical exam
- Imaging is not indicated and should not be performed before evaluation by a pediatric urologist
- Undescended testis can be intra-abdominal, in the inguinal canal, ectopic in the perineum, or in the upper scrotum
- If the testis was down at birth, the diagnosis is more likely retractile testis
- Retractile testis can be pulled down to the bottom of the scrotum
- Most retractile testes eventually will end up in the scrotum

Treatment

- If the testicle has not descended by 6 months of age, refer to a urologist for evaluation
- The ideal timing for surgical intervention is between 6 and 18 months of age

Prognosis

- Undescended testes have increased risk of cancer even after surgical correction
- Subfertility: Bilateral undescended testes have been associated with infertility in about half of cases

Testicular Cancer

Background

- Accounts for approximately 1–2% of all pediatric solid tumors
  - Typically occurs between ages 2 and 4 and then at puberty
- Compared to postpubertal testicular tumors, prepubertal testicular tumors are more commonly benign and, if malignant, then to have better prognosis
  - Teratoma is the most common benign testicular tumor in prepubertal boy
- Germ cell tumors are the most common pediatric testicular tumor
  - Yolk sac tumor is the most common testicular tumor in prepubertal boys

Clinical presentation

- Painless testicular mass (most common presentation). Occasionally detected in the setting of some other scrotal pathology such as hydrocele, epididymitis, and testicular torsion

Diagnosis

- Testicular ultrasound
- Tumor markers (AFP, LDH, β-HCG)
- Staging imaging: CT abdomen/pelvis
- Pubertal patients should be encouraged to perform regular self-exam

Management

- Urgent same-day referral to a pediatric urologist or to the emergency department. Once the diagnosis of a testicular tumor is made, surgical management should not be delayed
- Surgical: Radical orchiectomy

Varicoceles

Definition

- Abnormal dilation and tortuosity of the testicular vein and pampiniform plexus of spermatic cord
- Occurs most often on the left side. If present on the right, consider obtaining an abdominal ultrasound to evaluate for any renal or retroperitoneal masses

Clinical presentation

- Most patients are asymptomatic
- Larger varicocele may feel and appear like a bag of worms
- Testicular size must be checked for any asymmetry
- Can contribute to infertility in some cases
- Can cause scrotal pain

Management

- Obtain renal ultrasound
- Surgery may be indicated if there is reduced testicular growth, infertility, or pain

Hydroceles

Background

- Hydrocele is due to failure of fusion and obliteration of the processus vaginalis
- Noncommunicating hydroceles usually resolve by 1 year of age

Management

- Observation

- The following factors indicate hydrocele repair: Failure to resolve by age 2 years, continued discomfort, parental preference

Inguinal Hernia

Background
- Develop in 1–5% of children
- 5 to 10 × more common in boys and is more common in premature infants

Presentation
- Painless mass in the groin, which can contain abdominal contents that may wax and wane in size
  - This bulge may be present only in situations of increased abdominal pressure, such as in Valsalva maneuvers, crying, or straining

Management
- Inguinal hernias do not spontaneously heal and must be surgically repaired
- All pediatric inguinal hernias require operative treatment to prevent the development of complications such as inguinal hernia incarceration or strangulation
- Generally, a surgical consultation should be made at the time of diagnosis and repair

Kidney Stones

Background
- Urolithiasis is an uncommon disease in children, but recent studies have demonstrated an increasing incidence in the pediatric population
- Types of kidney stones
  - Calcium oxalate 40–65%
  - Calcium phosphate 14–30%
  - Struvite 10–20%
  - Cystine 5–10%
  - Uric acid 1–4%

Causes
- The most frequently reported abnormalities in children are hypercalciuria and hypocitraturia
- Struvite stones
  - Can grow quickly and form a large staghorn calculus with the bacteria becoming trapped in the stone
  - Proteus is the most common urease-forming bacterial species
  - Recurrent UTIs are the greatest risk for developing struvite stones

Clinical presentation
- Pain, usually colicky
- Dysuria and frequency
- Passage of blood, stones, or gravel
- Look for signs of renal or other metabolic diseases such as renal tubular acidosis, Dent disease, or Lesch-Nyhan syndrome
- Family history
- Dietary history

Diagnosis
- Urinalysis and urine culture
- Urine pH (< 6 for uric acid stones)
- Complete metabolic panel
- Uric acid
- Urine calcium (Ca) and creatinine
- 24-hour metabolic urine evaluation

Imaging
- Renal ultrasonography
- CT scan without contrast. Consider low-dose CT scan

Management
- The greatest risk factors for calcium kidney stone formation are low fluid and high sodium intake
- Decrease the risk of Ca oxalate by limiting intake to a modest amount of high-oxalate foods such as nuts and chocolates
- Recommended dietary allowance (RDA) should be encouraged

- No added salt diet
- Moderate amount of animal protein consumption
- Avoidance of excess vitamin C
- Thiazide diuretic if hypercalciuria and does not respond to a restricted sodium diet
- Antibiotic for infection-related (struvite)
- Flomax (medical expulsive therapy) to help with stone passage

Surgical treatment

- Most stones smaller than 5 mm pass spontaneously in children and do not require surgical intervention
- Stones that are larger than 5 mm may require nephrolithotomy or lithotripsy or endoscopies

Urethral Injuries

Background

- Trauma to the male urethra must be efficiently diagnosed and effectively treated to prevent serious long-term sequelae
- The etiology of a urethral injury can be classified as blunt or penetrating
- Iatrogenic injuries to the urethra occur when difficult urethral catheterization leads to mucosal injury with subsequent scarring and stricture formation
- Diagnosis of urethral injuries requires a reasonably high index of suspicion

Clinical presentation

- Hematuria or inability to void
- Decreased stream
- Blood at the meatus may be seen

Diagnosis

- The diagnosis of urethral trauma is made by retrograde urethrography

Management

- Consult pediatric urologist
- Bladder drainage must be established. Depending on the injury, the urologist may place a catheter or consider draining the bladder with a suprapubic catheter followed by delayed evaluation and reconstruction
- Surgical repair depends on the severity of injuries

PEARLS AND PITFALLS

- Refer children with recurrent febrile UTIs to a pediatric urologist for further anatomical workup and management. The decision regarding prophylactic antibiotics and their management is complex and should be shared by family and physician.
- The diagnosis of a UTI is based on a child having both symptoms and a positive urine culture.
- Refer children to a urologist if a testicle has not descended by 6 months of age.
- Testicular torsion accounts for 20–30% of acute scrotum cases and is a surgical emergency. All families with boys should be counseled and educated about testicular torsion, as it is common for boys to delay notifying an adult of symptoms due to embarrassment.
- Pubertal patients should be encouraged to perform regular self-exam.

References

1. Care of the uncircumcised penis. Elk Grove Village: American Academy of Pediatrics, 1999. http://www.cirp.org/library/normal/aap-care1999/. Accessed 3 Nov 2018.
2. Circumcision policy statement. American Academy of Pediatrics. Task force on circumcision. Pediatrics. 1999;103(3):686–93.

Suggested Reading

Bani Hani O, Prelog K, Smith GH. A method to assess posterior urethral valve ablation. J Urol. 2006;176(1):303–5.

Bomalaski MD, Anema JG, Coplen DE, Koo HP, Rozanski T, Bloom DA. Delayed presentation of posterior urethral valves: a not so benign condition. J Urol. 1999;162(6):2130–2.

Bushinsky DA, Coe FS, Moe OW. Nephrolithiasis. In: Brenner BM, editor. Brenner & Rector's the kidney, vol. 2. 9th ed. Philadelphia: Elsevier Saunders; 2012. p. 1455–507.

Care of the uncircumcised penis. Elk Grove Village: American Academy of Pediatrics. 1999. http://www.cirp.org/library/normal/aap-care1999/. Accessed 3 Nov 2018.

Hutson J. Undescended testis, torsion, and varicocele. In: Grosfeld JL, O'Neill JA, Coran AG, Fonkalsrud EW, editors. Pediatric surgery. Philadelphia: Mosby Elsevier; 2006. p. 1193–214.

Johnson CE, Corey HE, Elder JS. Urinary tract infections in childhood. Consens Pediatr. 2003;1:1–28.

Lannon CM, Bailey AGB, Fleischman AR. Circumcision policy statement. American Academy of Pediatrics. Task force on circumcision. Pediatrics. 1999;103:686–93.

Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Academy of Pediatrics. Committee on quality improvement. Subcommittee on UTI. Pediatrics. 1999;103(4 Pt 1):843–52. Erratum in Pediatrics. 1999;103(5 Pt 1):1052; 1999;104(1 Pt 1):118; 2000;105(1 Pt 1):141.

Weiss R, Duckett J, Spitzer A. Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). The International Reflux Study in Children. J Urol. 1992;148(5):1667–73.

Dermatology

26

Megan Craddock and Jennifer Ruth

SKIN DISORDERS OF THE NEWBORN

Erythema Toxicum

Background

- Cause unknown
- Occurs in 50% of infants
- Benign, self-limited condition in term infants
- Usually begins 24–48 h after birth

Clinical Presentation

- Discrete erythematous blotchy macules with central papule or pustule (Fig. 26.1)
- Affects the face, trunk, and extremities
- Spares the palms and soles
- Wright or Giemsa stain shows *eosinophils*
- Lasts 1 week or less

Management

- Reassurance

Transient Neonatal Pustular Melanosis

Background

- Cause unknown
- Classically occurs in dark-skinned newborns
- Benign, self-limited condition in term infants
- Present at birth

Clinical Presentation

- Fragile vesiculopustules and hyperpigmented macules with a collarette of scale
- Hyperpigmented macules may persist for several months
- Wright or Giemsa stain shows neutrophils

Management

- Reassurance

Miliaria

Background

- Obstruction of the eccrine ducts

Clinical Presentation

- *Miliaria crystallina*: superficial ductal obstruction, fragile vesicles resembling water droplets on the skin (Fig. 26.2)
- *Miliaria rubra*: non-follicular erythematous papules or pustules on the forehead, upper trunk, flexural areas, or covered skin

M. Craddock (✉)
Department of Dermatology and Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA
e-mail: mfcraddo@texaschildrens.org

J. Ruth (✉)
Department of Dermatology and Pediatrics, Dell Children's Medical Group, Austin, TX, USA
e-mail: jennifer.ruth@ascension.org

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_26

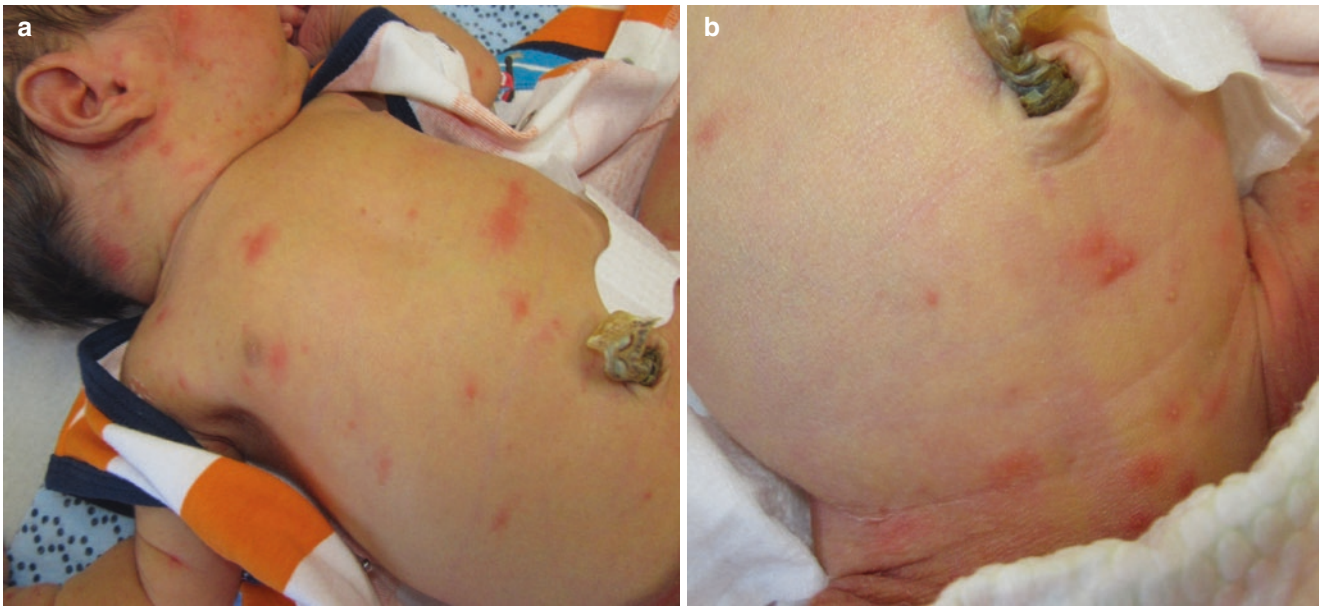


Fig. 26.1 (**a**) 5-day-old infant with erythema toxicum of the neck, chest, and abdomen (**b**) Scattered papules and pustules with surrounding erythema on the abdomen and suprapubic skin

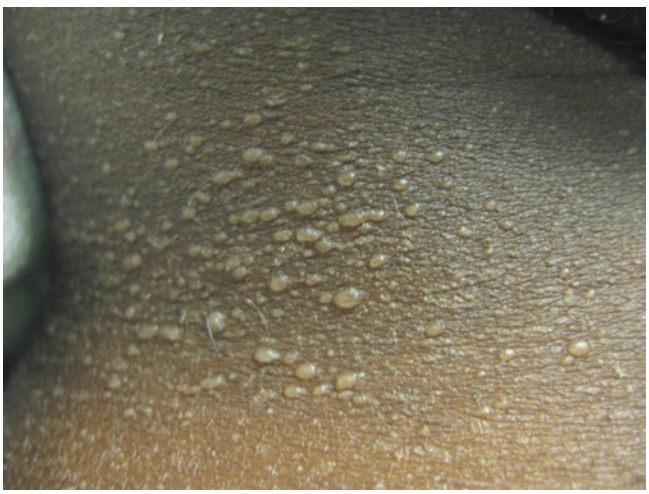


Fig. 26.2 Miliaria crystallina: Scattered fragile vesicles on the posterior neck of a child

- *Miliaria profunda:* deepest level of obstruction, white papules, can prevent adequate sweating

Management

- Avoid excessive heat, overdressing, or application of thick emollients in hot, humid climates
- Cool baths, air-conditioned environment, and lightweight cotton clothing

Nevus Sebaceus (of Jadassohn)

Background

- Hamartoma of sebaceous glands, hair follicles, and apocrine glands
- Rarely associated with neurologic, ocular, or skeletal abnormalities

Clinical Presentation

- Usually present at birth as a solitary, yellow-orange, round-to-oval, hairless plaque
- May become more verrucous during adolescence
- Most common on the scalp (Fig. 26.3)

Management

- Clinical observation vs. surgical excision
- Prophylactic excision is controversial but can be considered due to risk of thickening at puberty and small risk of developing benign > malignant neoplasms within the nevus

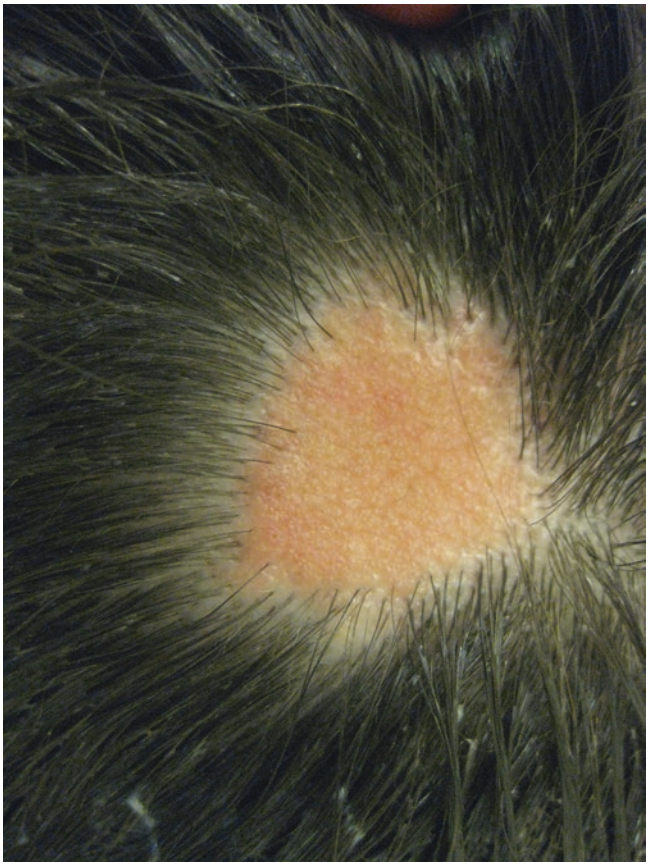


Fig. 26.3 Nevus sebaceous: Yellow-orange verrucous plaque on the scalp of an adolescent

Diaper Dermatitis (Table 26.1 and Fig. 26.4)

Table 26.1 Diaper dermatitis

Diaper rash	Irritant dermatitis	Candidiasis	Seborrheic dermatitis
Cause	Moisture, friction, enzymes in stool	*Candida* species	Unknown, may represent an inflammatory response to *Malassezia furfur*
Clinical presentation	Red patches that involve convex areas; inguinal creases are spared	Red patches involving convex areas and inguinal creases, satellite papules and pustules	Salmon-pink patches with greasy scale involving convex areas and inguinal creases; involvement of the scalp, face, and retroauricular skin may be present
Management	Frequent diaper changes, highly absorbent diapers, topical barrier creams or ointments with every diaper change	Topical antifungal cream	Topical antifungal cream or low-potency topical corticosteroid

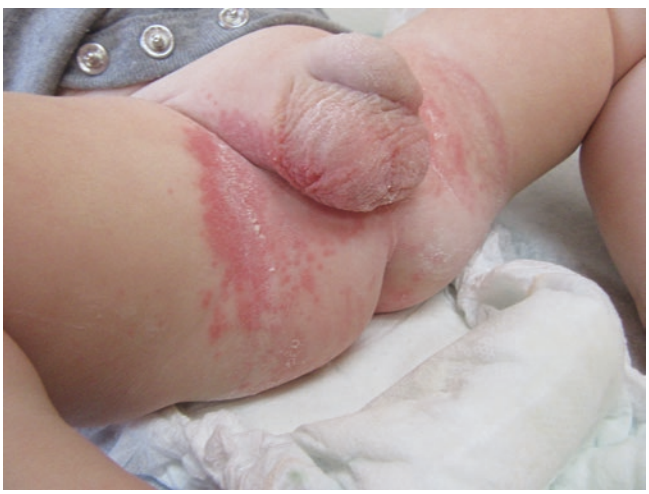


Fig. 26.4 Young male with a diaper dermatitis secondary to candida. Note the erythematous satellite papules and pustules

ECZEMATOUS DERMATITIS

Atopic Dermatitis

Background

- Chronic, inflammatory pruritic skin disorder
- Pathogenesis is multifactorial: genetic predisposition, immune dysregulation, epidermal barrier dysfunction, and environmental triggers
- Increased risk of developing other components of the atopic triad (asthma or allergic rhinitis)

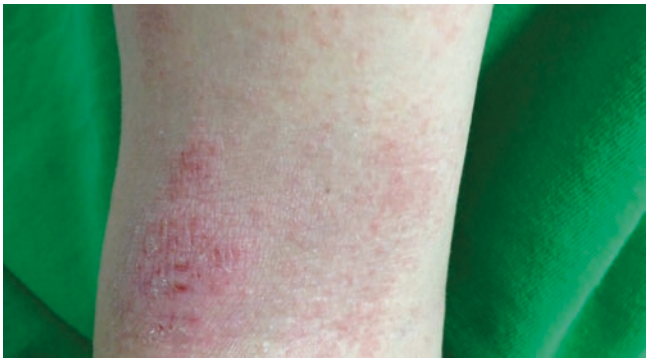


Fig. 26.5 14-year-old male with eczema affecting the antecubital fossa (Image courtesy of Sitratullah Olawunmi Kukoyi-Maiyegun, MD, Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas)

Clinical Presentation

- Symmetric, scaly, red patches and plaques, often with overlying crust
- Distribution of rash is dependent upon the age of the child
- Infants and toddlers: involvement of the face, trunk, and extensor extremities
- Childhood: flexural areas such as the antecubital and popliteal fossae (Fig. 26.5)
- Adolescents: flexural distribution but often develop lesions on the face, neck, and hands

Complications

- Increased risk of skin infections including *Staphylococcus aureus*, molluscum contagiosum, and herpes simplex virus
- Herpes simplex virus ("eczema herpeticum"): sudden onset of grouped vesicles and punched-out erosions, particularly within areas of atopic dermatitis (Fig. 26.6)

Variants

- Nummular eczema: coin-shaped, pruritic, scaly, or crusted papules or plaques
- Dyshidrosis: recurrent or chronic vesicles that affect the palms, lateral fingers, and soles
- Juvenile plantar dermatosis: erythematous scaly plaques involving the distal toes and soles with sparing of the interdigital spaces; cracking, fissures, or a "glazed appearance" can be seen

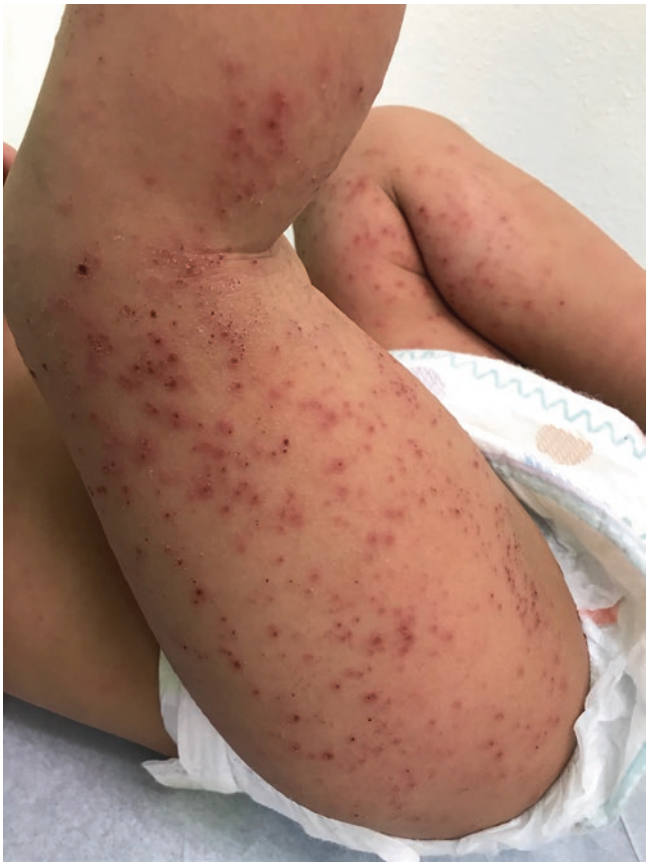


Fig. 26.6 Eczema herpeticum affecting the lower extremities of a toddler with known eczema. Note the scattered erythematous papules and punched-out erosions

Management

- Use of thick emollients such as ointments or creams is the cornerstone of therapy
- Apply topical corticosteroids twice daily to areas of inflammation until resolved
- Topical corticosteroids vary in strength from class VII (very low potency) to class I (very high potency). Therapeutic choice varies based upon severity and anatomic site, for example:
  - Low-potency corticosteroids such as hydrocortisone 2.5% ointment are preferred for delicate areas like the face, intertriginous skin, and genitals

  - Medium-potency corticosteroids such as triamcinolone 0.1% ointment are appropriate for the trunk or extremities
- Avoid the use of systemic corticosteroids
- Alternative therapies to low-potency topical corticosteroids include topical calcineurin inhibitors (tacrolimus or pimecrolimus) or a topical PDE4 inhibitor (crisaborole)
- Topical or systemic antibiotics as needed for secondary bacterial infections; bleach baths can be used to decrease bacterial colonization

Keratosis Pilaris

- Folliculocentric papules with a central core of keratin debris, may have associated erythema
- Usually located on the cheeks, extensor surface of the arms, and thighs (Fig. 26.7)
- Treatment is difficult; options include low-potency topical corticosteroids for associated erythema, topical retinoids, or emollients which contain an exfoliant (e.g. lactic acid)

Contact Dermatitis

Background

- May be irritant or allergic (delayed hypersensitivity reaction)

Perioral Irritant Contact Dermatitis

- Form of irritant contact dermatitis from licking lips
- Also known as lip-licker's dermatitis (Fig. 26.8)

Rhus Dermatitis (Poison Ivy)

- Form of allergic contact dermatitis caused by urushiol from plant sap
- Causes itching, erythema, papules, vesicles, or bullae in a linear or irregular distribution
- Fluid from ruptured vesicular or bullous lesions does not spread eruption
- Management: immediate washing with soap and water, cool compresses, topical corticosteroids, or antihistamines for pruritus; oral corticosteroids, if used, should be tapered slowly over several weeks

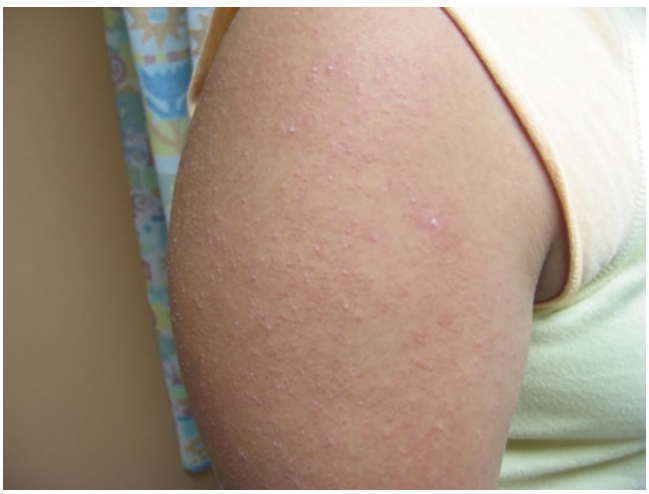


Fig. 26.7 Adolescent female with folliculocentric papules on the extensor surface of the right arm consistent with keratosis pilaris

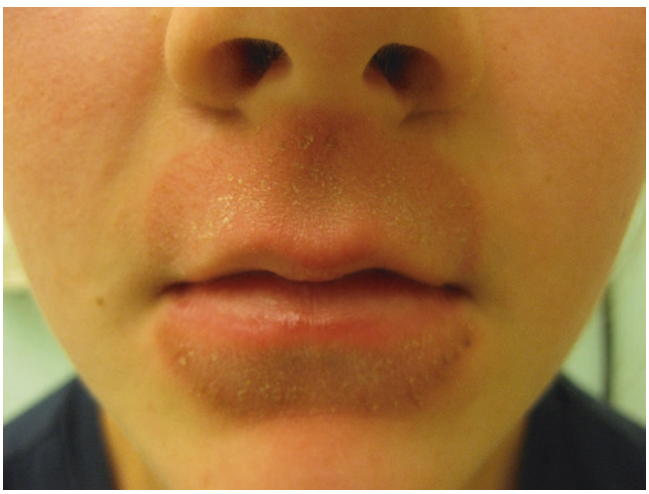


Fig. 26.8 Young male child with lip-licker's dermatitis

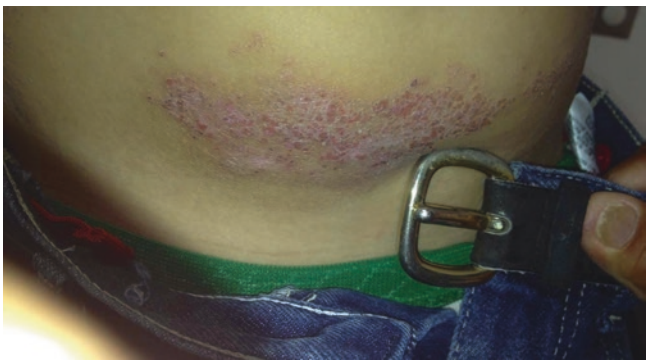


Fig. 26.9 10-year-old male with a nickel contact dermatitis

Nickel Dermatitis

- Form of allergic contact dermatitis that develops from exposure to jewelry or metal closures on clothing (Fig. 26.9)

Seborrheic Dermatitis

Background

- Cause unknown, may be an inflammatory response to *Malassezia furfur*

Clinical Presentation

- Salmon to pink patches with greasy scale involving the scalp, face, retroauricular creases, and diaper area
- Seborrheic dermatitis of the scalp (cradle cap) is common in infants, which peaks at 3 months of life (Fig. 26.10)

Management

- Mineral oil, ketoconazole or selenium sulfide shampoo, topical corticosteroids, or topical antifungals

Acrodermatitis Enteropathica

Background

- An autosomal recessive disorder affecting the uptake of zinc

Clinical Presentation

- Usually presents after being weaned from breast milk

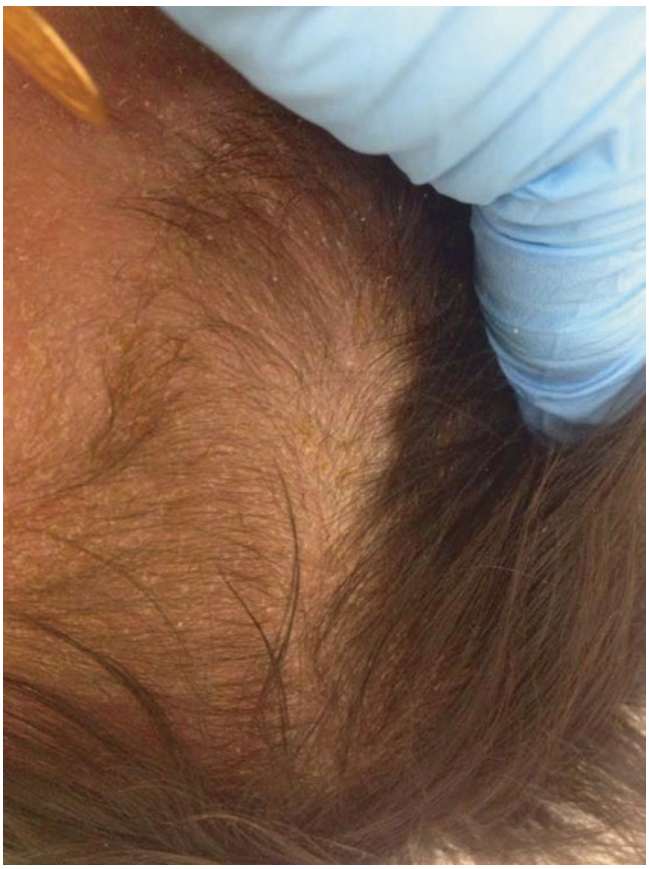


Fig. 26.10 2-month-old baby with seborrheic dermatitis of the scalp

- Zinc deficiency results in a triad of the following:
  - Well-demarcated eczematous to eroded plaques surrounding the mouth, diaper area, and distal extremities
  - Alopecia
  - Diarrhea

Management

- Zinc supplementation will lead to rapid improvement

ACNE

Acne Vulgaris

Background

- Obstruction of the pilosebaceous apparatus is due to hyperkeratinization and increased sebum production

- Inflammation is fueled by an increased density of *Propionibacterium acnes*, a normal resident flora
- Exacerbating factors: hormonal dysregulation/increased androgen states; anabolic steroids, corticosteroids, certain contraceptives, and topical products/mechanical factors that obstruct the pilosebaceous unit
- Types of acne: comedonal (open or closed comedones), inflammatory (papules, pustules, nodules, cysts), mixed (comedonal and inflammatory)

Clinical Presentation

- Open comedones (blackheads)
- Closed comedones (whiteheads): white papules without surrounding erythema
- Inflammatory acne: erythematous papules, pustules, cysts, and/or nodules (Fig. 26.11)
- Can be associated with post-inflammatory dyspigmentation or scarring

Differential Diagnosis

- Adenoma sebaceum (facial angiofibromas) may be mistaken for acne vulgaris

Management

- Topical therapies such as retinoids and benzoyl peroxide
- Antibiotics (topical or systemic), hormonal therapies, and oral retinoids may be considered for more severe disease
- Antibiotics should be used in combination with benzoyl peroxide to decrease *P. acnes* resistance

Neonatal and Infantile Acne

Background

- Neonatal acne starts in the first few weeks of life
- Infantile acne starts at 3–6 months of age

Clinical Presentation

- Face is the primary site of involvement
- Neonatal acne: small inflammatory papules and pustules most common (Fig. 26.12)
- Infantile acne: open and closed comedones most common
- Inflammatory lesions and scarring may occur, especially with the infantile form

Management

- Reassurance for neonatal acne (brief, self-limited eruption)
- Infantile acne: topical retinoids for comedonal lesions
- Topical benzoyl peroxide or topical antibiotics for inflammatory lesions

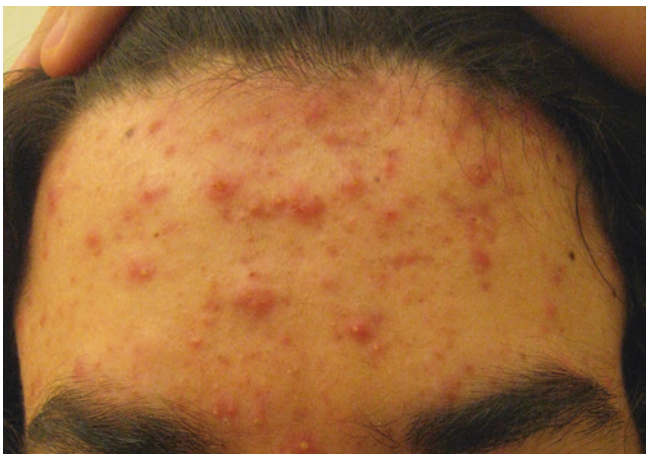


Fig. 26.11 Teenage male with papules, pustules, and rare nodules consistent with inflammatory acne vulgaris

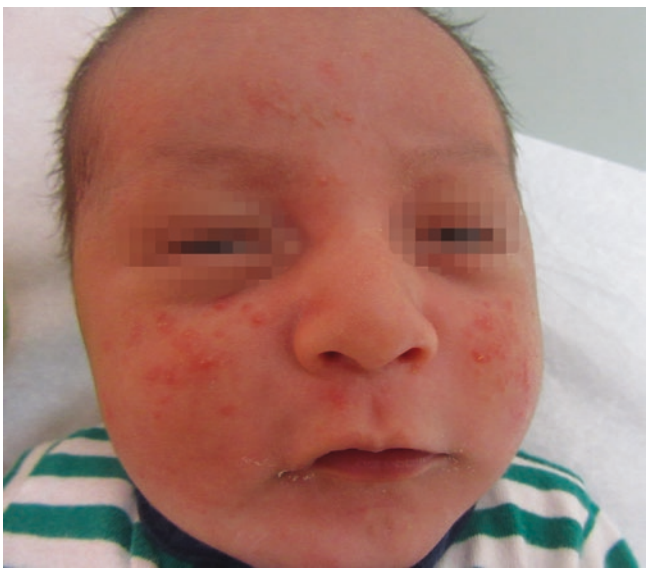


Fig. 26.12 Neonatal acne: Scattered erythematous papules and pustules on the forehead and cheeks

Periorificial Dermatitis

Background

- Common acneiform facial eruption in children
- Use of topical or inhaled corticosteroids often contributes to development

Clinical Presentation

- Red papules and papulopustules occur around the mouth, nose, and eyes (Fig. 26.13)

Management

- Topical antibiotics, such as metronidazole or clindamycin
- For severe cases, oral tetracyclines or erythromycin
- Stop the use of topical corticosteroids and wash face after use of inhaled corticosteroids
- Improvement is slow, often takes 6–8 weeks to clear

FUNGAL INFECTIONS

Tinea Capitis

Background

- *Trichophyton tonsurans* is the most common cause in the USA
- Most common in prepubertal children and uncommon in infants and adults
- African American children are disproportionately affected as compared to other ethnic groups
- Presence of alopecia, scaling, and occipital lymphadenopathy is highly suggestive

Clinical Presentation

- Alopecia: one or more round oval patches of partial to complete alopecia with associated *scaling* (Fig. 26.14); *T. tonsurans* causes hair breakage leaving behind black dots
- Seborrheic: mimics seborrheic dermatitis with patchy or diffuse white to grayscale; alopecia may be subtle
- Inflammatory or kerion: severely painful inflammatory reaction with deep, suppurative boggy lesions on the scalp (Fig. 26.15)
- Occipital lymphadenopathy is common
- A widespread papular dermatophytid rash, or id reaction, can occur after starting systemic treatment

Diagnosis

- Diagnosis is usually made clinically
- Fungal culture can be performed to confirm infection

Management

- Oral antifungal therapy is necessary for clearance due to involvement of the hair follicle

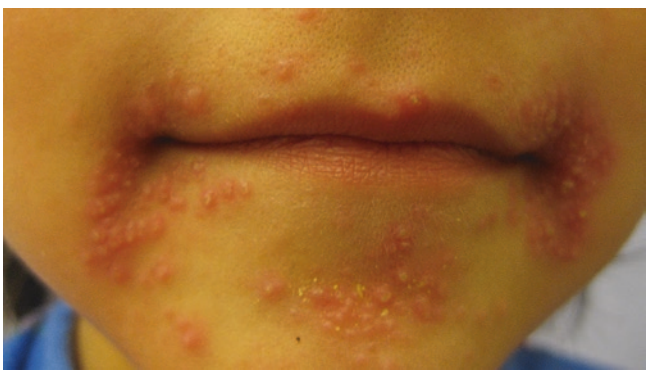


Fig. 26.13 Child with periorificial dermatitis. Note the erythematous papulopustules surrounding the mouth

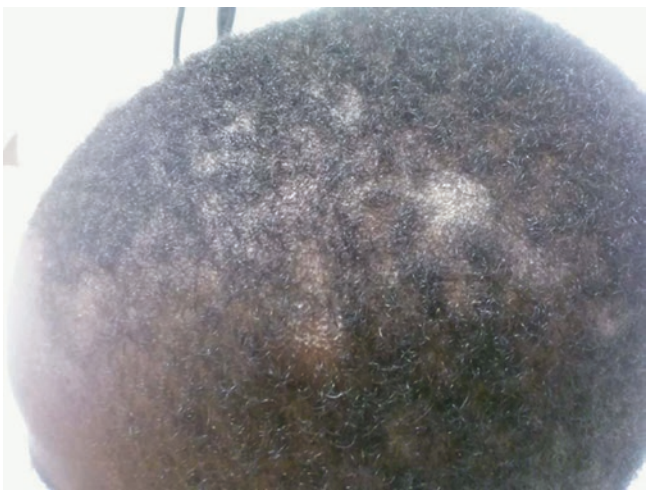


Fig. 26.14 6-year-old male with tinea capitis of the scalp. Skin findings include scalp scaling with associated alopecia

- Griseofulvin is the drug of choice (Table 26.2)
- Clearance requires at least 6 weeks or more of therapy
- Adjunctive topical therapy with selenium sulfide or ketoconazole shampoo twice weekly helps to reduce scales and curtail the spread of infection
- Incision and drainage of a kerion is not recommended
- Oral prednisone may be used for 2–4 weeks for severe inflammatory tinea capitis

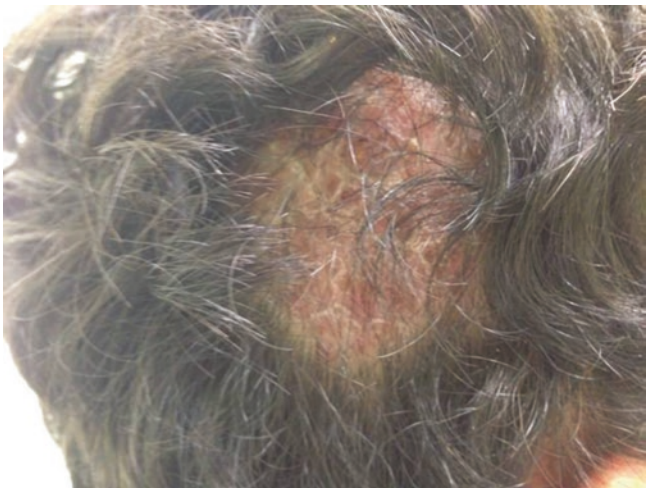


Fig. 26.15 Kerion secondary to tinea capitis. Note the erythematous indurated alopecia plaque on the occipital scalp

Tinea Corporis

Background

- Superficial fungal infection of the skin caused by a dermatophyte (T*richophyton*, *Microsporum*, and *Epidermophyton*)
- *Trichophyton rubrum* is the most common infectious agent in the world

Clinical Presentation

- Single or multiple annular (ring-like) lesions with a raised, erythematous, and scaly border with central clearing
- Lesions are variably pruritic

Management

- Topical antifungal agents are effective
- Topical treatment should be applied twice daily for at least 2–3 weeks
- Systemic therapy may be used for extensive tinea corporis, immunocompromised patients, or those cases refractory to topical therapy

Table 26.2 Common systemic antifungals

Drug name	Mechanism of action	Monitoring/warnings	Tips
Griseofulvin	Blocks mitotic spindle	No routine monitoring needed in healthy patients	Commonly used for tinea capitis
			Limited efficacy for onychomycosis
			Not effective for tinea versicolor
Terbinafine	Blocks cell wall synthesis (inhibits squalene epoxidase)	Advisable to check liver function before and during therapy	Not effective for tinea versicolor
			Commonly used for onychomycosis
			Effective for tinea capitis, especially *Trichophyton* species
Fluconazole	Blocks cell wall synthesis (inhibits lanosterol-14-alpha-demethylase)	Can prolong the QT interval	Effective for extensive/recurrent tinea versicolor
Itraconazole	Blocks cell wall synthesis (inhibits lanosterol-14-α-demethylase)	Can prolong the QT interval	Effective for extensive/recurrent tinea versicolor
		Do not use in patients with ventricular dysfunction	Can use pulse dosing for onychomycosis
		Advisable to check liver function before and during therapy	

Tinea Cruris

Background

- Dermatophyte infection of the groin or upper thighs
- Caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*
- A warm, humid environment and tight-fitting clothing are predisposing factors
- More common in men and rare before puberty

Clinical Presentation

- Erythematous patches and pustules on the inner thigh and inguinal creases
- Border of lesions is elevated with scale
- The scrotum and labia majora are commonly spared
- May be intensely pruritic; scratching leads to erosions, inflammation, and lichenification

Management

- Topical antifungal until clearance, usually 3–4 weeks
- Avoid tight-fitting clothing and dry after bathing
- May use absorbent powder such as Tinactin

Tinea Pedis

Background

- Dermatophyte infection of the feet
- Caused by *Trichophyton*, *Epidermophyton*, or *Microsporum*
- Common in adolescents and adults

Clinical Presentation

- Interdigital: erythema, fissures, scaling, and maceration in the interdigital spaces of the toes
- Vesicular: vesicles, bullae, and erosions on the instep of the foot
- Moccasin: erythema, fissure, and scaling of the plantar surface of the foot with extension to the lateral surfaces

Management

- Topical antifungals to be applied until the eruption clears
- Severe or persistent cases may require oral antifungal therapy
- Keep feet dry and wear well-ventilated shoes or sandals
- Recommend regular use of absorbent powders in recurrent cases

Tinea Versicolor

Background

- Caused by yeast forms of *Malassezia furfur* that invade the stratum corneum
- Occurs in adolescents and adults, rare in children

Clinical Presentation

- Small hypopigmented or hyperpigmented round or oval macules located on the trunk, proximal extremities, and/or neck (Fig. 26.16)
- Individual lesions may coalesce into large patches
- Sun exposure may accentuate the appearance in fair-skinned individuals

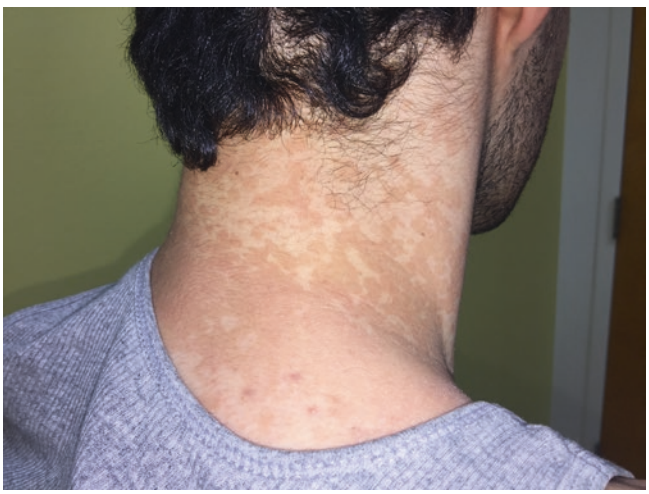


Fig. 26.16 Tinea versicolor: Hyperpigmented, thin scaly papules and plaques on the posterior neck of an adolescent

Diagnosis
- Diagnosis is usually made clinically
- KOH preparation will reveal short hyphae and spores (spaghetti and meatballs)

Management
- Topical antifungals such as selenium sulfide lotion or ketoconazole shampoo
- Oral antifungals such as fluconazole can be used for persistent or recurrent infections
- Normalization of pigmentation may take months

Onychomycosis

Background
- Fungal infection of the nail, usually due to dermatophytes such as *Trichophyton*, *Epidermophyton*, or *Microsporum*
- Toenails are more affected than fingernails
- Common in adolescents and adults

Clinical Presentation
- Commonly seen with tinea pedis or tinea manuum (dermatophyte infection of the hands)
- One or multiple nails may be involved
- Subungual onychomycosis: thickening of the nail with yellow discoloration
- Superficial white onychomycosis: white discoloration with fine powdery scale

Management
- Oral therapy is required for definitive treatment (see Table 26.2)
- Recurrence is common

INFESTATIONS

Scabies

Background
- Common skin infestation by *Sarcoptes scabiei*
- The microscopic scabies mite burrows into the upper layer of the skin where it lives and lays eggs
- Spreads by direct, prolonged, skin-to-skin contact

Clinical Presentation
- Pruritus, often more intense at night
- Papules, burrows (white-gray thread-like lines), and vesiculopustules
- Common locations: wrists, ankles, axillae, waist, groin, palms, and soles
- Infants may present with less common features such as involvement of the scalp or a robust hypersensitivity reaction to the mite characterized by red to brown nodules in the trunk, axillae, or groin

Diagnosis
- Clinical diagnosis
- Confirmatory test: skin scraping with mineral oil and use of a microscope to identify the mites, eggs, or feces

Management
- All contacts and family members of a child with scabies will require treatment even if asymptomatic
- Permethrin 5% cream is first-line treatment; perform two treatment applications spaced 1 week apart
- Thorough cleansing of all dirty clothing, towels, bedding, and car seat covers

Pediculosis

Background
- Pediculosis capitis (head lice) is caused by infestation of the human head with *Pediculus humanus capitis* (head louse)
- Head lice are transmitted via head-to-head contact or fomites
- Crab lice, an infestation of the pubic region, caused by *Phthirus pubis* (pubic louse), is often sexually transmitted
- Louse life cycle
  - Eggs/nits hatch after ~7 days
  - A louse reaches adulthood after ~16 days
  - An individual louse lives ~30 days

Clinical Presentation

- Pruritus
- Eggs, nits, and adult lice on the hair shaft
- For head lice, regional lymphadenopathy (cervical, suboccipital) is common
- For crab lice, gray-blue macules may be seen on the abdomen or inner thighs

Management

- Permethrin 1% topical liquid is first-line treatment for head lice and crab lice
- Perform two treatment applications spaced 1 week apart
- For crab lice, sexual partners need treatment

Bedbugs

Background

- *Cimex lectularius*, the common bedbug, is a nocturnal ectoparasite
- Bite reactions are caused by an immune reaction to the bug's saliva

Clinical Presentation

- Erythematous, edematous, pruritic papules on exposed areas of the body
- Classically occurs in clusters of three ("breakfast, lunch, and dinner")

Management

- Topical corticosteroids and antihistamines for pruritic papules/bites
- In-home bug treatment by a professional exterminator

Papular Urticaria

Background

- Common hypersensitivity reaction to insect bites

Clinical Presentation

- Pruritic, erythematous, urticarial papules
- Papules are grouped similar to arthropod bites
- Papules usually occur at sites of bites, but can also be generalized even to sites where a bite did not occur

Management

- Symptomatic treatment for pruritus with topical steroids and antihistamines
- Protect against insect bites with clothing and insect repellant

PAPULOSQUAMOUS DISORDERS

Psoriasis

Background

- Papulosquamous (elevated lesions with scale) condition with tendency to persist or recur for years
- An immune-mediated disorder that is likely influenced by both genetics and environment

Clinical Presentation

- Well-defined papules and plaques that are pink to deep red with adherent white to silver scale
- Removal of scale produces pinpoint bleeding (Auspitz sign)
- Commonly located on the scalp, elbows, knees, umbilicus, and gluteal cleft
- Infants may present with involvement of the diaper area
- Lesions appear in areas of trauma (Koebner phenomenon)
- Nail pitting, thickening, and discoloration may be seen

Management

- Topical corticosteroids (first-line of treatment)

- Phototherapy (narrow-band UVB) may be used in patients with moderate to severe disease
- Systemic therapy, for example, methotrexate or biologics (e.g. TNF-alpha [α] inhibitors), may be used in severe cases

Pityriasis Rosea

Background

- Self-limited condition of unclear etiology
- Seasonal incidence and clustering of cases suggest an infectious agent (postulated to be viral)

Clinical Presentation

- Often starts with a "herald patch," a single oval plaque with peripheral scale that can be mistaken for tinea corporis
- Days to weeks later, numerous oval scaly papules and plaques appear on the trunk (Fig. 26.17)
- The long axis of these lesions is oriented along lines of cleavage (resembles a Christmas tree)
- Pruritus is variable

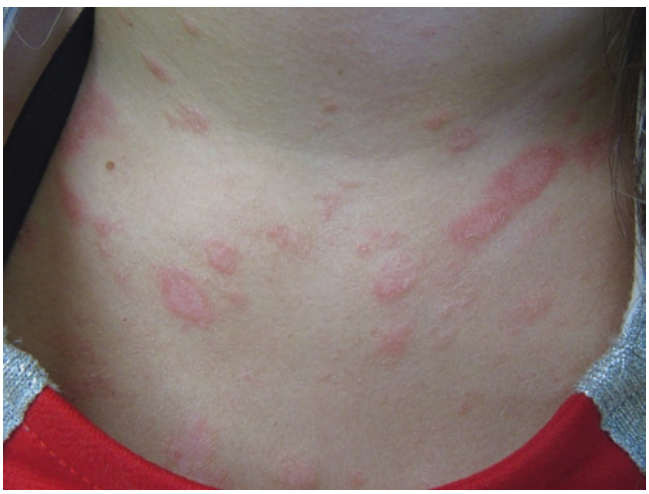


Fig. 26.17 Pityriasis rosea: Erythematous, scaly, and oval papules and plaques follow skin cleavage lines on the neck and chest of an adolescent

- New lesions appear for 2–3 weeks
- Eruption typically resolves over 6–8 weeks

Management

- Reassurance given the self-limited nature
- Symptomatic therapy (emollients, antihistamines, mild topical corticosteroids) if pruritus is present
- Differential diagnoses include psoriasis, tinea corporis, or secondary syphilis

LICHENOID DISORDERS

Lichen Nitidus

Background

- Occurs in school-age children
- Self-limited, benign condition of unclear etiology

Clinical Presentation

- Monomorphic, flat-topped, skin-colored papules
- Commonly located on the upper extremities, trunk, and genitals
- Lesions appear in areas of trauma (Koebner phenomenon)

Management

- Spontaneous resolution with time, may take months to years
- No curative therapy

Lichen Sclerosus

Background

- Predominantly occurs in prepubertal females, uncommon in males

Clinical Presentation

- Well-demarcated, pink to ivory white, flat-topped papules and plaques that become atrophic with time

- The anogenital region is most often affected
  - Females: Involvement of the vulva and perianal region results in the classic figure-of-8 pattern
  - Males: Involvement of the glans penis is referred to as balanitis xerotica obliterans, which can be a cause of acquired phimosis
  - May see purpura within lesions
  - Involvement commonly causes pain, pruritus, and bleeding with urination or defecation
- Extragenital involvement is often asymptomatic

Management

- Treatment is important as atrophy, and scarring can lead to alteration of normal anogenital anatomy
- Ultrapotent topical corticosteroids are first-line treatment
- If phimosis is present, circumcision may be required
- May improve at the time of puberty

VASCULAR TUMORS

Infantile Hemangioma (IH)

Background

- Most common benign soft tissue tumor in childhood
- Unclear etiology
- Risk factors for development of IH include prematurity, female gender, multiple gestation, advanced maternal age, preeclampsia, and placenta previa

Clinical Presentation

- Commonly located on the head and neck
- Most become evident at 2–3 weeks of age with predominant growth during the first 5 months of life
- IHs slowly improve over years with the majority of regression occuring by school age
- After resolution, scarring, discoloration, or fibrofatty tissue may be left behind
- Classified as superficial, deep, or mixed IHs
  - Superficial: bright-red, dome-shaped papules, plaques, or tumors; coined "strawberry hemangioma" (Fig. 26.18)
  - Deep: blue- to purple-hued subcutaneous nodule or tumor; may appear later and have a longer growth phase
  - Mixed: bright-red papule or plaque with an underlying subcutaneous component
- Most common complication is ulceration

Management

- Reassurance for most IHs
- Factors that influence decision to treat: size, location, functional impairment (e.g. obstruction of vision), and cosmetic impact
- Most effective treatment is oral beta-blockers
- Other treatment options: topical beta-blockers, topical/intralesional/oral corticosteroids, or surgical excision

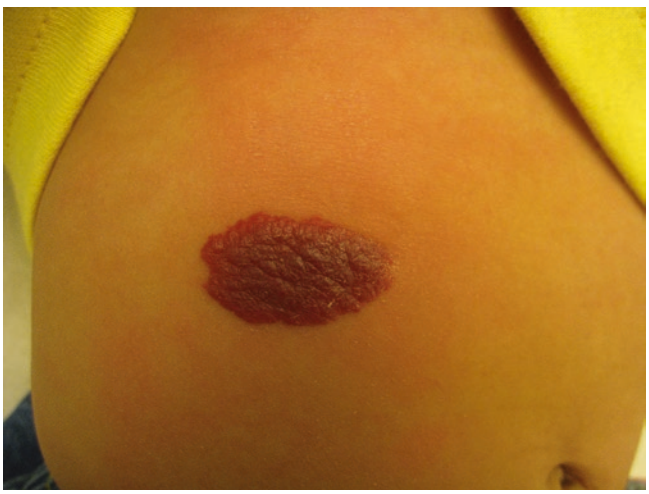


Fig. 26.18 6-month-old female with a superficial infantile hemangioma on the right abdomen

- Treatment for ulceration: wound care, antibiotics if secondarily infected, pulsed-dye laser, and/or oral beta-blockers

Infantile Hemangioma Variants

- Diffuse neonatal hemangiomatosis
  - Association of 5 or more cutaneous IHs with extracutaneous organ involvement (usually hepatic)
  - May see hypothyroidism, anemia, and thrombocytopenia
- PHACE syndrome
  - **P**osterior fossa malformation, **H**emangioma, **A**rterial anomalies, **C**ardiac anomalies, **E**ye abnormalities
  - The hallmark hemangioma is an extensive, segmental IH of the face
- Lumbosacral hemangiomas
  - Associated with lower body IH, spinal dysraphism, urogenital anomalies, bony deformities, anorectal malformations, and renal anomalies
  - Image to evaluate for underlying spinal anomalies
- Beard hemangiomas
  - Location on the lower lip, chin, and preauricular, mandibular, or neck areas
  - Extensive IH in the above locations may be associated with upper airway involvement; symptoms include cough, biphasic stridor, and hoarse voice

Kasabach-Merritt Phenomenon

Background

- Phenomenon associated with vascular tumors, specifically kaposiform hemangioendothelioma or tufted angioma
- Occurs most commonly during the first few weeks of life
- High mortality rate: 10–30%

Clinical Presentation

- Presents with rapid enlargement of the vascular tumor, thrombocytopenia, hemolytic anemia, and coagulopathy

Management

- Medical treatments include sirolimus, corticosteroids, and chemotherapy agents such as vincristine
- Avoid platelet transfusions as they can lead to platelet trapping

VASCULAR MALFORMATIONS

- Localized defects of vascular channel formation without associated endothelial proliferation

Capillary Malformations

- Nevus simplex
  - Common vascular lesion in infants that may be due to persistent fetal circulation
  - Also called salmon patch, stork bite (nape of the neck), or angel kiss (forehead/glabella) (Fig. 26.19)
  - Dull-pink macules and patches usually located on the midface, posterior neck, and scalp
  - Facial lesions usually fade by 2 years, but may become prominent with crying or straining
- Port wine stain (PWS)
  - Also called nevus flammeus
  - Represents a true capillary malformation
  - Congenital pink to dark red macules and patches that persist throughout life and grow in proportion to the child
  - Stains may darken or thicken with age
  - PWSs are usually not associated with underlying disorders

Fig. 26.19 Nevus simplex in an infant (**a**) Erythematous patches on the forehead, glabella, upper eyelids, and upper cutaneous lip (**b**) Erythematous patch on the occipital scalp and neck

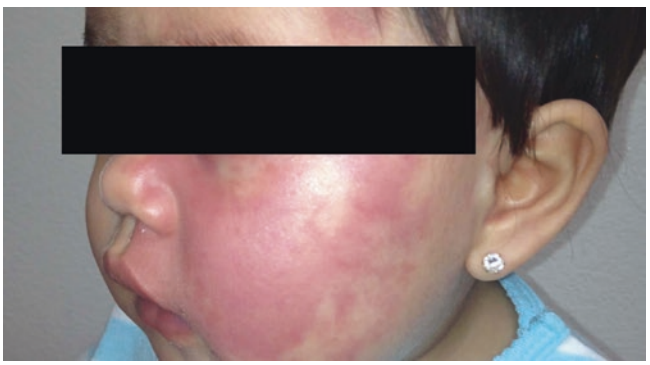


Fig. 26.20 9-month-old female with Sturge-Weber syndrome with associated glaucoma and seizures (Courtesy of Sitratullah O. Kukoyi-Maiyegun, MD, Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas)

  - Sturge-Weber syndrome: association of a facial port wine stain (usually involving the distribution of the first branch of the trigeminal nerve (V1) +/− other trigeminal dermatomes), leptomeningeal angiomatosis (usually causing seizures), and glaucoma (Fig. 26.20)

Management

- Pulsed-dye laser can be used to lighten the PWS
- Infants with a large facial PWS involving V1 or multiple trigeminal dermatomes warrant specialty referral (dermatology, ophthalmology, neurology) to evaluate for Sturge-Weber syndrome

Arteriovenous Malformation

Background

- Rare, dangerous vascular malformation with arterial and venous components and arteriovenous shunting

Clinical Presentation

- Cephalic location is most common
- May present with a red patch simulating a PWS, a pulsating mass with thrill, or necrosis and ulceration
- Occasional association with cardiac compromise

Management

- Ultrasound, MRI, and arteriography can help to confirm the diagnosis
- Treatment is challenging, but may include embolization and excision

HYPERSENSITIVITY REACTIONS

Urticaria

Background

- Type I hypersensitivity reaction with skin manifestations
- Activation of mast cells leads to degranulation and release of vasoactive mediators such as histamine, leukotrienes, and prostaglandins
- Acute urticaria lasts < 6 weeks; chronic urticaria lasts > 6 weeks
- The majority of acute urticaria in children is secondary to infection, usually a virus

Clinical Presentation

- Well-circumscribed erythematous pruritic wheals on the skin and mucous membranes (Fig. 26.21)
- Transient skin lesions; each lesion commonly lasts less than 12–24 h
- May be polycyclic, annular, or serpiginous; annular lesions may be confused with erythema multiforme
- Urticaria multiforme describes a morphologic subtype with erythematous annular or polycyclic wheals with a dusky or ecchymotic center (Fig. 26.22)

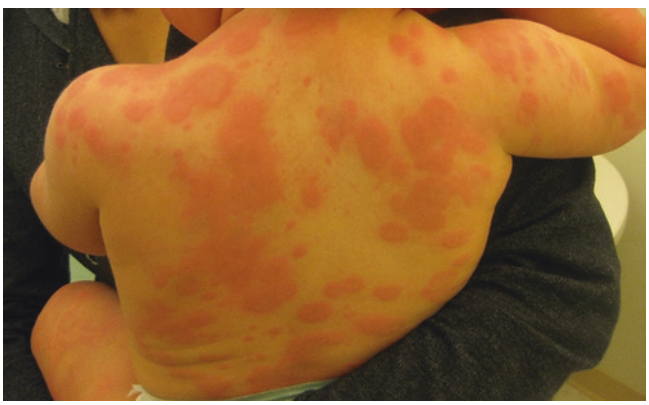


Fig. 26.21 2-year-old female with urticaria secondary to a recent viral infection

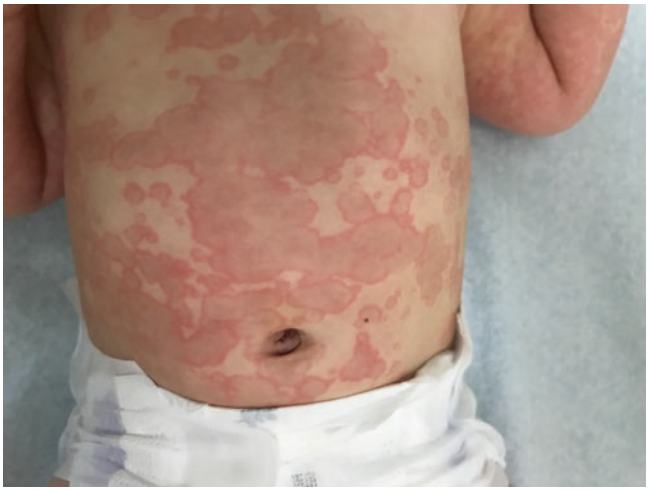


Fig. 26.22 Urticaria multiforme: Erythematous annular wheals with a dusky center scattered on the back of an infant

Management

- Reassurance; majority of urticaria will resolve within 2 weeks
- Symptomatic treatment with non-sedating histamine (H1) blockers such as cetirizine, loratadine, or fexofenadine during the day and sedating histamine blockers at night such as diphenhydramine or hydroxyzine
- For chronic urticaria, further evaluation is warranted by a dermatologist or allergist

Cutaneous Lupus Erythematosus (CLE)

Background

- May be an isolated finding or associated with underlying systemic lupus erythematosus
- Classification includes acute CLE, subacute CLE, and chronic CLE

Clinical Presentation

- Acute CLE: malar or generalized photodistributed rash, often associated with systemic disease
  - Erythematous, scaly papules or plaques involving the nasal bridge and cheeks ("butterfly rash"); when present on the dorsal hands, the rash typically spares the skin overlying the joints

- Subacute CLE: uncommon in pediatric patients, annular or polycyclic erythematous plaques involving the upper trunk and upper extremities, mild systemic manifestations if present
- Chronic CLE: can be classified as discoid lupus or lupus panniculitis; these are rare in children
  - Discoid lupus: well-circumscribed erythematous indurated plaques most common on the face and ears, if untreated can lead to dyspigmentation and atrophy, may be associated with systemic disease
  - Lupus panniculitis: well-circumscribed indurated subcutaneous papules or nodules most common on the face, upper arms, thighs, or buttocks; may lead to significant disfigurement

Management

- Evaluation for underlying systemic disease especially if other symptoms are present
- Strict sun protection, topical anti-inflammatory agents such as topical corticosteroids, and occasionally anti-malarials (hydroxychloroquine) or oral corticosteroids

Erythema Multiforme (EM)

Background

- Self-limited hypersensitivity reaction with the majority of cases secondary to herpes simplex virus
- Commonly lasts 1–4 weeks and can be recurrent
- May involve both the skin and mucous membranes

Clinical Presentation

- Symmetric, fixed, erythematous targetoid (3 zones of color/concentric circles) papules or plaques often on the distal extremities
- Up to 50% of patients may have mucous membrane involvement
- Mild symptoms may be present such as fever, malaise, myalgia, and arthralgia

Management

- Resolution within 1–4 weeks
- If recurrent, may consider prophylactic treatment with acyclovir

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (Table 26.3)

- Variants of the same hypersensitivity syndrome categorized by the extent of epidermal detachment

Table 26.3 Differences between Stevens-Johnson syndrome and toxic epidermal necrolysis

	Stevens-Johnson syndrome	Toxic epidermal necrolysis
Cause	Medications or infection	Medications
Pattern of skin lesions	Erythematous macules or papules, target-like lesions, vesicles and erosions	Erythematous macules and papules, target-like lesions, and diffuse epidermal detachment
Mucous membrane involvement	Severe mucosal involvement of ≥ 2 sites such as the ocular, oral, or genital mucosa	Severe mucosal involvement
Body surface area with epidermal detachment (%)	Less than 10%	More than 30%
Management	Removal of offending agent, supportive care; systemic treatment is controversial but may include systemic corticosteroids, IVIG, and TNF-α inhibitors	Admission to ICU or burn center, removal of offending drug; treatment is controversial but may include systemic corticosteroids, IVIG, and TNF-α inhibitors

IVIG Intravenous immunoglobulin

- SJS: < 10% of epidermal loss
- SJS/TEN overlap: 10–30% of epidermal loss
- Toxic epidermal necrolysis (TEN): > 30% of epidermal loss (Fig. 26.23)
- Infection (e.g. Mycoplasma) and less commonly drugs (see list below), may cause SJS
- Majority of cases of TEN are secondary to drugs—allopurinol, antiepileptic agents (carbamazepine, lamotrigine, phenytoin), NSAIDs, sulfonamides, barbiturates, and penicillin

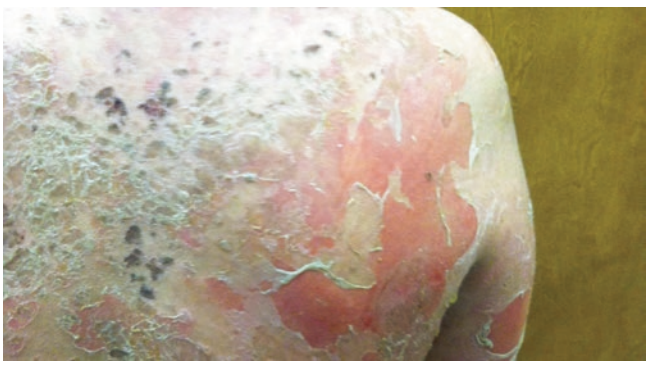


Fig. 26.23 Toxic epidermal necrolysis

VIRAL INFECTIONS OF THE SKIN

Molluscum Contagiosum

Background

- Common viral infection of the skin in young children
- Caused by a DNA poxvirus called the *Molluscum contagiosum* virus

Clinical Presentation

- Skin-colored to pink, domed, pearly papules with central depression (Fig. 26.24)
- Lesions can trigger a surrounding dermatitis ("molluscum dermatitis")
- Involvement is often more extensive in patients with atopic dermatitis

Management

- Treatment is not necessary as spontaneous resolution occurs in several months to years
- Potential therapeutic options: watchful waiting, intralesional candida antigen injections, topical

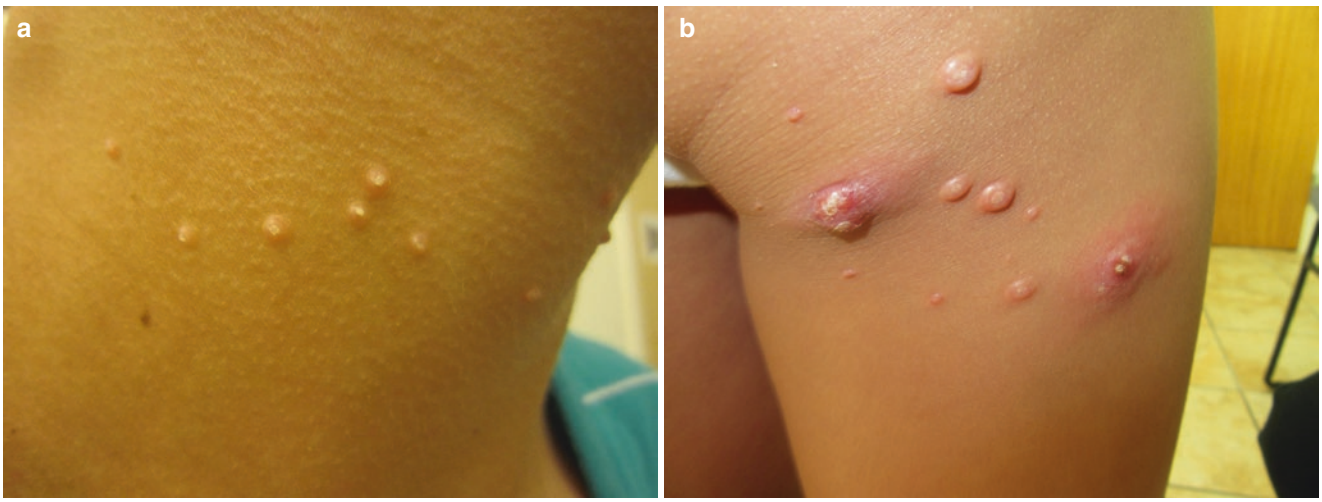


Fig. 26.24 Molluscum contagiosum (**a**) School-age child with molluscum contagiosum on the anterior neck (**b**) Toddler with molluscum contagiosum of the lateral lower extremity. There are two erythematous, indurated molluscum lesions secondary to immune reaction

therapies (cantharidin, imiquimod), or destructive modalities (liquid nitrogen, curettage)
- If pruritic, the molluscum dermatitis can be treated with twice-daily application of a low-potency topical corticosteroid

Verruca Vulgaris

Background
- Common viral infection caused by the human papillomavirus (HPV)

Clinical Presentation
- Single or multiple, skin-colored, verrucous papules
- Often located on the hands, but may be present on any skin surface (Fig. 26.25)

Management
- No specific antiviral therapy
- Potential therapeutic options: watchful waiting (often spontaneously resolve), topical salicylic acid, liquid nitrogen, immunotherapy (imiquimod, candida antigen injections, oral cimetidine)

Condyloma Acuminatum

Background
- Manifestation of HPV infection in the anogenital region
- Can spread via sexual transmission or benign transmission (autoinoculation, vertical transmission, fomites)

Clinical Presentation
- Skin-colored, soft, verrucous papules in the anogenital region

Management
- Be mindful of potential for sexual transmission/screen when appropriate
- Potential therapeutic options: watchful waiting, topical therapies (podophyllin, trichloroacetic acid, imiquimod), and destructive modalities (cryotherapy, electrodesiccation, curettage)

BACTERIAL INFECTIONS OF THE SKIN

Impetigo

Background
- Primarily caused by *S. aureus* and sometimes by group A beta-hemolytic streptococci (GABHS)
- Two forms: bullous and non-bullous
- Non-bullous impetigo is more common

Clinical Presentation
- Non-bullous form often presents with honey-colored scabs formed from dried serum

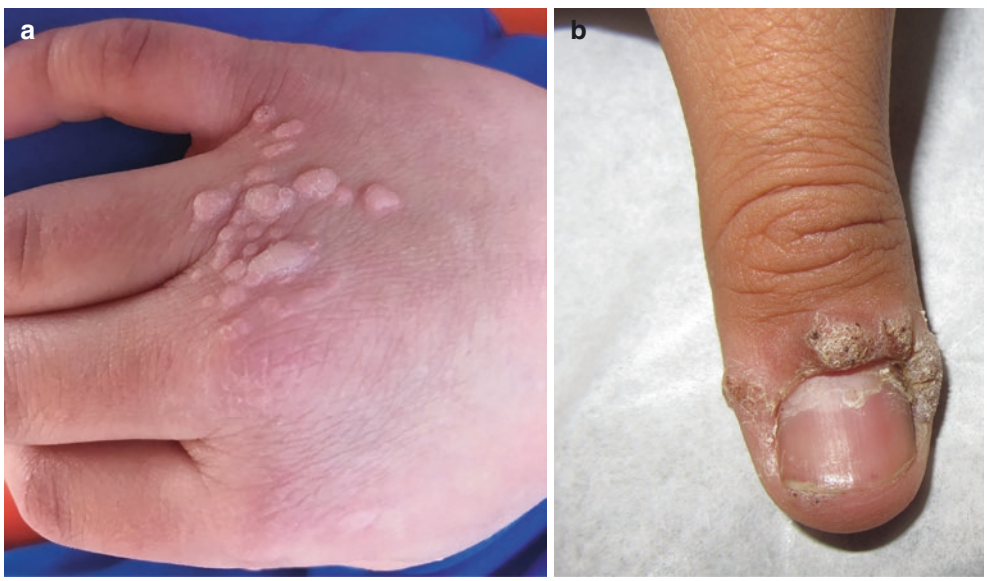


Fig. 26.25 (**a**) Child with multiple verrucae on the dorsal hand. (**b**) Child with periungual verruca vulgaris

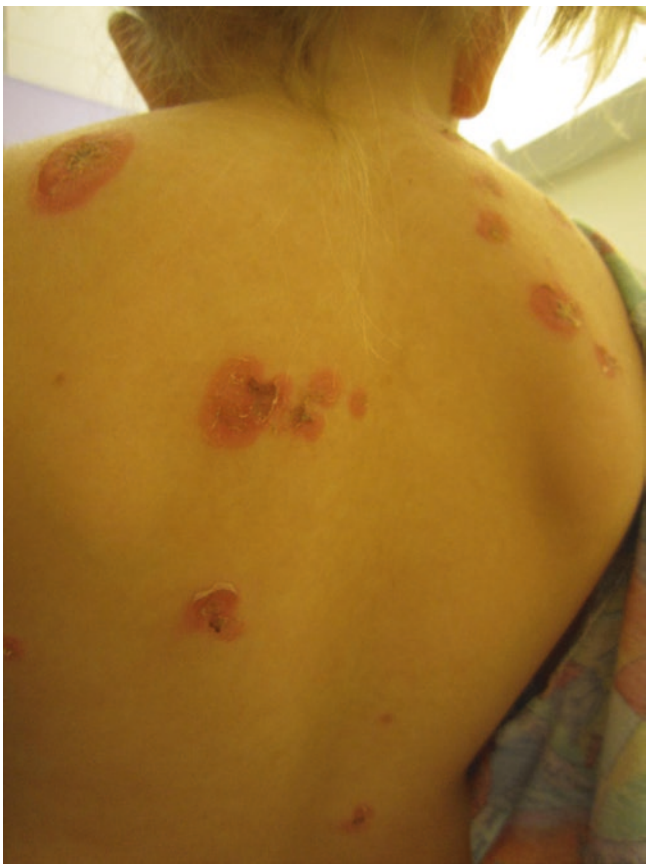


Fig. 26.26 Young female child with impetigo on the back secondary to *Staphylococcus aureus*

- Bullous form is characterized by flaccid bullae and shallow erosions surrounded by residual blister roof (Fig. 26.26)

Management
- Topical anti-staphylococcal antibiotic for mild cases
- More extensive cases warrant wound culture and systemic antibiotics

Staphylococcal Scalded Skin Syndrome (SSSS)

Background
- Blistering skin disease caused by an exfoliative toxin produced by *S. aureus*
- Most common in neonates or young children

Clinical Presentation
- Prominent erythema, fragile blisters, and subsequently denuded skin; skin is painful
- Favors the flexural areas and periorificial skin; involvement around the mouth can present with crusting and radial fissures
- Nikolsky sign: Firm pressure at the edge of the blister causes further progression/lateral spread of the cleavage plane
- Usually associated fever and malaise

Management
- Hospitalization for systemic anti-staphylococcal antibiotic, wound care, pain control, fluid and electrolyte management

Cellulitis

Background
- Acute infection of the skin and subcutaneous tissues most often due to *S. aureus* or GABHS
- Usually caused by trauma to the skin

Clinical Presentation
- Local pain, tenderness, swelling, and erythema that progresses rapidly and may involve large areas of the skin
- Systemic manifestations include fever, chills, malaise, lymphangitis, and bacteremia
- Erysipelas is a superficial form of cellulitis, classically caused by GABHS, that has prominent lymphatic involvement

Management
- Targeted systemic antibiotics that cover for both *S. aureus* and GABHS
- Hospitalization may be required for seriously ill patients or those not responding to oral antibiotics

Intertrigo

Background
- Rubbing and occlusion of skin surfaces results in erosions and skin irritation
- May become secondarily infected with bacteria or *Candida* species

Clinical Presentation

- Erythematous and superficial erosions located in skinfolds

Management

- Apply adsorbent powder to keep affected areas dry
- Severe cases may benefit from low-potency topical corticosteroids
- Antifungal therapy if *Candida* infection or antibiotics if bacterial infection is suspected

Necrotizing Fasciitis

Background

- Infection of the deeper subcutaneous tissues and fascia
- Several bacteria can cause necrotizing fasciitis (GABHS, *S. aureus*, *Clostridium perfringens*, *Bacteroides fragilis*, *Aeromonas hydrophila*)

Clinical Presentation

- Painful, extensive, rapidly progressive necrosis and gangrene of the skin and underlying tissue
- Patients are usually ill and have a high temperature and toxic appearance

Management

- Hospitalization for broad-spectrum antimicrobial therapy, surgical debridement, and pain control

DISORDERS OF PIGMENTATION

Albinism

Background

- Absent or decreased melanin biosynthesis of the eye, hair follicles, and skin
- Includes syndromic and nonsyndromic forms of albinism
- Nonsyndromic forms include oculocutaneous albinism (OCA) types I–VII
- Syndromic forms of albinism include Hermansky-Pudlak, Griscelli, and Chediak-Higashi syndromes

Clinical Presentation

- Nonsyndromic forms of OCA:
  - Affected persons have light skin, hair, and eyes regardless of ethnic background
  - Dependent upon the OCA type, eyes, hair, and skin vary in pigmentation; some develop lentigines/pigmented nevi; risk of cutaneous malignancy varies
  - Eye manifestations: photophobia, strabismus, nystagmus, and decreased visual acuity
- Syndromic forms of OCA:
  - Hermansky-Pudlak syndrome: pigment dilution of the skin and eyes, hemorrhagic diathesis secondary to platelet dysfunction, and complications such as granulomatous colitis, pulmonary fibrosis, cardiomyopathy, or renal failure
  - Griscelli syndrome: pigment dilution of the skin with silvery hair; different types may manifest immune or neurologic dysfunction
  - Chediak-Higashi syndrome: pigment dilution of the skin and eyes with silvery hair, pyogenic infection (*S. aureus*, GABHS, and *Streptococcus pneumoniae*), bleeding diathesis, and neurologic deterioration with age

Management

- Strict sun protection and evaluation by a dermatologist and ophthalmologist
- If concerned for a syndromic form of OCA, evaluation by a hematologist and/or neurologist may be appropriate

Pityriasis Alba

- Nonspecific dermatitis followed by post-inflammatory hypopigmentation
- Small, poorly defined, hypopigmented, scaly macules and patches predominantly on the face

- Encourage sun protection and moisturization of the skin
- If erythema is present, a mild topical corticosteroid or topical calcineurin inhibitor may be used

Vitiligo

Background

- An immune-mediated disorder leading to depigmentation of the hair, skin, and mucosa
- Can be characterized as focal, segmental, or generalized
- Family history of vitiligo is present in 30% of patients as well as an increased incidence of autoimmune disease

Clinical Presentation

- May be partially or completely depigmented macules or patches (Fig. 26.27)

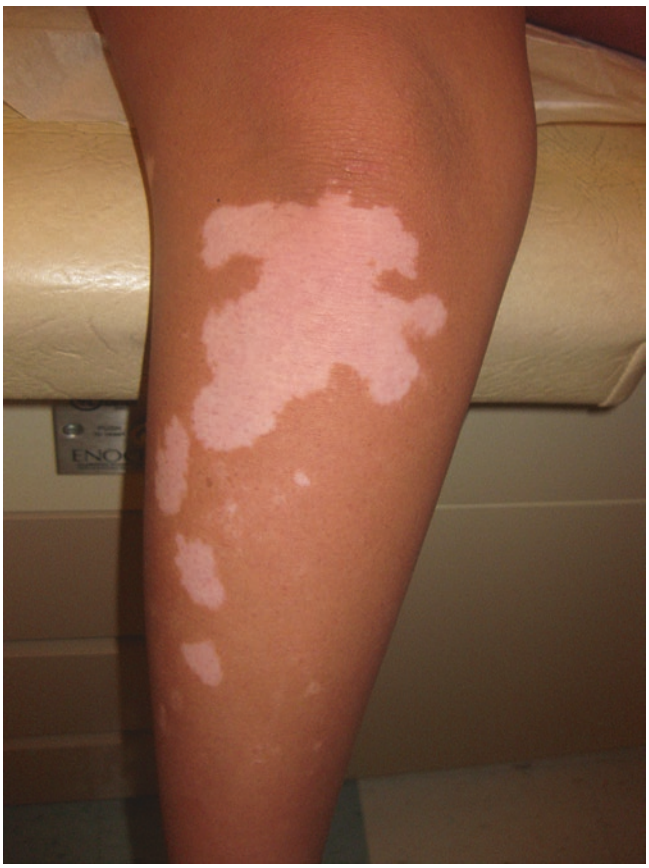


Fig. 26.27 Vitiligo: Depigmented patches on the lower extremity of a child

- Development of lesions commonly begins on the face, dorsal hands, and neck; other sites of involvement are body folds (axillae, groin), orifices (eyelids, nostrils, genitals, perianal skin), and bony prominences (elbows, knees, skins)
- White hair can be seen
- Halo nevi are common in prepubertal children (pigmented nevi with surrounding depigmentation)
- Pigmentation returns from the hair follicle as small, "freckle-like" spots within the area of depigmentation

Management

- Sun protection to affected areas
- Repigmentation can be difficult but is most successful on the head and neck
- Treatments include anti-inflammatory agents such as topical corticosteroids, topical calcineurin inhibitors, and NB-UVB phototherapy

Post-inflammatory Hypo-/Hyperpigmentation

Background

- Self-limited dyspigmentation preceded by inflammatory dermatoses
- Pathogenesis of both is unclear

Clinical Presentation

- Post-inflammatory hypopigmentation: ill-defined hypopigmented macules and patches
- Post-inflammatory hyperpigmentation: ill-defined hyperpigmented macules and patches

Management

- Provide reassurance
- Sun protection as this becomes more cosmetically apparent with sun exposure
- Self-limited and will resolve over months to years
- Treatment of preceding inflammatory dermatosis if appropriate

Nevus of Ota

- Unilateral, irregular brown to blue-gray pigmentation of the face in the distribution of the first and second divisions of the trigeminal nerve
- Two-thirds of patients have associated dyspigmentation of the sclera of the ipsilateral eye
- May darken at puberty and have a speckled appearance
- Associated with glaucoma (10% of patients) and melanoma of the eye, skin, and brain (rare)
- Monitoring by dermatology and ophthalmology; if there is a cosmetic concern, may treat with laser therapy

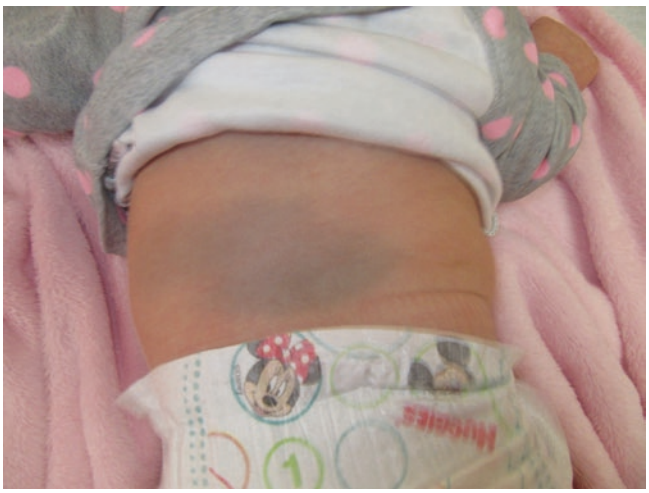


Fig. 26.28 Dermal melanocytosis: Blue-gray patch on the lumbosacral area of an infant

Nevus of Ito

- Unilateral, irregular brown to blue-gray pigmentation of the neck, shoulder, supraclavicular and deltoid areas, and/or upper arm skin
- May darken at puberty
- If a cosmetic concern, may treat with laser therapy

Dermal Melanocytosis

- Commonly referred to as Mongolian spots
- Ill-defined brown to blue-gray pigmentation commonly on the lumbosacral skin and buttocks (Fig. 26.28)
- Present at birth and fades with time, occasionally present in adulthood
- Most common in dark-skinned persons
- If extensive and numerous, consider underlying lysosomal storage disorders

Café-au-Lait Macules (CALMs)

- Oval to round, tan to brown macules or patches present at birth or shortly thereafter (Fig. 26.29)
- Present in approximately 30% of normal children, can occur anywhere on the body

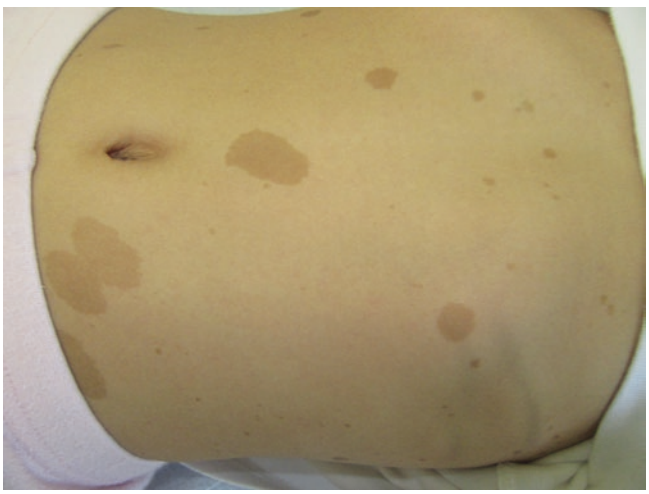


Fig. 26.29 *Café-au-lait* spots. Scattered tan macules and patches on the abdomen of a child

- If more than 5 CALMs are present, consider an underlying genetic condition such as neurofibromatosis or Legius syndrome
- Consider McCune-Albright syndrome if a large, unilateral CALM is present in a dermatomal distribution

MELANOCYTIC TUMORS

Congenital Melanocytic Nevi (CMN)

- Lesions with an increased number of melanocytes, usually present at birth or within the first year of life (Fig. 26.30)

Fig. 26.30 Congenital melanocytic nevus: Homogenous dark-brown nevoid plaque on the trunk of a child

- Classification is based upon the projected largest diameter in adulthood:
  - Small: < 1.5 cm
  - Medium: 1.5–19.9 cm
  - Large: > 20 cm
- Exact risk of melanoma is debatable, however, large CMN carry a greater risk than small or medium CMN
- Large CMN of the head, neck, or back, especially those with multiple "satellite" nevi, are risk factors for neurocutaneous melanosis (proliferation of melanocytes in the central nervous system that has the potential to cause neurologic symptoms or develop melanoma)
- Treatment must be individualized based on CMN site, size, and evolution
- All need clinical monitoring and education regarding sun protection

Melanoma

Background

- Potentially a fatal form of skin cancer
- Rare in children, especially prior to puberty
- Risk factors include sun exposure, family history of melanoma, numerous nevi (> 50–100), large CMN, immunosuppression, and fair skin

Clinical Presentation

- May develop from a preexisting mole or may be a new growth
- Features that should raise concern for melanoma include the following:
  - **A**symmetry, irregular **b**orders, multiple **c**olors, large or enlarging **d**iameter, and **e**volution (ABCDE)
  - An enlarging pink +/− bleeding papule
  - Any "ugly duckling" nevus (a nevus that differs significantly in clinical appearance from a child's other nevi)

Management

- Early detection and prompt referral to a dermatologist
- Education regarding the risks of sun exposure and discussion of sun protective measures
- Short-term effects of sun exposure: visible damage to the skin including sunburn, tanning, and freckles
- Long-term effects of sun exposure: wrinkles, age/sun spots, and skin cancer
- Protective measures: sun avoidance, sun-protective clothing (including wide-brimmed hats), and broad-spectrum, SPF30+ sunscreen
- Lifetime practice of sun avoidance and sunscreen use decreases the lifetime risk of UV light-induced skin cancers by ~80%

DERMAL TUMORS

Granuloma Annulare (GA)

- Common in school-age children
- Pathogenesis of GA is unknown
- Skin-colored, non-scaly papules or plaques in a ring-like distribution on the dorsal wrists, hands, ankles, and feet (Fig. 26.31)
- May be mistaken for tinea corporis
- No effective treatment spontaneous resolution within months to years

Mastocytosis

Background

- Group of disorders characterized by the accumulation of mast cells within the skin and potentially other organs
- Cutaneous variants common in pediatrics include mastocytomas, urticaria pigmentosa, and diffuse cutaneous mastocytosis (Fig. 26.32)

Clinical Presentation

- Mastocytomas: solitary or multiple skin-colored to yellow-orange papules or plaques; become urticarial-like when rubbed (Darier sign); vesicles or bullae can also be seen

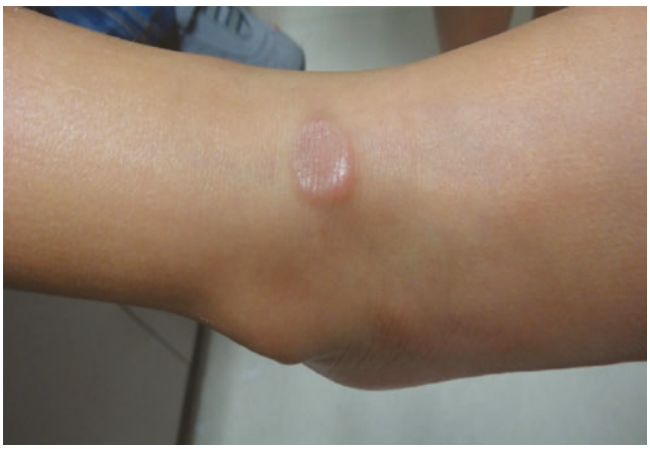


Fig. 26.31 4-year-old boy with granuloma annulare (Courtesy of Sitratullah O. Kukoyi-Maiyegun, MD, Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas)

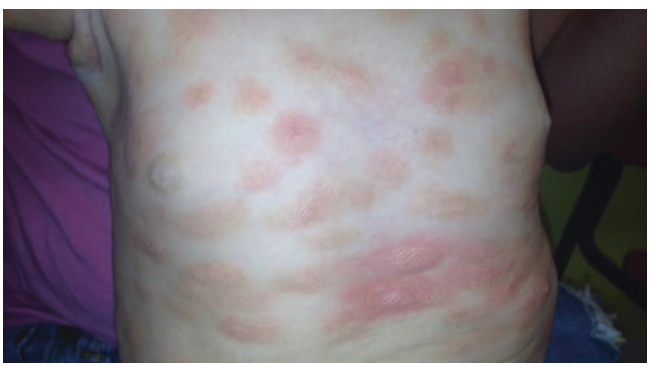


Fig. 26.32 Mastocytosis: Scattered yellow-brown plaques, some with associated erythema on the trunk of an infant

- Urticaria pigmentosa: multiple red-brown macules and papules with a widespread distribution; Darier sign and bullae can be seen
- Diffuse cutaneous mastocytosis: uncommon; diffuse mast cell infiltration of the skin; causes reddish-brown discoloration, skin thickening, and numerous blisters
- Systemic disease: itching, flushing, vomiting/diarrhea/abdominal pain, respiratory distress

Management

- Symptomatic treatment with non-sedating and sedating histamine (H1) receptor antagonists
- If GI symptoms are present, consider treatment with cromolyn sodium
- Localized forms of the disease often improve with age
- If vesicles or bullae are present, a topical corticosteroid can be applied
- Avoid mast cell triggers: certain medications (e.g., NSAIDs), local anesthetics (e.g., tetracaine), general anesthesia (e.g., d-tubocurarine), iodine-containing contrast, and venoms

Dermoid Cyst

- Nontender, mobile, subcutaneous nodule most common along the orbital ridge
- Small percent of dermoid cysts or sinuses are located in the midline and require imaging to rule out extension to the CNS
- Treatment includes surgical excision

HAIR DISORDERS

Alopecia Areata

Background

- Autoimmune, nonscarring hair loss disorder in children and adults

Clinical Presentation

- Sudden appearance of circular areas of hair loss, most common on the scalp (Fig. 26.33)

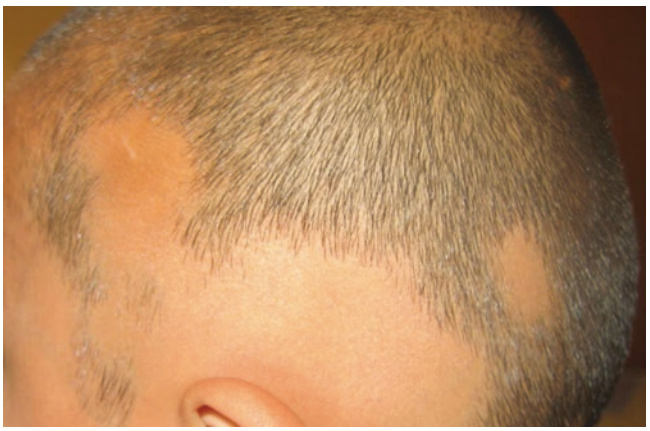


Fig. 26.33 Alopecia areata: Well-defined patches of alopecia with no associated erythema or scale

- Classified as localized, ophiasis (band-like hair loss of the temporal and occipital scalp), totalis (loss of all scalp hair), and universalis (loss of all scalp and body hair)
- Appearance of underlying skin is smooth and commonly without erythema
- Nail pitting can be seen

Management

- Reassurance; spontaneous hair regrowth usually occurs with localized disease
- Treatments include topical or intralesional corticosteroids, topical minoxidil, and topical immunotherapy (e.g. squaric acid)

Trichotillomania

- Self-induced pulling and breakage of the hair, most common on the scalp
- Associated with psychological distress, habitual pulling (e.g. prior to sleeping, television watching), or compulsive behavioral disorders
- Characterized by irregular patches of hair loss with hair of varying lengths
- Treatment can be difficult; strong physician, patient, and parent relationship is important; behavioral modifications; psychiatric therapy if appropriate

Telogen Effluvium

- Most common form of hair loss in children
- Diffuse thinning of hair secondary to a stressful event; examples include an illness, surgery, childbirth, or medication change
- Hair loss is seen ~6 to 16 weeks following stressor
- Reassurance; hair regrowth occurs over months

Anagen Effluvium

- Hair loss secondary to the reduction of hair shaft production during the growth (anagen) phase
- Commonly occurs in children receiving chemotherapy or radiation

Traction Alopecia

- Hair loss secondary to excessive pulling (tight ponytails, braids, etc.), most prominent at the margins of the hairline
- If untreated, may lead to scarring and permanent hair loss
- Treatment: relaxed hairstyles and avoidance of other stressors to the hair (such as heat and chemicals)

GENODERMATOSES

Epidermolysis Bullosa (EB)

Background

- Group of genetic disorders characterized by skin fragility and bullous lesions secondary to friction or trauma
- Genetic mutations occur within components of the basement membrane zone of the skin
- Major subtypes of EB include EB simplex, junctional EB, and dystrophic EB

Clinical Presentation

- **EB simplex**
  - Blister formation on the palms and soles secondary to trauma
  - Heals without scarring
- **Junctional EB**
  - Can range from mild to severe
  - Generalized severe junctional EB: 50% mortality rate in early childhood; blistering occurs on the skin, oral mucosa, esophagus, and airway; perioral granulation tissue, dental enamel hypoplasia, growth retardation, and scarring
  - Other variants of junctional EB include localized, junctional EB with pyloric atresia, and generalized intermediate junctional EB
- **Dystrophic EB**
  - Dominant dystrophic EB: Blisters on the skin result in scarring, mild mucous membrane involvement, and nail dystrophy
  - Recessive dystrophic EB (RDEB): life-threatening bullous disease with severe scarring leading to fusion of the fingers and toes, esophageal involvement with resultant stenosis, dental caries, nail dystrophy, and growth retardation
  - RDEB patients have an increased risk of cutaneous squamous cell carcinoma which can lead to death

Management

- Wound care for skin fragility and skin blistering
- Evaluation by a multidisciplinary team is important

Incontinentia Pigmenti

Background

- X-linked dominant disorder that affects the eyes, teeth, CNS, and skin
- Approximately 65% of cases are sporadic mutations
- Mutation in the nuclear factor-kB essential modulator (NEMO, IKBKG)

Clinical Presentation

- Cutaneous lesions appear in the first few weeks of life
- 4 stages of cutaneous lesions that may not appear in sequential order or can overlap
  - Stage 1: crops of inflammatory vesicles or pustules that occur in a whorled pattern (blaschkoid distribution)
  - Stage 2: verrucous papules most prominent on the extremities, hands, and feet
  - Stage 3: brown to blue-gray macules and patches; pigmentation may persist for years
  - Stage 4: hypopigmented and atrophic plaques most common on the trunk and extremities
- Scarring alopecia and nail dystrophy can be seen
- Dental anomalies include delayed dentition, partial anodontia, and conical/pegged shaped teeth
- ~30% of patients have CNS involvement, commonly seizures
- ~35% of patients have ocular disease such as strabismus, cataracts, optic atrophy, and retinal neovascularization/detachment

Management

- Cutaneous lesions will clear and do not require treatment
- Early ophthalmologic evaluation is important to discover and treat retinal disease if present
- Neurologic evaluation if seizures or developmental delay is present

Ectodermal Dysplasia

Background

- ~150 inherited disorders characterized by abnormalities of ectoderm-derived tissues (such as the skin, hair, teeth, and nails)

- Select disorders within this group include the following:
  - Hypohidrotic ectodermal dysplasia
  - Hidrotic ectodermal dysplasia
  - Ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome
  - Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome

Clinical Presentation

- Hypohidrotic ectodermal dysplasia: reduced or absent sweating, conical teeth, characteristic facies (frontal bossing, saddle nose, thick/everted lips), sparse hair, often associated atopy
- Hidrotic ectodermal dysplasia: nail changes, thin hair, thickening of the palms and soles; teeth and sweating are normal
- EEC: ectrodactyly (split hand/foot deformities), ectodermal dysplasia (sparse hair, teeth abnormalities), clefting, abnormalities of the lacrimal tract
- AEC: ankyloblepharon (strands of tissue between the eyelids), ectodermal defects (erosions of the scalp, sparse/fine hair, nail changes, hypohidrosis), clefting

Management

- No curative therapy
- Multidisciplinary support required
- Supportive measures such as artificial sweat for patients with hypohidrotic ectodermal dysplasia and wound care for scalp erosions of patients with AEC

Ichthyosis Vulgaris

- Most common form of ichthyosis, shows autosomal semi-dominant inheritance
- Characterized by gray, polygonal scales commonly involving the lower extremities
- Groin and flexural areas are usually spared
- Hyperlinear palms and associated atopy often seen
- Moisturization is key; emollients containing lactic acid or urea are helpful for reducing scaling

MISCELLANEOUS

Langerhans Cell Histiocytosis (LCH)

Background

- Infiltration of Langerhans cells, bone marrow-derived antigen-presenting cells, into various organs
- Unknown pathogenesis
- Skin and bones are the most commonly involved organs; skin changes are usually the presenting complaint
- Involvement may be unifocal, multifocal, or disseminated; extensive disease has a poor prognosis

Clinical Presentation

- Skin:
  - Classically a red, scaly dermatitis of the scalp, axillae, and diaper area that can mimic seborrheic dermatitis; resistant to standard treatments for seborrheic dermatitis (distinguishing feature)
  - Red to brown papules that may have overlying hemorrhage, erosion, or crust
- Bone: pain and swelling caused by lytic lesions, usually affects the skull or long bones
- CNS: diabetes insipidus, hyperreflexia, cranial nerve defects
- Other organ systems that may be involved include the lungs (pulmonary dysfunction), spleen (splenomegaly), bone marrow (cytopenias), lymph nodes (lymphadenopathy), etc

Management

- Patients with suspected LCH require an extensive workup that often includes imaging, laboratory studies, and biopsy; referral to hematology and dermatology is important

- Degree of therapy is driven by extent of involvement
- Skin-limited disease does not require therapy, but can be treated with topical corticosteroids
- Vital organ dysfunction may warrant aggressive systemic therapy with corticosteroids and chemotherapy
- Long-term monitoring

Acanthosis Nigricans

- Presents as velvety-brown plaques within skinfolds such as the neck and axillae (Fig. 26.34)
- Pathogenesis unknown
- May be associated with obesity, insulin resistance, or malignancy (rare in pediatrics)
- Treatment is difficult; weight reduction and healthy lifestyle if secondary to obesity or insulin resistance; topical keratolytics or topical retinoids may improve cosmetic appearance

Factitious Disorders

- Self-inflicted lesions on the skin secondary to psychological stressors, may be associated with secondary gain

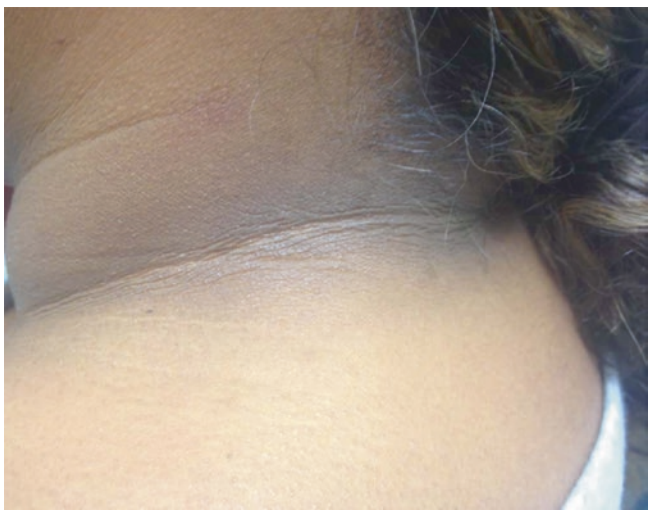


Fig. 26.34 Acanthosis nigricans in a teenager with type II diabetes mellitus

- Mode of injury to the skin can vary: scratching, cutting, picking, burning, etc
- Face, upper trunk, and upper extremities are most often involved; pay attention to the handedness of the patient; linear, geometric, and well-demarcated areas of skin injury are seen
- Treatment can be difficult; strong physician, patient, and parent relationship is important; behavior modifications; psychiatric therapy if appropriate

PEARLS AND PITFALLS

Pearls

- The pustules of erythema toxicum contain **eosinophils**, while the pustules of transient neonatal pustular melanosis contain **neutrophils**
- If erythema, vesicles, or bullae occur in a line, consider an outside cause such as rhus dermatitis/poison ivy
- Bites in clusters of three ("breakfast, lunch, and dinner") are suggestive of bed bugs
- Lichen sclerosus of the anogenital region necessitates aggressive therapy with high-potency topical steroids
- Infantile hemangiomas have a characteristic growth pattern (rapid growth during the first ~5 months of life and slow involution over years)
- A nevus simplex will fade with time, but a port wine stain will persist for life and may become darker or thicker
- Erythematous, scaly papules or plaques involving the nasal bridge and cheeks ("butterfly rash") should raise concern for acute CLE
- A lesion of urticaria will last < 24 h; a lesion of erythema multiforme will last for days to weeks
- The Nikolsky sign is seen with both SJS and SSSS; SJS involves < 10% of the skin (especially the trunk) and > 2 mucosal sites, whereas SSSS favors the flexures and periorificial skin

- Alopecia areata causes complete hair loss (hair falls out by the roots) with underlying smooth skin
- The first sign of NF is usually CALMs; the first sign of TS is usually hypomelanotic macules
- Ectodermal dysplasias commonly involve the skin, hair, teeth, and nails

Pitfalls

- Atopic dermatitis in the diaper area is uncommon; rashes in the diaper area should prompt consideration of irritant diaper dermatitis, seborrheic dermatitis, psoriasis, acrodermatitis enteropathica, LCH, and skin infections (such as candida)
- Facial angiofibromas of TS can be mistaken for acne vulgaris
- Periorificial dermatitis is made worse by use of topical or inhaled corticosteroids
- Topical antifungal therapy is inadequate for onychomycosis and tinea capitis; oral antifungal therapy is necessary for clearance
- Scabies is not adequately treated unless all household family members are treated at the same time (even if they are asymptomatic)
- The herald patch of pityriasis rosea can mimic an isolated patch of tinea corporis
- Not all infantile hemangiomas occur in isolation; 5+ infantile hemangiomas, segmental facial hemangiomas, or large hemangiomas of the lower body or lower face/neck can have important associations (liver hemangiomas, PHACE syndrome, spinal abnormalities, and airway hemangiomas, respectively)
- Urticaria can have a dusky center ("urticaria multiforme"); this is different from erythema multiforme where lesions are targetoid with 3 zones of color
- Molluscum contagiosum can trigger a surrounding dermatitis that mimics atopic dermatitis
- Granuloma annulare is red and annular but lacks scale, thus distinguishing it from tinea corporis
- LCH can mimic seborrheic dermatitis (consider LCH in cases of treatment-resistant seborrheic dermatitis)

Acknowledgement The authors gratefully acknowledge the contributions of Sitratullah Olawunmi Kukoyi-Maiyegun, MD, Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas, to the first edition of this chapter, some images from which have been incorporated into this edition as well.

Suggested Reading

Browning JC. An update on Pityriasis rosea and other similar childhood exanthems. Curr Opin Pediatr. 2009;2(4):481–5.

Crespo-Erchiga V, Florencio VD. Malassezia yeasts and pityriasis versicolor. Curr Opin Infect Dis. 2006;19(2):139–47.

Eichenfeld LF, Frieden IJ. Neonatal and infant dermatology. 3rd ed. Philadelphia: Elsevier Saunders; 2015.

Johr RH, Schachner LA. Neonatal dermatologic challenges. Pediatr Rev. 1997;18(3):86–94.

Krowchuk DP, Mancini AJ, editors. Tinea versicolor. In: Pediatric dermatology a quick reference guide. 2nd ed. Elk Grove Village: American Academy of Pediatrics; 2012. p. 255–60.

Maverakis E, Fung MA, Lynch PJ, Draznin M, Michael DJ, Ruben B, Fazel N. Acrodermatitis enteropathica and an overview of zinc metabolism. J Am Acad Dermatol. 2007;56(1):116–24.

Morelli JG. The skin: diseases of the neonate. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier/Saunders Elsevier; 2011a. p. 2218–20.

Morelli JG. The skin: disorders of the hair. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier/Saunders Elsevier; 2011b. p. 2289–93.

Paller AS, Mancini AJ. Hurwitz clinical pediatric dermatology. 5th ed. Philadelphia: Elsevier Saunders; 2016.

Psychosocial Issues and Child Abuse

27

Sitratullah O. Kukoyi-Maiyegun

FAMILY AND ENVIRONMENTAL ISSUES

Death

- Understanding of death and expression of grief are determined by chronological age and levels of cognitive development. These are coupled with circumstances of death as well as the family's cultural and religious background.
- Levels of cognitive and behavioral development differ by age:
  - Children < 2 years: sensorimotor stage.
  - Children 2–6 years: preoperational stage.
  - Children 6–10 years: concrete operational stage.
  - Adolescents: formal operational stage.
- Grief reactions occur in different domains that include the emotional, cognitive, physical, and social domains (Table 27.1):
  - Usual expressions of grief include repeated questioning, somatic complaints, regressive behaviors, separation anxiety, school phobia, or academic difficulty.
  - Adolescents may present with increased high-risk behavior with drugs, alcohol, delinquency, or precocious sexual activity.

Table 27.1 Usual and unusual grief reaction at different ages

Age	Usual grief reaction	Unusual grief reaction
Preschool	Separation anxiety, decreased appetite, irritability, and regression < 6 months	Persistence of symptoms > 6 months
School-age	Poor academic performance, school phobia, and physical complaint < 3 months	Persistence of symptoms > 3 months
Adolescent	Somatic complaint < 3 months	Increased high-risk behavior, withdrawal from peer interaction

The Concept of the Stages of Grief Introduced by Kubler-Ross

- Denial
- Anger
- Bargaining
- Depression
- Acceptance

Management

- When death is anticipated, information about expectations and effective counseling will help family bereavement.
- A dying child benefits from open communication about death.

S. O. Kukoyi-Maiyegun (✉)
Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Science Center, El Paso, TX, USA
e-mail: sitratullah.maiyegun@ttuhsc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_27

- Encourage family members to be with their child after death, e.g., holding, rocking, or bathing their child's body.
- Siblings may help in funeral planning, e.g., choosing the burial clothing.
- The pediatrician can provide counseling and support by listening to and communicating well with the family.
- Scheduling an appointment with the family about 1 month after the death to evaluate the family's coping ability.
- Pediatricians need resources and support within the medical community to help cope most effectively with the death of a patient.

Divorce

Long-Lasting Effects **of Divorce or Separation on the Child and the Family**

- Academic underachievement, depression, delinquency, and high-risk behaviors such as drug use and early sexual activity.
- Families may experience increased financial difficulties.
- Children exposed to high-conflict parental interactions are significantly more likely to exhibit externalizing behavioral problems, emotional dysregulation, and decreased academic performance.

Protective Factors That May Increase the Likelihood of Long-Term Positive Psychological Adjustment

- Parents must allow adequate time for children to adjust to divorce before forming any new relationship.
- The slow introduction to a new partner.
- Cooperative co-parenting is most helpful in children's adjustment to divorce.
- Structured routine provides stability, helps with both short and long-term adjustment, and leads to better outcomes.
- Regular schedule with flexibility for change.

Management

- Consistency in parenting techniques and discipline as a way to promote stability and predictability.
- Pediatrician should avoid taking sides or overidentifying with one parent vs. another.
- Report to a child protective service (CPS) if there is suspicion of abuse or neglect or significant parental substance abuse.
- Provide counseling and consult to appropriate resources in cases of significant parental mental health problems.
- Refrain from providing legal advice and refer those questions to the parent's legal counsel.
- Monitor the emotional and behavioral adjustment of children of divorced parents.
- Parents are encouraged to speak positively about each other and to avoid blaming one another for the divorce in front of children.
- Encourage agreement between parents and coordination of parenting plans to avoid escalation of conflict and improve co-parenting cooperation, thus saving significant legal fees.

Discipline

- Disciplinary approaches depend on the child's developmental stage.
- Time-out for negative behavior is an effective strategy for age 1 year to early adolescence.
- Time-out will be effective if parents also provide time-in with short nonverbal physical contact on a frequent basis for acceptable behavior.
- Extinction is a method by which the parent withdraws all attention (and thus reinforcement) from a child's undesirable behavior. This may initially increase the intensity of the undesirable behavior (extinction burst), but with parental perseverance, the undesirable behavior will diminish.

- In planned ignoring, the parents gradually ignore the child's behavior; this method tends to take longer but does not lead to an increased undesirable behavior.
- **Family chip system (ages 3–7 years):**
  - Fake coin currency can be used as a chip.
  - A child earns chips for desired behavior, e.g., brushing teeth or going to school without a tantrum.
  - The child can watch television (TV) or play a video game in exchange for chips.
  - A child loses chips for undesired behavior, e.g., fighting with a sibling, yelling, etc. The child may not play video games or watch TV.

Sibling Rivalry

- Sibling rivalry and jealousy are common.

Causes

- Unequal amounts of parents' attention, discipline, and responsiveness
- Family stress
- Birth order
- Birth of a new sibling
- Personality
- Children very close in age and of the same gender
- 1 or both children intellectually gifted

Management

- Children should initially be allowed to resolve their differences on their own.
- Parents need to intervene in the case of physical or verbal abuse; the fighting siblings should be separated and told violence is not allowed.
- Parents should focus on the individual needs of each child, giving each the time and attention necessary to feel loved and secure.
- Parents should be vigilant to favoritism.
- The ideal time to prepare for supportive relationships between siblings is during the months prior to the new baby's arrival.
- Referral to a therapist may be considered if the behavior continues to be challenging and unresponsive to initial parental interventions.

Separation Anxiety and School Refusal

General Considerations

- Separation anxiety disorder is one of the most common causes of school refusal.
- Separation anxiety is developmentally appropriate in the preschool child and during the first few months of school in kindergarten or first grade.
- School refusal related to anxiety differs from conduct problems and subsequent truancy.
- Youth who exhibit truancy generally do not report other symptoms of anxiety or issues of separation from parents.

Treatment

- In school refusal due to separation anxiety disorder, the child needs to go back to the school environment as soon as possible.
- Decrease in stress, proper sleep hygiene, healthy eating, regular exercise, predictable routine, and social supports.
- Cognitive behavioral therapy.
- Pharmacotherapy: selective serotonin reuptake inhibitors (SSRIs).

Media

Impact of Mass Media

- Pediatricians should routinely ask about the amount of recreational screen time.
- Children younger than 2 years of age should not watch television (TV).

- Solitary TV viewing should be discouraged in young children.
- Limiting TV viewing, including other forms of screen time, to 2 h/day or less for all children.
- Parents should supervise the proper use of the internet and social networking sites.
- Media can be beneficial in enhancing learning, health, and connection with others.
- Discourage parents from having a TV or internet-connected device in a child's bedroom, as it causes sleep disturbance (sleep latency prolongation) and increases the risk of adverse effects from media.
- Education of parents on links between TV viewing, obesity, and diminished academic performance.

Potential Negative Effects of TV Viewing on Children

- Increased aggressive behavior, inattention, acceptance of violence, obesity, substance use, sleep problems, obscured distinction between fantasy and reality, trivialization of sex and sexuality
- Increased passivity, obesity, and risk of suicidal behavior
- Less time spent on healthier activities and increased risk of adverse effects from media

Foster Care

Background

- Foster care is a system in which a minor is placed into a ward, a group home, or the private home of a state-certified caregiver who is compensated for expenses.
- Parental neglect is the main reason children are placed in foster care.
- Approximately 1 in 5 children in foster care has been a victim of physical abuse.
- Foster care is intended to be a short-term solution until a permanent placement or adoption can be made.

Legal Issues

- Usually arranged through the government or a social service agency.
- All legal decisions are made by the state through the family court and child protection agency; the foster parent is responsible for the day-to-day care.
- Legal guardians/foster parents can consent to medical treatment for children under their care.

Management

- Within 72 h of foster care placement, evaluate these children for abuse, neglect, acute infections, mental health issues, and immediate concerns related to chronic medical conditions.
- Within 30 days of entrance into foster care, the child should be evaluated for any physical, mental, developmental, and dental problems in order to develop a coordinated management.
- Family-based foster care is generally preferred to other forms of out-of-home care.

Complications

- Children in foster care suffer more physical, psychological, and cognitive or mental health problems.

Immigrants and Internationally Adopted Children

General Considerations

- Depending on their country of origin, international adoptees may be at risk of certain infectious diseases, particularly parasitic infections.
- Children adopted from institutional or orphanage care settings are more at risk of medical and developmental problems than their counterparts who have resided in foster care.
- The pediatrician should closely review any information about the child's medical history (if available) before and after adoption.

- Family or parental leaves are recommended to provide enough time, security, and love when the adopted child arrives.
- During the transition period, adoptive children may experience withdrawal, temper tantrums, and sleep and feeding problems.

Evaluation of the Immigrants

- Depends on the country of origin and living condition, e.g., orphan or a refugee camp

Immunization Record

- Immunization record from other countries is acceptable as long as it contains documenting date, dose, and the name of the vaccines.
- If no immunization record or any method of documentation is available, all the required vaccines should be given all over.

Evaluation of Adopted Children

- Comprehensive physical examination, immunization status, and appropriate catch-up immunization
- **Nutrition:**
  - Anemia
  - Malnutrition
  - Rickets
  - Iodine deficiency
- **Growth and development:**
  - Estimated age
  - Vision and hearing
  - Dental caries
  - Congenital defects
  - Developmental delay
- **Investigations:**
  - Blood specimens for complete blood count (CBC), serum lead concentration, hepatitis B, human immunodeficiency virus (HIV), and syphilis infection status; stool sent for ova and parasites, *Giardia lamblia*, and *Cryptosporidium*
  - A tuberculin skin test placed regardless of bacillus Calmette-Guérin vaccine status
  - Hepatitis C serologies, if emigrating from hepatitis C-endemic area
  - Newborn metabolic screen for infants

Cultural Issues in Medical Care

- Culture can refer to race, ethnicity, nationality, religion, or sexual orientation.
- A culturally competent practice provides an atmosphere in which patients and families can participate in shared decision-making.
- The clinician should work with individual families to provide health care that is compatible with the beliefs and values of the patient and family.

Providing Culturally Competent Care

- Explain the medical condition, diagnosis, and treatment in terms the patient and family can understand and in their native language.
- Breaking the language barrier:
  - Use a medical interpreter in person or by other methods, e.g., by phone or video.
  - Maintain eye contact with the patient or family member when using in-person medical interpreter.
- Determine if the patient and parents accept the plan of care.
- Provide more information and renegotiate if there is any conflict regarding the investigations, diagnosis, or devised treatment plan.

SPECIFIC PROBLEMS AND CONDITIONS

Gifted Child

- Children with significantly advanced skills and abilities in any developmental domain.
- Academically gifted children can become bored and rebellious in school if they lack stimulating challenges.

- Giftedness should be part of the differential diagnosis for academic failure in school.
- Can be associated with social and emotional effects on the child, family functioning, and family dynamics.

Clinical Presentation

- Alertness during infancy
- Early language development
- Advanced vocabulary
- Abstract thinking and the ability to generate original ideas
- Exceptional problem-solving and memory skills
- Early development of empathy, concern with truth and fairness in play, a mature sense of humor, leadership in cooperative play, and perfectionism
- Cognitive and academic skills often exceeding social, emotional, and motor skills

Associated Conditions

- Attention-deficit/hyperactivity disorder
- Asperger syndrome
- Oppositional defiant disorder
- Learning disabilities

Management

- Provide appropriate academic or extracurricular opportunities for a child with particular learning abilities.
- Provide enrichment:
  - A child with particular skill and interest can be encouraged to research the topic further.
  - A child who has mastered the reading or mathematical concepts for her/his grade level may be allowed to take up studies in logic, learn a new language, explore music or art history, or begin studying science.
- Prevent overscheduling the child, allow time for the typical daily activities of childhood, such as chores and recreation.
- Advancing them ahead in school years may not be the most appropriate approach to meet their educational needs; advancement also effectively accelerates and shortens childhood.
- Homeschooling may impair interpersonal experiences and socialization.

Vulnerable Child Syndrome (VCS)

Background

- Excessive, unfounded parental concerns, anxiety, and a high frequency of health-care use.
- Affected children may suffer from sleep disorders, school problems, discipline problems, and hypochondria.
- Parent perceives a child as being at risk of illness or harm because of a previous threat to their health.

Risk Factors

- Family stress, low levels of social support, low socioeconomic status, parents who rate their own health as poor
- Postpartum depression, obsessive-compulsive behavior, anxiety, unresolved grief over the death of a child or family member
- Maternal history of fertility problems or previous miscarriages, threatened abortion or health concerns of the fetus, prematurity, hyperbilirubinemia, congenital anomalies
- Preceding serious illness or injury to this child or a sibling, presence of a condition that is benign or resolved but considered serious to the parent (e.g., functional heart murmur, colic), known familial or inheritable conditions

Exacerbating Factors

- Environmental stress
- Family stress
- Lack of social support
- Low socioeconomic status
- Poor rating of mother's health

Effect on Children

- Exaggerated separation anxiety

- Sleep disorders
- Peer relationships, self-control, discipline problems
- School underachievement
- Hypochondria
- Child becoming abusive to their parents

Management

- Early recognition and treatment.
- Inquire regarding the sources of the parental anxiety; reeducate them about their child's health.
- Inquire about the connection between past threats and present concerns.
- Clarification of the child's resolved health conditions and reassurance.
- Clear and close communication with parents or guardians that past experiences with illness can affect their perception of their child's health.
- When new concerns arise, a thorough history and physical examination are primary.
- Extensive laboratory evaluation, radiologic studies, and referral to subspecialists should be avoided unless medically indicated.
- Regularly scheduled follow-up visits to discuss health concerns and behavioral issues.

Transition of Adolescents to Young Adulthood for Vulnerable Populations

Background

- Adolescents with chronic medical conditions and disabilities have immense challenges transitioning to adult medical care.
- These could affect all domains of daily living such as health care, education, vocation, and independent living.

General Considerations

- These vulnerable populations should have written transition plans by 14 years of age, which should be updated annually.
- The timing of transition to an adult healthcare practitioner should be individualized for each patient and not based solely on age.
- Encourage patients and families to identify an adult health care practitioner and involve the practitioner during the transition process.
- The portable medical summary and written transition plan can be transferred to the new medical home to facilitate the sharing of information.

Management

- Early discussion of future goals with the patient, family, and other members of the team to coordinate the process.
- Promote independence and shared decision-making.
- Identification of potential obstacles to a successful transition in the domains of health care, education, vocation, and independent living.
- Parents should be encouraged to acknowledge the sexuality of their adolescent and young adult children as well as to foster the development of their social independence.
- The role of a surrogate decision-maker should be discussed for those with severe intellectual disabilities or mental health conditions.
- Full independence regarding medical or other decisions may not be appropriate.

Chronic Illness and Handicapping Conditions

General Effect of a Child with Chronic Conditions on the Family

- Parents of children with handicapping conditions may exhibit grief reactions, and this could affect the siblings.
- Increased risk of child abuse among handicapped children.
- Chronic conditions (e.g., ADHD, asthma, seizures, inflammatory bowel disease) may lead to psychosocial issues.

- Use of home medical equipment (e.g., oxygen monitors, physical therapy, transportation, hygiene) may have psychosocial effects on family dynamics.

Psychosocial Factors

- Disease-specific parental stress regarding a child's chronic medical condition is likely to improve the management of the disorder, as long as that stress is not overwhelming.
- Excessive parental stress about their child's chronic medical condition can impair their ability to manage the disorder.
- Chronic medical conditions in children often have an overall negative impact on parental psychological functioning.

Management

- As a medical home, the pediatrician's office should coordinate specialist referrals for disease management.
- Any child with a chronic medical condition can qualify for a 504 educational plan designed to prevent the condition from having a significant impact on the child's academic career.
- Early intervention programs provide education-related services to infants and toddlers with a developmental delay up to 3 years of age.
- Individualized education plans (IEPs) address the needs of children who qualify for special education by authorizing appropriate education-related services
- 504 modification plans provide education-related services to children with chronic or disabling conditions who do not qualify for special education.
- Supportive and nonthreatening discussion with parents whose children have chronic diseases.
- Appropriate ethical decisions relating to children with chronic and handicapping diseases.
- A pediatrician can help the family in the facilitation of a normal progression of a chronically ill or handicapped child to adult behavior, including separation from parents and emerging sexuality in spite of chronic illness.

Chronic Pain Syndrome

- It is a constellation of syndromes that usually do not respond to the medical model of care.
- Chronic pain syndrome is a diagnosis of exclusion. Other conditions must be ruled out before diagnosis.
- Chronic pain syndrome often occurs concurrently with irritable bowel syndrome, chronic fatigue syndrome, interstitial cystitis, chronic headache, functional abdominal pain, or conversion disorders.
- Pain is subjective, and repeated painful experiences can result in altered pain sensitivity and behavioral disturbances.
- Dealing with and tolerance to pain vary with a child's developmental stage.

Management of Chronic Pain Syndrome

- Open communication, reassurance, and parental presence.
- The treatment should focus on restoration of normal function (minimal disability), better quality of life, reduction of use of medication, and prevention of relapse of chronic symptoms.
- Physical and occupational therapies.
- Exercise, desensitization, stress management, and counseling.
- Cognitive-behavioral therapy (CBT).
- Rule out all organic causes.

Transplantation

- Growth impairment is common after all solid organ transplants.
- Etiologies of growth impairment may be multifactorial.

- Increased risk of neurocognitive changes and education failure.
- Psychosocial stresses: waiting for future transplantation and the guilt of realizing that to receive a lifesaving organ, someone else must die.
- The parents' financial burden of time lost from work and fear of child's possible organ rejection, organ loss, malignancy, and death.

Management

- Formal neurocognitive assessment of academic strengths and weaknesses
- Support groups for pretransplantation and posttransplantation periods
- Adherence with clinic follow-up and medication regimens

CHILD ABUSE AND NEGLECT

Family and Societal Violence

Risk Factors

- Maternal depression.
- Substance use/abuse.
- Physical injuries may indicate intimate partner violence.

Possible Precipitants of Violence

- Pregnancy
- Efforts by the partner to leave the home
- Seeking separation or divorce
- Moving to a shelter

Effect of Violence on Children

- Exposure to stress, abuse, neglect, and violence in growing children leads to anatomic changes and physiologic changes in the brain.
- Increased risk of physical and behavioral problems in adults who were abused as children.

Management

- Early identification and reporting, especially if suspected child abuse.
- Emergency social work or child protective services.
- Parental engagement in all aspects of their children's lives is a recommended intervention in the treatment of aggressive youth.

Child Abuse

Background

- Neglect is the most common form of child abuse.
- The caregiver is the abuser of a child in 90% of child abuse cases.
- Failure to thrive may be a manifestation of abuse or neglect in children.
- Siblings of abused children are at increased risk of abuse.
- Intimate-partner violence is frequently a risk factor for child abuse.
- Fractures are present in a minority of physically abused children.
- Physical abuse is the most common cause of serious intracranial injuries during the first year after birth.
- Shaking is a possible cause of coma in the absence of signs of cutaneous trauma.
- Foster home placement is associated with continued risk of child abuse.
- Many abused and neglected children are not removed from their parents or placed in foster care.

Risk Factors

- Handicap, hyperactivity
- Social/situational stressors (e.g., poverty, isolation, family discord, multiple births, parent-child conflicts)
- Parental stress (e.g., abused as a child, depression, substance abuse)
- Abusive and neglectful parents often having severely unrealistic expectations for their child's behavior

Clinical Presentation

- Poisonous ingestions may be manifestations of child abuse.
- **Bruises:**
  - Keys to the diagnosis of cutaneous injury include the child's developmental stage, location, and pattern.
  - Abnormal bruises will be multiple in different planes and different stages of healing.
  - Patterned bruises (belt marks, whips, straps), human bite marks, and frenulum tear.
- **Burns:**
  - A nonaccidental burn injury usually involves the lower extremities and is symmetric.
  - Immersion burns, when a child is forcibly held in hot water, show a clear delineation between the burned and healthy skin and uniform depth.
  - They may have a stocking or glove pattern (foot or hand held under scalding water) (Fig. 27.1).
  - Immersion burns may have a doughnut pattern in the buttocks (child pressed into scalding water).
  - No splash or spill injury indicates that the child was held in place.
- **Common fractures suggestive of child abuse:**
  - Abusive fractures are seen in children younger than 18 months.
  - Any fracture can be the result of abuse, especially in a nonambulatory child.
  - Postero-medial rib fractures near the costovertebral junction (Fig. 27.2).
  - Classic metaphyseal lesion in infants.
  - Multiple fractures at different sites and different stages of healing.
  - Spiral/oblique or metaphyseal fractures of the humerus (Fig. 27.3).
  - Spiral/oblique or metaphyseal fractures of the femur (especially in preambulatory children).
  - Fractures of the scapula and sternum are rarely accidental.

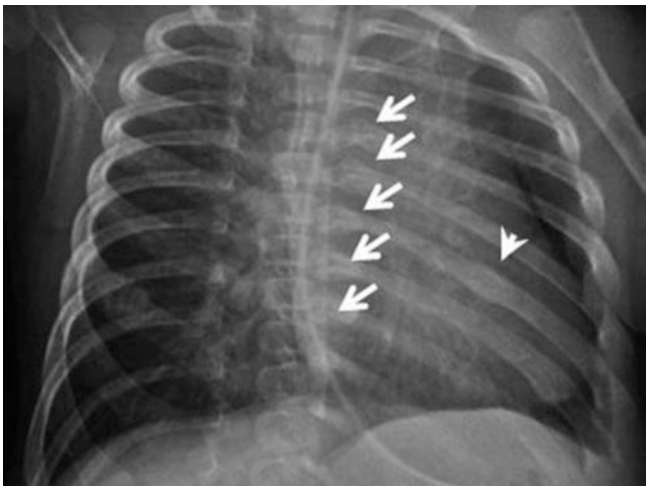


Fig. 27.2 Bone survey for suspected child abuse showing callus formation posteriorly in ribs 5–9 on the left side (*arrows*). Callus formation is seen also on the left seventh more laterally (*arrowhead*)

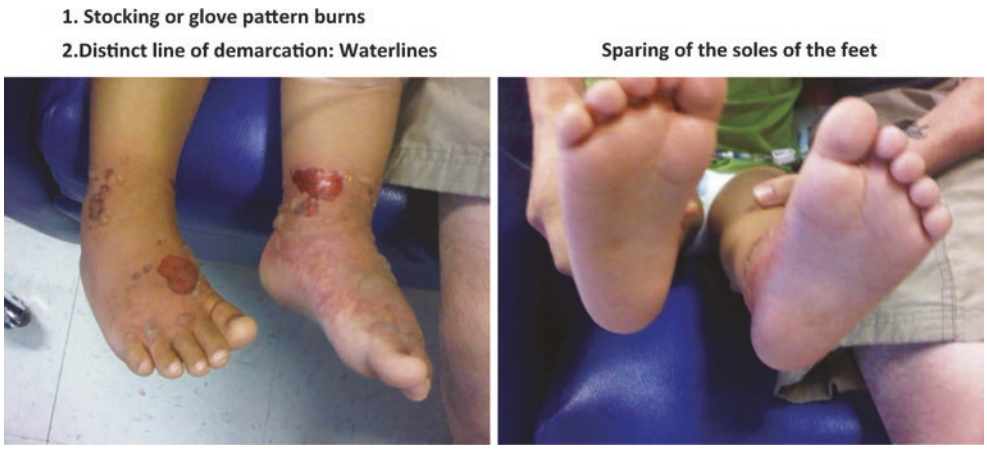


Fig. 27.1 *Left:* Stocking pattern burns and a distinct line of demarcation: waterlines. *Right:* Sparing of the soles of the feet

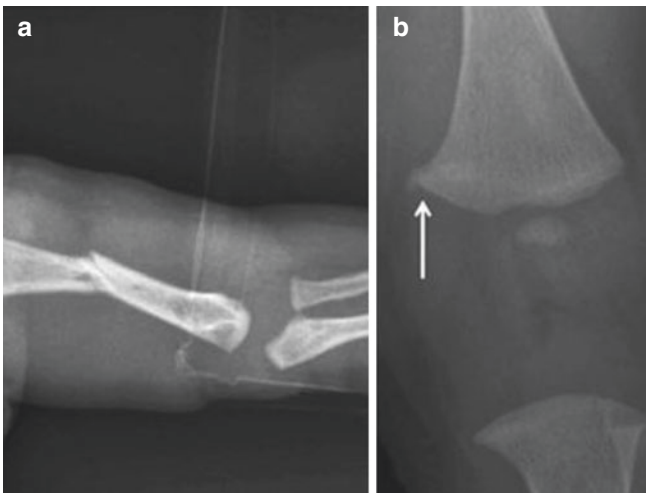


Fig. 27.3 5-month-old boy brought to the emergency department with swelling and deformity of the left arm. (**a**) Radiograph shows a midshaft humeral fracture. **(b)** Bone survey showing metaphyseal corner fracture in the left distal femur (*arrow*)

  - Chip fracture of metaphysis is commonly due to wrenching or pulling injuries.
  - Dislocated elbow, clavicular fracture, and toddler fracture of the tibia are infrequently indicative of physical abuse.

Clinical Features Commonly Mistaken for Child Abuse

- Normal bruises occur over a bony prominence—forehead, knees, elbows, and shins:
  - Facial scratches on infants from their fingernails
  - Bruises that appear in the same stage of healing
- Mongolian spot, coining, cupping, and urticaria pigmentosa.
- Accidental burn injuries usually involve the upper part of the body due to exploration and are usually asymmetric:
  - Spill or splash injury is characterized by irregular margins and nonuniform depth.
- Contact burns will show branding type and mirror the object used.
- Differential diagnosis of inflicted burns includes staphylococcal impetigo, herpes, contact dermatitis, and toxic epidermal necrolysis.
- Fractures:
  - Osteogenesis imperfecta
  - Hypophosphatasia
  - Infantile cortical hyperostosis
  - Osteoid osteoma

Diagnosis

- Suggestive history and physical examination.
- The skeletal survey is mandatory in suspected child abuse or a child with a subdural hematoma.
- Radionuclide bone scan can reveal subtle areas of skeletal trauma that may not be seen on plain-film radiographic studies of bones.
- The absence of neurologic symptoms in infants with intracranial injuries should not exclude the need for imaging.

Management

- Report to a state child protective service.
- Team approach needed in the management of child abuse.
- An ophthalmology consultation is needed to identify retinal hemorrhages in suspected head trauma due to shaking.

Report Child Abuse

- Child abuse must be reported to a state child protection agency.
- Under state laws, physicians are legally obligated to report suspected abuse or neglect as soon as possible.
- Physicians are protected by law from liability when they make a report or provide information in good faith to CPS or law enforcement agents.
- Unsubstantiated report/finding by a child protection agency does not necessarily mean that abuse or neglect did not occur.
- Failure to substantiate child abuse may be due to failure to locate the child, failure to locate the parents, parents' refusal to speak to investigators, duplicate reports, child's refusal to repeat history, and non-English-speaking family.

Neglect

Background

- Neglect is the most common form of child maltreatment.

Types of Neglect

- **Medical neglect:** Caregiver failed to provide adequate medical care for a child.
- **Physical neglect:** Caregiver was unable to provide basic needs (nutrition, shelter, clothes)—child abandonment.
- **Educational neglect:** Caregiver failed to enroll the child in school or provide home-schooling, allowed frequent absenteeism, or ignored special education needs.
- **Emotional neglect:** Caregiver kept the child isolated, withheld emotional support, and exposed the child to interpersonal violence or substance abuse.
- **Supervisory neglect:** Caregiver left the child alone or improperly supervised and failed to keep the child from safety hazards.

Management of Child Neglect

- Physicians are legally obligated to report cases of suspected child neglect to a child welfare agency.

Sexual Abuse

Background

- The incidence of sexual abuse cases that came to the attention of investigators or other community professionals was 2.4/1000 US children under the age of 18 years.
- Child sexual abuse involves physical contact between the victim and the perpetrator, with or without oral, anal, or vaginal penetration.
- There may not be touching; the child may be forced to watch sexual acts or pornography.
- The delay between the onset of abuse and disclosure is common.
- Sexual victimization is more common among girls than boys.
- Boys are less likely to disclose sexual abuse and might be victimized more often than the reported ratio.
- Teenagers have the highest rates of sexual assault.
- The child knows most perpetrators of sexual abuse before the abuse occurs.
- Physical disabilities, prior sexual victimization, and absence of a protective parent are other potential risk factors.
- There is increased incidence of sexually transmitted disease (STD) associated with sexual abuse.

Clinical Presentation

- An explicit description and imitation of adult sexual behavior by children may indicate either victimization or observation of sexual acts (not fantasy).
- Sexually abused children also can present with nonspecific physical or emotional complaints.
- Unexplained abdominal pain, genital pain, encopresis, school failure, or sleep disturbance.
- Complaint of genital pain and genital discharge may infrequently indicate sexual abuse.
- When sexual abuse is suspected, the child should be interviewed alone.
- Verbatim statements by a child may qualify as evidence in a criminal court.

Medical History-Taking

- In suspected sexual abuse, the first detailed interview of a child is diagnostically critical.
- It is essential to avoid repetitive interviewing of an allegedly sexually abused child.
- Repetitive interviewing is unnecessarily stressful and may create rote quality to responses, increases the likelihood of leading questions, increases chance of learned responses, and increases the chances of inconsistency/retraction.

- The use of anatomically correct dolls for interviewing has advantages in a child who is nonverbal but who can point; there may be a risk of overinterpretation.

Examination

- Explanations to parents and the child before, during, and after the examination can ease stress.
- Supportive, non-offending caretakers can also be comforting to the child.
- Older patients can indicate if they prefer to undergo the examination with or without their caretaker in the examination room.
- The use of chaperones is essential during the examination of pediatric patients.
- Examination positions include supine lithotomy, supine frog-leg, and knee-chest position.
- Patients who refuse should not be forced to undergo an examination.
- A normal physical examination does not exclude the possibility of sexual abuse or prior penetration.
- Most sexual abuse victims have normal anogenital examinations.
- Findings indicative of trauma include laceration or bruising of the hymen, genital or perianal bruising, and hymenal transection.
- Labial adhesions, vulvar erythema, and anal tags are not signs of abuse.

Legal Issues

- STD in a prepubertal child is presumptive evidence of sexual abuse.
- Gold standard tests to diagnose sexually transmitted infections in children should be used.
- Evidence of seminal fluid is infrequently found in sexually abused children.
- Seminal fluid is unlikely to be found/persist beyond 72 h in a sexually abused child.
- Sexual abuse can recur even when families are receiving treatment.
- HIV, *Chlamydia trachomatis*, gonorrhea, and syphilis are diagnostic of sexual abuse unless otherwise proven.

Investigations

***Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infection**

- Infection may be acquired from the mother at birth.
- Specimens from the rectum, male urethra, vagina, and urine can be tested for C*hlamydia trachomatis* and *Neisseria gonorrhoeae*.
- Throat specimens can also be tested for gonorrhea.
- Nucleic acid amplification tests (NAATs) for chlamydia and gonorrhea infections in urine.
- Repeat chlamydia and gonorrhea testing within 2 weeks after the last contact is indicated in cases in which prophylactic treatment was not given.

Trichomonas vaginalis

- Wet mounts and other studies of vaginal discharge can identify *Trichomonas vaginalis* and bacterial vaginosis.
- Bacterial vaginosis can be unrelated to sexual abuse.

Herpes Simplex Virus

- Polymerase chain reaction testing or culture of genital lesions can test for herpes simplex virus.

Others

- Send serologic studies for HIV, syphilis, and hepatitis B.
- Laboratory testing at the time of initial presentation and convalescent testing for syphilis and HIV are indicated at 6, 12, and 24 weeks post-assault.
- Anogenital warts (condyloma acuminata) and genital herpes simplex are suspicious but not diagnostic of abuse.

- Pregnancy testing should be performed where indicated based on the patient's pubertal stage.

Management

- Sexual abuse must be reported to a state child protection agency as soon as possible.
- Treatment plans address physical health, mental health, child safety, and psychosocial concerns.
- Gonorrhea, chlamydia infection, trichomonas infection, and bacterial vaginosis:
  - Prophylactic antibiotics for patients who present within 72 h of an assault.
  - These prophylactic antibiotics are generally not prescribed for prepubertal patients because the incidence of sexually transmitted infection is low.
  - There is a low risk of spread to the upper genital tract.
- HIV postexposure prophylaxis:
  - A 28-day course of a 2- to 3-drug regimen initiated as soon as possible within 72 h of potential exposure and careful follow-up
- Pregnancy prevention:
  - Emergency contraception should be offered when female pubertal patients present within 72 h till 120 h.
- Mental health issues need to be addressed; urgent psychiatric referral if there are suicidal ideations.
- It is very important not to assign blame to the victim in helping families cope with sexual abuse.

Caregiver-Fabricated Illness (Munchausen Syndrome by Proxy)

- Caregiver falsely claims that the child has a physical or psychological signs or symptoms of illness or causes injury or disease in the child with the intention of deceiving others.
- Caregiver-fabricated illness may result in harm to the child through unnecessary procedures and treatments.
- Caregiver may cause recurrent sepsis from injecting fluids; chronic diarrhea from laxatives; false renal stones from pebbles; fever from heated thermometer; or rashes from trauma, sugar, or blood in the urine.
- Mothers have been identified as the sole perpetrators in the majority of cases.

Clues to Caregiver-Fabricated Illness

- The patient has bizarre symptoms.
- History, physical examination findings, and appearance of health are inconsistent.
- The caregiver is not satisfied with normal or reassuring test results.
- A sibling of the patient has an unexplained illness.
- The caregiver uses social media to solicit donations based on the child's illness.
- The caregiver has a history of somatization disorder.
- Parents and children with this condition may exhibit significant ongoing psychological problems.

Management

- Requires a multidisciplinary child protection team that includes the state social service agencies.
- Consult child protection agents, communicate with the patient's specialists, and/or submit a detailed report to the state child welfare agency upon suspecting the diagnosis rather than waiting until the evaluation or unnecessary treatment is complete.
- Family therapy to address ongoing family issues.

PEARLS AND PITFALLS

- Expression of grief is determined by chronological age and level of cognitive development.
- Divorce and/or separation has long-term devastating effects on all aspects of the life of the child and family.

- Adolescents with chronic medical conditions and disabilities should have written transition plans by 14 years of age, which should be updated annually.
- Children exposed to high-conflict parental interactions may have difficulty forming meaningful relationships.
- During adoption, the pediatrician should help review any information about the child's medical history (if available) before and after adoption.
- Limit screen time (TV, internet, etc.) to 2 h/day.
- Foster care is intended to be a short-term solution until a permanent placement or adoption can be made.
- Encopresis occurs with an 80% male predominance and often a positive family history.
- Somatization disorders occur in children who are genetically predisposed.
- Chronic pain syndromes are diagnoses of exclusion. Other conditions must be ruled out before diagnosis.
- Sibling rivalry and jealousy are common.
- Anxiety disorders have a genetic predisposition and environmental factors.
- Night waking may be associated with separation anxiety.
- Organ transplantation can have psychosocial and financial stresses on the family.
- Under state laws, physicians are legally obligated to report any suspected abuse and neglect.
- Neglect is the most common form of child maltreatment.
- STD in a prepubertal child is presumptive evidence of sexual abuse.

Suggested Reading

American Academy of Pediatrics, Committee on Fetus and Newborn; Fetus and Newborn Committee. Prevention and management of pain in the neonate: an update. Pediatrics. 2006;118:2231–41.

Asnes AG, Leventhal JM. Managing child abuse: general principles. Pediatr Rev. 2010;31:47–55.

Bhargava S. Diagnosis and management of common sleep problems in children. Pediatr Rev. 2011;32(3):91–9.

Brown P, Tierney C. Munchausen syndrome by proxy. Pediatr Rev. 2009;30:414–5.

Dubowitz H, Feigelman S, Lane W, Kim J. Pediatric primary care to help prevent child maltreatment: the Safe Environment for Every Kid (SEEK) model. Pediatrics. 2009;123:858–64.

Flaherty EG, Sege RD, Griffith J, et al. From suspicion of physical child abuse to reporting: primary care clinician decision-making. Pediatrics. 2008;122:611–9.

Fortin K, Jenny C. Sexual abuse. Pediatr Rev. 2012;33:19–32.

Gold LM, Kirkpatrick BS, Fricker FJ, Zitelli BJ. Psychosocial issues in pediatric organ transplantation: the parents' perspective. Pediatrics. 1986;77:738–44.

Holsti L, Grunau RE. Considerations for using sucrose to reduce procedural pain in preterm infants. Pediatrics. 2010;125:1042–7.

Pagel JF. Nightmares and disorders of dreaming. Am Fam Physician. 2000;61:2037–42, 2044.

Pipan M, Blum N. Basics of child behavior and primary care management of common behavioral problems. In: Voight RG, Macias MM, Myers SM, editors. Developmental and behavioral pediatrics. Elk Grove Village: Pediatrics; 2011. p. 49–50.

Zeltzer LK, Krane EJ. Pediatric pain management. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011. p. 360–75.

Zuckerman B. Nightmares and night terrors. In: Parker S, Zuckerman B, Augustyn M, editors. Developmental and behavioral pediatrics: a handbook for primary care. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 251–2.

Ethics

28

Marwa Abdou

GENERAL

Negligence and Malpractice

- Pediatricians are expected to adhere to the highest level of professional conduct
- If their behavior is found to be substandard and a patient is harmed as a result, the pediatrician can be sued for malpractice
- Pediatricians are sued most commonly for errors in diagnosis related to several conditions, e.g.,
  - Meningitis
  - Pneumonia
  - Appendicitis
  - Asthma
  - Developmental dysplasia of the hip

Battery

- Performing a procedure or providing treatment without informed consent
- Treatment that is substantially different from that to which the patient consented is considered battery even with the best intentions
- Unauthorized substitution of one doctor for another comes within the definition of battery, especially when it involves invasive procedures, e.g.,
  - Circumcision performed on a newborn by a pediatrician other than the physician the mother consented to perform the procedure

Good Samaritan Laws

- Laws that protect pediatricians and caregivers from prosecution for medical mistakes, as long as the caregivers are acting voluntarily

ETHICAL PRINCIPLES

Autonomy

- It is the patient's right to make decisions and act on them freely and without interference
- The physician must understand the risks, benefits, and alternatives of any proposed therapy or procedure in order to help the patient or guardian of the child make a decision that is consistent with his or her values
- **Example:** If a patient refuses a specific treatment or procedure, it is the physician's obligation to respect that autonomy and not forcefully override the refusal

Beneficence

- The primary ethical principle in pediatrics
- Beneficence is doing good for others and acting in the patient's best interest. This includes the consideration of treatment efficacy and

M. Abdou (✉)
Department of Pediatrics, Texas Tech University Health Science Center, El Paso, TX, USA
e-mail: marwaali@doctor.com

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_28

the potential to lessen disability or complications
- **Example:** Referring a child to an expert in the field in order to provide the best treatment available

Nonmaleficence

- The principle of *do no harm*
- **Example:** Not ordering a head computed tomography (CT) scan to a well-appearing child with a minor head laceration

Veracity

- The principle of telling the truth
- **Example:** Informing an adolescent regarding their diagnosis

Fidelity

- The quality of being faithful and maintaining confidentiality
- **Example:** Maintaining the privacy of an emancipated minor with a sexually transmitted disease (STD)

Confidentiality

- Not to divulge a patient's personal information without his or her permission

Justice

- The principle of being fair
- The ideal distribution of risks and benefits; prudently legislating potential conflict
- **Example:** Clinical research trials in children

MEDICAL DECISION-MAKING

Parental Authority

Parents' rights
- Parents have the right to make decisions for their children
- Affection and close family ties make parents the most suitable party to reach the best decision for their children
- Parents will carry the consequences of any decision made

Limitations
- Parents have no right to refuse life-saving treatment for a child
- Pediatricians may seek help from a hospital ethics committee or the court if time allows, e.g., parents refusing critical treatment or an operation that is not immediately life-threatening

Medical Decisions in Complex Conditions

Supportive team in making difficult decisions
- Psychosocial interdisciplinary team
- Pediatric palliative care team
- Social worker
- Case manager
- Child life specialist
- Chaplain
- Psychologist
- Bereavement specialist
- Palliative care physician

Description of Team Functions
- Social workers: Quickly link families to government-sponsored insurance programs, financial support; help resolve custody or guardianship issues

- Case managers: Work closely with social workers and other clinicians to help coordinate outpatient appointments, tests, and treatments
- Child life specialists: Able to explain the current situation and upcoming procedures in terms that the child can understand
- Chaplains: Care for the spiritual needs of the patient and family
- Psychologists: Trained to listen to and help with the spoken and unspoken concerns of the family and/or patient
- Bereavement specialists: Build rapport and help the patient and family deal with anticipatory grief regarding the diminishment of the child's expected lifespan or the very real possibility of the child's actual death
- Palliative care physicians: Can begin therapy while awaiting a referral to the appropriate sub-specialist
- **Example:** A child with respiratory distress who is dying:
  - It is ethically acceptable to treat symptoms of respiratory distress in a dying patient even if it may hasten death because of the "doctrine of double effect"
  - Narcotics and benzodiazepines at standard doses are effective medications to treat the discomfort of respiratory distress in dying patients
  - The medication has 2 effects:
    - Positive (treating symptoms)
    - Negative (hastening death)
  - The intent of the positive effect can be honored

General rules

- Pediatricians are not obligated to provide futile care, which includes prolonged or invasive therapies on patients who are not likely to derive benefit from them
- Pediatricians must provide parents or guardians with relevant risks and benefits of the available options and provide specific recommendations
- Pediatricians should not offer a list of vague choices

End-of-life planning

- A multidisciplinary team approach to inform the family and provide more time for them to decide in the best interest of the child
- The discussion about end-of-life care should take place early in the course of a chronic disease
- Withdrawal of life-sustaining medical therapies should occur with agreement from those accountable after they have been allowed adequate time to make a fully informed decision

CONSENTS

Informed Consent

- Approval of the legal guardian of the child and/or of the competent child for medical interventions following appropriate and clear information

Elements of informed consent

- Provision of information about the nature of the illness or condition; proposed diagnostic steps and/or treatments; the probability of their success, the potential risks, and benefits make up the elements of informed consent
- Information about the uncertainties of the proposed treatment and alternative treatments, including the option of no treatment or comfort measures only

- Assessment of patient and surrogate understanding and medical decision-making capacity should be made
- Ensure that there is a voluntary agreement with the plan

Assent by Pediatric Patients

Informed assent

- A child's agreement to medical procedures in circumstances where he or she is not legally authorized or lacks enough understanding for giving consent competently
- Doctors should carefully listen to the opinion and wishes of children who are not able to give full consent and should strive to obtain their assent
- Assent from children even as young as 7 years can foster the moral growth and development of autonomy in young patients

Benefits of informed assent

- Helps the patient to achieve a developmentally appropriate awareness of the nature of his or her condition
- Tells the patient what he or she can expect with tests and treatments
- Makes a clinical assessment of the patient's understanding of the situation and the factors influencing how he or she is responding
- Solicits an expression of the patient's willingness to accept the proposed care
- Children and adolescents have a right to give their opinion on medical decision-making in clinical practice and research

Principles in Medical Decision-Making

- Pediatricians have the responsibility to determine the ability and competence of the child for giving his or her consent or assent
- All children, even those not judged as competent, have a right to receive information given in a way that they can understand and to give their assent
- This consent/assent process must promote and protect the dignity, privacy, and confidentiality of the child and his or her family
- Consent or assent is required for all aspects of medical care—for preventive, diagnostic, or therapeutic measures, and for research

Refusal of Treatment or Procedure by a Child

- A child may refuse a treatment or procedure that is not necessary to save life or prevent serious harm
- Children should generally be allowed to participate in their own medical decision-making when possible
- Mature and emancipated minors may be able to make their own decisions

Refusal of Treatment or Procedure by Parents or Guardians

Possible causes of disagreement

- Different religious beliefs
- Moral values
- Believing that the treatment is not necessary or preferring other alternatives that may not be the best for the child

Appropriate action in cases of disagreement

- The best initial step, in general, is to try to understand why the parents are refusing the treatment or the procedure and try to convince them
- If the treatment is necessary to save life or prevent serious harm, e.g., refusing antibiotic treatment for meningitis, blood transfusions in cases of life-threatening anemia, or chemotherapy that offers a good chance of cure in an otherwise universally fatal cancer:
  - Proceed with the treatment or procedure without informed consent

  - The pediatrician has the duty to act in the best interest of the child
- If not life-threatening or there is no immediate harm, but the risks and complications are evident without treatment:
  - Consult the institutional ethics committee or refer to the court
  - May call the state child protection agencies for medical negligence
  - May terminate the physician-patient-parent relationship
- Low risk or no imminent danger to the child, e.g., refusing hepatitis B, or vitamin K in the hospital after birth:
  - Explore the reason why parents are refusing the vaccine or vitamin K
  - Explain why physicians strongly recommend vitamin K or hepatitis B vaccinations for all newborns
  - Inform the parents of the medical indications and the risks, and the pediatrician should try to convince the parents to consent, e.g., the hemorrhagic disease in the newborn is a life-threatening illness that is easily preventable by giving vitamin K; should the disease process begin, it is difficult to treat
  - May ask the parents to sign a declination form, indicating that the vitamin K or hepatitis B has been recommended and the risks have been explained
- Parents may refuse non-emergent treatment or procedures, e.g., treatment of acne, suturing lacerations, etc.

Adolescent Consent in Special Situations

- Adolescents have the right to consent to the investigation and treatment of sexually transmitted diseases, contraceptive services, and prenatal care
- Adolescents can access mental health and substance abuse prevention and treatment services
- Pediatricians should protect adolescent confidentiality unless there is abuse or serious risk of harm

Examples:

Parents requesting drug testing of their adolescent without his or her knowledge (surreptitious drug testing) → The best approach:

- Building a trusting relationship with the adolescent and parents is the best next step
- Interview the adolescent alone; the conversation may lead to a discussion about drugs and other potentially risky activities
- Do not test the child without his or her knowledge, as that will inevitably seriously impair the physician-patient relationship
- Try to convince the parents that this is the best approach, because even if the child is indeed a drug addict, he or she may resist intervention efforts

Adolescent requesting birth control pills → The best approach:

- Maintain confidentiality and trust
- Oral contraceptives are much safer for adolescents than is pregnancy
- An adolescent who seeks contraception is acting responsibly and maturely, and this is an opportunity for an open conversation
- Ask if she has a boyfriend? What is his age? If he is much older, there may be a possibility that this is an abusive relationship
- Report abusive relationships to appropriate authorities. The age of consent may differ from state to state
- Convince the adolescent to inform her parents or another trusted adult
- Inform the adolescent that her parents may know about the prescription if she is under their insurance health plan
- Counsel about the risk of sexually transmitted diseases

A 16-year-old female who is the mother of a 2-month-old infant and who requires surgery to remove her gallbladder

- She can provide informed consent for herself (emancipated minor)

Emancipated minors can give informed consent for medical care if:

- He/she is married
- In the military
- A parent
- Self-supporting while not living with parents
- A high school graduate

ETHICS IN GENETICS

Use of Technology for Genetic Studies in Genetic Counseling

- Families can find out earlier about possible genetic variations that could affect their children by using genetic testing for example:
  - Whole exome sequencing
  - Maternal noninvasive prenatal screening (NIPS)/cell free placental DNA testing

Duties of pediatricians

- Providing accurate, up-to-date, and balanced information following a prenatal or postnatal diagnosis of a genetic condition will help in a smooth and positive transition
- Not to focus exclusively on the genomic outcomes and medical issues to avoid the risk of leaving parents feeling anxious and frightened
- Even with a full spectrum of information, patients are still likely to undergo an adjustment process and some degree of grief

Predictive Genetic Testing

- Predictive genetic testing of children for adult-onset genetic disorders is not recommended until the child reaches adulthood or adolescence. If the child has a mature decision-making capacity, genetic counseling can be considered, with informed consent
- Pediatricians should be very cautious about ordering predictive genetic testing for minors without parental consent, as this testing can have serious psychological, social, and medical ramifications for the minor and other family members
- The anticipated outcomes of a condition can change based on the social support, healthcare, and services available to individuals with different conditions, e.g.,
  - Positive cases of Huntington's disease, which usually manifest during adulthood

ETHICS IN COCHLEAR IMPLANTS

Background (see Chap. 18 Ear, Nose, and Throat (ENT) for more information)

- Traditional methods used for deaf education include: American Sign Language, which is very successful if started early in life, and oralism, which is speechreading with some limitations as some words have same lip movements

Variable outcome

- Some children who receive implants are able to function well in the hearing world
- Others continue to require special assistance or to use sign language along with spoken language

Duty of pediatricians

- Pediatricians need to understand the options and be prepared to help parents sort through the complex data and multiple options to arrive at a decision that is best for themselves and their children

IMPERILED NEWBORN INFANTS

Newborns between 23 and 24 weeks of gestation

- Such neonates are at a high rate of mortality and high risk of diminished quality of life

- Ongoing discussions about care at the time of birth should be made jointly with the family before delivery
- Parental wishes regarding resuscitation should be respected

Viability
- Viability is a reasonable chance of survival with advanced medical support
- No uniform agreement exists as to the exact timing of fetal viability

Non-initiation of resuscitation may be appropriate in the following cases:
- Confirmed gestation less than 23 weeks
- Birth weight less than 400 g
- Anencephaly
- Confirmed lethal genetic disorder or malformation

DEATH AND DYING CHILDREN

Death
- Irreversible cessation of circulatory or respiratory functions or irreversible cessation of all functions of the entire brain, including the brainstem

Determination of death by either of the following criteria
- Neurologic
- Circulatory

Brain death declaration requires that the following examinations be done twice
- Physical examination
- Apnea testing

Death is declared after the second examination confirms brain death
- Cerebral blood flow scanning and electroencephalography should be performed **only** if any component of the physical examination or apnea testing cannot be performed (for more details, see Chap. 8 Critical Care)

Action when a child is declared dead
- If consent for organ donation is declined by the family, breathing and circulatory support should be discontinued
- No recommendation or consent is required

ORGAN DONATION/ TRANSPLANTATION

Time of approach
- The family should not be approached by anyone about organ donation before the declaration of death

Appropriate steps in approaching the family about organ donation
- Confirmation and declaration of death
- Obtaining consent from the family for organ recovery
- Inform local organ procurement organization (OPO)
- The family should be approached by the OPO representative regarding organ donation

RESEARCH INVOLVING CHILDREN

Critical Criteria Required to Conduct a Clinical or Drug Trial in Children

- Consent of guardians and the child (7 years and older)
- The informed consent should be written in a language that can be easily understood, at a sixth to eighth grade reading level for adult participants
- Trial design appropriate to the research question
  - Targeted to help understand, prevent, or alleviate a serious condition that specifically affects the pediatric population
  - Congruent with all local, regional, and national regulatory guidelines and laws

  - Meaningful and measurable outcomes
  - Adequate comparative data and adequate enrollment numbers
  - Conducted in the best interest of the child
  - Minimize harm or a minor increase over minimal risk
  - Scientifically applicable
  - Independent data and safety monitoring committee (DSMC) for all phase 3 drug trials

Financial incentives

- Healthcare providers are prohibited to receive financial incentives for recruiting children to participate in clinical drug research

Parents and minor rights

- Retain the right to withdraw consent/assent and participation in the study at any time during the process

COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

Classification

- Natural products, e.g., botanicals, vitamins and minerals, and probiotics
- Mind and body practices, e.g., acupuncture, relaxation techniques

Ethical considerations

- Seek reliable, evidence-based information about the safety and effectiveness of specific therapies and therapists
- Identify risks or potential harmful effects
- If therapy is both safe and effective→ recommend the therapy
- If the therapy is not safe and is not effective → discourage its use
- If the therapy is not safe but is effective → monitor closely or discourage its use
- Nonjudgmental approach to the use of CAM can prevent harm resulting from interactions with traditional medical therapy
- Religious beliefs of the family must be respected
- Parents must be held accountable for withholding medical care when doing so would likely result in death or suffering

Examples:

Fish Oil

- May improve the symptoms of attention-deficit/hyperactivity disorder (ADHD) in some children
- Minimal adverse effects

Melatonin

- Used for functional sleep disorders to decrease sleep latency
- Long-term studies on the safety and efficacy of pediatric use are lacking

Probiotics

- Used for treatment of acute infectious diarrhea; however, *Lactobacillus rhamnosus* is not effective for the treatment of acute gastroenteritis in young children
- May decrease functional abdominal pain symptoms in some children
- Used in the prevention of atopic dermatitis in predisposed children, however, probiotics not effective for atopic dermatitis
- Used in preventing necrotizing enterocolitis and late-onset sepsis in preterm infants

Manipulative, movement, and body-based practices

- For example, osteopathic manipulation, chiropractic adjustments, and massage
- Serious complications are possible with chiropractic treatment of children; however, such adverse effects are rare and related to high-velocity, extension, and rotational spinal manipulation
- It is critical to exclude abnormal anatomic or neurologic findings before any manual or manipulative therapy is used on a child or adolescent

Acupuncture

- Acupuncture is performed using solid-core, small-gauge sterile needles to penetrate the skin
- Used in the treatment of pediatric headache and migraine and treatment of postoperative pain
- Acupuncture is generally safe in the pediatric population when practiced by an appropriately trained practitioner

Spirituality

- Spiritual healing includes prayer
- The belief that praying for someone else can help cure their illness
- Mind-body therapies may delay the diagnosis or treatment of serious illness

MEDICAL TESTIMONY

- It is ethical for pediatrician to testify as an expert witness
- Recommendation according to the American Academy of Pediatrics: Physicians should contribute as medical experts only to cases in which they possess true expertise and related experience

Pediatricians responsibilities

- Ensure that their testimony is:
  - Complete, accurate, and unbiased
  - Based on a complete understanding of current medical evidence and standard of care
- Transcripts of courtroom testimony in medical malpractice cases may be submitted for peer review

CONFLICT OF INTEREST

Definition

- Any situation that creates a risk that professional judgment or actions regarding a primary interest will be excessively influenced by a secondary interest
- Conflicts of interest can occur in research, education, and clinical practice

Examples of financial conflict of interest

- Accepting gifts from pharmaceutical companies
- Receiving outside funding for educational programs
- Having relationships with pharmaceutical companies

Disclosure of any potential conflicts of interest is an essential step in mitigating them

PEARLS AND PITFALLS

- Performing a procedure or providing treatment without informed consent is considered a battery even with good intention.
- The 4 principles of medical ethics are respect for autonomy, beneficence, nonmaleficence, and justice.
- Clinicians should make every effort to work with families to find mutually acceptable decisions for the medical care of their children.
- When parents refuse a proposed treatment procedure, the best initial step is to engage them in dialogue to try to understand why they are rejecting it and to try to convince them of its efficacy.
- In complicated cases, multidisciplinary meeting with all involved specialists might help.
- When disagreements persist between families and the medical team, consultation with the institutional ethics committee may be helpful.
- If the CAM is not safe and is not effective, discourage its use.

Suggested Reading

American Academy of Pediatrics Committee on Fetus and Newborn, Bell EF. Noninitiation or withdrawal of intensive care for high-risk newborns. Pediatrics. 2007;119:401–3.

Committee on Pediatric Research. Policy statement: promoting education, mentorship, and support for pediatric research. Pediatrics. 2014;133:943–9.

De Lourdes Levy M, Larcher V, Kurz R, Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Informed consent/assent in children. Statement of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). Eur J Pediatr. 2003;162:629–33.

Fanaroff JM. Medical malpractice/expert testimony/disclosure of errors. Pediatr Rev. 2010;31:e24–7.

Karkazis K, Rossi WC. Ethics for the pediatrician: disorders of sex development: optimizing care. Pediatr Rev. 2010;31:e82–5.

Lantos J. The patient-parent-pediatrician relationship: everyday ethics in the office. Pediatr Rev. 2015;36(1):22–9; quiz 30.

Nakagawa TA, Ashwal S, Mathur M, Mysore MR, Bruce D, Conway EE Jr, Society of Critical Care Medicine; Section on Critical Care and Section on Neurology of the American Academy of Pediatrics; Child Neurology Society, et al. Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. Pediatrics. 2011;128:e720–40. Crit Care Med. 2011;39:2139–55.

Opel DJ, Olson ME. Bioethics education and resources. Pediatr Rev. 2012;33:370–3.

Opel DJ, Feemster KA, Omer SB, Orenstein WA, Richter M, Lantos JD. A 6-month-old with vaccine-hesitant parents. Pediatrics. 2014;133:526–30.

Saul RA, Meredith SH. Beyond the genetic diagnosis: providing parents what they want to know. Pediatr Rev. 2016;37:269–78.

Sitratullah O. Kukoyi-Maiyegun

BIAS AND STUDY DESIGN

Bias

- Bias is the result of differences between the study groups
- Bias is a systematic error in the study design that can decrease the ability to find a relationship between the exposure and the outcome of interest
- Bias should be minimized in the study design
- Some forms of bias can attempt to be accounted for in statistical analysis

Common types of bias

1. **Confounding bias**—Occurs when an association between an exposure and an outcome is distorted by another variable. Example: Smoking → Lung cancer. However, certain members of the study group were exposed to environmental toxins, so the environmental toxins would be a confounding variable
2. **Selection bias**—Occurs when the subjects selected truly do not represent the intended population to be studied, i.e., nonrandomization of the study group
3. **Recall bias**—Occurs when research subjects inaccurately recall previous exposures or events. Example: A parent with a child who has cancer may link certain exposures to the cancer
4. **Pygmalion effect bias**—Occurs when the researcher's belief in a specific treatment modality efficacy changes the outcome of the treatment
5. **Hawthorne effect**—Occurs when the subjects of the research study change their own behavior. Example: Some people in the "smoking group" stop smoking during the study
6. **Procedure bias**—Occurs when research subjects are not treated equally

How to reduce bias:

1. Randomization—Subjects should be randomly selected
2. The use of a double-blind study so that neither researchers nor test subjects can identify the true treatment, e.g., neither party has any idea as to who is receiving the active drug and who is receiving the sugar pill (placebo)
3. Maximize follow-up so that the number of subjects who are lost is kept to a minimum
4. Researchers should try to minimize their own prejudices and opinions about a particular treatment
5. Use of a standardized protocol that is applied to all subjects of the research study

Study Designs

Randomized controlled trials

- Best study design to evaluate the risks and benefits of a proposed new treatment

S. O. Kukoyi-Maiyegun (✉)
Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Science Center, El Paso, TX, USA
e-mail: sitratullah.maiyegun@ttuhsc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_29

- Establishes causal relationships between treatments and outcomes
- Optimal way to evaluate the effect of 2 different treatments for a disease
- Has high internal validity
- Reduced risk of confounding variable
- Reduced external validity
- Expensive, time-consuming variables

Cohort studies

- A population-based cohort study is best for obtaining valid information about the prognosis of a condition over time
- A prospective study that stratifies subjects into groups based on the presence or absence of a proposed risk factor and then follows the subjects prospectively for outcome
- Can reveal important details about the natural history of the condition being studied
- Useful for sequential events
- Can study multiple outcomes from exposures
- Requires large sample size
- Risk of confounding variables
- Difficult to study rare outcomes
- Prospective: expensive

Case-control studies

- Useful to study individuals with a disease compared to individuals without the disease to evaluate risk factors and outcomes for the disease
- Case-control study groups are defined by the outcome and exposures ascertained retrospectively
- Useful for rare outcomes
- Can study several exposures
- Inexpensive
- Risk of confounding variables

Cross-sectional studies

- Best method to ascertain the efficacy of a diagnostic test by comparing a new diagnostic or screening test with a known gold standard test in the same population group
- Causation cannot be determined from cross-sectional prevalence studies
- Can study multiple outcomes and exposures
- Cannot infer causality
- Risk of confounding variables
- Less useful for rare exposures or outcomes

Case studies

- Useful for rare outcomes
- Convenient and inexpensive
- Lack of a comparison group
- Cannot infer causality
- Risk of confounding variables

Case series

- Descriptive study design that is inexpensive and convenient but with limited uses
- Best used for generation of etiologic hypotheses, health planning purposes, and allocation of resources

Systematic reviews

- A comprehensive review of the literature on a clinical question
- Includes a descriptive results section summarizing the findings and addressing the qualities of the included studies

Meta-analysis

- Uses statistical methods to combine the results of multiple studies on a given topic
- Compilation of evidence that potentially has greater power to inform clinical decisions than would an individual study in the systematic review or meta-analysis
- If the quality of the studies included in the systematic review or meta-analysis is poor, the summary conclusions are similarly inadequate

Case reports

- Aid in recognizing and describing new disease processes or rare manifestations
- Describe the disease in the context of comorbidities and individual characteristics
- Identify drug adverse effects

- Help to illustrate the diagnostic process and help students apply the literature to an individual patient
- Help identify emerging health conditions
- Show how exposures and disease outcomes are related
- Can stimulate important research questions and help guide hypotheses
- Are purely descriptive and one of the weakest forms of evidence
- Cannot be used to make inferences about the broader population
- Cannot prove causality

Anecdotal evidence

- Clinician's personal experience
- Shares some characteristics with case reports
- Lacks the strength of data collected via rigorous methodology that also involves significant numbers
- Can suggest hypotheses and lead to the creation of credible studies

Descriptive epidemiologic studies

- Follow-up on case reports
- Used to describe patterns of disease in the population according to person, place, and time
- Do not test a predefined hypothesis or determine a cause-and-effect relationship
- Used to develop hypotheses for subsequent analytic studies
- Use a variety of tools, including surveillance reports, cross-sectional analyses, and surveys

Statistically significant vs. clinically significant studies

- In both studies, results are unlikely to be the result of chance
- Statistical significance does not imply clinical significance
- Clinically significant results should be generalizable and reproducible
- Clinically significant study results should have an effect that suggests an alteration in practice or decision making

EPIDEMIOLOGICAL RESEARCH METHODS

Prevalence vs. Incidence

Both provide important information that leads to the prioritization of public health issues, development of public health initiatives, and the development of future studies

Prevalence

- The percent of a group of people with a specific condition in the population being studied
- Prevalence is the total number of existing cases of a disease/total population being studied

Incidence

- The total number of new cases within a specific period of time
- Number of new cases in a specific time period/total population at risk during that same time period

Prevalence vs. incidence

- Prevalence will be greater than incidence in chronic conditions
- Prevalence and incidence will about the same in acute conditions

Screening and Diagnostic Testing: Four Square Model (Fig. 29.1)

False positive

- A false positive (FP) occurs when the test reports a positive result for a person who is disease-free

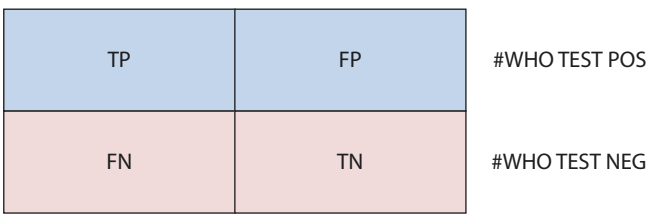


Fig. 29.1 Foursquare. *TP* true positive, *FP* false positive, *FN* false negative, *TN* true negative

False negative

- A false negative (FN) occurs when the test reports a negative result for a person who actually has the disease

Sensitivity: Screening

- Probability of correctly identifying those who truly have the disease
- True positives (TP)/patients with the disease
- TP/(TP + FN) (see Fig. 29.1)
- A highly sensitive test helps rule out disease because the higher the sensitivity, the lower the number of false negatives

Specificity: Confirmation

- Probability of correctly identifying those who do not have the disease
- True negatives/patients who do not have disease
- TN/(FP + TN)
- A highly specific test is used to confirm disease after a screening test and "rules in" disease because the higher the specificity, the lower the number of false positives.

Useful mnemonics

- SPIN—**SP**ecific tests rule **IN** the condition when they're positive
- SNOUT—**S**e**N**sitive tests rule **OUT** the condition when they're negative

Summary

- A good screening test is a rapid, inexpensive assay and has a good sensitivity (i.e., a negative test is reliable)
- A positive or equivocal test should generally be confirmed with a more specific confirmatory assay
- Example: HIV screening is done with enzyme-linked immunosorbent assay (ELISA) and then confirmed with a western blot (protein immunoblot)

Positive Predictive Value (PPV)

- Probability of correctly identifying those who truly have the disease among those whose tests are positive
- Likelihood that a patient with a positive test has the condition
- PPV = TP/(TP + FP)
- Predictive values are dependent on the prevalence of the disease
- The higher the prevalence of a disease, the higher the PPV of the test

Negative Predictive Value (NPV)

- Probability of correctly identifying those not having the disease given a negative test
- Likelihood that a patient with a negative test that truly does not have the disease
- TN/(FN + TN)

Likelihood Ratio (LR)

- Probability that an individual with disease has a positive test result divided by the probability that an individual without disease has a positive test result
- The degree to which the results of the test change the probability
- The LR combines the sensitivity and specificity of the test into a single measure
- The LR for a positive test can be calculated from the sensitivity and specificity as follows: Sensitivity/(1-specificity), when sensitivity and specificity are expressed as decimals.
- Post test probability can be determined by using the Fagan nomogram.
- Fagan nomogram:

  - A tool that allows the determination of post-test probability given the pretest probability of disease and the LR for the diagnostic test
  - The pretest probability of disease can be estimated based on disease prevalence

DESCRIPTIVE STATISTICS

Validity (Accuracy) vs. Reliability (Precision)

Validity (accuracy)

- Addresses whether an instrument or test actually measures what it is intended to measure
- Validity assesses how accurate and how true the test measurements are
- Criterion validity is the degree to which the measurement correlates with an external criterion or another instrument or test that is considered valid
  - Convergent validity is the degree to which independent measures of the same construct are highly correlated
  - Predictive validity is the ability of an instrument or test to predict some future criterion
  - Discriminant validity requires that an instrument or test shows little or no correlation with measures from which it differs
- Content validity refers to the extent to which aspects of items that make up an instrument or test are representative of a particular construct
  - Face validity is a judgment about whether elements of an instrument make intuitive sense
  - Sampling validity refers to whether the instrument incorporates all of the aspects under study

Reliability (Precision)

- The consistency or repeatability of scores
- Test–retest reliability assesses whether an instrument or test yields the same results each time it is used with the same study sample under the same study conditions
- Internal consistency reliability is a measure of the consistency of the items within a test
- Interrater reliability is the degree to which 2 raters independently score an observation similarly

Sample size

- Increasing sample size improves the ability to detect adverse events
- For studies in which the difference in measured effect is small, a larger sample size is required to detect a statistically significant difference
- Power is the statistical probability that a study will not mistakenly accept a null hypothesis and conclude that there was no effect when there actually was one
- Having a larger sample size increases the power of the study
- A larger sample size reduces the likelihood of making a type I or type II error

Odds Ratio and Risk Types (Table 29.1)

Odds ratio

- Defined as the odds of having a disease in the exposed group divided by the odds of having the disease in the unexposed group
- Odds ratio calculates the relative risk (RR) if the prevalence of the disease is low. It can be calculated for case-control study (retrospective study)

Odds ratio formula = A × D/B × C

Interpretation

- OR > 1—Exposure is associated with a higher odds of an outcome

Table 29.1 Calculating the odds ratio

	Disease present (+)	Disease absent (−)
Risk factor/exposure (+)	A	B
Risk factor/exposure (−)	C	D

- OR < 1—Exposure is associated with a lower odds of an outcome
- OR = 1—No effect of the exposure on an outcome

- Example: Exposure = cigarette smoke. Outcome: lung cancer. If the OR > 1 → Smoking is associated with higher odds of lung cancer

Risk: Probability of a Disease Outcome

1. **Absolute risk**—Ratio of the number of people exposed to a risk factor that developed disease to all of those who were exposed to the risk factor

$$\text{Absolute risk} = A / A + B$$

2. **Relative risk**—Disease risk in the exposed group divided by disease risk in unexposed group. It can be calculated for cohort study (prospective study).

   For a rare disease, OR approximates R

$$\text{Relative risk} = A / (A + B) / C / (C + D)$$

3. **Attributable risk**—Difference in risk between the exposed and unexposed groups

$$\text{Attributable risk} = A / A + B - C / C + D$$

Statistical Hypothesis (Null Hypothesis vs. Alternative Hypothesis)

Null hypothesis

- The null hypothesis is referred to as the hypothesis of "no difference"
- There is no statistically significant relationship between the 2 variables that are being studied
- Example: Does exercise reduce cholesterol levels?
- Null hypothesis: Exercising daily has no effect on cholesterol levels

Alternative hypothesis

- The alternative hypothesis is referred to as the hypothesis of "difference"
- There is a statistically significant difference between the 2 variables that are being studied
- Example: Does exercise reduce cholesterol levels?
- Alternative hypothesis: Exercising daily has an effect on cholesterol level by lowering cholesterol levels.

Type I error (alpha)

- A type I error (false-positive, also known as a rejection error) is rejection of a null hypothesis that is actually true in the population
- The investigator concludes that there is a significant difference between the groups when, in fact, there is no true difference
- This risk can be reduced by setting a more stringent *P* value (e.g., .01 instead of .05)
- A difference was seen that truly does not exist

Type II error (beta)

- A type II error (false negative, also known as an acceptance error) is failure to reject the null hypothesis that is actually false
- The investigator concludes that there is no difference when a difference actually exists in the population
- Increasing the sample size will reduce the risk of these errors
- A difference that was not seen but which truly exists

Power of a study

- The probability of rejecting the null hypothesis or the probability that there is a treatment effect (i.e., exercising daily reduces cholesterol levels)

- The larger the sample size, the higher the statistical power
- Power = 1 minus the probability of a type II error (beta)

Standard deviation (SD)

- A measure of the variability of individual values around the mean or average value
- When data are grouped closely together, the SD is small. When data are highly variable, the SD is large
- One standard deviation—68% of the numbers fall within the mean (average)
- 2 standard deviations—95% of the numbers fall within the mean
- 3 standard deviations—99.7% of the numbers fall within the mean

Standard error of the mean (SEM)

- Describes the variability in a distribution of sample means
- Mathematically, it is the sample SD divided by the square root of the sample size
- SEM = Standard deviation/sample size
- So as the sample size increases, the standard error decreases
- SEM is a smaller number than the SD

***P* value**

- The *P* value is the probability of obtaining a test statistic result at least as extreme as the one that was actually observed, assuming that the null hypothesis is true
- A researcher will often "reject the null hypothesis" when the *P* value turns out to be less than a predetermined significance level, often 0.05 or 0.01. Such a result indicates that the observed result would be highly unlikely under the null hypothesis
- Many common statistical tests, such as chi-square test or Student t test, produce test statistics that can be interpreted using *P* values
- An informal interpretation of a *P* value, based on a significance level of about 10%, might be:
  - $P \leq 0.01$: Very strong presumption against null hypothesis
  - $P \leq 0.05$: Strong presumption against null hypothesis
  - $0.05 < P \leq 0.1$: Low presumption against null hypothesis
  - $P > 0.1$: No presumption against the null hypothesis

Confidence intervals

- A confidence interval is a range of values with a specified probability that a given parameter falls in that range
- Often 95% (*P* value of 0.05) or 99% (*P* value of 0.01)
- If the confidence interval includes a 0 or a 1, then the null hypothesis cannot be rejected

Intention-to-treat analysis

- In an intention-to-treat analysis, study participants are analyzed according to their randomized assignment, regardless of changes that may occur after randomization
- Intention-to-treat analysis prevents the loss of statistical power that may be encountered with a failure to complete study protocols (dropout) or noncompliance

Number needed to treat

- The total number of patients who need to be treated to prevent an adverse event or bad outcome
- Number needed to treat = 1/absolute risk reduction (ARR)
- Example if the ARR is 20% then the number needed to treat = 1/0.2, which is 5. Thus 5 people need to be treated to prevent one bad outcome
- The number needed to harm is a measure that indicates how many persons on average need to be exposed to a risk factor over a specific period to cause harm in an average of one person who would not otherwise have been harmed

PEARLS AND PITFALLS

- Bias is a systematic error in the design study that can decrease the ability to find a relationship between the exposure and the outcome of interest.
- A randomized controlled study is the optimal way to evaluate the effect of 2 different treatments for a disease.
- Statistical significance does not imply clinical significance.
- A good screening test is a rapid, inexpensive assay and has a good sensitivity (i.e., a negative test is reliable).
- Having a larger sample size increases the power of a study.
- Standard deviation is a measure of the variability of individual values around the mean or average value.
- A confidence interval is a range of values with a specified probability that a given parameter falls in that range.

Suggested Reading

Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. J Clin Epidemiol. 2010;63(5):502–12.

Copeland-Linder N. Research and statistics: reliability and validity in pediatric practice. Pediatr Rev. 2009;30(7):278–9.

Ferrante di Ruffano L, Hyde CJ, McCaffery KJ, Bossuyt PM, Deeks JJ. Assessing the value of diagnostic tests: a framework for designing and evaluating trials. BMJ. 2012;344:e686.

Hernandez RG, Rowe PC. Research and statistics: cohort studies. Pediatr Rev. 2009;30(9):364–5.

Moore EM, Johnson SB. Research and statistics: case reports, anecdotal evidence, and descriptive epidemiologic studies in pediatric practice. Pediatr Rev. 2009;30(8):323–4.

Norris S, Atkins D, Bruening W, Fox S, Johnson E, Kane R, et al. Selecting observational studies for comparing medical interventions. In: Methods guide for effectiveness and comparative effectiveness reviews [Internet]. Rockville: Agency for Healthcare Research and Quality; 2010.

Palaia A. Research and statistics: study design and data sources. Pediatr Rev. 2013;34(8):371–2.

Perry-Parrish C, Dodge R. Research and statistics: validity hierarchy for study design and study type. Pediatr Rev. 2010;31(1):27–9.

Patient Safety and Quality Improvement

30

Osama I. Naga

MEDICAL ERRORS

- A medical error is an act that has the potential to cause patient harm, regardless of whether or not harm reaches the patient.

Preventable adverse event
- A medical error that results in harm to the patient

Potential adverse events or near misses
- Medical errors that do not cause harm to the patient

Types of potential adverse events or near misses:
- Intercepted: An error that is recognized and corrected before it reaches the patient
- Nonintercepted: An error that reaches the patient but does not result in harm

Preventable medical errors
- ***Examples:***
  - Failure to provide preventive treatment.
  - Failure to provide both the hepatitis B vaccine and hepatitis B immunoglobulin to an infant born to an HBsAg-positive mother within 12 h.
  - Patient who is allergic to penicillin is prescribed amoxicillin and develops a skin rash after drug administration.

Nonpreventable medical errors
- ***Example***: Patient with no history of allergic reaction to penicillin develops a severe allergic reaction to amoxicillin.

Causes of medical errors
- Inadequate or poor communication
- Insufficient information flow
- Human issues
- Patient issues
- Workflow and staffing issues
- Technical breakdowns/failures
- Policies and procedures that are inadequate

How to address medical error
- Either the medical error caused harm or not, the physician must analyze the event to prevent its reoccurrence and to improve the safety system.
- All providers must be responsible for the quality of patient care and safety.

***Example:* A nurse administered the incorrect medication.**
- Investigate the flaw or problem within the system that allowed or facilitated the mistake.
- Try to understand how and why the event occurred, instead of focusing on just blaming or punishing the nurse.
- Changing how medications are stored, labeled, or packaged may prevent the error from occurring again.
- This course of action does not negate the nurse's personal responsibility.

O. I. Naga (✉)
Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, USA
e-mail: osama.naga@ttuhsc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_30

Sentinel Event

- A sentinel event is an unexpected occurrence of death or serious physical or psychological injury.
- Near miss sentinel event: If the risk and potential consequences of a recurrence may lead to a serious adverse outcome.
- A sentinel event may or may not be due to a medical error.

Root Cause Analysis (RCA) Process

- A process for identifying the primary or causal factors that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event.
- Once a sentinel event has been identified, investigation must be immediately undertaken to determine the root causes that have led to the event as well as to implement an action plan to monitor for and to minimize any future risk that this event will recur.

Diagnostic Errors

- Diagnostic errors in the form of missed or incorrect diagnosis account for most pediatric malpractice cases.
- The most common diseases associated with diagnostic errors: pneumonia, meningitis, appendicitis, and testicular torsion.
- Most pediatricians have at least 1 diagnostic error per month, e.g., misdiagnosis of viral pharyngitis as acute streptococcal pharyngitis—a viral illness diagnosed as a bacterial illness.

Treatment Errors

Causes of medication errors

- Calculation error
- Dosage form confusion
- Illegible handwriting
- Incorrect documentation/data
- Knowledge deficit
- Performance error and poor communication

Significance

- Harm may or may not reach the patient (e.g., mistake caught early by physician, parents, or pharmacist).
- The severity of harm varies from minimal to serious adverse effects or even death.

Prevention

- Avoid abbreviations of drug names (e.g., "MS" may mean "morphine sulfate" or "magnesium sulfate").
- Confirm that the patient's weight is correct for weight-based dosages.
- Ensure that the weight-based dose does not exceed the recommended adult dose
- Identify drug allergies in patients.
- Write out instructions rather than using abbreviations, e.g., "Take 1 tablet twice a day" rather than "bid." Avoid vague instructions such as "Take as directed."
- The concentration of the medication and the frequency of administration should be clearly noted on prescriptions.
- Avoid use of a terminal zero to the right of the decimal point (e.g., use 5 rather than 5.0) to minimize 10-fold dosing errors.
- Use a zero to the left of a dose less than 1 (e.g., use 0.1 rather than 0.1) to avoid 10-fold dosing errors.
- Spell out dosage units rather than using abbreviations (e.g., milligram or microgram rather than mg or μg; units rather than "u").
- The pharmacist and nurse must verify all medication orders.
- When giving a verbal order, request that the name of the medication and directions for use be read back.

Decrease the risk of medication administration errors by parents

- Liquid medications should be dosed in milliliters, not teaspoons or tablespoons.

- Medications should be dosed to the nearest 0.1, 0.5, or 1 mL.
- Appropriate-volume milliliter-based dosing devices should be distributed with the medication.
  - Syringes are the preferred dosing device.
  - Measuring cups and spoons calibrated and marked in milliliters are acceptable alternatives.
- Advanced counseling strategies to ensure parental understanding and adequate health literacy and numeracy should be offered.

Role of the institution in reducing medication errors

- Provide education and training to hospital staff.
- Computerized systems to check dose and dosage schedules, drug interactions, allergies, and duplicate therapies.
- Standardize equipment (such as infusion pumps and weight scales) throughout the institution.
- Standardize measurement systems throughout the institution, for example, using only kilograms for weight, rather than using pounds in 1 department and kilograms in another.
- Avoid use of verbal orders whenever possible.
- Have a pharmacist participate in daily clinical rounds.
- Adjust for look-alike and sound-alike medications.
- Remove high-risk medications.

REPORTING MEDICAL ERRORS

- Reporting medical error is paramount to establishing a system capable of preventing future mistakes and improving the safety of care.
- Both voluntary and mandatory reporting systems will help to prevent the recurrence of a similar event.

Voluntary error reporting

- Errors reported, with little or no patient harm, can provide information critical to improving patient safety.

Barriers to voluntary reporting

- Fear of punitive action
- Lack of feedback
- The incident report takes a long time to complete
- Lack of physician access to electronic incident reporting systems
- Interruption of patient care to complete an incident report

Factors that may enhance voluntary reporting

- Education about which errors should be reported, even if trivial or causing no harm
- Encouraging a nonpunitive culture for reporting and reviewing adverse events
- Feedback on a regular basis about errors reported and about individual events
- Evidence that reporting of errors has successfully led to system changes
- Electronic format for reports
- Protecting the confidentiality of the author of the incident report

Mandatory error reporting

- Example of mandatory reporting
  - Suspected child physical or sexual abuse
  - Deaths not related to anticipated disease progression
  - Medical equipment malfunction or misuse leading to serious patient harm or death
  - Discharge of a patient incapable of making medical decisions to an unauthorized person

Medical error disclosure

- Once a medical error has been detected, it must be disclosed to the patient and family.
- Providers should consider offering an apology, and disclosing medical errors.

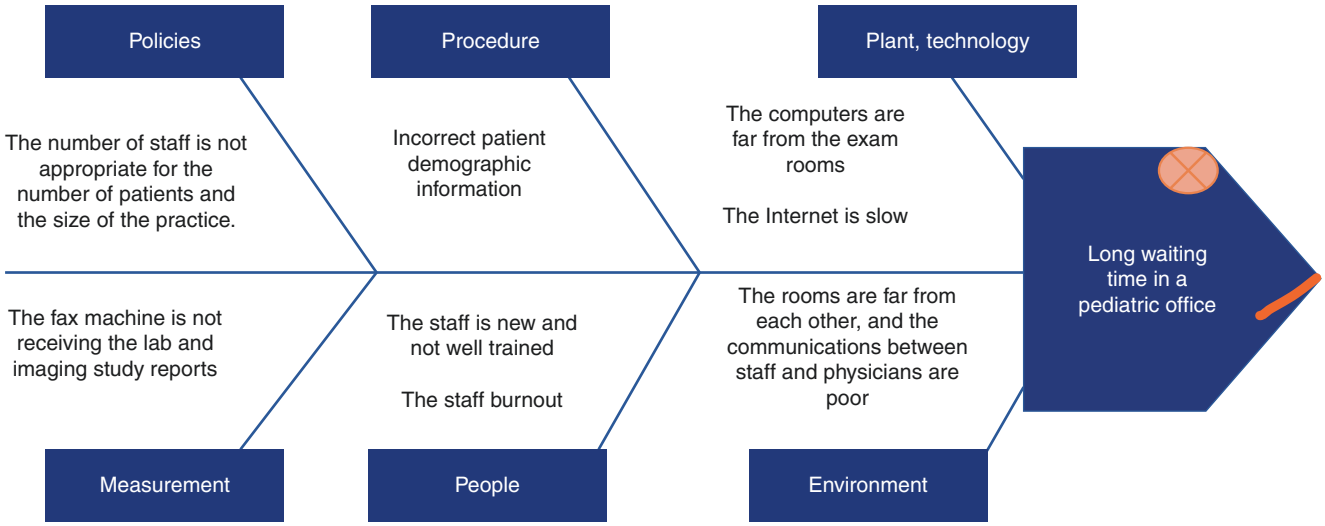


Fig. 30.1 A fishbone diagram as used in root cause analysis can help brainstorming by team members to identify the root cause of long wait times in a busy pediatric practice

- Patients desire and deserve disclosure of errors that have caused them harm.
- Disclosure of medical errors by physicians helps build trust in the clinician.
- Frank disclosure of medical errors by physicians decreases the likelihood of parents seeking legal action.

Recommendations

- Ensure that patient and family remain at the center of communication.
- Communicate clearly about how the medical error occurred and what will be done to prevent its recurring in the future.
- Support personnel to answer the family's questions.
- Promptly share with the family any new information obtained from investigation.
- Address all patient and family concerns as soon as possible.

QUALITY IMPROVEMENT (QI)

- To cultivate an effective team, encourage transparency, collaboration, teamwork, and learning from mistakes.
- Root cause analysis to identify problems and their solutions.
- For each cause found, the team should continue to "drill down" by repeatedly asking "Why is that?" until the root causes are identified.
- The fishbone diagram as used in root cause analysis can help brainstorming by team members to identify the root causes of problems, leading to improvement in the quality of care (Fig. 30.1).

PATIENT SAFETY

Handoffs

- A handoff takes place when a patient or a patient's medical information is transferred from one provider to another and/or from one healthcare venue to another.
- The resident duty hour restrictions implemented several years ago have increased the frequency of patient handoffs.
- The use of a mnemonic is recommended to structure patient handoffs. This will decrease the risk of miscommunication and help

ensure that all important elements are included. For example**:** *I-PASS*: *I*llness severity, *P*atient summary, *A*ction list, *S*ituation awareness and contingency plans, and *S*ynthesis by receiver.
- Methods of communications:
  - Printed patient summary documents (sign-out documents)
  - Verbal communication
- Use of *both* a sign-out document and verbal communication together are recommended.
- Sign-out and verbal documents generally remain accurate for only a short period (patient's clinical condition may change in 6 h or less).
- The ideal method of handoff is using an electronic summary that is continuously updated to reflect clinical changes.

Fostering a Culture of Safety

- Encourage communication and teamwork to meet high patient safety standards.
- Provide an open, fair, and transparent environment for the disclosure of medical errors to better identify means to decrease or eliminate them in the future.

Examples of fostering a culture of safety
- Use at least 2 patient identifiers when providing care, treatment, and services:
  - Check the patient's name, hospital number, and date of birth on both the wristband and hospital chart before obtaining blood or administering medicine.
- Report critical results of tests and diagnostic procedures on a timely basis.
- Maintain and communicate accurate patient medication information:
  - Obtain a list of patient medications on admission to a healthcare facility.
- Identify patients at risk for suicide.
  - Conduct a risk assessment to identify patients at risk for suicide.

Never Events

- Serious reportable hospital events that should never occur
- Serious—resulting in death or significant disability
- Should not occur:
  - Clearly identifiable and measurable
  - Usually preventable

Examples of never events
- **Surgical event**
  - A surgical procedure performed on the wrong body part
- **Product or device event**
  - Contaminated drug or instrument provided by the healthcare setting
- **Patient protection event**
  - An adolescent with suicide attempts or self-harm, resulting in serious disability, while being cared for in a healthcare facility
- **Care management event**
  - Patient death or serious injury associated with a medication error (e.g., errors involving the wrong drug, wrong dose, wrong patient, wrong time, wrong rate, wrong preparation, or wrong route of administration)
- **Environmental event**
  - Patient's death due to an oxygen line designed to deliver oxygen to the patient containing no oxygen
- **Criminal event**
  - Abduction of a newborn from the newborn nursery

PEARLS AND PITFALLS

- Punishing the provider for medical mistakes is not the ultimate solution; it is merely a temporary fix. Addressing the real cause and implementing the real solution will prevent the same mistake for reoccurring.

- Near miss: If the potential harm from a medical error does not reach the patient.
- Sentinel event: Medical error leading to a patient's unexpected death or serious physical or psychological injury.

Suggested Reading

Bartman T, McClead RE. Principles of quality improvement and patient safety. Pediatr Rev. 2016;37(10):407–17.

Crowley E, Williams R, Cousins D. Medication errors in children: a descriptive summary of medication error reports submitted to the United States Pharmacopeia. Curr Ther Res. 2001;62(9):627–40.

Haig KM, Sutton S, Whittington J. National patient safety goals. SBAR: a shared mental model for improving communication between clinicians. Jt Comm J Qual Patient Saf. 2006;32(3):167–75.

Institute of Medicine (US) Committee on Quality of Health Care in America. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academies Press (US); 2001. https://www.ncbi.nlm.nih.gov/books/NBK222274/. Accessed 20 Dec 2018.

McClead RE, Brady M. Sentinel events/patient safety events. Pediatr Rev. 2016;37(10):448–50.

Pereira-Argenziano L, Levy FH. Patient safety and quality improvement: terminology. Pediatr Rev. 2015;36(9):403–11.

Pharmacology and Pain Management

31

Osama I. Naga

GENERAL PEDIATRIC PHARMACOLOGY

Absorption (Table 31.1)

- Absorption is the process by which a drug enters the bloodstream or another body compartment from the site of administration.
- Drugs administered via the intravenous (IV) route are 100% bioavailable, meaning that the entire drug dose has reached the circulation.
- Due to diminished intestinal motility and delayed gastric emptying in neonates and infants, it takes longer for a drug to reach a similar plasma concentration as in older children after oral administration.

Table 31.1 Absorption of drugs

Drug	Drug-food interaction
Acetaminophen	Food may delay absorption
Tetracycline, doxycycline, minocycline	Milk and dairy products affect the absorption
Antihistamines, e.g., cetirizine	Food may delay the absorption
Iron	Acidic juices may enhance the iron absorption
	Antacids interfere with iron absorption
Levothyroxine	Grapefruit, soybeans, and soy milk may interfere with absorption
Griseofulvin	Should be taken with whole milk or other food containing fat for optimum bioavailability
NSAIDs, e.g., ibuprofen	Food or milk may prevent stomach irritation

NSAID Nonsteroidal anti-inflammatory drugs

Bioavailability

- Bioavailability is defined as the rate and extent to which the active drug is absorbed and becomes available at the site of drug action to produce a pharmacologic response

Hepatic Metabolism

- The cytochrome P450 (CYP) isoenzymes in the liver, primarily 3A4, 2D6, 1A2, 2C9, and 2C19, are responsible for the oxidation of 75% of all drugs (Table 31.2)

O. I. Naga (✉)
Department of Pediatrics, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, USA
e-mail: osama.naga@ttuhsc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_31

Table 31.2 Cytochrome P450 (CYP) enzyme inhibitors and inducers and potential interactions

Cytochrome P450 (CYP) enzyme inhibitors	*Potential interactions*
Amiodarone, cimetidine, fluconazole, fluoxetine, metronidazole, trimethoprim/sulfamethoxazole, diphenhydramine, clarithromycin, itraconazole, erythromycin	May increase the risk of toxicity when combined with certain drugs, e.g., methotrexate, tacrolimus
Cytochrome P450 (CYP) enzyme inducers	*Potential interactions*
Carbamazepine, phenobarbital, rifampin, glucocorticoids	Decrease the activity of certain drugs, e.g., warfarin, digoxin, and oral contraceptives

Drug-Drug Interactions

- Pediatricians should screen routinely for potential drug-drug, drug-herbal product, or drug-food interactions before prescribing a new medication, e.g.:
  - Beta-blocker prescribed for hypertension or migraines inhibits the activity of a beta agonist given to treat an asthma exacerbation
  - The effect of a broad-spectrum antibiotic on warfarin by eradicating the gut flora needed to metabolize the anticoagulant
  - Increased potential toxicity of phenytoin when combined with sulfa drugs, e.g., trimethoprim/sulfamethoxazole

Renal Elimination

Examples of drugs predominantly eliminated by the kidneys:

- NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aminoglycosides, sulfamethoxazole/trimethoprim, vancomycin, ciprofloxacin, antivirals, amphotericin B

Dose adjustment of renally eliminated medications, e.g.:

- Patients with primary pathologic kidney disease.
- Patients with lower muscle mass (e.g., neonates, females, malnourished patients).
- Patients with vomiting and diarrhea, or dehydrated, and at the same time using diuretics may develop increased serum drug concentrations with routine dosing and potential attainment of a toxic level.
- The dosing interval of renally eliminated drugs, e.g., gentamicin or vancomycin, may need to be prolonged when coadministered with ibuprofen or indomethacin or in neonates with a history of birth hypoxia/asphyxia or cyanotic congenital heart disease.
- A postoperative cardiac patient who has poor renal perfusion and who requires antibiotics for concerns of sepsis may require a less frequent dosing interval for vancomycin, an antibiotic that is cleared renally.

Methods of dose adjustment clinically

- **Trough level** (Fig. 31.1)
  - The lowest concentration reached by a drug before the next dose is administered.
  - Trough routinely used for certain drug monitoring, e.g., gentamicin, or vancomycin.
  - Trough concentrations are obtained at the end of a dosing interval just before the next dose is administered to verify that the drug's concentration is still in the therapeutic range and to prevent drug toxicity.
  - If the first trough level obtained is acceptable, repeat the trough levels at 4–6 days into therapy to ensure nontoxic level.
  - If the trough level is higher than acceptable, the drug should not be given, and another level checked 6 h later. This should be repeated as needed until a safe level is obtained.
- **Peak level** (see Fig. 31.1)
  - The highest concentration reached by a drug after the dose is administered
  - Peak level should be obtained 30 min after the infusion of gentamicin or vancomycin
  - Peak levels are not necessary for cases being treated with a course of antibiotics without a positive culture

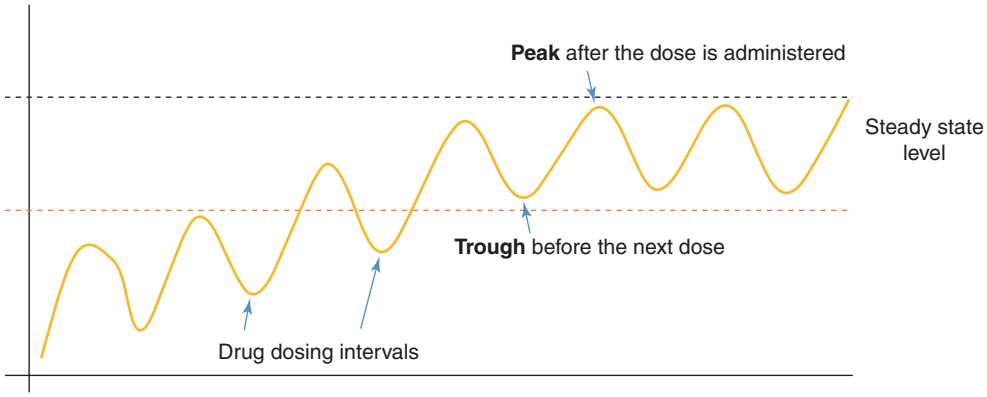


Fig. 31.1 Trough, peak, and steady-state levels of a drug curve

  - If a blood culture is positive and an organism and sensitivities are identified, both peak and trough levels should be obtained to ensure adequate dosing
- **Creatinine and glomerular filtration rate**
  - Creatinine clearance and glomerular filtration rate are used for adjustment of dosage of renally eliminated medications

Half-Life (t½)

- t½ is the time it takes the plasma concentration of a drug to decrease by half.
- 50% of the drug will remain after 1 t½, 25% will remain after 2 t½, 12.5% after 3 t½, 6.25% after 4 t½, and 3.125 after 5 t½. Thus, approximately 97% of the drug will have left the system after 5 t½.
- The t½ can vary from hours to days and even months among different medications.
- Half-life informs our decisions related to drug-dosing intervals to maximize efficacy and limit toxicity (Table 31.3).
- To achieve a steady state with drug concentration greater than 97% requires 5 t½; drug must be administered at constant intervals.
- When measuring drug levels, proper timing is essential for accurate therapeutic monitoring, e.g.: (see Fig. 31.1):
  - Vancomycin trough level usually measured before third or fourth dose when the drug reaches steady state level (Time to Steady State: 18–39 h) in infants and children

Table 31.3 Examples of t½ and drug dosing intervals

Drug	Half-life (t½)	Drug-dosing intervals
Adenosine	< 10 s	Give all doses with a rapid IV push
Morphine	2–3 h	Doses every 3–4 h as needed
Propranolol	4–6 h	Doses can be divided every 6–8 h
Fluoxetine	4–6 days	Once a day
Levothyroxine	6–7 days	Once a day
Amiodarone	60 days approximately	Once a day (oral form)

IV intravenous

  - Gentamicin trough level usually measured before second dose when the drug reaches steady state level (Time to Steady State: 20–40 h) in neonates

Practical advice when Prescribing Medications

- When prescribing for children, it is appropriate to use a pediatric reference source
- An incorrect dose, particularly in infants, could have catastrophic adverse effects
- It is good practice for two people to double check dose calculations, such as the prescriber and dispensing pharmacist
- Usually, the calculated dose should not exceed the adult dose
- The recommended dose may not be the optimum dose for some children. It may then be necessary to adjust the dose according to the clinical response

- Ensure that the calculated dose can be administered safely to the child
- Doses can be rounded to ensure that parents can accurately measure them

Drug Reactions

- Immunologic reactions include (see also Chap. 11 "Allergy and Immunology")
  - Type I (E-mediated)
  - Type II (cytotoxic)
  - Type III (immune complex)
  - Type IV (delayed)
- Nonimmunologic drug reactions include:
  - Pseudo-allergic reactions caused by direct mast cell degranulation, e.g., red man syndrome with an infusion of vancomycin
  - Idiosyncratic reactions, e.g., drug-induced hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency and aspirin sensitivity causing bronchospasm

The FDA Adverse Event Reporting System (FAERS)

- Example of cases that should be reported to the U.S. Food and Drug Administration (FDA): A serious adverse drug event:
  - Death
  - Hospitalization
  - Disability
  - Birth defect

ANTIBIOTICS

Aminoglycosides, e.g., Gentamicin, Tobramycin, and Amikacin

Mechanism of action

- Inhibit bacterial protein synthesis by binding to bacterial 30S ribosome

Drug activity

- Against aerobic Gram-negative organism, e.g., *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)
- Some activity against *Staphylococcal* species, *Mycobacterium, Entamoeba histolytica, Cryptosporidium parvum*

Drug toxicity

- Nephrotoxicity and ototoxicity

Beta Lactam Antibiotics

Classes of beta lactam antibiotics

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams

Mechanism of action

- Inhibit cell wall synthesis by binding and inhibiting cell wall proteins called penicillin-binding proteins (PBPs)

Penicillins, e.g., Crystalline Penicillin

Indications

- Periodontal infections
- Erysipeloid
- Group A and group B *streptococci*
- Syphilis
- Meningococcal meningitis and meningococcemia

Ampicillin

Bacterial coverage

- Similar to penicillin, but its spectrum extends to some Gram-negative bacteria

Indications

- *Listeria monocytogenes* meningitis
- Enterococcal infections

- UTIs caused by susceptible strains of *Escherichia coli*

Amoxicillin-Clavulanate (Augmentin; GlaxoSmithKline)

Bacterial coverage

- Addition of beta-lactamase inhibitors increase coverage to MSSA
- Extended coverage for respiratory infections, e.g., sinusitis, otitis media, bronchitis

Drug of choice for bite wounds

- *Pasteurella* is susceptible to penicillin.
- *Pasteurella* and *S. aureus* are the likely organisms in most animal bites.

Penicillinase-Resistant Penicillins, e.g., Nafcillin or Oxacillin

- Drug of choice only for staphylococcal infection (MSSA), but the resistance is rapidly expanding.

Anti-Pseudomonal Penicillins, e.g., Piperacillin and Ticarcillin

Bacterial coverage

- Extended Gram-negative coverage, including *Pseudomonas* species, *S. aureus*, and *H. influenzae*
- Addition of beta-lactamase inhibitors:
  - Piperacillin-tazobactam (Zosyn; Pfizer)
- Drug of choice, e.g., *Pseudomonas aeruginosa*

Cephalosporins (Penicillinase-Resistant)

- First-generation cephalosporin, e.g., cefazolin and cephalexin
  - Bacterial coverage
    - Many Gram-positive cocci, including MSSA and most *Streptococcus*
    - No reliable CNS penetration; do not use for meningitis or arteriovenous (AV) shunt infections.
  - Indications
    - Skin and soft tissue infection
- Second-generation cephalosporins, e.g., cefaclor, cefoxitin, cefuroxime, and cefotetan
  - Bacterial coverage
    - Maintains Gram-positive activity but less than first generation
    - Greater coverage for Gram-negative bacteria than first generation, e.g., *H. influenzae*, *Enterobacter aerogenes*, and some *Neisseria*
    - Extends the coverage to respiratory Gram-negative, e.g., *H. influenzae* and *Moraxella*
    - Has variable activity against gut anaerobes except cefuroxime
    - Not used for meningitis
  - Indications
    - Abdominal surgeries
    - Community-acquired pneumonia
    - Pelvic inflammatory disease
- Third-generation cephalosporins
  - Bacterial coverage
    - Extended Gram-negative activity, loss of Gram-positive activity
    - Good cerebrospinal fluid (CSF) penetration
    - Has greater activity in deep tissue infections and less toxicity than aminoglycosides
    - Only few drugs are active against *P. aeruginosa*, e.g., ceftazidime
  - Ceftriaxone
    - Has the longest half-life and effective against most *S. pneumoniae*
    - Crosses the blood-brain barrier and indicated as the primary therapy for meningitis
    - Ceftriaxone can be used as a single agent for empiric treatment of meningitis

while lab results are pending; except in neonates, ampicillin needs to be added to cover for *Listeria*
  - Cefotaxime
    - Bacterial coverage is the same as ceftriaxone
    - Preferred in neonates or < 30 days old
- Fourth-generation cephalosporin, e.g., cefepime
  - Bacterial coverage
    - Equal Gram-positive as the first-generation cephalosporins
    - Equal Gram-negative as the third-generation cephalosporins
    - Excellent *Pseudomonas* coverage
- Fifth-generation cephalosporin, e.g., ceftaroline
  - Bacterial coverage
    - Increased Gram-positive coverage, some Gram-negative
    - U.S. Food and Drug Administration (FDA) approved for community-acquired pneumonia and skin/soft tissue infections, including MRSA for infants and children > 2 months of age

Carbapenems, e.g., Imipenem/Cilastatin, Meropenem, and Ertapenem

- Imipenem is a very broad-spectrum carbapenem antibiotic.
- Very active against *Bacteroides fragilis*.
- Kills most *Enterobacteriaceae*, *Pseudomonas*, and Gram-positive bacteria and is inhibitory for *Listeria* and *Enterococcus faecalis*.
- Imipenem can lower the seizure threshold and should not be used in patients with seizures or renal insufficiency.
- Meropenem is a carbapenem with a longer half-life, less likely than imipenem to cause seizures.
- Ertapenem has limited activity against *Enterococcus* sp. and *P. aeruginosa*.

Monobactam, e.g., Aztreonam

- Aztreonam is often used in patients who are allergic to penicillin or who cannot tolerate aminoglycosides.
- Aztreonam has strong activity against susceptible aerobic and facultative Gram-negative bacteria, including *P. aeruginosa* and most *Enterobacteriaceae*.
- Aztreonam is not active against Gram-positive cocci or anaerobes.

Other Commonly Used Antibiotics

Clindamycin

Mechanism of action
- Inhibits bacterial protein synthesis by binding to 50S ribosomal subunit.

Bacterial coverage
- Active against many strains of MRSA
- Active against anaerobes
- Active against most staphylococcal and streptococcal infections

Adverse effects
- Diarrhea, including *C. difficile* enterocolitis

Macrolides, e.g., Azithromycin and Clarithromycin

Mechanism of action
- Inhibits bacterial protein synthesis by binding to 50S ribosomes
- Azithromycin does not inhibit cytochrome P-450 as erythromycin or clarithromycin do

Bacterial coverage
- Azithromycin is the drug of choice for pertussis, *Mycoplasma,* and *Chlamydia*

Adverse effects
- Gastrointestinal (GI) irritation

- Hypertrophic pyloric stenosis if used in children less than 1 month of age

Rifampin

Bacterial coverage
- Tuberculosis
- Invasive *H. influenzae*

Indications
- Close contacts to a child who has invasive meningococcal infection.
- Combination with vancomycin in certain staphylococcal infections (ventriculoperitoneal (VP) shunt, osteomyelitis, endocarditis)
- Persistent group A streptococcal pharyngitis in combination with beta-lactam antibiotics
- MRSA carriage eradication attempt

Fluoroquinolones, e.g., Ciprofloxacin

AAP recommendation of fluoroquinolones use in children
- If the pathogen is multidrug resistant
- No safe and other effective alternative
- Parenteral therapy is not feasible
- No other effective alternative oral agents

Bacterial coverage
- UTIs caused by multidrug resistant Gram-negatives rods
- Resistant Gram-negative rods:
  - *P. aeruginosa*
  - GI and respiratory tract infection
  - Chronic or acute osteomyelitis

Adverse effects
- Fluoroquinolones in children cause arthralgia that resolves after drug withdrawal.
- Tendon rupture, especially Achilles tendon and often bilateral, is a rare complication (1 in 5000)

Tetracycline

Bacterial coverage
- Tetracycline provides coverage against tick-borne organisms, e.g., Lyme disease, Rocky Mountain spotted fever
- Doxycycline and minocycline are used for acne (*Propionibacterium acnes*)
- Doxycycline may also treat MRSA

Adverse effects
- Tetracycline causes staining of dental enamel
- Tetracycline is not recommended in children less than 8 years old
- Tetracycline can be used in children younger than 8 years in life-threatening situations, e.g., Rocky Mountain spotted fever (doxycycline is the drug of choice)
- Doxycycline does not cause staining of permanent teeth compared to tetracycline

Trimethoprim/Sulfamethoxazole

Bacterial coverage
- *Pneumocystis jiroveci* pneumonia, which is common in immunocompromised patients, e.g., HIV
- Urinary tract infection, treatment, and prophylaxis (one drug of choice in susceptible patients)
- MRSA infection.
- Gastroenteritis due to *Salmonella, Shigella,* and *Isospora belli*
- *Burkholderia cepacia.*
- *Brucella.*

Adverse effects
- Rash
- Neutropenia
- Stevens–Johnson syndrome

Vancomycin

Mechanism of action

- Inhibits bacterial cell wall synthesis by binding tightly to peptidoglycan precursors and blocking polymerization

Bacterial coverage

- Confirmed Gram-positive infection in patient seriously ill or allergic to beta-lactam antibiotics
- Initial empiric treatment in a child (> 2 months) with meningitis in combination with third-generation cephalosporin
- MRSA infection
- Prophylaxis before prosthetic device implantation requiring major surgery
- Enterally for *C. difficile*
- Acute infectious endocarditis if *S. aureus* is the likely cause

Adverse effects

- Red man syndrome, or red neck syndrome
  - Vancomycin releases histamine that can cause pruritus and erythema of the head and neck.
  - This is a related drug infusion problem; just slow down the infusion rate.
- Ototoxicity and nephrotoxicity (monitor drug toxicity with trough levels)
- Misuse of vancomycin can cause development of resistance

Indications

- *C. difficile* diarrhea (given orally, not systemically absorbed)
- *S. aureus* infections, including MRSA

Summary of antibiotics and adverse reactions

(Table 31.4).

Table 31.4 Antibiotics and common adverse effects

Commonly used antibiotics	Common adverse effects	Comments
Penicillins, e.g., amoxicillin, amoxicillin/clavulanic acid (Augmentin; GSK), piperacillin/tazobactam (Zosyn; Pfizer)	Non-IgE-mediated: vomiting, diarrhea, headache, or a non-urticarial, nonpruritic rash	Most cases of penicillin allergies are non-IgE-mediated
	IgE-mediated type1 hypersensitivity: urticarial rash, angioedema, anaphylaxis (0.3–3%)	Desensitization is necessary for pregnant with neurosyphilis, congenital syphilis, or tertiary syphilis
Cephalosporins, e.g., cephalexin, cefazolin, cefuroxime, cefdinir, cefixime, ceftriaxone	Nausea, vomiting, diarrhea, rash, AST and ALT elevation, allergic reaction.	Low risk of allergic reaction to first-generation cephalosporins in penicillin-allergic patients (3–7%) and much lower risk for third-generation cephalosporins
Aminoglycosides, e.g., gentamicin, tobramycin	Nephrotoxicity/ototoxicity	Monitor toxicity with trough levels, renal function, and audiology testing
Glycopeptides, e.g., vancomycin	Red man syndrome; pruritic erythematous rash, and flushing	Reduce IV infusion rate (infusion-related reaction)
Antituberculosis drugs, e.g., rifampin, isoniazid, pyrazinamide, ethambutol	Nausea, vomiting, diarrhea, anorexia, hemolytic anemia, liver toxicity, peripheral neuropathy	Vitamin B6 (pyridoxine) ➔ prevents peripheral neuropathy with isoniazid
	Orange body fluids (rifampin)	
Macrolides, e.g., erythromycin, azithromycin, clarithromycin	Nausea, vomiting, abdominal pain, diarrhea, anorexia, taste changes (clarithromycin)	Coated or delayed-release pill should not be opened, chewed, or crushed
Sulfonamides, e.g., trimethoprim-sulfamethoxazole, sulfadiazine (Bactrim; Roche)	Nausea/vomiting, diarrhea, anorexia, abdominal pain, rash, photosensitivity, headache, dizziness	Sunscreen, sun avoidance, and protective clothing are recommended
Tetracyclines, e.g., tetracycline, doxycycline, minocycline	Nausea, vomiting, diarrhea, anorexia, abdominal pain, photosensitivity, tooth discoloration in children < 8 years	Sunscreen, sun avoidance, and protective clothing are recommended
		Give at any age to children with suspected RMSF

IgE Immunoglobulin E, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *RMSF* Rocky Mountain spotted fever

ANTIVIRALS

Acyclovir

Mechanism of action
- Terminates the viral deoxyribonucleic acid (DNA) synthesis when incorporated into the viral DNA chain

Appropriate use
- HSV type 1 and HSV type 2
- Varicella
- Treatment of recurrent primary genital HSV2 or primary HSV1 mucocutaneous infections
- Intravenous (IV) acyclovir is the drug of choice for treatment of HSV encephalitis.

Major adverse effects
- Acute renal failure due to precipitation in the renal tubules (proper hydration and slower infusion can minimize this problem)
- Nausea, vomiting, and diarrhea

Valacyclovir

Background
- Newer potent oral antiviral (Inhibits DNA polymerase; incorporates into viral DNA)

Indications
- HSV1
- HSV2
- Varicella-Zoster virus (VZV)

Ganciclovir (IV) and Valganciclovir (Oral)

Indications
- Congenital and acquired cytomegalovirus (CMV) infection

Major adverse effects of ganciclovir and valganciclovir
- Neutropenia and other cytopenias that may interrupt therapy or require granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)

Foscarnet

- CMV infection

Other Antiviral Agents, Against DNA Viruses

- Famciclovir, valganciclovir, penciclovir, and cidofovir

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Mechanism of action
- These drugs inhibit replication of HIV by interfering with the reverse transcriptase enzyme

Indication
- HIV infection

Examples of NRTIs and side effects (Table 31.5)
- Zidovudine (ZDV)
  - Significant adverse effect: Bone marrow suppression

Table 31.5 Adverse effects of common antiretroviral medications

Common antiretroviral therapy	Common adverse effects
Zidovudine	Bone marrow suppression
Tenofovir	Nausea, vomiting, diarrhea
Emtricitabine	Headache, insomnia, diarrhea, nausea, skin discoloration
Lamivudine	Headache, nausea, less common; pancreatitis
Indinavir	Nausea, abdominal pain, hyperbilirubinemia, nephrolithiasis
Ritonavir	Nausea, headache, vomiting, taste aversion
Fosamprenavir	Nausea, vomiting, perioral paresthesias, rash, lipid abnormalities
Raltegravir	Nausea, headache, dizziness, diarrhea, fatigue

- Didanosine (ddI)
  - Significant adverse effects: Pancreatitis and peripheral neuropathy
- Stavudine (d4T)
  - Contraindication: Cannot be combined with ddI in pregnant women; can cause fatal lactic acidosis
  - Adverse effects: Pancreatitis and peripheral neuropathy
- Abacavir
  - Most serious adverse effect is fatal hypersensitivity

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)

Indication

- HIV infection

Examples of NNRTIs and side effects

- Efavirenz: safe in first trimester pregnancy
  - Adverse effects: neuropsychiatric effects, QT prolongation
- Nevirapine: prevents mother-to-child transmission
  - Adverse effect: Rash

Protease Inhibitors

Mechanism of action

- Inhibit the HIV protease enzyme that is involved with processing the completed virus

Indication

- HIV infection

Examples of protease inhibitors and side effects

- Ritonavir: boosts concentration of other protease inhibitors
  - Adverse effect: hyperlipidemia
- Nelfinavir
  - Adverse effects: diarrhea and nausea
- Lopinavir
  - Adverse effect: insulin resistance
- Atazanavir
  - Adverse effect: proximal tubulopathy (renal)
- Darunavir
  - Adverse effects: rash and nausea

ANTIPARASITICS (TABLE 31.6)

Permethrin

- Excellent safety profile
- 5% permethrin cream is the drug of choice for treatment of scabies
- 1% permethrin topical solution is effective for head lice
- Paralyzes the parasite to cause death
- Not recommended in infants younger than 2 months and during pregnancy

Malathion

- The most effective drug in the treatment of pediculosis or head lice
- Ovicidal activity
- Single topical application is effective in resistant cases

Table 31.6 Indications and adverse effects of common antiparasitic medications

Antiparasitic	Indications	Adverse effects
Albendazole/ mebendazole	Ascariasis, hookworms, enterobiasis, trichuriasis, trichinosis, toxocariasis	Headache, abdominal pain, reversible alopecia, elevated liver enzymes, leukopenia
Ivermectin	Cutaneous larva migrans, strongyloidiasis, scabies	Pruritus, fever, rash, myalgia, headache, constipation, diarrhea, abdominal distension
Praziquantel	Schistosomiasis, taeniasis, diphyllobothriasis	Loss of appetite, dizziness, drowsiness, headache, malaise

Metronidazole

Mechanism of action

- Metronidazole is nitroimidazole bactericidal drug

Indications

- Anaerobic bacteria
- *Clostridium difficile*
- *Trichomonas vaginalis*
- *Gardnerella vaginalis*
- *Treponema pallidum*
- Oral spirochetes
- *Helicobacter pylori*

Chloroquine (Table 31.7)

Indication

- Drug of choice for malaria prophylaxis in the sensitive chloroquine regions, e.g., Central and South America
- Drug should be administered 1–2 weeks before traveling

Adverse effects

- GI upset, headache, dizziness, blurred vision, insomnia, and pruritus

Other Antimalarials: Atovaquone/Proguanil, Doxycycline, and Mefloquine

- Commonly used for prophylaxis for malaria in chloroquine-resistant regions, e.g., Africa and the Middle East
- Mefloquine has FDA black box warning; causes psychosis

ANTIFUNGALS (TABLE 31.8)

Amphotericin B

Indication

- Active against broad array of fungi, e.g., *Candida*, *Aspergillus, Zygomycetes, Histoplasma*, *Coccidioides immitis*

Table 31.7 Indications, and side effects of common antiprotozoal medications

Antiprotozoal	Indications	Adverse effects
Atovaquone-proguanil (Malarone; GSK)	Chloroquine-resistant malaria or unknown resistance regions	Abdominal pain, elevated liver enzymes, headache, vomiting, asthenia
Chloroquine phosphate	Chloroquine-sensitive malaria regions	Macular degeneration, psychosis, agitation, nausea, vomiting, abdominal pain
Hydroxychloroquine	Chloroquine-sensitive malaria regions	Rash, pruritus, skin pigmentation, alopecia, abdominal pain, diarrhea, anorexia

Table 31.8 Indications, monitoring of toxicity and adverse effects of common antifungal drugs

Antifungal	Indications	Monitoring and adverse effects
Amphotericin B	Mucocutaneous candidiasis, systemic candida, *Aspergillus* and *Cryptococcus* species	Hypokalemia, hypomagnesemia Monitor electrolytes, hematologic, renal, and liver function
Terbinafine	Tinea capitis, tinea corporis, tinea pedis, tinea cruris, onychomycosis	AST, ALT; do not use if liver dysfunction
Griseofulvin	Tinea capitis, tinea corporis, tinea pedis, tinea cruris	No monitoring is required
Fluconazole	Tinea capitis, tinea corporis, tinea pedis, tinea cruris, mucocutaneous candidiasis	Liver function test; exercise caution if liver dysfunction
Nystatin suspension	Mucocutaneous candidiasis	Nausea, vomiting, abdominal pain, diarrhea

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Toxicity

- Febrile drug reaction
- Hypokalemia
- Hypomagnesemia
- Nephrotoxicity (liposomal preparation is equally effective and less nephrotoxic)

Fluconazole

Indications

- As equally effective as amphotericin B for treatment of invasive *Candida albicans* in neonates
- Treatment of oropharyngeal or esophageal candidiasis in immunocompromised patients
- Treatment of vulvovaginal *Candida*
- Treatment of cryptococcal meningitis

Griseofulvin

- Standard first-line therapy for tinea capitis
- No laboratory assessment of hepatic enzyme if used < 8 weeks
- Serum liver enzyme monitoring every 8 weeks; prolonged therapy is a risk of hepatotoxicity
- Consumed with fatty meals, e.g., peanut butter, for maximum absorption

DIURETICS

Furosemide (Table 31.9)

- Loop diuretic: Inhibits reabsorption of sodium and chloride ions at proximal and distal renal tubules and the loop of Henle by interfering with chloride-binding cotransport system, resulting in increased excretion of water, calcium, magnesium, sodium, and chloride

Adverse effects

- Hypochloremia
- Hypokalemia
- Alkalosis

Table 31.9 Difference between furosemide, hydrochlorothiazide, and spironolactone diuretics

Furosemide	Hydrochlorothiazide	Spironolactone
Hypokalemia	Hypokalemia	Hyperkalemia
Metabolic alkalosis	Metabolic alkalosis	Metabolic acidosis
Hypocalcemia	Hypercalcemia	Increases testosterone clearance

- Hypocalcemia
- Hyperuricemia
- Ototoxicity
- Nephrotoxicity

Thiazide Diuretics (Hydrochlorothiazide)

- Thiazide diuretic inhibits sodium reabsorption in distal renal tubules, resulting in increased excretion of water, sodium, potassium, and hydrogen.

Adverse effects

- Hyponatremia
- Hypochloremia
- Hypercalcemia
- Hyperuricemia

Spironolactone

- Aldosterone antagonist with a diuretic and antihypertensive effects; competitive binding of receptors at aldosterone-dependent Na-K exchange site in distal tubules results in increased excretion of sodium, chloride, and water and retention of potassium and hydrogen
- Increases testosterone clearance and estradiol production; blocks conversion of potent androgens to weaker ones in peripheral tissues

Adverse effects

- Hyperkalemia
- Metabolic acidosis
- Gynecomastia

Acetazolamide

- Carbonic anhydrase inhibitor that decreases the rate of aqueous humor formation, in that way decreasing intraocular pressure
- Inhibits hydrogen ion excretion in renal tubule, increasing sodium, potassium, bicarbonate, and water excretion and producing alkaline diuresis

Mannitol

- Osmotic diuretic causes diuresis
- Reduces the intracranial pressure and intraocular pressure

OVER-THE-COUNTER MEDICATIONS

Cough and Cold Products (Table 31.10)

- Nonprescription (over-the-counter [OTC]) and prescription cough and cold preparations have not been adequately studied in children younger than 6 years of age, and thus they are not recommended for treating the common cold symptoms in young children

Teething

Benzocaine

- Benzocaine gels and liquids for mouth and gum pain have been linked to methemoglobinemia, which causes a reduction in blood oxygen and can be fatal.
- All other oral health products with benzocaine are contraindicated for children less than 2 years for teething relief.
- Instead of teething gels or tablets, the American Academy of Pediatrics recommends gently rubbing or massaging the child's gums with a finger and giving the child a cool (not cold) teething ring or a clean, wet, cool washcloth to chew on.

ANTIHYPERTENSIVE MEDICATIONS (TABLE 31.11)

Propranolol, Atenolol, Metoprolol

Common Uses

- Hypertension
- Supraventricular tachycardia (SVT)

Propranolol for treatment of infantile hemangioma

- Starting dose at 1 mg/kg/day divided q 8 h and check heart rate and blood pressure 1and 2 h after the first dose

Table 31.10 Side effects of over the counter common cold and allergy medications

Cough and cold remedies	Brand name	Adverse effects
Diphenhydramine	Benadryl (J&J)	Hypertension, tachycardia, confusion, constipation, diarrhea, paresthesia
Brompheniramine/ dextromethorphan/ pseudoephedrine	Bromfed DM (Morton Grove Pharmaceuticals)	Sedation, potential abuse, palpitations, anxiety, hypotension, urticaria, diplopia
Dextromethorphan	Robitussin (Pfizer) (Delsym)	Hallucinations, stupor, nystagmus, dystonia, seizures, tachycardia, respiratory depression, coma, potential abuse
Guaifenesin	Mucinex (Reckitt Benckiser)	Nausea, vomiting, diarrhea, abdominal pain, kidney stones
Phenylephrine	Sudafed PE (J&J)	Hypertension, chest pain, bradycardia, peripheral vasoconstriction, arrhythmias, respiratory depression, hallucinations
Pseudoephedrine	Children's Sudafed (J&J)	Palpitations, tachycardia, bradycardia, nausea, insomnia, dizziness, psychosis, urticaria

Table 31.11 Classes, and mechanism of action of antihypertensive agents

Class	Antihypertensive agent	Mechanism of action
Angiotensin-converting enzyme (ACE) inhibitor	Captopril	Blocks the conversion of angiotensin I to angiotensin II and the degradation of the vasodilatory molecule bradykinin through the blockade of the kinin-kallikrein system
	Enalapril	
	Lisinopril (> 6 years of age)	
Angiotensin receptor blocker (ARB)	Irbesartan	Blocks the binding of angiotensin II to type 1 angiotensin II receptors
	Losartan	
Calcium channel blocker (CCB)	Amlodipine	Lowers blood pressure by blocking the influx of calcium into smooth muscle, resulting in arteriole dilatation and reduced peripheral resistance
	Felodipine	
	Isradipine	
	Nifedipine XR	
β-Blocker	Atenolol	Decreases blood pressure through several different mechanisms, including inhibition of renin secretion, reduction of peripheral resistance, lowering of cardiac output, and decreasing plasma volume
	Metoprolol	
	Propranolol	
	Labetalol	
Diuretic	Hydrochlorothiazide	Lowers blood pressure by decreasing plasma volume and lowering peripheral resistance
	Furosemide	
	Spironolactone	
Central α-blocker	Clonidine	Centrally acting α2-agonist that stimulates α2-receptors to lower peripheral resistance and heart rate
Vasodilator	Hydralazine	Acts directly on vascular smooth muscle to reduce vascular wall tension and peripheral vascular resistance
	Minoxidil	

- Increase the dose gradually every 3–7 days to therapeutic dose 2 mg/kg/day divided q 8 h
- Monitor heart rate and blood pressure

Adverse effects

- Bradycardia
- Hypotension
- Hypoglycemia (hypoglycemia-induced seizures)
- bronchospasm
- Depression

ANTI-ULCERS

H2-Blocking Drugs

- Histamine-2 receptor antagonists (H2RAs) decrease acid production by binding to the histamine-2 receptor on the gastric parietal cell
- Examples of these medications include ranitidine, famotidine, cimetidine, and nizatidine
- Ranitidine reaches a peak plasma concentration 2.5 h after ingestion in children and has a half-life of 6 h
- H2RAs are considered safe for use in children and are commonly used as first-line therapy in infants

Adverse effects

- Irritability, head banging, and headaches
- Cimetidine use is associated with gynecomastia
- Tachyphylaxis has been observed with chronic H2RA use

Proton Pump Inhibitors (PPIs)

- PPIs suppress gastric acid production by irreversibly blocking H^+ and K^+ ATPase, which is the final step in parietal cell acid secretion.

- PPIs are more effective than H2RAs in blocking acid production.
- PPIs must be given daily before meals and can take several days for maximal acid suppression effect.
- Examples: omeprazole, lansoprazole, and esomeprazole.

Adverse effects

- Headache, diarrhea, constipation, and nausea
- In neonates, acid suppression is associated with a higher carriage rate of candida and a higher incidence of necrotizing enterocolitis

ANTIEMETICS

- 5-hydroxytryptamine (serotonin) receptor antagonist
  - Example: Ondansetron
  - Routine use of ondansetron does not improve the outcome in children without dehydration
  - Side effects: headache, dizziness, and constipation. The most worrisome side effect is QT-prolongation, it should be avoided in patients with known prolonged QTc
- Antihistamines
  - Examples: Diphenhydramine, meclizine, promethazine
  - H_1-antagonist and has limited dopaminergic (D_2) effects
  - Side effect: sedation
- Muscarinic M_1 receptor antagonist
  - Example: Hyoscine (also known as scopolamine)
  - Used to treat motion sickness or prophylactically in the perioperative setting
  - Side effects: dry mouth, vision changes, or drowsiness
- Dopamine receptor antagonist (D_2)
  - Example: Metoclopramide
  - Metoclopramide has significant promotility effects and can increase gastric emptying
  - Side effects: dizziness, headache and extrapyramidal symptoms to include dystonia and tardive dyskinesia

SEDATION

Minimal Sedation (Anxiolysis)

- Anxiolysis with the maintenance of consciousness
- Example: Intranasal midazolam for short and brief procedures e.g., laceration repair in a child who is crying and very anxious

Moderate Sedation (Conscious Sedation)

- Controlled depressed consciousness
- Airway reflexes and airway patency are maintained
- Patient responds appropriately to age-appropriate commands ("Open your mouth") and to touch

Deep Sedation

- Controlled depressed consciousness
- Airway reflexes and airway patency may not be maintained
- Ability to independently maintain ventilatory function may be impaired
- Patient not easily aroused but responds purposefully following repeated or painful stimulation

General Anesthesia

- Loss of consciousness occurs.
- Impaired airway reflexes, airway patency, and ventilatory function.
- Children are not arousable.
- Not responsive to painful stimulation.

Recommendations for fasting or *nothing by mouth* (NPO) before sedation and anesthesia

- 2 hours fasting for clear liquids
- 4 hours fasting for breast milk
- 6 hours fasting for formula
- 8 hours fasting for solids

Medications for Procedural Sedation

- Opioid analgesics ➔ morphine sulfate, fentanyl
- Benzodiazepines ➔ midazolam, diazepam
- Barbiturates ➔ pentobarbital, methohexital, thiopental
- Miscellaneous agents ➔ nitrous oxide, ketamine, propofol, dexmedetomidine

Morphine

- Among the oldest opioids
- Indications
  - Analgesia, sedation
- Side effects
  - Respiratory depression, nausea and vomiting, pruritus, constipation, miosis, tolerance, and physical dependence

Fentanyl

- Rapid onset of action opioid
- Most commonly used opioid for short, painful procedures
- Intranasal fentanyl is a good option for children with severe pain seen in the emergency department and prehospital settings
- Doses of fentanyl delivered via a transmucosal route have similar analgesic action to intravenous opioids
- Fentanyl is preferred over morphine in patients with renal insufficiency
- Chest wall rigidity can occur with even low doses, especially in neonates and infants, and can lead to significant impairment of ventilation

Midazolam

- Rapid and predictable onset of action
- Short recovery time
- Causes amnesia
- Mild depression of hypoxic ventilatory drive

Ketamine

- Commonly used for procedural sedation
- Preserves the airway reflexes
- Minimal effect on the respiratory drive
- Bronchodilatory effects and is especially effective with bronchospasms
- Good safety profile in children

Propofol

- A purely sedative agent without any analgesic or amnestic properties
- Rapid onset of action (within 40 s)
- Used for induction and maintenance of general anesthesia
- Used for procedural sedation

Nitrous oxide

- Causes anxiolysis, amnesia, and mild-to-moderate analgesia.
- Administered as an inhalant via a handheld mask or mouthpiece.
- Effects are rapidly lost once inhalation ceases, and recovery occurs within 5 min.
- Nitrous oxide has little effect on the cardiovascular and respiratory systems.

Sedation Protocol

- Ketamine ➔ Lowest rate of adverse effects if used alone
- Ketamine + midazolam + atropine ➔ Adding midazolam counter the emergence delirium
- Midazolam + Fentanyl ➔ High risk of respiratory depression (decrease the frequency of fentanyl infusion to no more than every 3 min)

Reversal Agents

- Opioids ➔ Naloxone
- Benzodiazepine ➔ Flumazenil

Preprocedural Evaluation

- History and physical examination are critical before clearing a child for sedation or anesthesia
  - Ask about past medical history, previous sedation or anesthesia
  - Last solid and liquid oral intake
  - Recent illness
  - Current medications, allergies, or side effects of medications
  - Family history
  - Upper respiratory infection symptoms; history of reactive airway disease
  - Airway, cardiac, pulmonary, and neurological examination

Intraprocedural Monitoring:

Monitoring during procedural sedation

- Continuous oxygen saturation and heart rate monitoring
- Monitor vital signs and blood pressure every 15 min for conscious sedation and every 5 min for deep sedation
- Monitor state of consciousness and response to stimulation

Discharge Criteria After Sedation or Anesthesia

- Vital signs should be within normal range of age.
- Child should be able to ambulate as appropriate for age and without assistance.
- Child should be able to tolerate oral intake.

Sedation for simple and short procedures (Table 31.12)

Table 31.12 Antihistamines with sedative effects

Medications	Dose
Diphenhydramine (PO, IV, IM)	1 mg/kg; maximum 50 mg/dose
Hydroxyzine (PO)	2 mg/kg/day divided every 6–8 h; maximum 600 mg/24 h

PO per os, *IV* intravenous, *IM* intramuscular

PAIN MANAGEMENT

Pain Management in Neonates

Non-pharmacologic pain management

- For minor procedures, e.g., heel stick, venipuncture, subcutaneous injections:
  - Oral sucrose/glucose
  - Breastfeeding
  - Nonnutritive sucking
  - Skin to skin contact "kangaroo care"
  - Facilitated tuck (holding the arms and legs in a flexed position)
  - Swaddling
  - Limiting environmental stimuli, lateral positioning, the use of supportive bedding, and attention to behavioral clues
  - Minimize the frequency and number of procedures.

Pharmacologic pain management

- Topical anesthetic for painful procedures, e.g., lumbar puncture
  - Topical anesthetics can effectively reduce pain, e.g., lidocaine
  - Give sufficient length of time before the procedure (usually 30 min for neonates)
- Acetaminophen
  - Administered orally postoperatively has been shown to reduce morphine requirements.
  - Should not be used alone for severe pain.
  - Use during the later postoperative period.
  - Use after minor procedures, e.g., circumcision.
- Morphine for postoperative pain

Pain Management in Older Children

Pain scale assessment (Fig. 31.2)

Postoperative pain management

Morphine IV

- Moderate-severe pain after surgeries
- Use the lowest effective dose
- Acute pain may counteract the respiratory depression induced by morphine

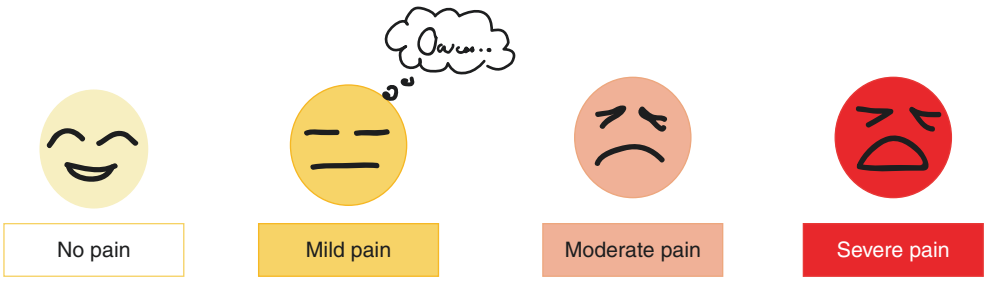


Fig. 31.2 Pain scale assessment, no pain, mild pain, moderate and severe pain

- Repeated doses every four to 6 h based on additional pain assessment (see Fig. 31.2)
- Using appropriate dosing of acetaminophen after surgery may reduce the requirements for morphine or opioids in general

Ketorolac IV

- Nonsteroidal anti-inflammatory drug
- Not associated with common opioid side effects, such as respiratory depression, nausea, vomiting, urinary retention, or sedation
- Attention must be paid to postoperative bleeding after tonsillectomy

Acetaminophen (rectal)

- Provides good analgesic and morphine-sparing effects, even in neonates and infants, after major surgery

Post-operative pain management with conversion to oral agents

- Ibuprofen
- Acetaminophen
- Hydrocodone

Opioids as outpatient

- Because of side effects such as drowsiness and constipation, some surgeons avoid using opioids after surgeries, taking pain scale assessment into consideration
- In mild to moderate pain, may alternate ibuprofen and acetaminophen instead
- Appropriate dosing of acetaminophen and ibuprofen may reduce postoperative opioid requirements
- Substitute codeine with acetaminophen/ibuprofen or oxycodone
- Reserve opioids for moderate to severe pain, e.g., after bone surgeries

Codeine

- No longer recommended in pediatrics
- Can cause severe nausea and vomiting
- 3% to 5% of population over metabolize, potentially leading to catastrophic overdose

PEARLS AND PITFALLS

- If planning to check the serum level of a drug, measure the serum level after the steady-state serum level is achieved, which is about five half-lives.
- Red man syndrome is a common adverse drug reaction of vancomycin; it is infusion rate related. It is not an allergic reaction.
- Red man syndrome symptoms vary from mild flushing, urticaria, and pruritus to severe manifestations, which include generalized erythema, intense pruritus, and distributive shock.
- Red man syndrome can be avoided by infusing the vancomycin over 60 min, and symptoms can be ameliorated by discontinuing or slowing the infusion, diphenhydramine is not effective is treating these symptoms.
- Trough level is measured before the next dose of a drug, and peak level is measured after the dose is administered.
- Peak levels are not necessary for cases being treated with a course of antibiotics without a positive culture.

- Most cases of penicillin allergies are non-IgE-mediated; there is a low risk of allergic reaction to first-generation cephalosporins in penicillin-allergic patients and much lower risk for third-generation cephalosporins.
- Infants receiving acyclovir suppressive therapy after neonatal herpes simplex infection should have CBC at 2 and 4 weeks after starting treatment and then monthly to calculate the absolute neutrophil count and monitor for the development of neutropenia.
- Nonprescription (OTC) and prescription for cough and cold medications are not recommended for treating common cold in children younger than 6 years of age.
- Most common side effects of ADHD medications are loss of appetite, abdominal pain, and headaches; these symptoms may be lessened if the medication is taken with food.
- Ketorolac used postoperatively is not associated with common opioid side effects such as respiratory depression, nausea, vomiting, urinary retention, or sedation.
- Appropriate dosing of acetaminophen and ibuprofen after surgery may reduce postoperative opioid requirements.

Suggested Reading

Akdis AC, Sicherer SH. Allergy and the immunologic basis of atopic disease. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 20th ed. Philadelphia: Elsevier Saunders; 2016. p. 1074–7.

American Academy of Pediatrics, Committee on Fetus and Newborn, Canadian Paediatric Society, Fetus and Newborn Committee. Prevention and management of pain in the neonate. An update. Adv Neonatal Care. 2007;7(3):151–60.

Barnes S, Yaster M, Kudchadkar SR. Pediatric sedation management. Pediatr Rev. 2016;37(5):203–12.

Batchelor HK. Influence of food on paediatric gastrointestinal drug absorption following oral administration: a review. Children (Basel). 2015;2(2):244–71.

Chang WT. Pediatric sedation. Medscape [Internet]. Updated 8 May 2018. Medscape. New York: WebMD. https://emedicine.medscape.com/article/804045-overview#a8. Accessed 26 Dec 2018.

De Sutter AIM, van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. Cochrane Database Syst Rev. 2012;2:CD004976.

Drugs.com [Internet]. Common side effects from antibiotics, and allergies and reactions. n.d. Updated 3 Mar 2017. Drugs.com. https://www.drugs.com/article/antibiotic-sideeffects-allergies-reactions.html. Accessed 21 Oct 2018.

Ginsburg CM, McCracken GH Jr, Petruska M, Olsen K. Effect of feeding on bioavailability of griseofulvin in children. J Pediatr. 1983;102(2):309–11.

Gupta AK, MacLeod MA, Foley KA, Gupta G, Friedlander SF. Fungal skin infections. Pediatr Rev. 2017;38(1):8–22.

Lowry JA, Leeder JS. Over-the-counter medications: update on cough and cold preparations. Pediatr Rev. 2015;36(7):286–97. quiz 298

Myers AL, Gaedigk A, Dai H, James LP, Jones BL, Neville KA. Defining risk factors for red man syndrome in children and adults. Pediatr Infect Dis J. 2012;31(5):464–8.

Rakovchik EE, Fein DM. Nonsteroidal anti-inflammatory drug and salicylate poisoning. Pediatr Rev. 2016;37(1):48–50.

Sandritter TL, McLaughlin M, Artman M, Lowry J. The interplay between pharmacokinetics and pharmacodynamics. Pediatr Rev. 2017;38(5):195–206.

Tom-Revzon C. Drug interactions. Pediatr Rev. 2006;27(8):315–7.

Wagner J, Abdel-Rahman SM. Pediatric pharmacokinetics. Pediatr Rev. 2013;34(6):258–69.

Weaver DJ Jr. Hypertension in children and adolescents. Pediatr Rev. 2017;38(8):369–82.

Radiology Review

32

Wendy G. Kim and Michael George

CARDIOTHORACIC RADIOLOGY

Case 1

Preterm infant born at 32 weeks gestational age presenting with respiratory distress

Imaging findings (Fig. 32.1): Frontal chest radiograph demonstrates diffuse granular opacities and obscured vascular markings. Typically, patients with this finding will demonstrate lower lung volumes, due to alveolar collapse, prior to intubation.

Diagnosis: Surfactant deficiency disease (respiratory distress syndrome).

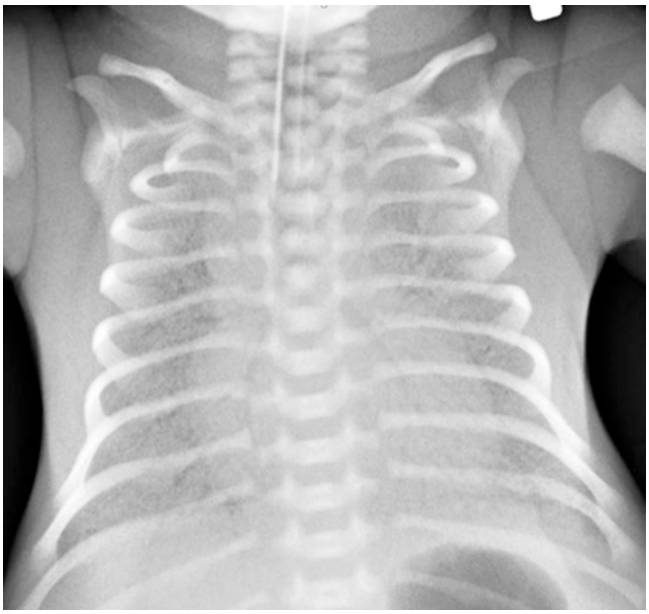


Fig. 32.1

W. G. Kim (✉) · M. George
Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: Wendy.Kim@childrens.harvard.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_32

Case 2

8-day-old infant born prematurely with a history of surfactant deficiency developing respiratory instability and decreased breath sounds on the right

Imaging findings (Fig. 32.2): Frontal chest radiograph (**a**) demonstrates tubular and cystic lucencies throughout the right lung representing air dissecting into the interstitium (*arrows*). Subsequent radiograph (**b**) shows a large lucency (∗) surrounding the right lung with resultant contralateral mediastinal shift.

Diagnosis: Pulmonary interstitial emphysema and resultant tension pneumothorax.

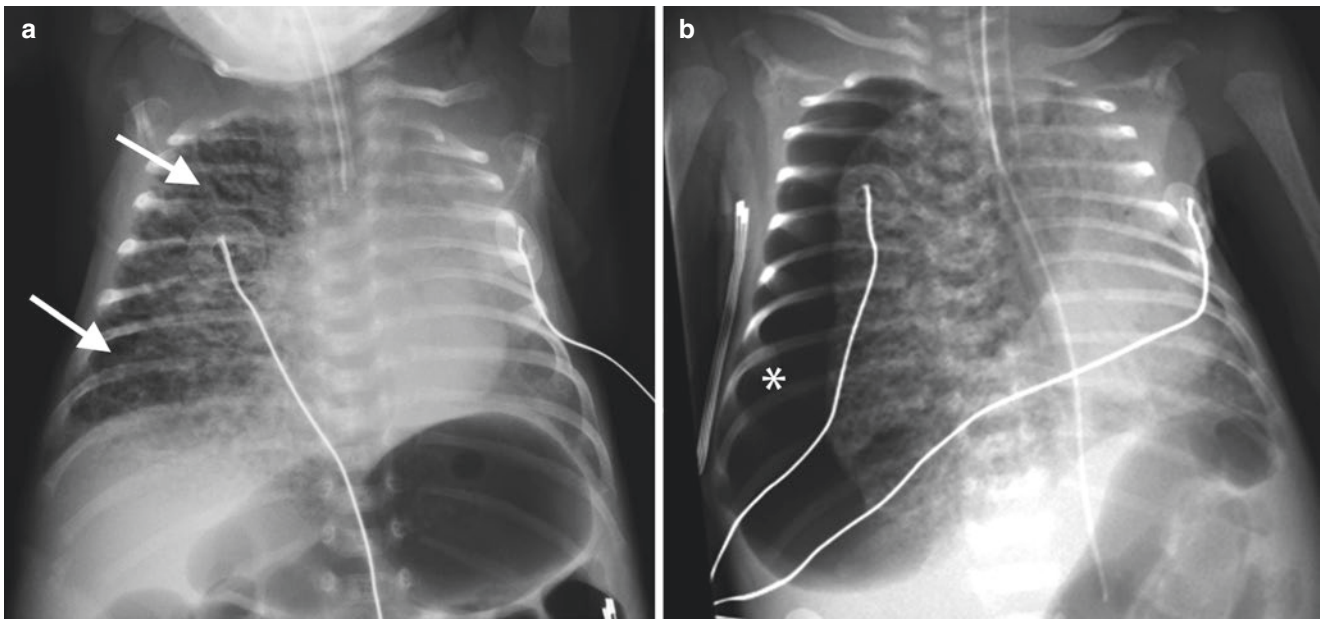


Fig. 32.2

Case 3

Post-term infant with history of prolonged delivery and amniotic meconium staining presenting with respiratory distress

Imaging findings (Fig. 32.3): Frontal chest radiograph demonstrates coarse, ropy perihilar opacities, and segmental areas of air trapping (*arrowheads*). Lung volumes are large.

Diagnosis: Meconium aspiration syndrome.

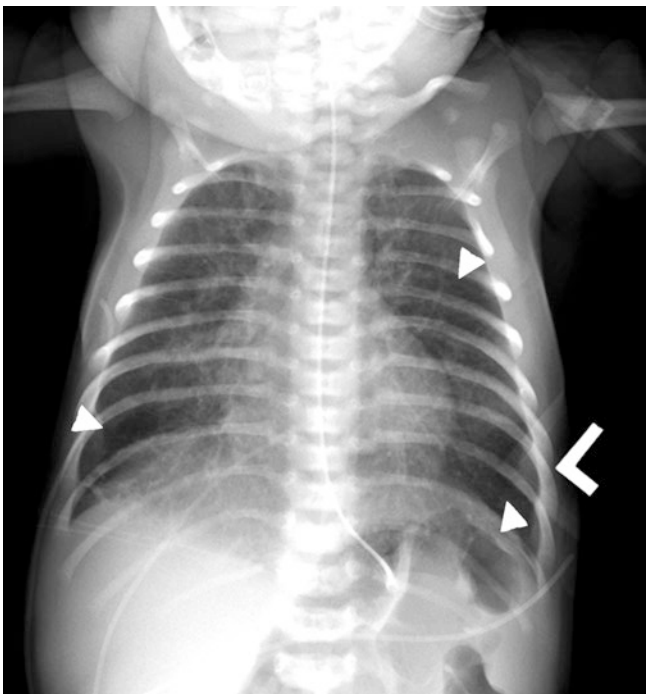


Fig. 32.3

Case 4

Newborn infant with respiratory distress and absent breath sounds on the left

Imaging findings (Fig. 32.4): Frontal chest radiograph demonstrates multiple tubular and rounded lucencies in the left hemithorax with contralateral mediastinal shift. The left diaphragm is indistinct. Note the nasogastric tube terminating above the left hemidiaphragm (*arrow*).

Diagnosis: Congenital diaphragmatic hernia (Bochdalek hernia), which occurs most commonly on the left. A right-sided hernia, or any hernia including the liver, is associated with a worse prognosis, often due to degree of ipsilateral lung hypoplasia.

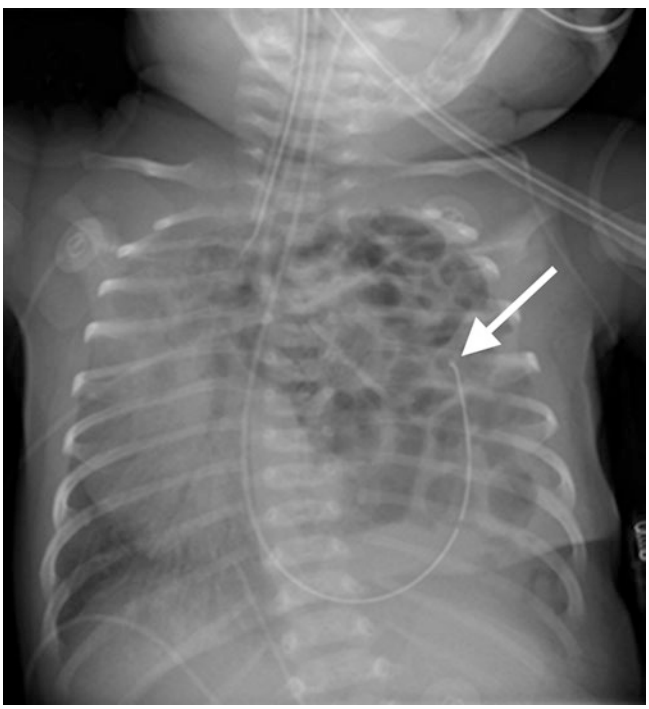


Fig. 32.4

Case 5

Newborn infant with prenatal diagnosis of chest mass

Imaging findings (Fig. 32.5): Frontal chest radiograph (**a**) shows an area of lucency in the right lower lobe (*arrow*)**.** Coronal chest CT (**b**) demonstrates a predominantly right lower lobe multicystic lesion.

Diagnosis: Congenital pulmonary airway malformation, type II. The lack of systemic arterial supply distinguishes this lesion from a pulmonary sequestration or hybrid lesion.

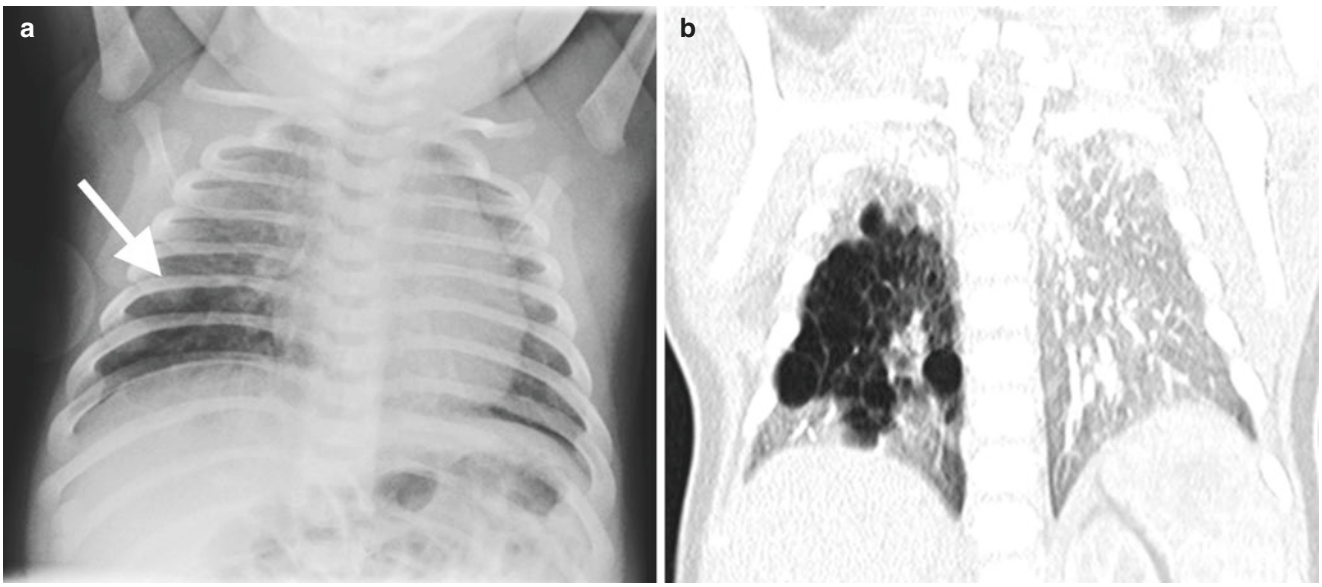


Fig. 32.5

Case 6

1-month-old infant presenting with respiratory distress

Imaging findings (Fig. 32.6): Frontal radiograph of the chest (**a**) shows asymmetric hyperlucency of the left lung (∗) with mild rightward mediastinal shift. Axial CT of the chest (**b**) shows hyperinflation of the left upper lobe with attenuation of the pulmonary vasculature. There is mediastinal shift and compressive atelectasis of the dependent left lower lobe (*arrows*).

Diagnosis: Congenital lobar emphysema, which most commonly involves the left upper lobe.

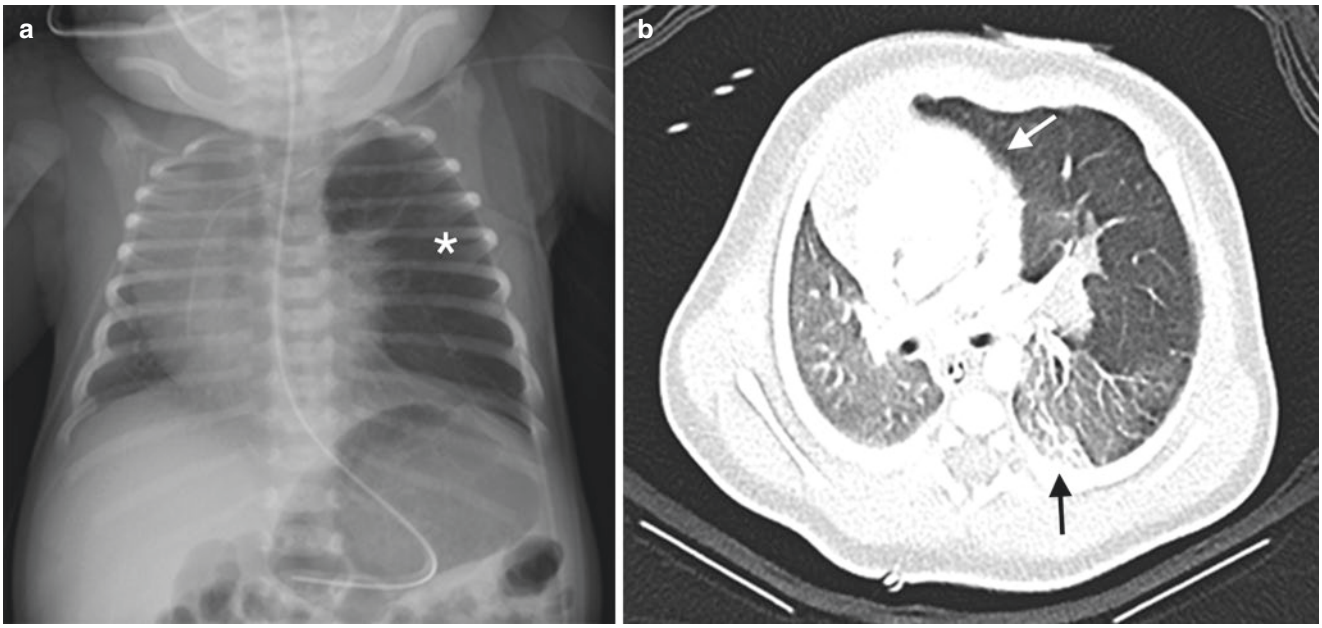


Fig. 32.6

Case 7

Newborn infant with heart murmur and limb abnormalities presenting with difficulty feeding and inability to pass a nasogastric tube

Imaging findings (Fig. 32.7): Frontal chest radiograph (**a**) demonstrates a nasogastric tube terminating in the upper mediastinum in the expected location of the proximal esophagus (*arrow*). Intraoperative fluoroscopic image of the chest (**b**) demonstrates enteric contrast administered retrograde via gastrostomy extending up only a short segment of the distal esophagus (*arrowhead*), approximately 6 cm from the proximal esophageal tube.

Diagnosis: Long gap esophageal atresia with tracheoesophageal fistula in the setting of VACTERL association (Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies, and Limb abnormalities).

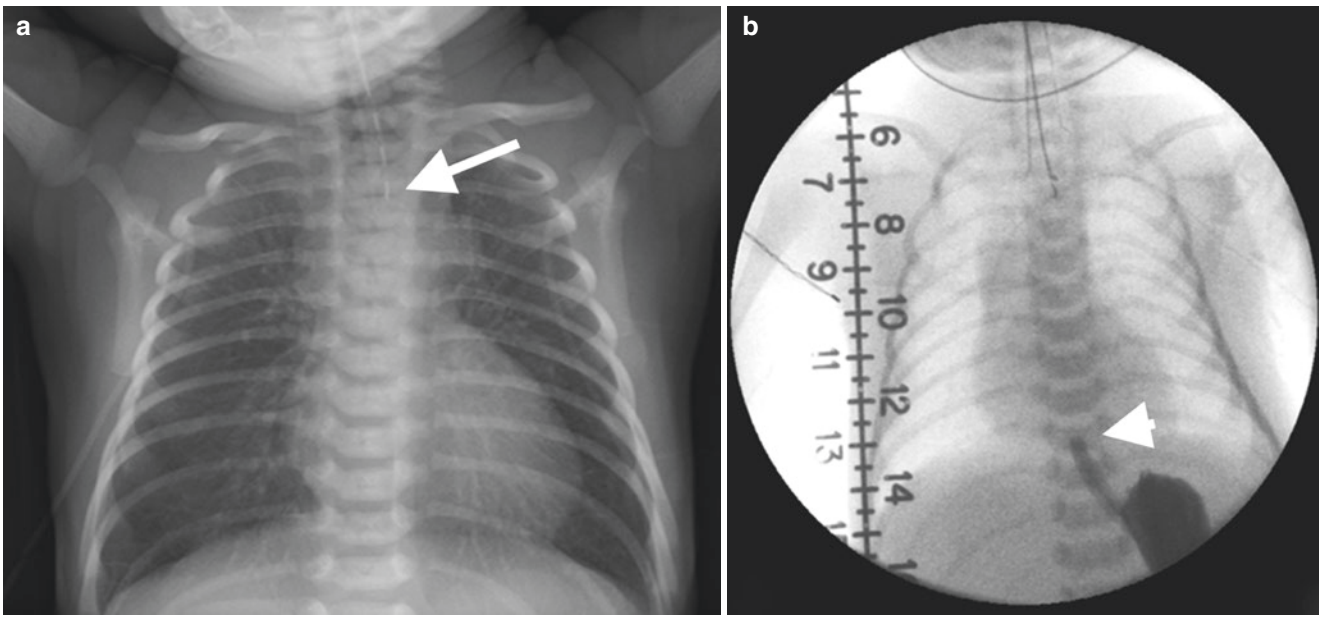


Fig. 32.7

Case 8

Newborn infant presenting with cyanosis, arrhythmia, and holosystolic murmur

Imaging findings (Fig. 32.8): Frontal chest radiograph demonstrates a markedly enlarged cardiac silhouette, often referred to as a "box shaped" due to asymmetric enlargement of the right heart.

Diagnosis: Ebstein's anomaly.

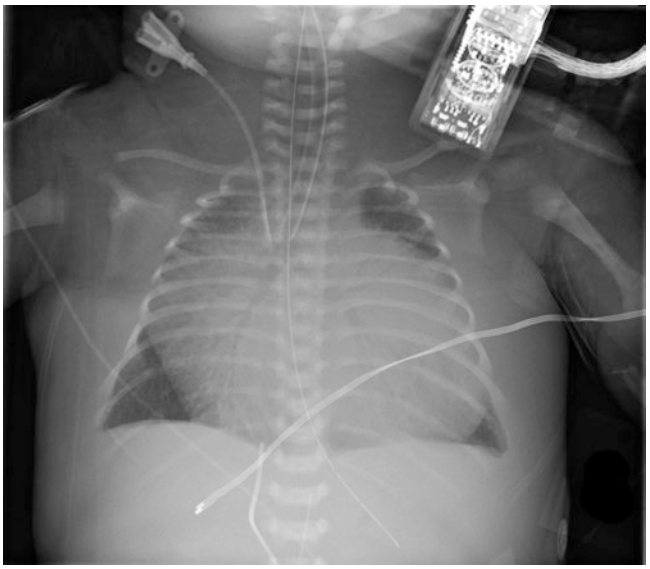


Fig. 32.8

Case 9

Newborn infant presenting with cyanosis and systolic murmur

Imaging findings (Fig. 32.9): Frontal chest radiograph demonstrates a "boot-shaped" heart with upturned cardiac apex due to right ventricular hypertrophy. Note the decreased pulmonary vascular markings.

Diagnosis: Tetralogy of Fallot. The degree of pulmonary oligemia reflects the severity of pulmonary stenosis and subsequent right to left shunt across the ventricular septal defect (VSD).

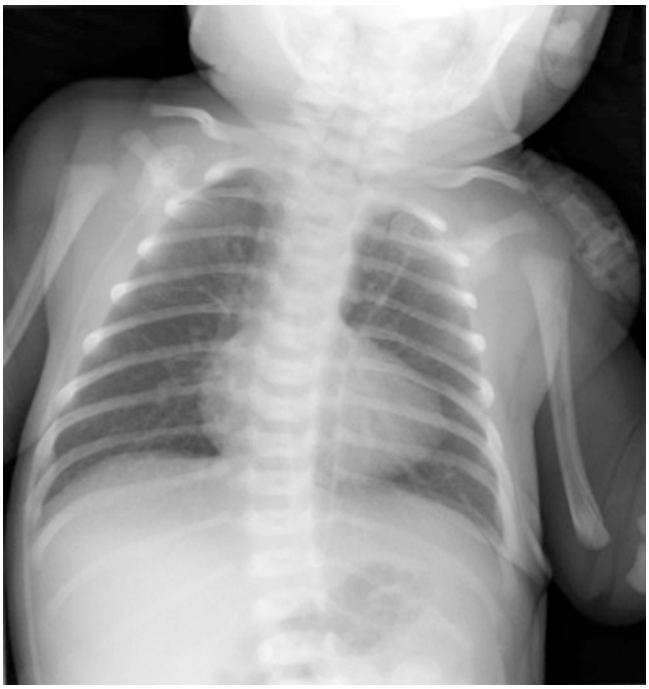


Fig. 32.9

Case 10

15-month-old male presenting with inspiratory stridor and barking cough

Imaging findings (Fig. 32.10): Anteroposterior (AP) radiograph of the neck (**a**) demonstrates smooth tapering of the subglottic trachea, with loss of normal shouldering of the aryepiglottic folds (*arrow*)**.** There is ballooning of the hypopharynx (∗) on lateral view (**b**) due to air trapping.

Diagnosis: Croup (laryngotracheobronchitis).

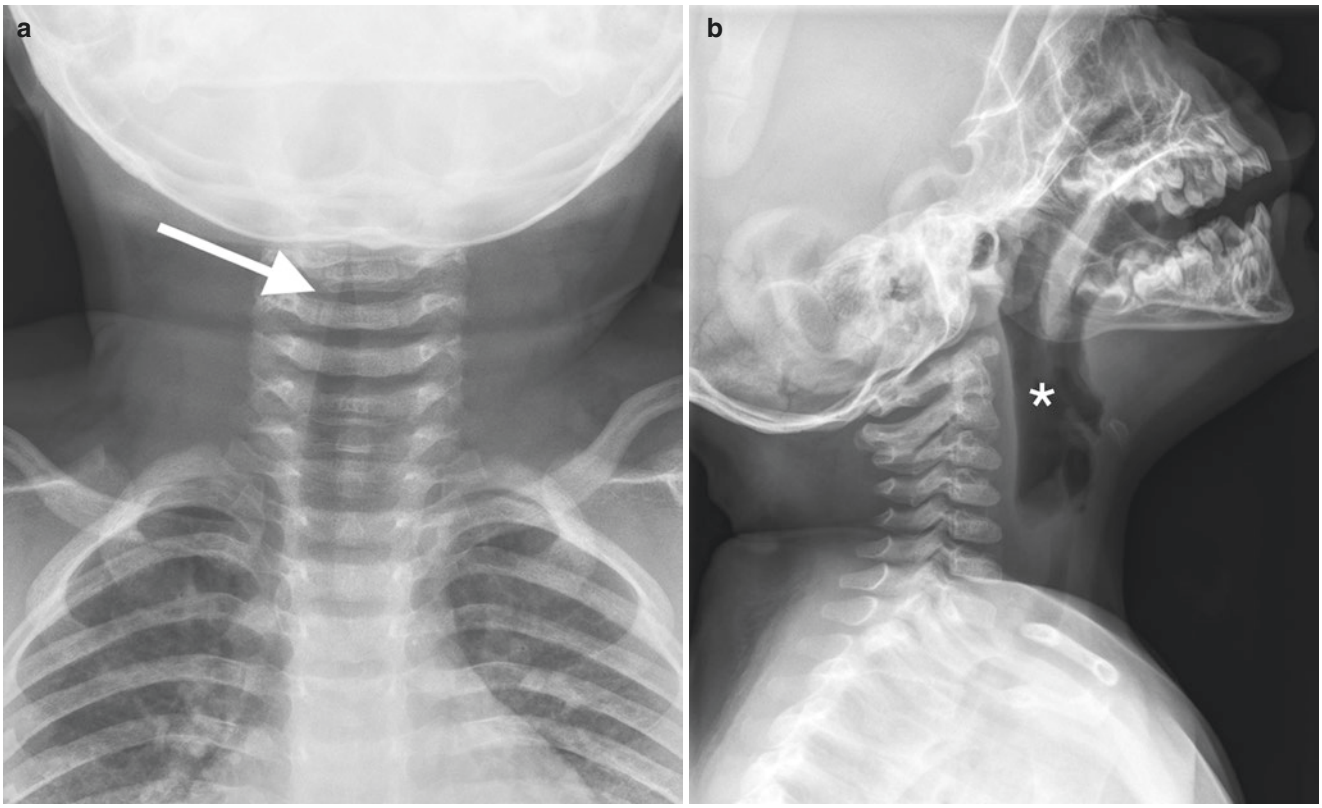


Fig. 32.10

Case 11

2-year-old female presenting with wheezing and found choking and coughing while playing with small toys

Imaging findings (Fig. 32.11): Frontal supine (**a**) and right lateral decubitus (**b**) radiographs of the chest demonstrate asymmetric lucency and hyperinflation in the right lung (∗). The right lung does not collapse when placed in the right decubitus position and remains more lucent than the left lung.

Diagnosis: Foreign body aspiration, most likely in the right mainstem bronchus.

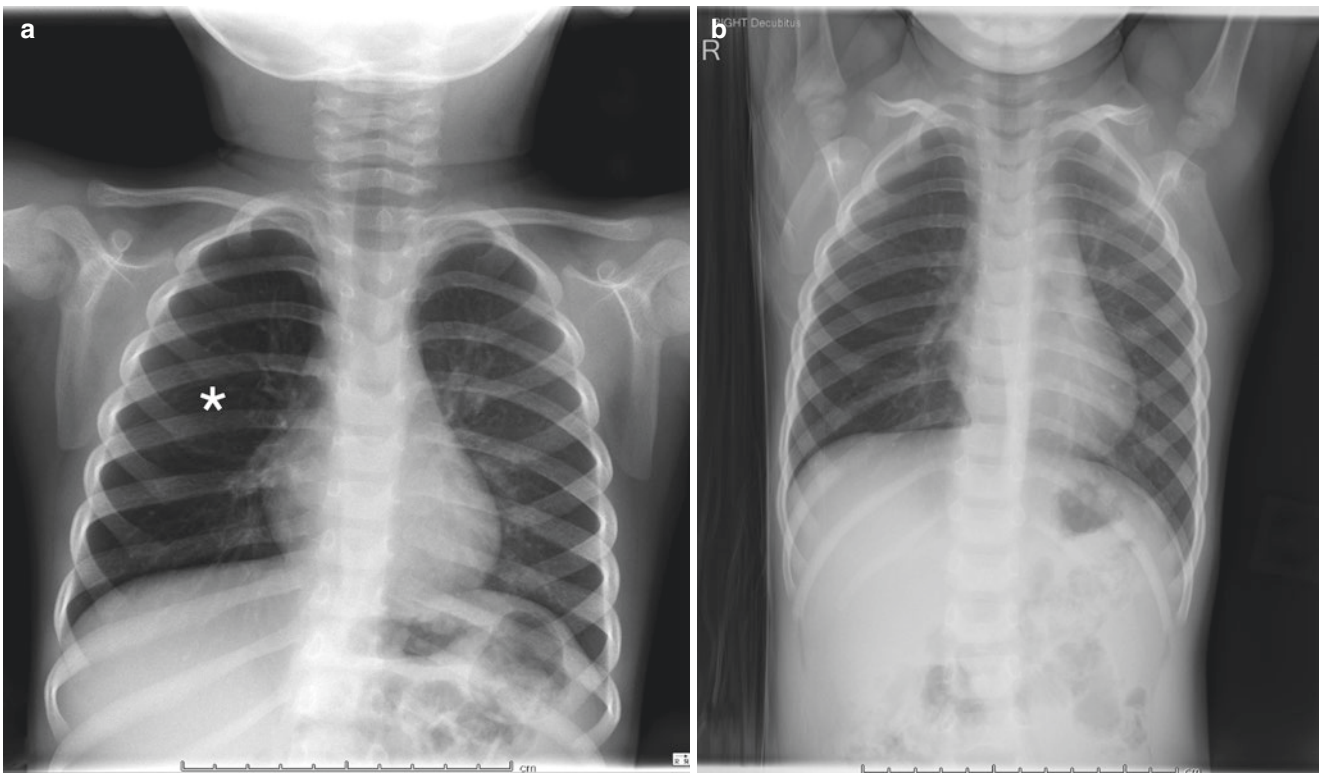


Fig. 32.11

Case 12

5-year-old male presenting with fever and cough

Imaging findings (Fig. 32.12): Frontal (**a**) and lateral (**b**) radiographs of the chest demonstrates a rounded airspace opacity in the right upper lobe (*arrows*)**.**

Diagnosis: Round pneumonia. This appearance can be seen in children under 8 years old due to underdevelopment of pores of Kohn, or collateral airways, which limits the spread of infection.

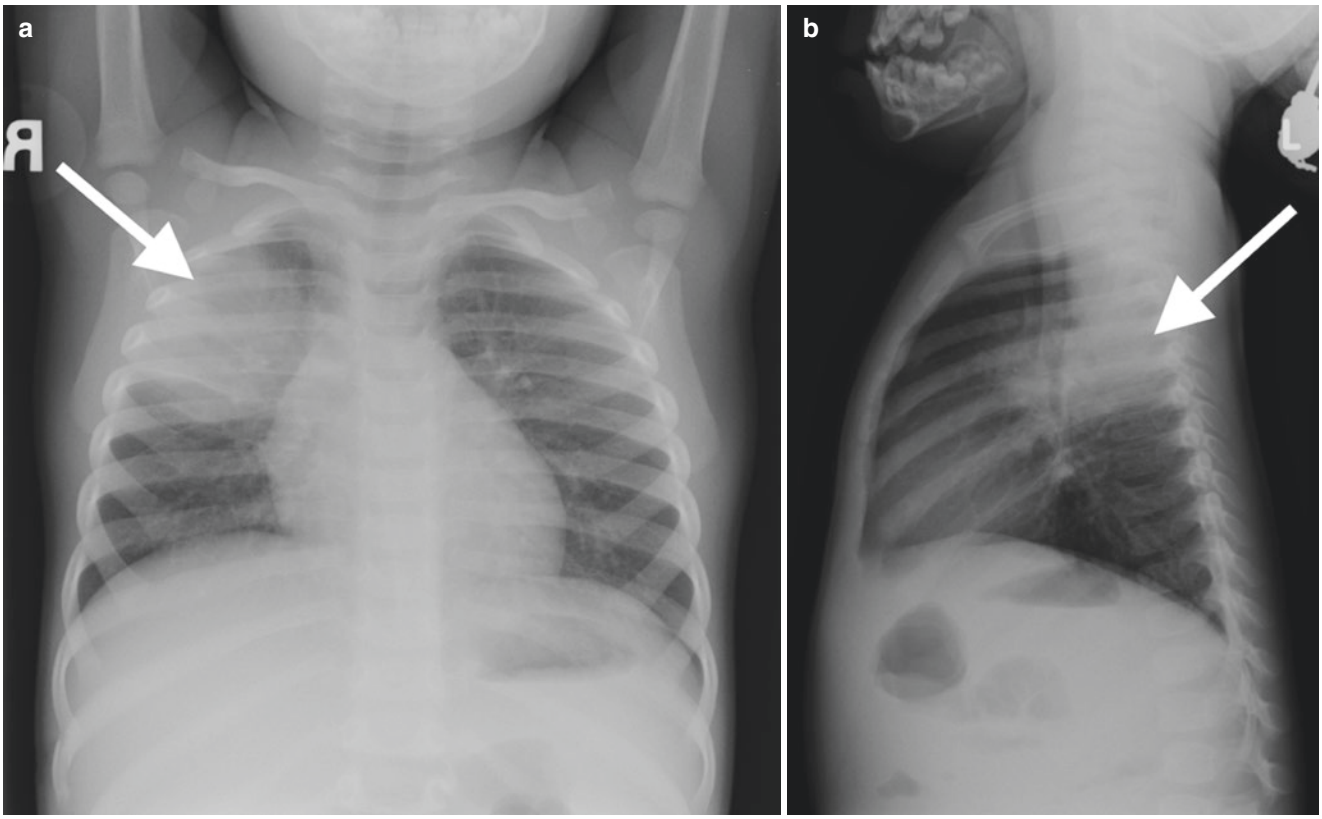


Fig. 32.12

Case 13

12-year-old female presenting with fever and cough

Imaging findings (Fig. 32.13): Frontal (**a**) and lateral (**b**) radiographs of the chest demonstrate dense opacification of the right lower lobe, obscuring the right hemidiaphragm. There are also opacities in the right middle lobe, which obscure the right heart border.

Diagnosis: Lobar pneumonia.

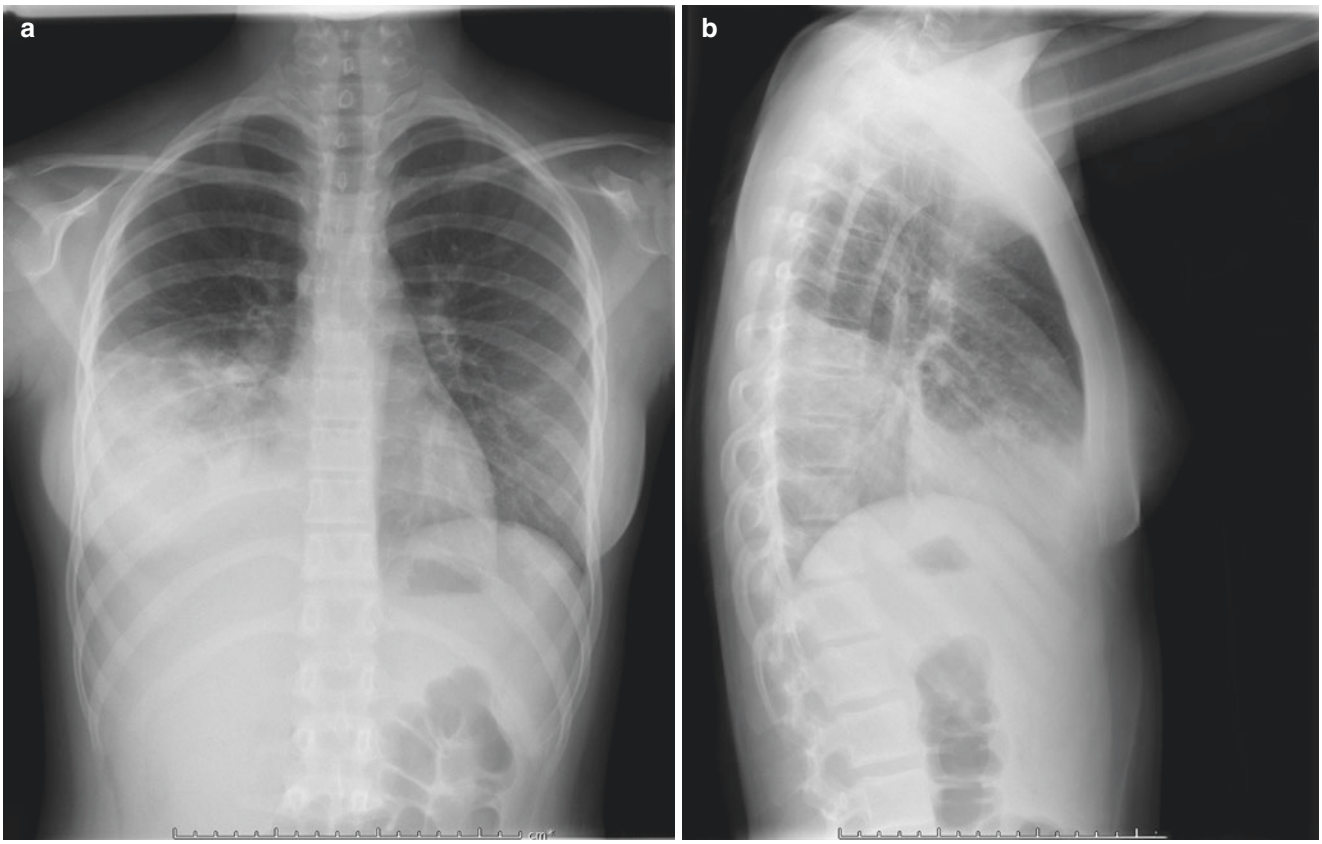


Fig. 32.13

Case 14

2-month-old female with 10 days of fever, with additional history revealing that the patient's grandmother was recently diagnosed with active tuberculosis

Imaging findings (Fig. 32.14): Frontal radiograph of the chest (**a**) demonstrates a rounded right hilar opacity (*arrow*). Coronal CT (**b**) demonstrates extensive mediastinal and hilar hypoattenuating lymph nodes (*arrowheads*), in keeping with necrotic lymphadenopathy.

Diagnosis: Active tuberculosis.

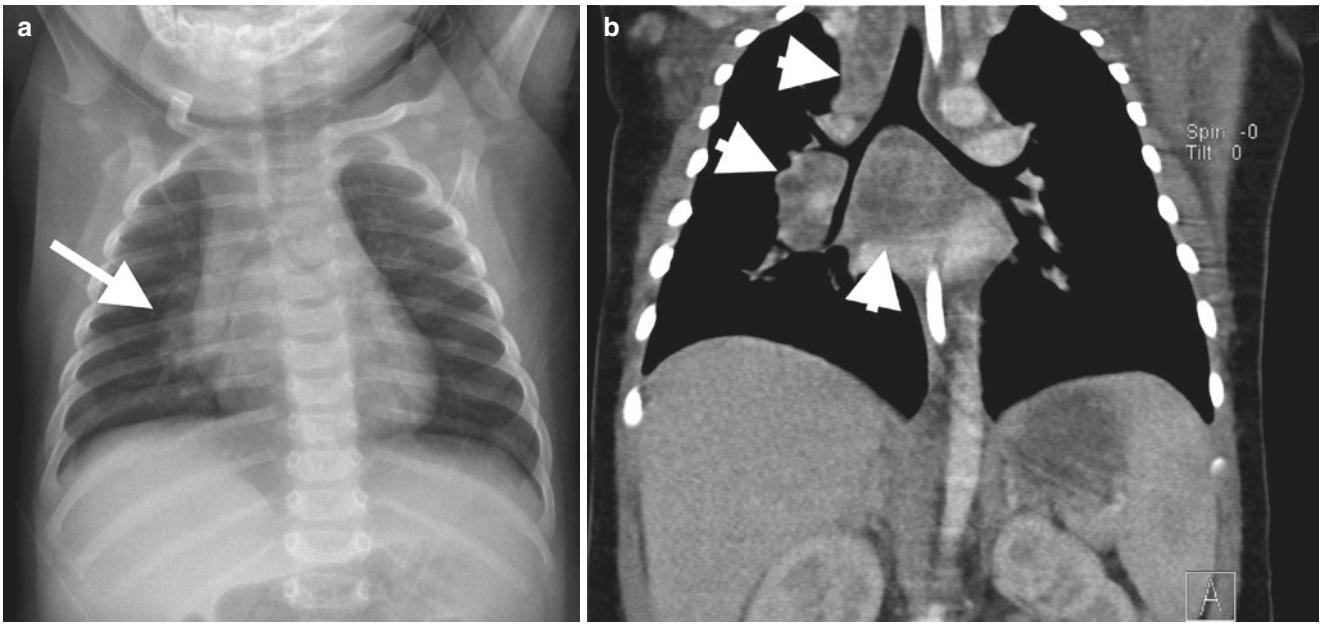


Fig. 32.14

Case 15

15-year-old female on oral contraceptives presenting with shortness of breath and pleuritic chest pain

Imaging findings (Fig. 32.15): CT angiography of the chest with axial (**a**) and coronal (**b**) maximum intensity projection (MIP) images demonstrates multiple filling defects in the main and lobar pulmonary arterial branches bilaterally (*arrows*)**.**

Diagnosis: Pulmonary thromboembolism.

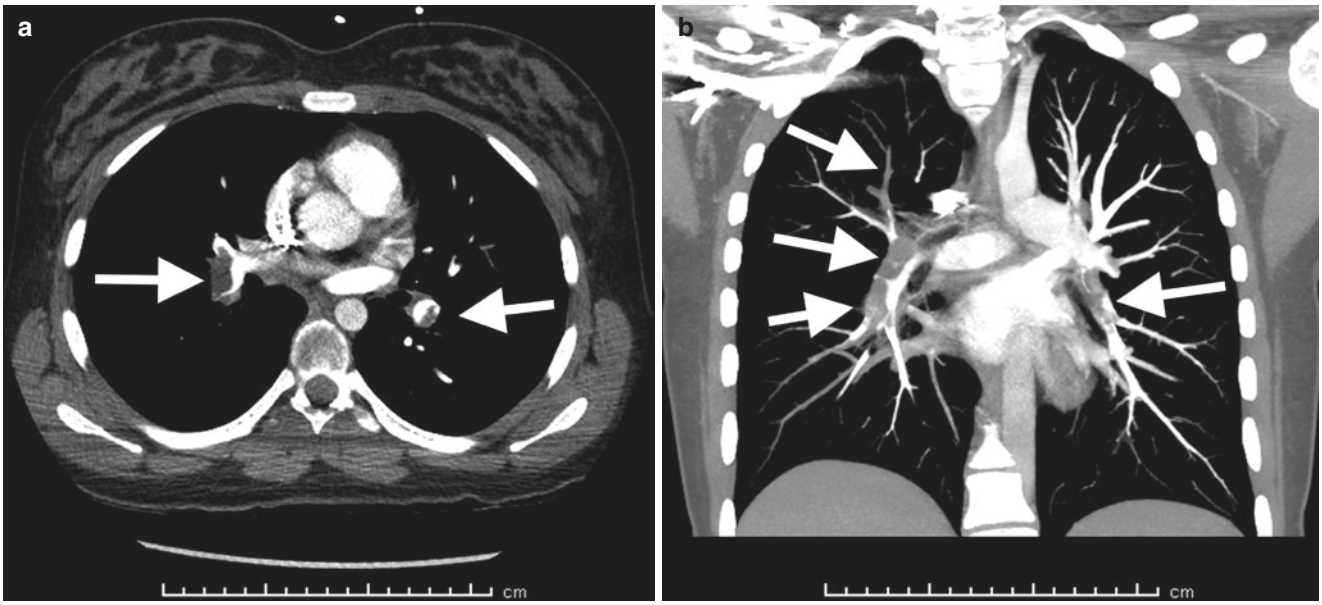


Fig. 32.15

Case 16

16-year-old male with chronic cough, exercise intolerance, and frequent bulky, greasy stools

Imaging findings (Fig. 32.16): Frontal radiograph of the chest demonstrates hyperinflation of the lungs, upper lobe predominant cystic bronchiectasis and bronchial wall thickening, apical pleural thickening, and small nodular opacities in the peripheral lungs.

Diagnosis: Cystic fibrosis. The peripheral nodular opacities typically reflect mucus plugging in terminal bronchioles.

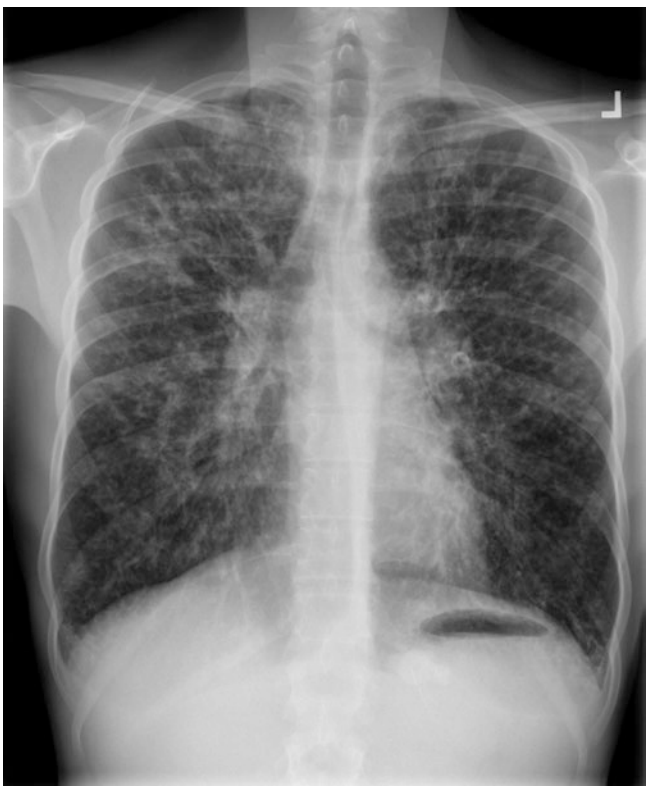


Fig. 32.16

Case 17

Previously healthy 14-year-old female admitted to the hospital with right lower lobe mycoplasma pneumonia, presenting with acute respiratory failure and clinical deterioration

Imaging findings (Fig. 32.17): Frontal radiograph of the chest demonstrates diffuse coalescent airspace opacities. The patient was intubated and cannulated for veno-venous extracorporeal membrane oxygenation. A small pleural effusion is present on the right.

Diagnosis: Acute respiratory distress syndrome (ARDS).

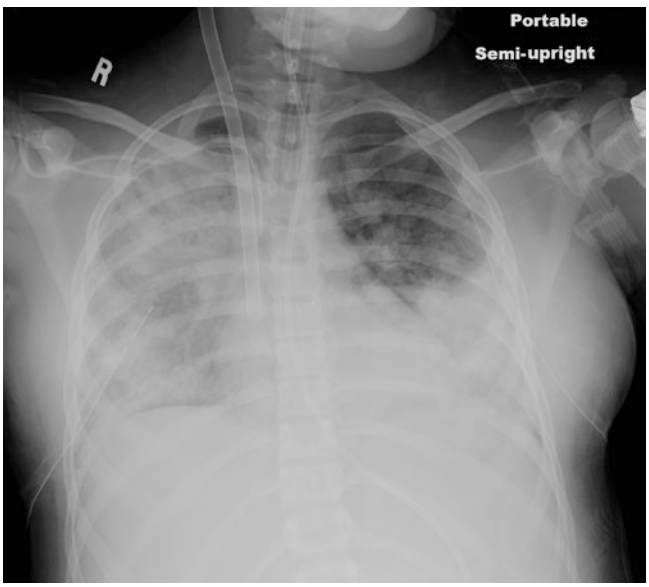


Fig. 32.17

Case 18

16-year-old female presenting with several days of malaise, chest discomfort, and loss of appetite

Imaging findings (Fig. 32.18): Frontal radiograph of the chest (**a**) demonstrates an abnormal and markedly widened mediastinal contour (*arrows*). Lateral radiograph (**b**) localizes the abnormality to the anterior mediastinum with loss of the retrosternal clear space (*arrow*). CT of the chest with contrast (c) demonstrates a heterogeneous, enhancing, lobular soft tissue mass in the anterior mediastinum (∗). The mass surrounds the mediastinal vessels without compressing them.

Diagnosis: Lymphoma.

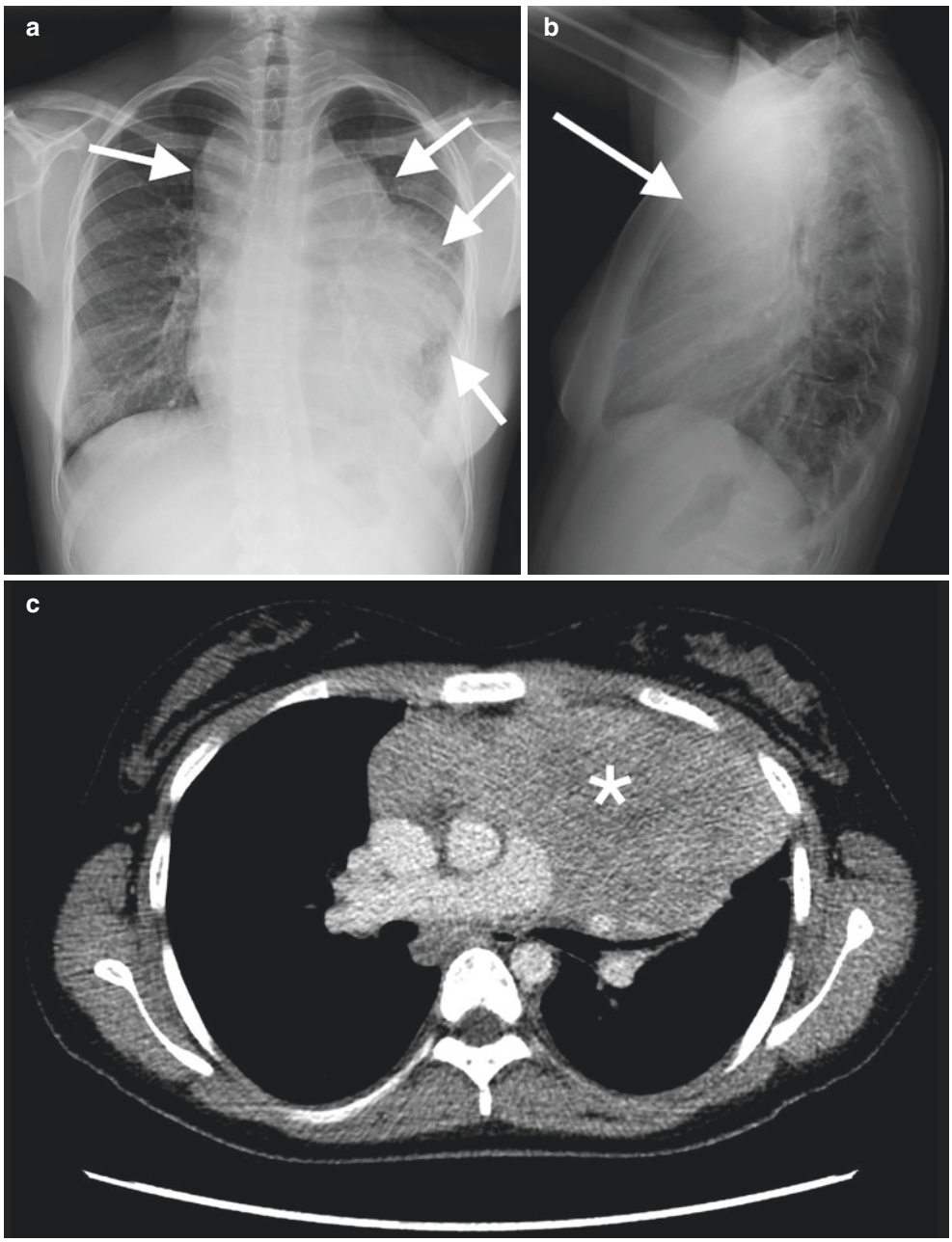


Fig. 32.18

GASTROINTESTINAL RADIOLOGY

Case 19

12-day-old infant with history of prematurity, presenting with abdominal distension

Imaging findings (Fig. 32.19): Frontal supine (**a**) and cross table lateral (**b**) radiographs of the abdomen demonstrate markedly distended, featureless bowel loops with intramural lucencies that outline the bowel walls (*arrows*). Branching lucencies over the liver are also noted, indicative of portal venous gas (*arrowheads*).

Diagnosis: Pneumatosis intestinalis and portal venous gas in the setting of necrotizing enterocolitis.

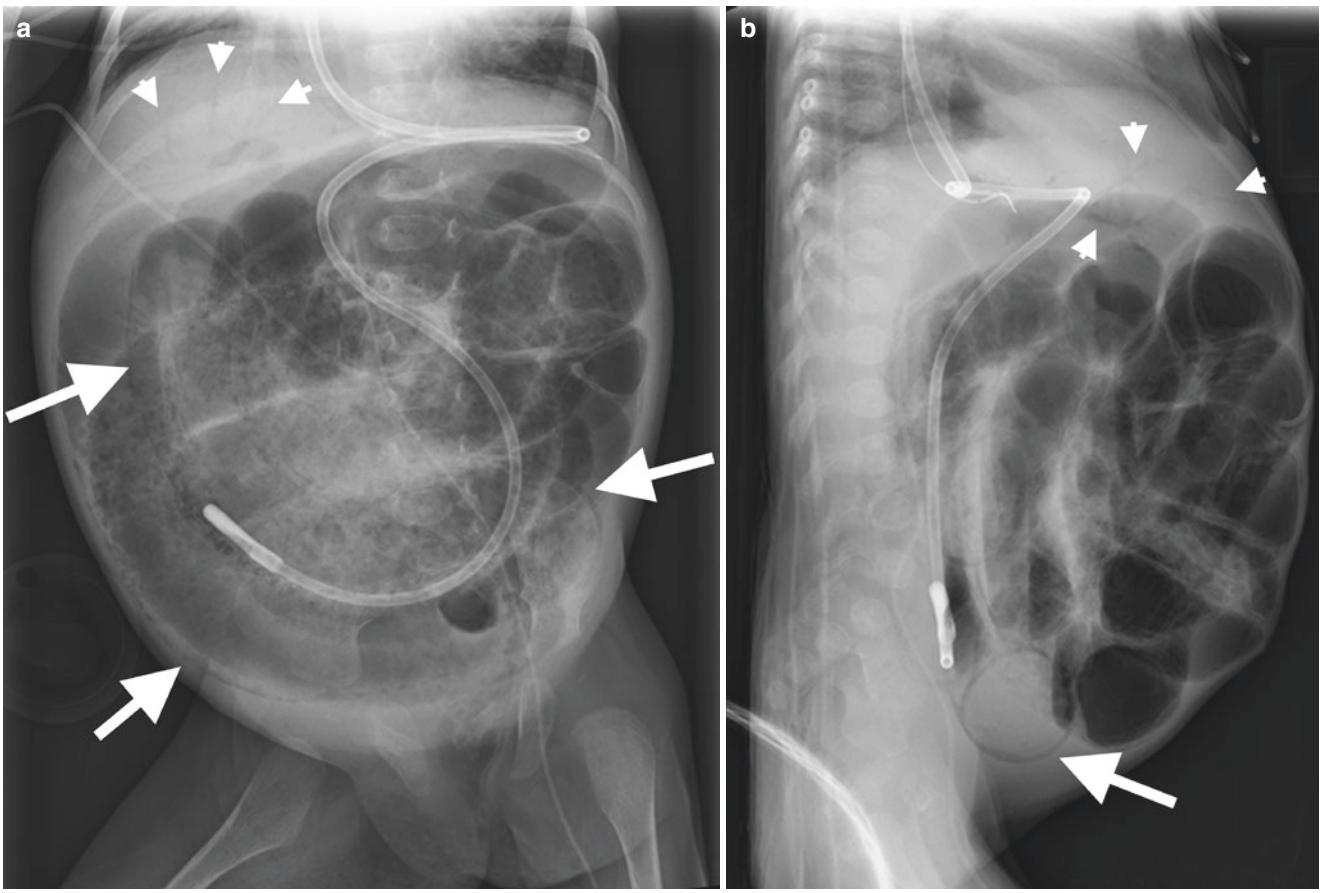


Fig. 32.19

Case 20

12-day-old infant born at 29 weeks gestational age presenting with abdominal distension and hypotension

Imaging findings (Fig. 32.20): Frontal radiograph of the abdomen (**a**) demonstrates abnormal featureless appearing tubular bowel loops with a large vague lucency under the mid diaphragm outlining the falciform ligament (*arrow*). A subsequent lateral decubitus radiograph (**b**) better demonstrates the abnormal lucency which is now seen in the antidependent abdomen adjacent to the liver (*arrow*).

Diagnosis: Bowel perforation with pneumoperitoneum.

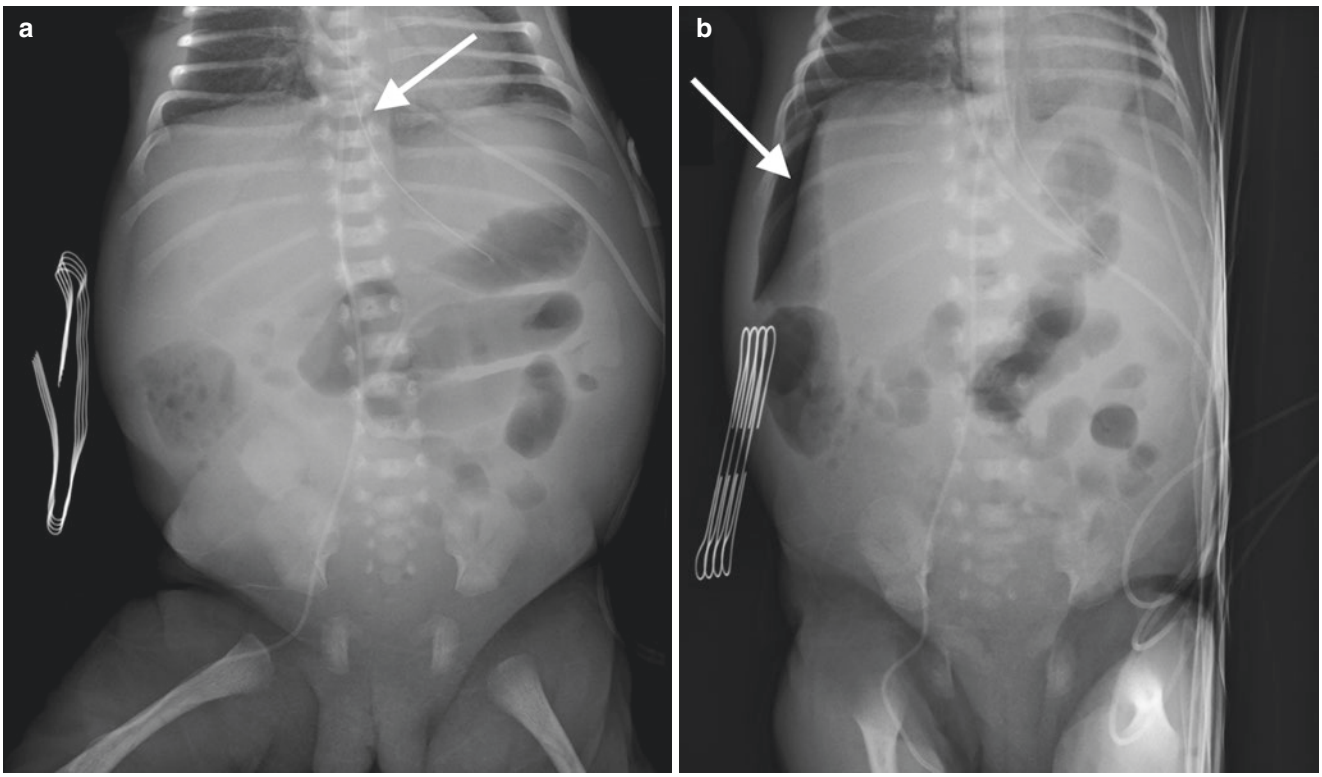


Fig. 32.20

Case 21

1-year-old with abdominal pain

Imaging findings (Fig. 32.21): Abdominal radiograph demonstrates amorphous calcifications (*arrows*) throughout the abdomen, many in a curvilinear pattern, indicative of diffuse peritoneal calcification.

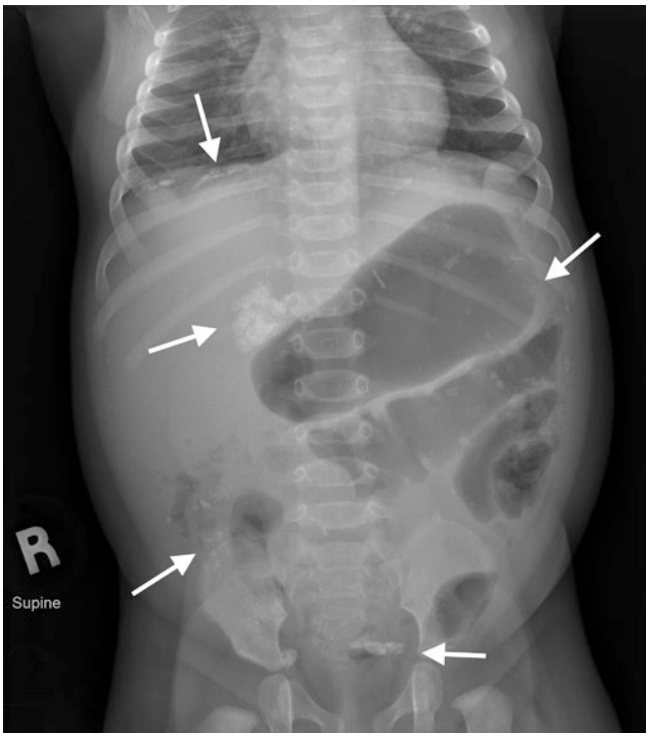


Fig. 32.21

Diagnosis: Meconium peritonitis, an incidental finding indicating in utero bowel perforation and chemical peritonitis due to meconium.

Case 22

3-week-old male presenting with projectile non-bilious, non-bloody emesis after feeding

Imaging findings (Fig. 32.22): Transverse gray-scale ultrasound image of the epigastric region demonstrates an abnormally elongated pyloric channel (*dashed line*, > 14 mm) with thickened hypoechoic muscular layer (*solid line*, > 3 mm). Note the fluid within the gastric antrum (*arrow*) and lack of fluid in the duodenal bulb (*arrowhead*). No gastric contents were seen traversing the pylorus during the ultrasound exam.

Diagnosis: Hypertrophic pyloric stenosis.

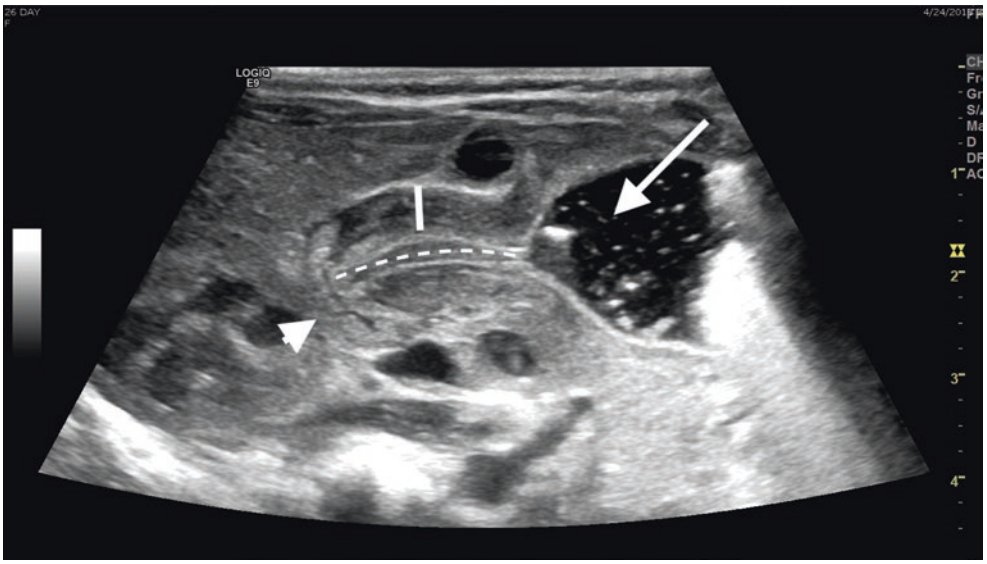


Fig. 32.22

Case 23

14-year-old male presenting with nausea, vomiting, and periumbilical pain that migrated to the right lower quadrant, with laboratory results revealing a white blood cell count of 18,000

Imaging findings (Fig. 32.23): Focused right lower quadrant ultrasound image demonstrates a dilated (> 6 mm), tubular, and thickened appendix (*arrows*). An echogenic shadowing structure is seen within the lumen of the appendix (∗), most in keeping with an appendicolith. Note the fluid and echogenic fat surrounding the appendix, denoting periappendiceal edema.

Diagnosis: Acute appendicitis.

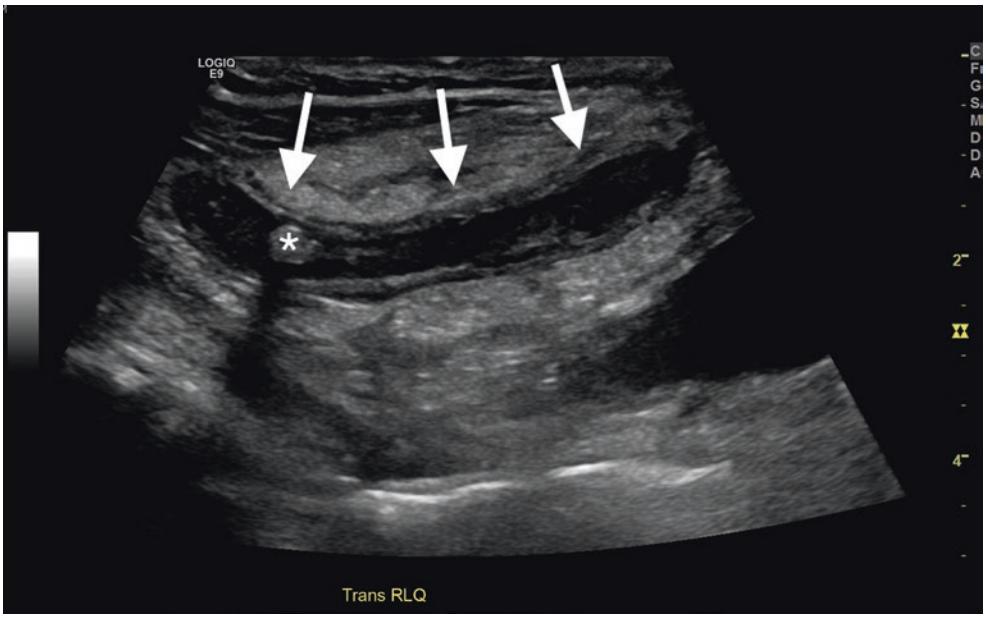


Fig. 32.23

Case 24

4-day-old male presenting with bilious emesis, abdominal distension, and feeding intolerance

Imaging findings (Fig. 32.24): Upper GI fluoroscopic image of the abdomen during administration of water-soluble enteric contrast demonstrates an abnormal corkscrew appearance of the proximal duodenum (*arrow*), which does not cross midline.

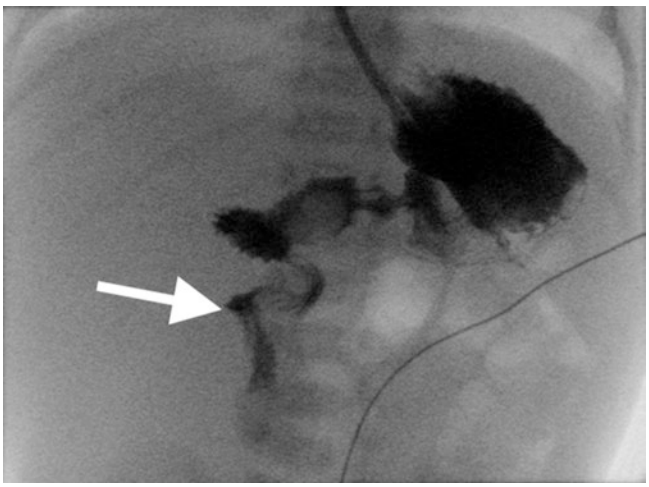


Fig. 32.24

Diagnosis: Malrotation with volvulus. The second and fourth segments of the duodenum should course retroperitoneally, and the duodenojejunal junction should be located at the same level of the duodenal bulb at approximately the L1 vertebral body on the left.

Case 25

2-year-old male with recent history of viral upper respiratory tract infection presenting with intermittent bouts of severe abdominal pain and lethargy, with a palpable tubular mass in the upper abdomen on examination

Imaging findings (Fig. 32.25): Frontal abdominal radiograph (**a**) demonstrates a rounded soft tissue filling defect within the mid transverse colon (*arrow*). Right lower quadrant ultrasound images (b, c) reveal a targetoid appearance of multiple alternating layers of bowel wall (*arrows*) and interposed mesenteric fat (∗), lymph nodes (∗), and fluid (∗).

Diagnosis: Ileocolic intussusception.

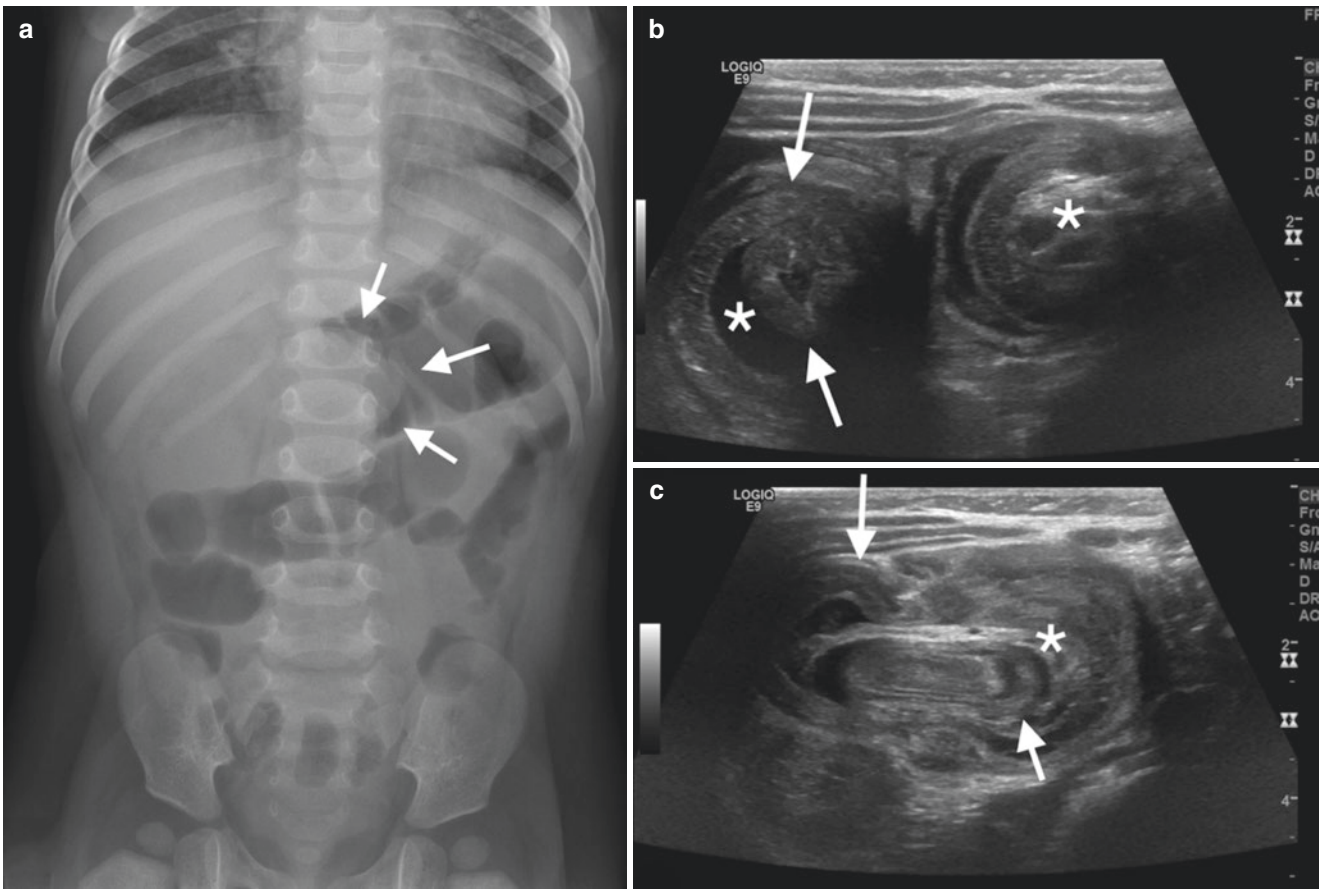


Fig. 32.25

Case 26

Newborn infant with trisomy 21 and history of polyhydramnios, presenting with bilious emesis

Imaging findings (Fig. 32.26): Radiograph of the abdomen demonstrates a "double-bubble" appearance of gaseous distension of the stomach (*arrow*) and duodenal bulb (*arrowhead*) with absence of gas distally.

Diagnosis: Duodenal atresia.

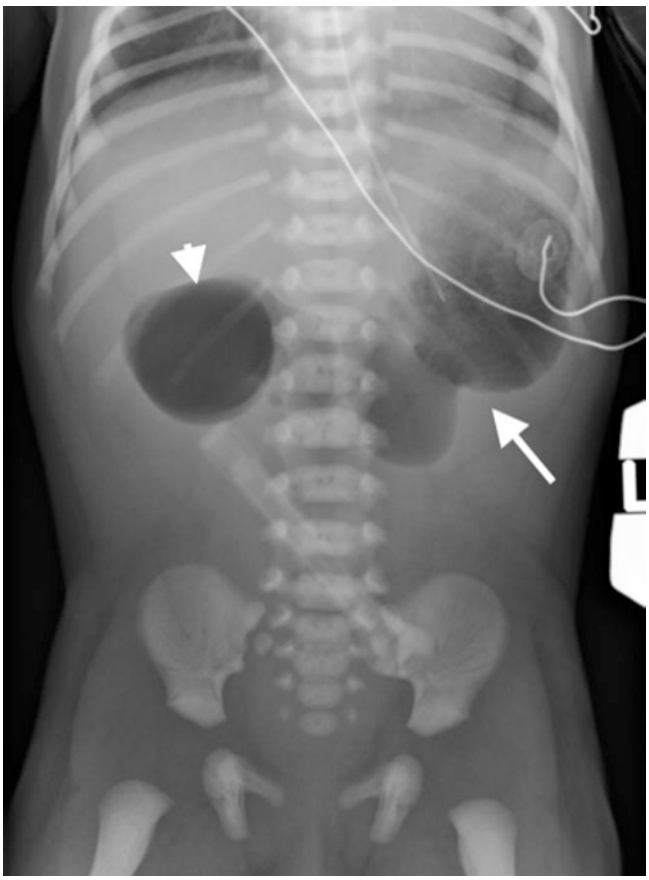


Fig. 32.26

Case 27

12-day-old infant with a diagnosis of 2q22.1 chromosomal deletion with multiple congenital abnormalities, presenting with abdominal distension

Imaging findings (Fig. 32.27): Abdominal radiograph (**a**) demonstrates gas distension of the distal colon in the left hemiabdomen (*arrow*). Fluoroscopic contrast enema (**b**) demonstrates a small caliber rectum with a transition point (*arrow*) at the rectosigmoid junction and dilatation of the colon proximally. Normally, the rectum should be larger in caliber than the sigmoid colon (rectosigmoid ratio > 1).

Diagnosis: Hirschsprung disease.

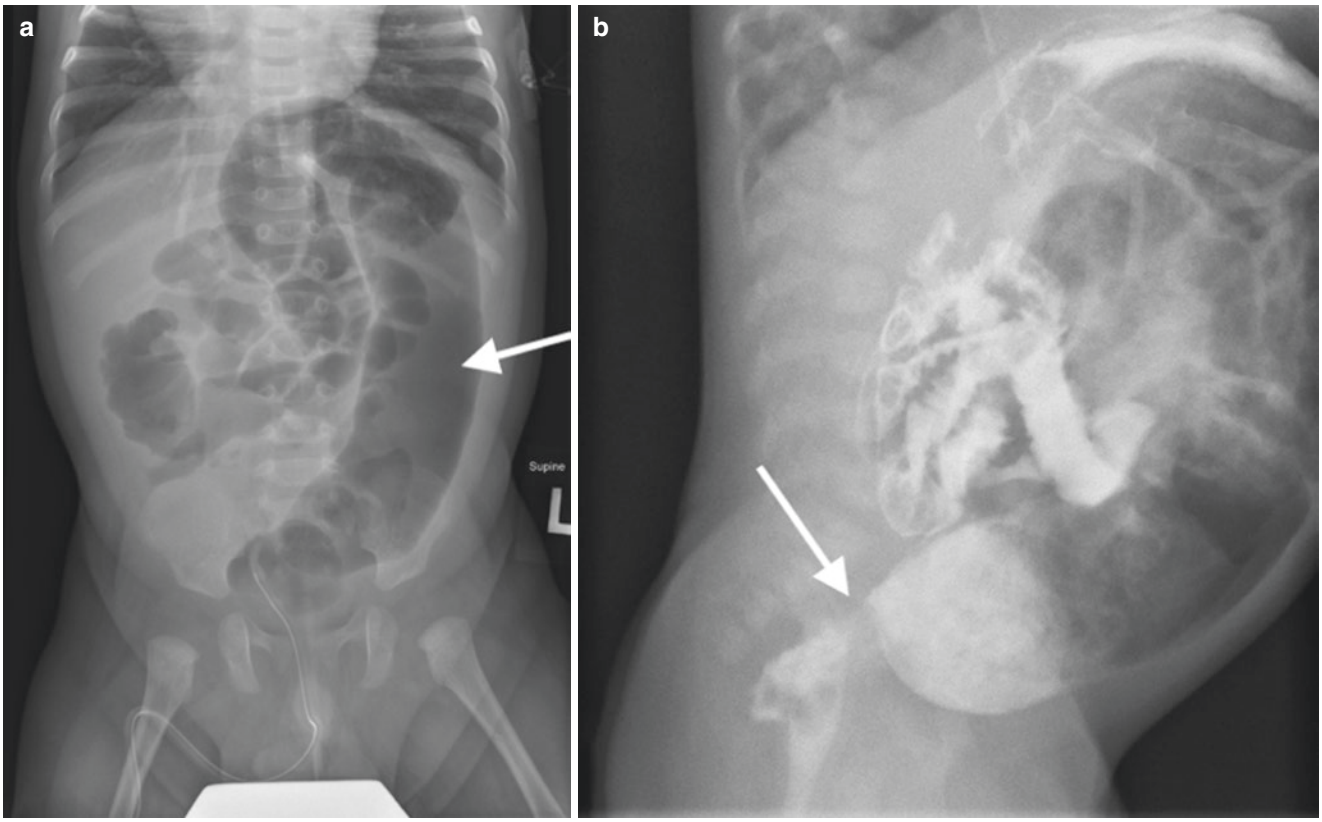


Fig. 32.27

Case 28

9-month-old male with a non-reducible left-sided scrotal mass

Imaging findings (Fig. 32.28): Ultrasound image of the left scrotum shows a structure extending from the inguinal canal adjacent to the spermatic cord. This structure demonstrates walls with alternating hypoechoic and hyperechoic layers (*arrow*), indicative of gut signature. Note the small adjacent hydrocele (*arrowhead*).

Diagnosis: Incarcerated inguinal hernia.

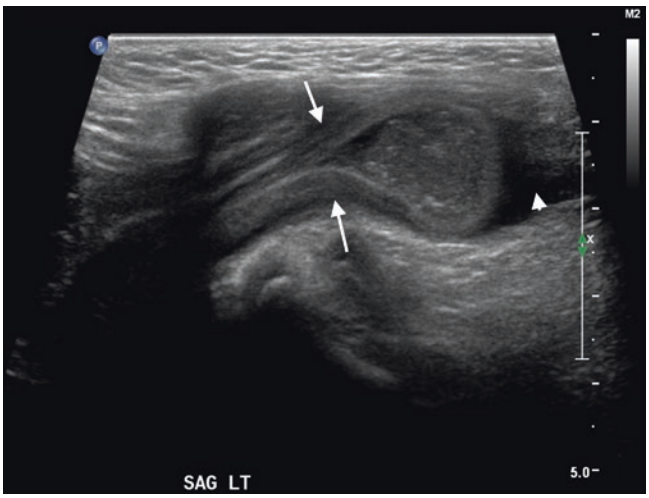


Fig. 32.28

Case 29

2-week-old infant presenting with jaundice and conjugated hyperbilirubinemia

Imaging findings (Fig. 32.29): Hepatobiliary iminodiacetic acid scintigraphy (HIDA scan) shows uptake of radiotracer into the liver but no excretion into the small bowel. This was confirmed on 24-h delayed imaging. No gallbladder was identified.

Diagnosis: Biliary atresia.

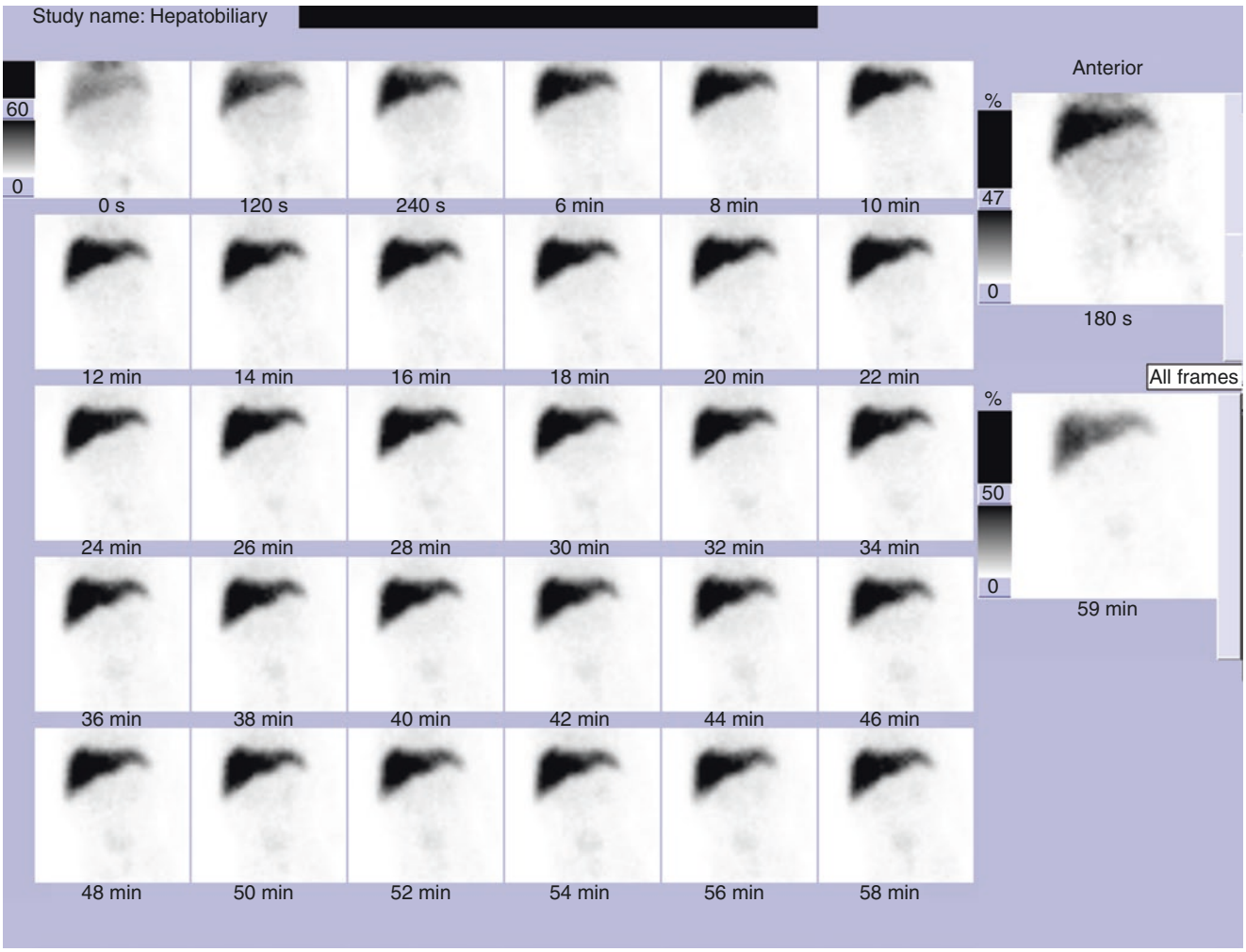


Fig. 32.29

Case 30

10-year-old male presenting with lower gastrointestinal bleeding

Imaging findings (Fig. 32.30): Dynamic abdominal scintigraphy with technetium-99m-labeled sodium pertechnetate demonstrates an intense focus of persistent abnormal tracer activity in the right lower quadrant (*arrow*). There is normal uptake of tracer by the stomach.

Diagnosis: Functioning ectopic gastric mucosa (Meckel's diverticulum).

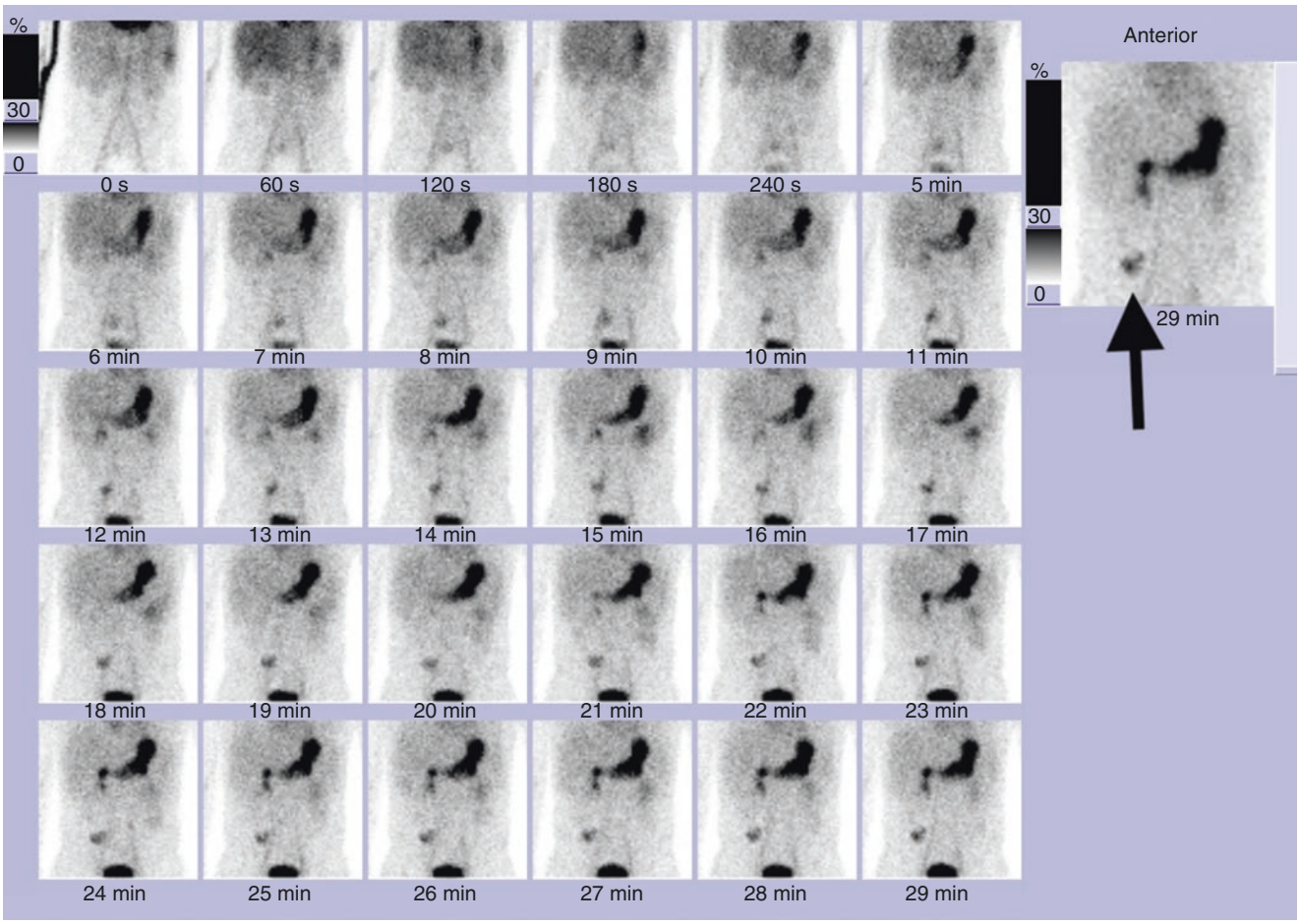


Fig. 32.30

Case 31

2-year-old child presenting with throat pain

Imaging findings (Fig. 32.31): Frontal (**a**) and lateral (**b**) radiographs of the chest show a discoid metallic foreign body projecting over the upper esophagus at the level of the aortic arch. The double rim and slight step off along the edges of the object distinguish this from a simple coin. Ingested foreign bodies in the esophagus are most commonly seen at the levels of the thoracic inlet, the aortic arch, and gastroesophageal junction.

Diagnosis: Button battery ingestion.

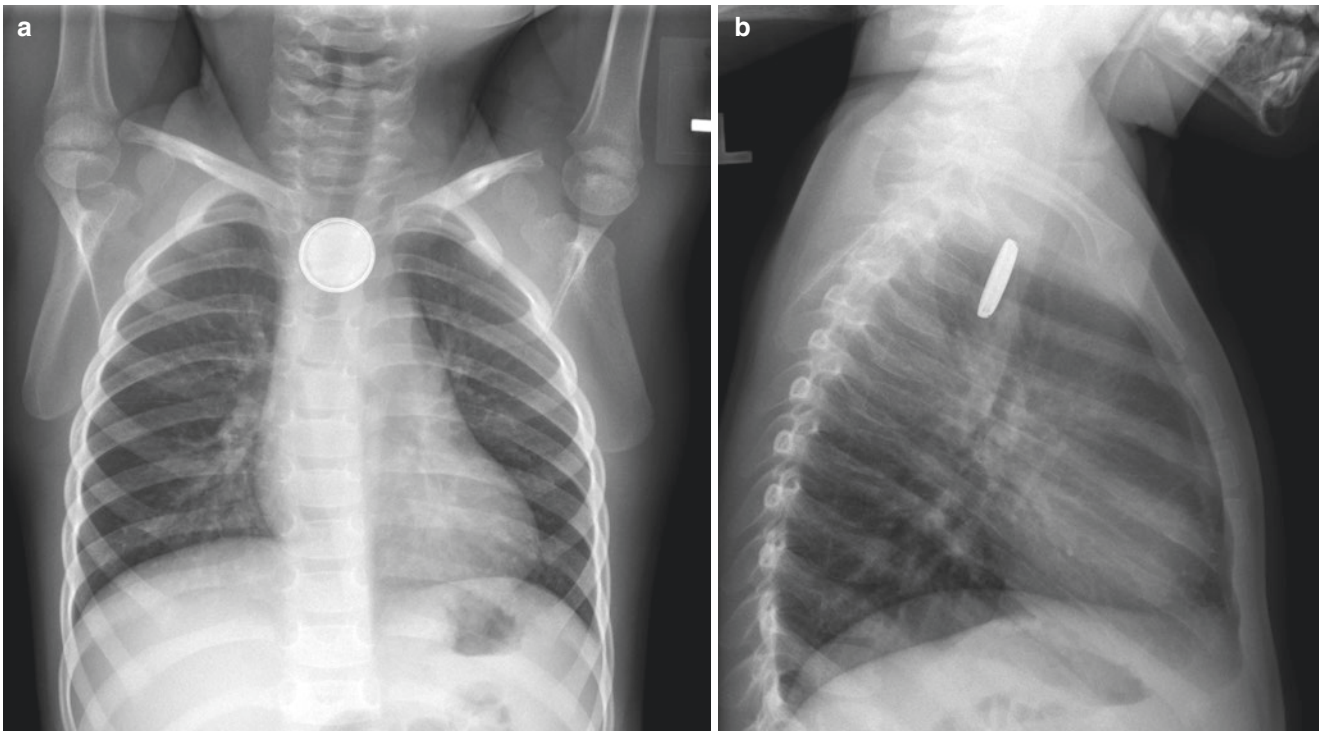


Fig. 32.31

Case 32

2-year-old with history of gastroschisis, presenting with abdominal pain and distention

Imaging findings (Fig. 32.32): Frontal and lateral decubitus radiographs (**a, b**) of the abdomen demonstrate markedly dilated loops of small bowel with multiple air-fluid levels (*arrows*). There is also a paucity of gas in the sigmoid colon and rectum (∗).

Diagnosis: Small bowel obstruction.

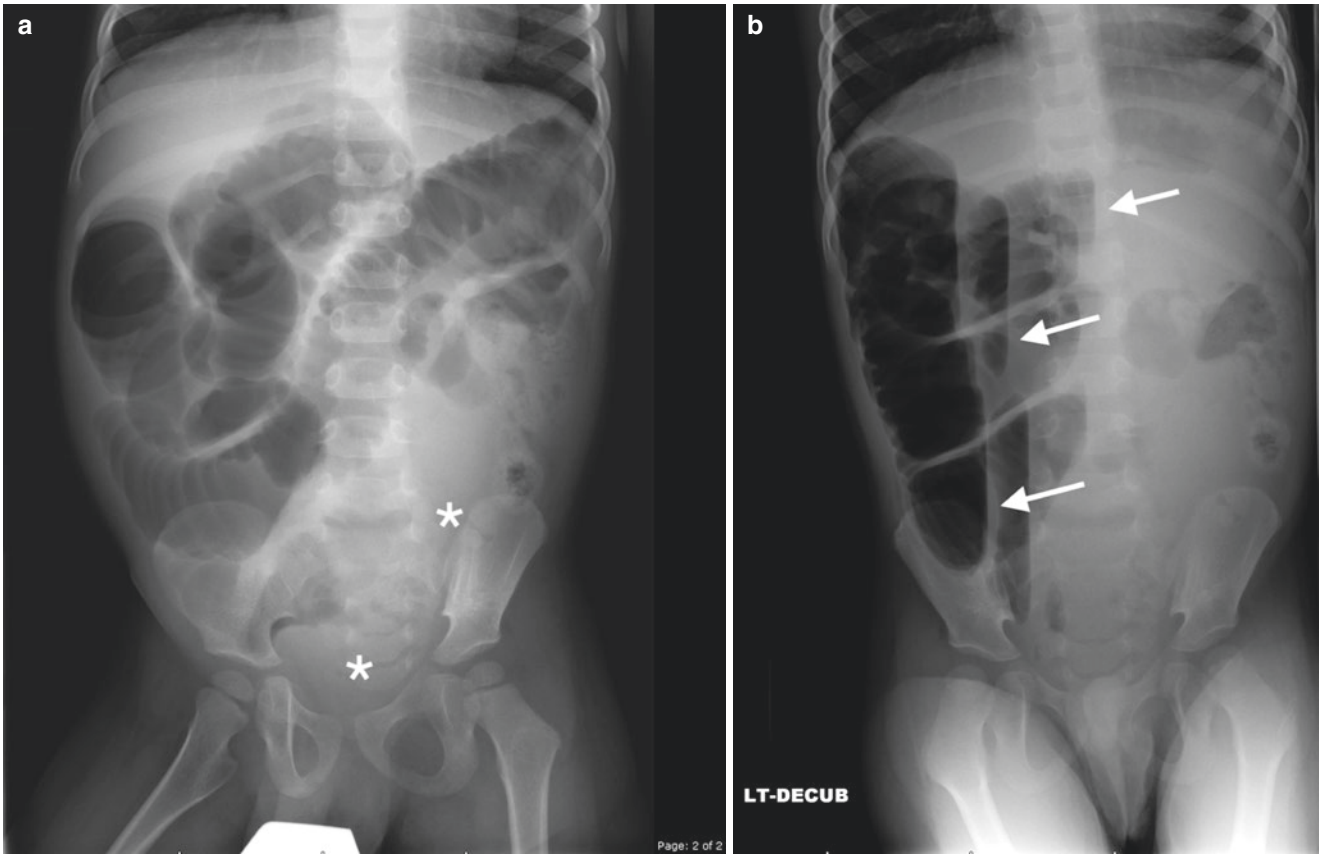


Fig. 32.32

Case 33

12-year-old male with several weeks of intermittent abdominal pain and diarrhea

Imaging findings (Fig. 32.33): MR enterography was performed. Gadolinium contrast-enhanced coronal (**a**) and axial (**b**) T1-weighted, fat-saturated MR images show enhancement and thickening of a long segment of the terminal ileum in the right lower quadrant (*arrows*). Note also the engorgement of the mesenteric vessels (*arrowheads*).

Diagnosis: Crohn's disease with terminal ileitis.

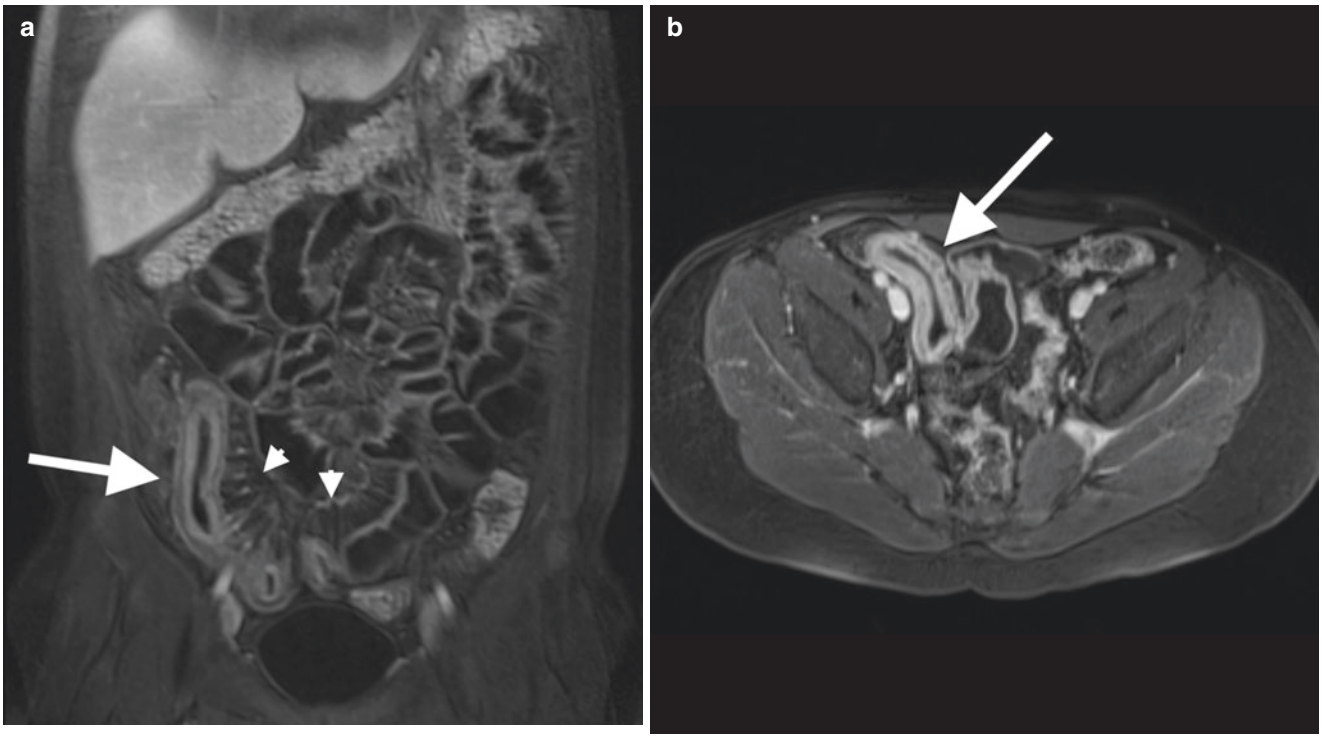


Fig. 32.33

Case 34

3-year-old male presenting with abdominal pain and failure to thrive, with a palpable left upper quadrant mass on examination and an abnormal abdominal ultrasound which prompted further evaluation with CT

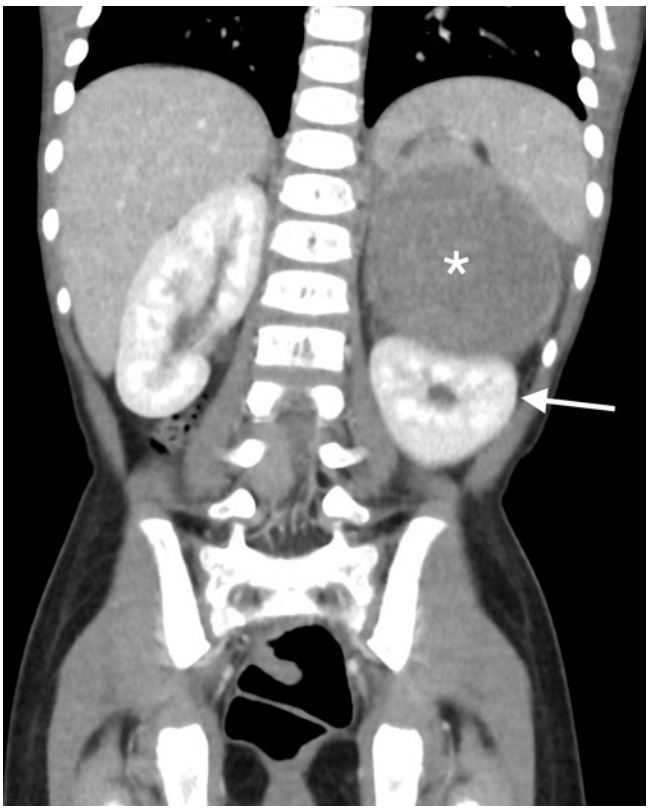


Fig. 32.34

Imaging findings (Fig. 32.34): Coronal contrast-enhanced CT of the abdomen demonstrates a large, round, and heterogeneously enhancing left suprarenal mass (∗). The left kidney is displaced inferiorly (*arrow*).

Diagnosis: Neuroblastoma.

GENITOURINARY RADIOLOGY

Case 35

1-month-old infant presenting with discharge from the umbilicus

Imaging findings (Fig. 32.35): Sagittal ultrasound of the midline lower abdomen demonstrates a fluid-filled tract (*arrows*) extending from the dome of the bladder to the umbilicus. Thickening of the soft tissues surrounding the umbilicus suggests inflammation.

Diagnosis: Infected patent urachus.

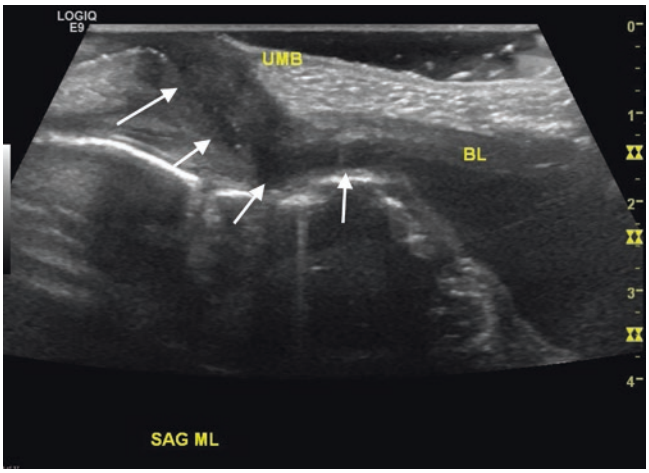


Fig. 32.35

Case 36

Newborn male infant with prenatal diagnosis of hydronephrosis

Imaging findings (Fig. 32.36): Fluoroscopic cyclic voiding cystourethrogram was performed. An oblique fluoroscopic image of the pelvis during voiding demonstrates abnormal dilatation and elongation of the posterior urethra (*arrow*) proximal to a thin radiolucent band of tissue (*arrowhead*). Note also the trabecular appearance of the bladder (∗) due to muscular hypertrophy.

Diagnosis: Posterior urethral valve causing bladder outlet obstruction.

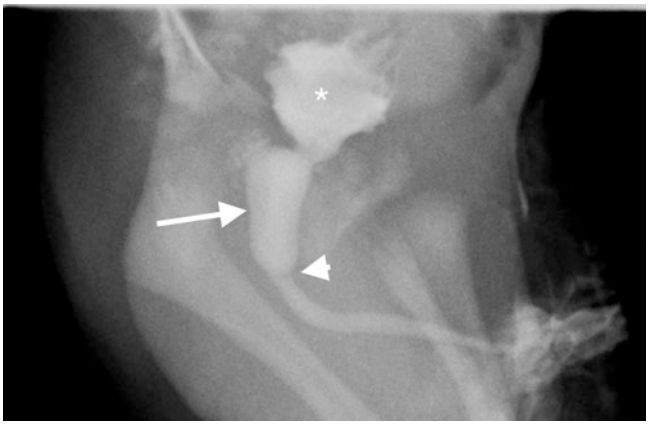


Fig. 32.36

Case 37

16-month-old male with febrile urinary tract infection

Imaging finding (Fig. 32.37): Fluoroscopic voiding cystourethrography demonstrates abnormal reflux of contrast into dilated renal collecting systems bilaterally. There is mild distension and blunting of the renal calyces in the right kidney and moderate distention of the renal pelvis and calyces in the left kidney. The left ureter is also dilated and tortuous.

Diagnosis: Left grade IV and right grade III vesicoureteral reflux.

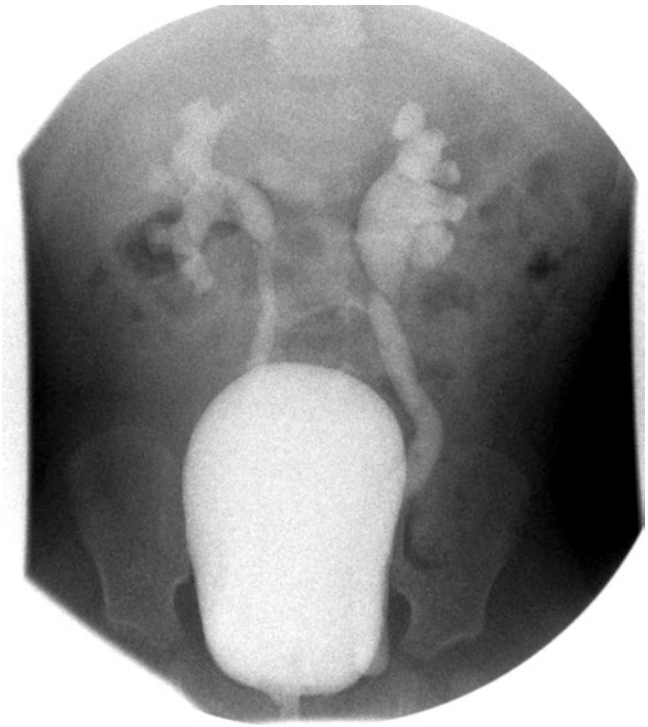


Fig. 32.37

Case 38

1-week-old infant with history of oligohydramnios, presenting with hypertension and bulging flanks on examination

Imaging findings (Fig. 32.38): Ultrasound images of the left and right kidneys (**a**) demonstrate markedly enlarged, echogenic kidneys with diffuse, innumerable small cystic lesions, and loss of corticomedullary differentiation. Coronal T2-weighted, fat-saturated MR image (**b**) shows the extent to which the kidneys occupy a majority of the abdomen.

Diagnosis: Autosomal recessive polycystic kidney disease.

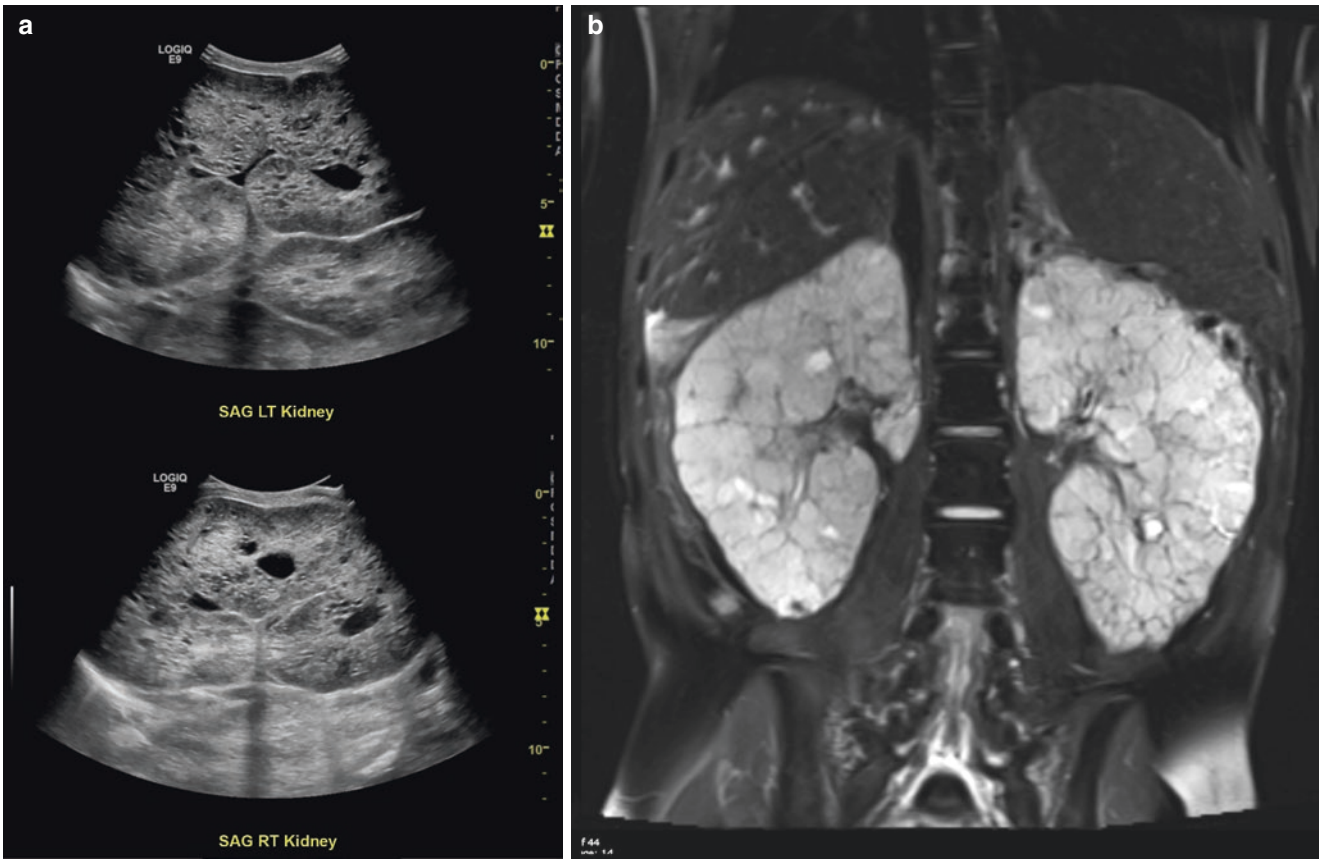


Fig. 32.38

Case 39

3-year-old male with hemihypertrophy presenting with a palpable abdominal mass on examination and an abnormal abdominal ultrasound which prompted further evaluation with contrast-enhanced CT

Imaging findings (Fig. 32.39): Coronal contrast-enhanced CT of the abdomen demonstrates a large, heterogeneous, rounded mass centered at the superior pole of the left kidney (∗). Note the thin rim of renal parenchyma inferiorly (*arrows*) stretching around the mass.

Diagnosis: Wilms tumor.

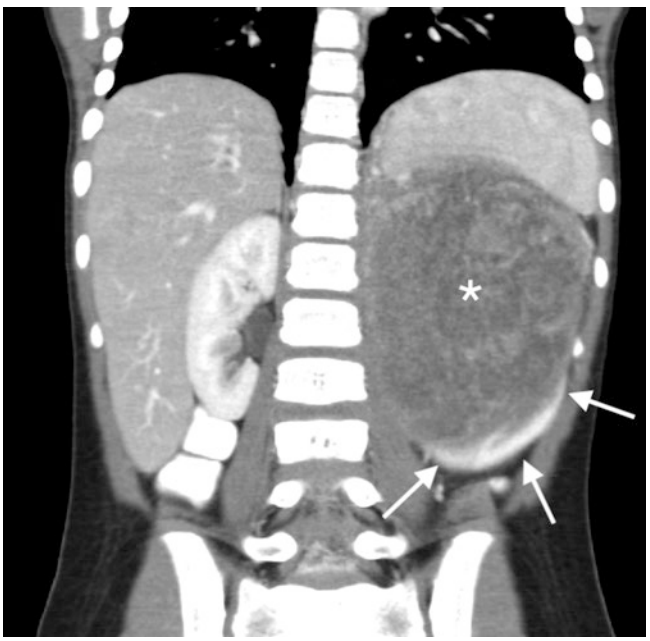


Fig. 32.39

Case 40

Newborn infant with prenatal diagnosis of a left adrenal mass

Imaging findings (Fig. 32.40): Ultrasound image (**a**) demonstrates a left suprarenal mass with complex cystic features and multiple septations (*arrows*). Multiple follow-up ultrasounds were obtained, which showed sequential decrease in size. Follow-up imaging at 9 months of age (**b**) demonstrates complete resolution of the mass.

Diagnosis: Adrenal hemorrhage.

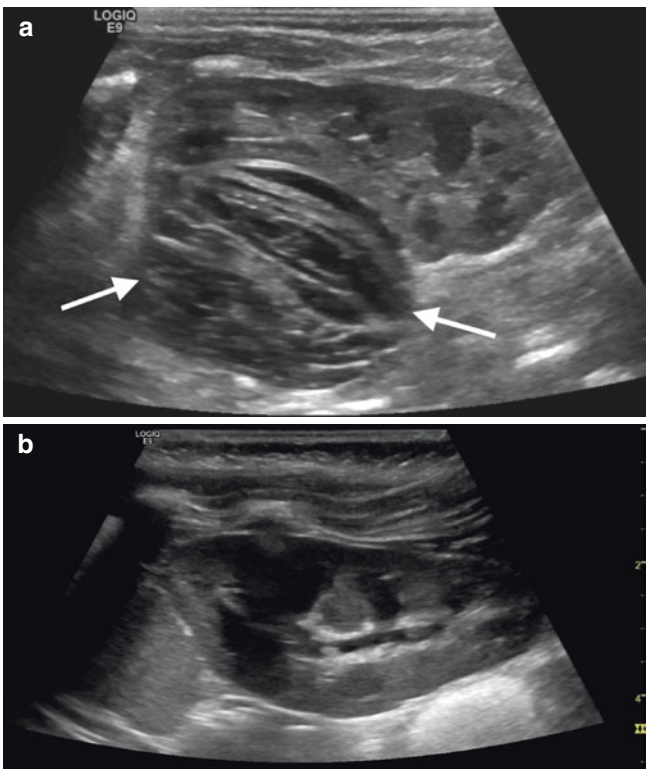


Fig. 32.40

Case 41

15-year-old premenarchal female presenting with recurrent pelvic pain

Imaging findings (Fig. 32.41): Sagittal ultrasound image of the pelvis demonstrates a markedly distended endometrial (∗) and cervical (*arrowhead*) canal with homogeneous echogenic material.

Diagnosis: Hematometrocolpos, in this case secondary to an imperforate hymen.

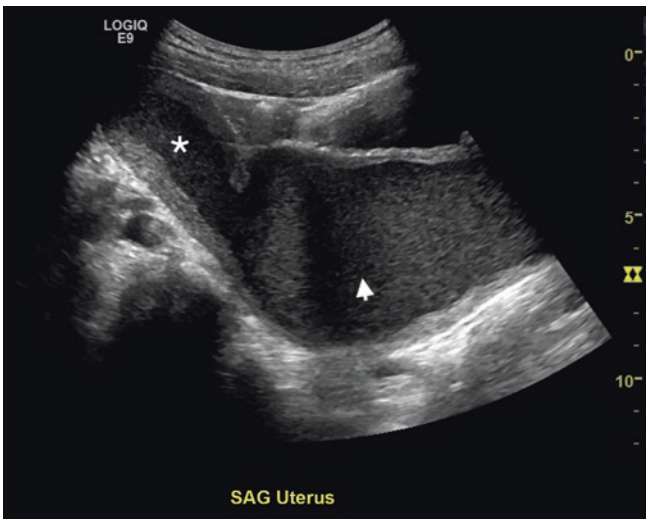


Fig. 32.41

Case 42

15-year-old female presenting with acute-onset right-sided pelvic pain and vomiting

Imaging findings (Fig. 32.42): Transverse ultrasound image of the pelvis (**a**) demonstrates an asymmetrically enlarged and heterogeneously hypoechoic right ovary (*arrow*). Sagittal image of the right ovary (**b**) shows peripheralized follicles (*arrows*) and lack of color Doppler flow.

Diagnosis: Right ovarian torsion.

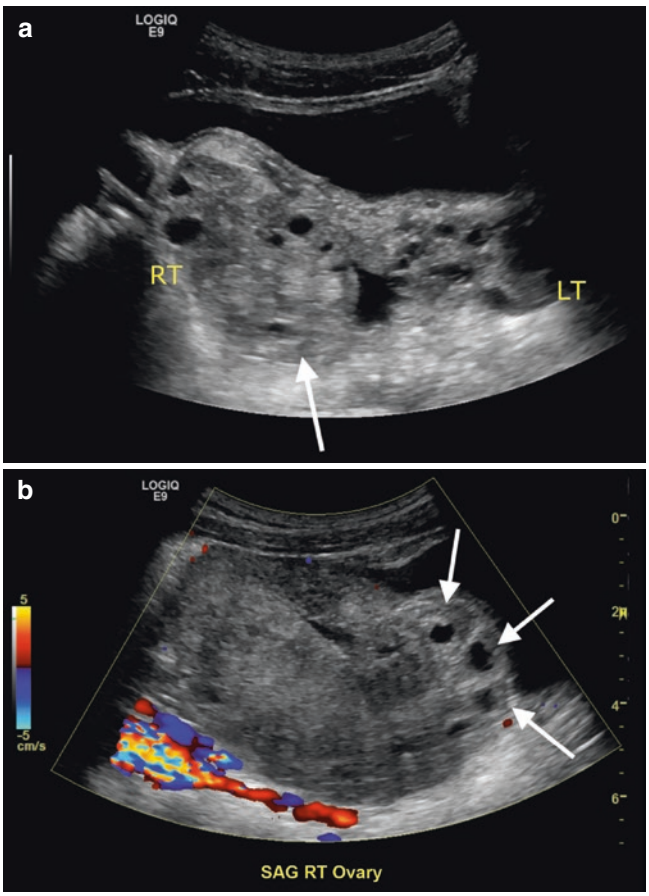


Fig. 32.42

Case 43

12-year-old male presenting with right-sided testicular pain for 4 h

Imaging findings (Fig. 32.43): Transverse ultrasound image of the scrotum (**a**) demonstrates asymmetrically diminished Doppler flow to the right testis (∗). Sagittal ultrasound image of the right scrotum (**b**) demonstrates an abnormal contour of the spermatic cord and epididymal head (*arrow*), indicative of a bell clapper deformity. There is a small associated hydrocele.

Diagnosis: Acute right testicular torsion.

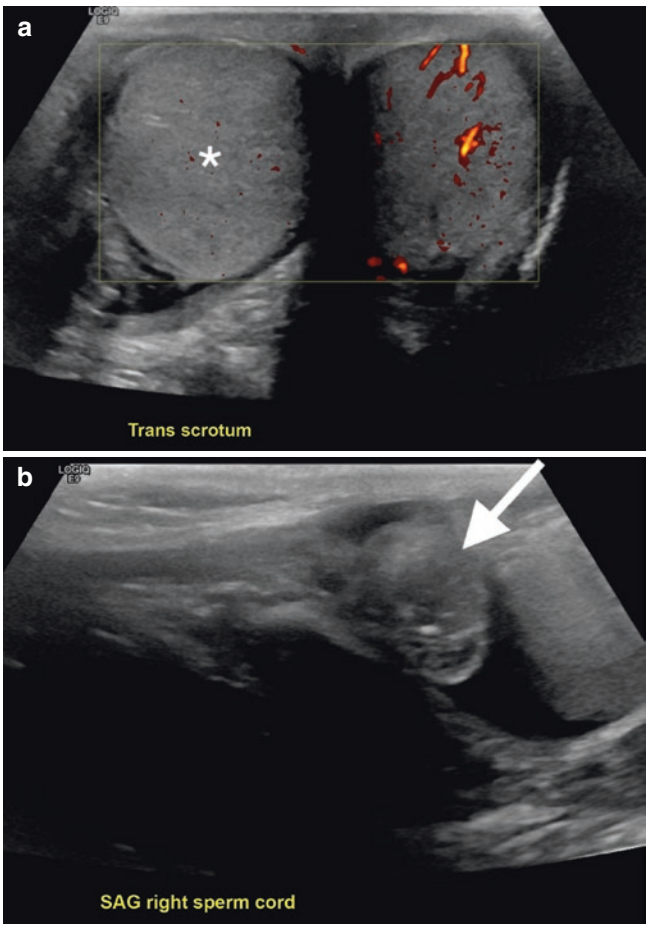


Fig. 32.43

Case 44

19-month-old male presenting with hematuria

Imaging findings (Fig. 32.44): Transverse ultrasound image of the bladder **(a)** demonstrates an intraluminal, exophytic, lobular mass near the base of the bladder. There is color flow within this mass on Doppler ultrasound **(b)**, indicative of vascularity.

Diagnosis: Rhabdomyosarcoma of the bladder.

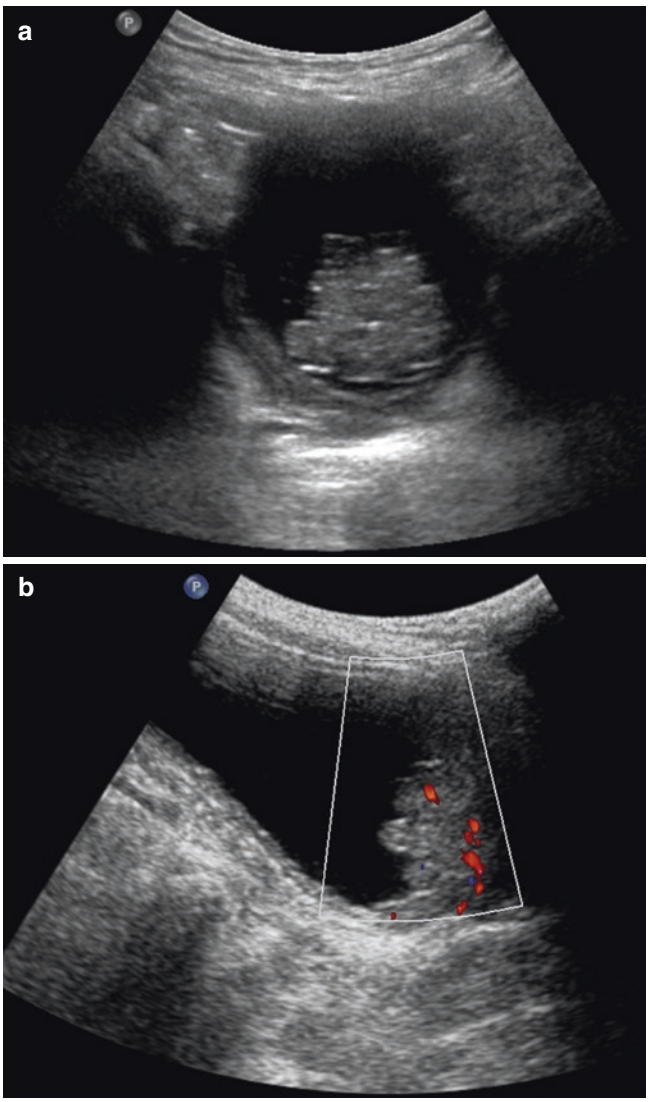


Fig. 32.44

Case 45

16-year-old sexually active female presenting with pelvic pain, fever, and cervical motion tenderness

Imaging findings (Fig. 32.45): Ultrasound image of the pelvis **(a)** demonstrates a complex cystic mass in the left adnexal region (*arrow*). The surrounding mesenteric fat is echogenic, suggestive of adjacent inflammation. Note the normal right ovary (∗). Post-gadolinium enhanced axial T1-weighted MRI of the pelvis (**b**) demonstrates a complex, rim enhancing tubular structure (*arrow*) in the left hemipelvis, with extensive adjacent enhancement.

Diagnosis: Tubo-ovarian abscess.

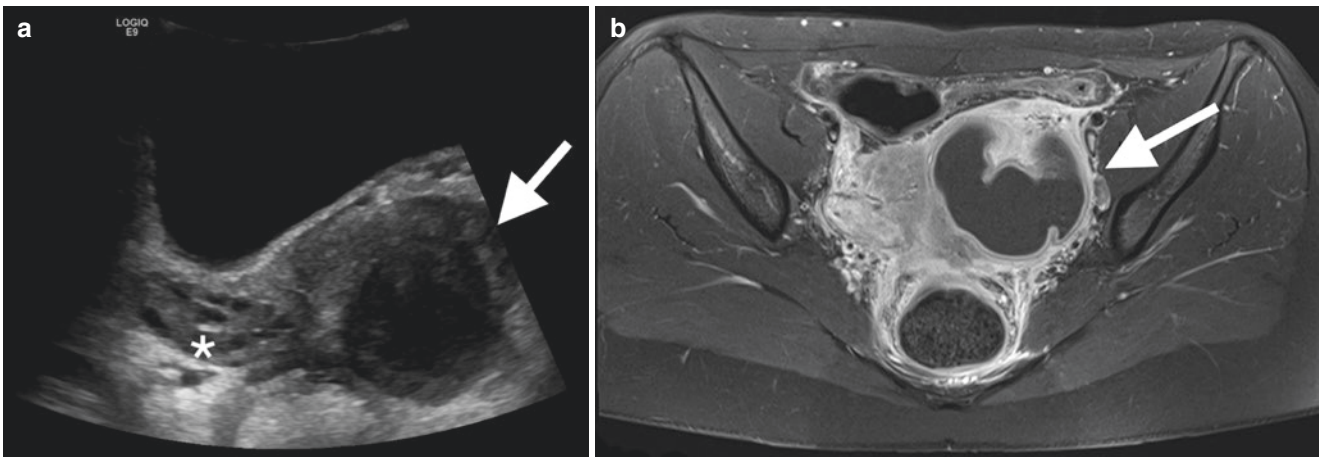


Fig. 32.45

MUSCULOSKELETAL RADIOLOGY

Case 46

12-year-old male with ankle pain after a basketball injury

Imaging findings (Fig. 32.46): Frontal and lateral radiographs of the ankle demonstrate an oblique lucency through the tibial metaphysis (*arrows*). On the lateral view, there is clear widening of the physis anteriorly (*arrowhead*). No epiphyseal component is appreciated.

Diagnosis: Salter Harris II fracture.

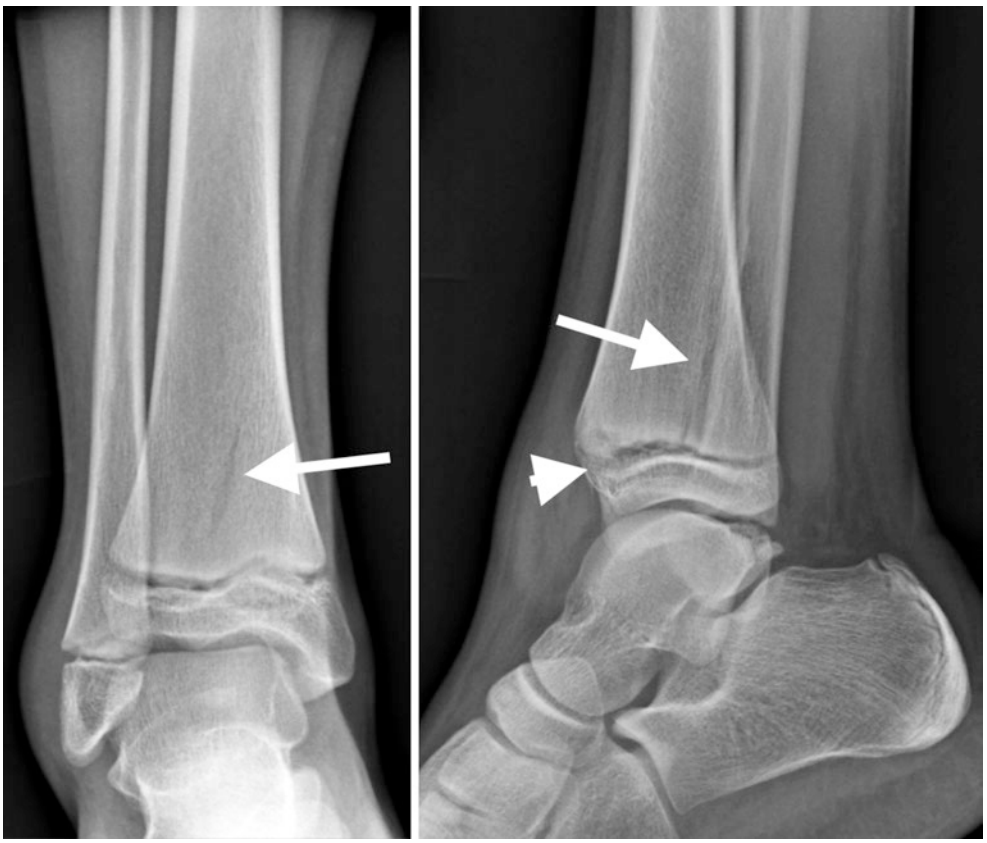


Fig. 32.46

Case 47

15-month-old female presenting to the emergency room with fussiness, with multiple bruises noted on physical examination

Imaging findings (Fig. 32.47): Frontal radiograph (**a**) of the right wrist demonstrates triangular bone fragments along the lateral aspect of the distal radial metaphysis and medial aspect of the distal ulnar metaphysis (*arrows*), in keeping with corner fractures. Lateral radiograph (**b**) shows the radial fracture extending to both the anterior and posterior corners of the distal radius (*arrowheads*), which has a "bucket-handle" appearance. This patient had similar appearing fractures in the tibia as well. Towne view of the skull (c) in the same patient shows a left occipital fracture.

Diagnosis: Non-accidental trauma with classic metaphyseal lesions and skull fracture.

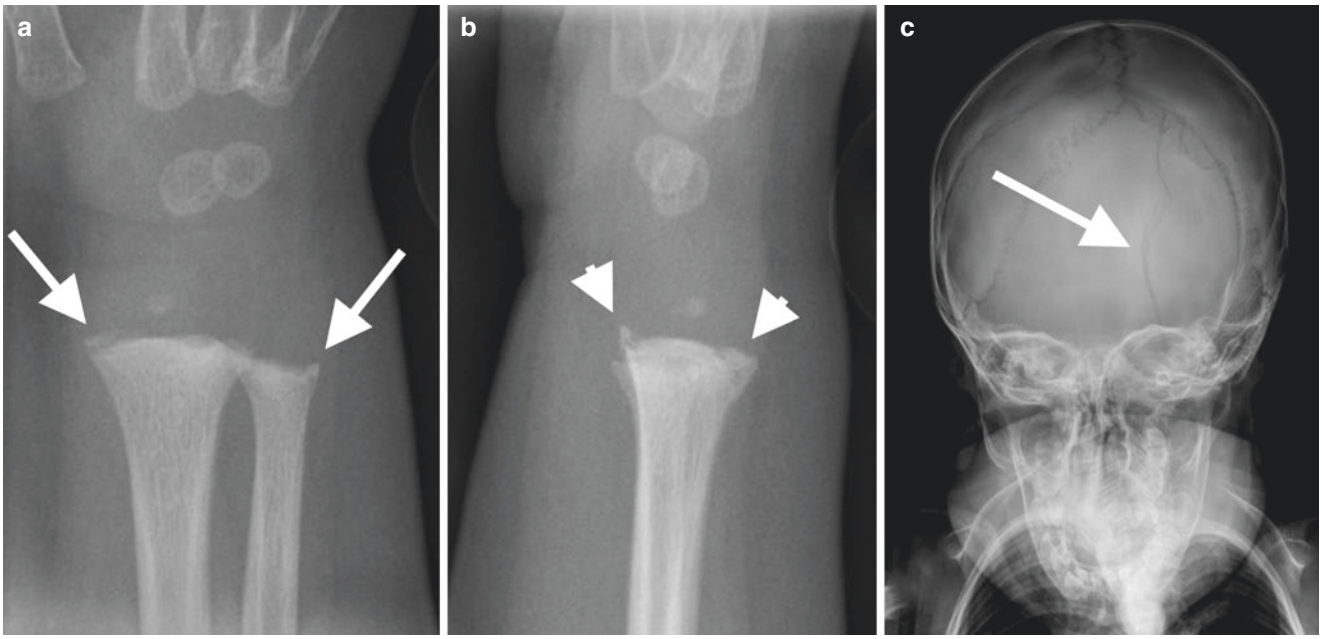


Fig. 32.47

Case 48

4-year-old female with a history of multiple fractures

Imaging findings (Fig. 32.48): Frontal radiograph of the hips and lower extremities demonstrates numerous healed fractures of the right iliac wing, femoral shafts, and distal tibial diaphysis bilaterally (*arrows*). The bones are diffusely demineralized with thinning of the cortex. Numerous growth arrest lines are present (∗).

Diagnosis: Osteogenesis imperfecta.

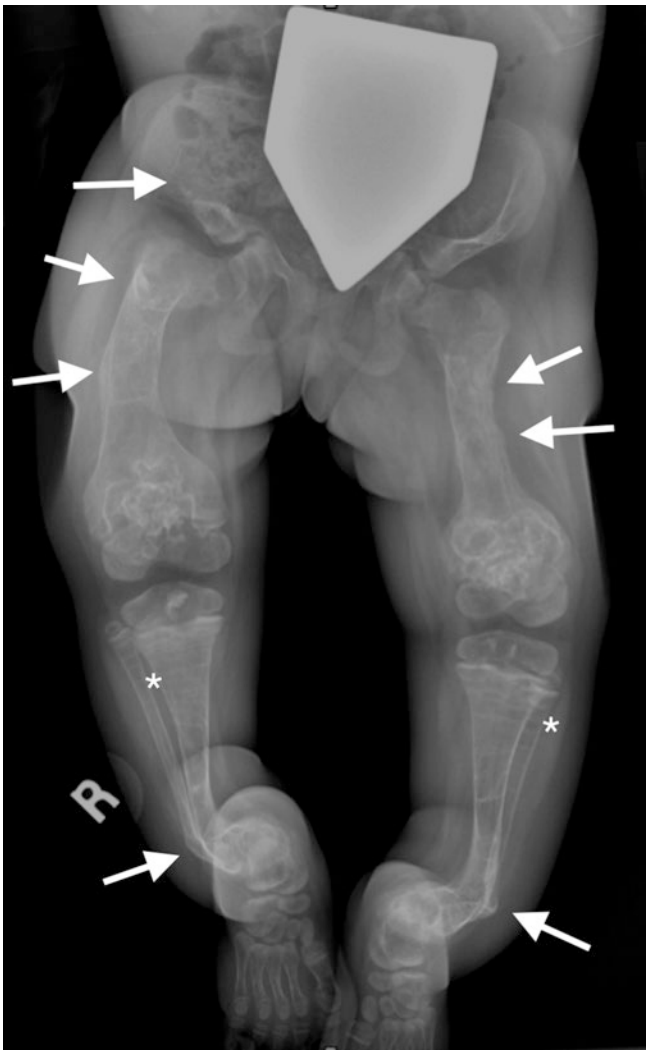


Fig. 32.48

Case 49

17-month-old female presenting to the emergency room with fevers and right knee warmth

Imaging findings (Fig. 32.49): Frontal radiograph of the right knee (**a**) demonstrates a subtle lucency in the medial distal femoral metaphysis (*arrow*). T1 weighted coronal MRI (**b**) of the right knee demonstrates loss of normal fatty signal in the same region (*arrow*). This is accompanied by high signal on the T2-weighted MRI (**c**), indicative of marrow edema (*arrow*). Additional edema is noted in the overlying soft tissues and medial epiphysis (*arrowheads*).

Diagnosis: Acute osteomyelitis.

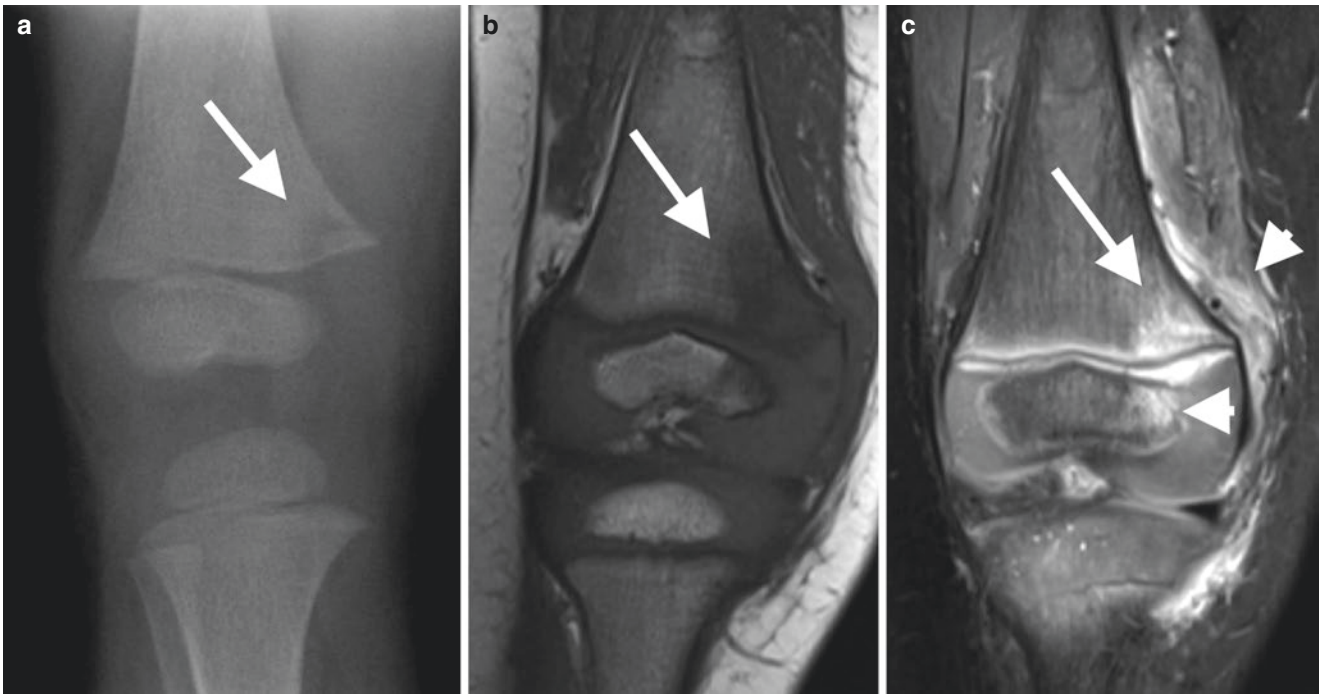


Fig. 32.49

Case 50

2-year-old male with history of chronic renal disease presenting with weakening grip

Imaging findings (Fig. 32.50): Frontal radiographs of the wrists demonstrates fraying, cupping, and expansion of the distal radial and ulnar metaphyses bilaterally (*arrows*).

Diagnosis: Rickets.

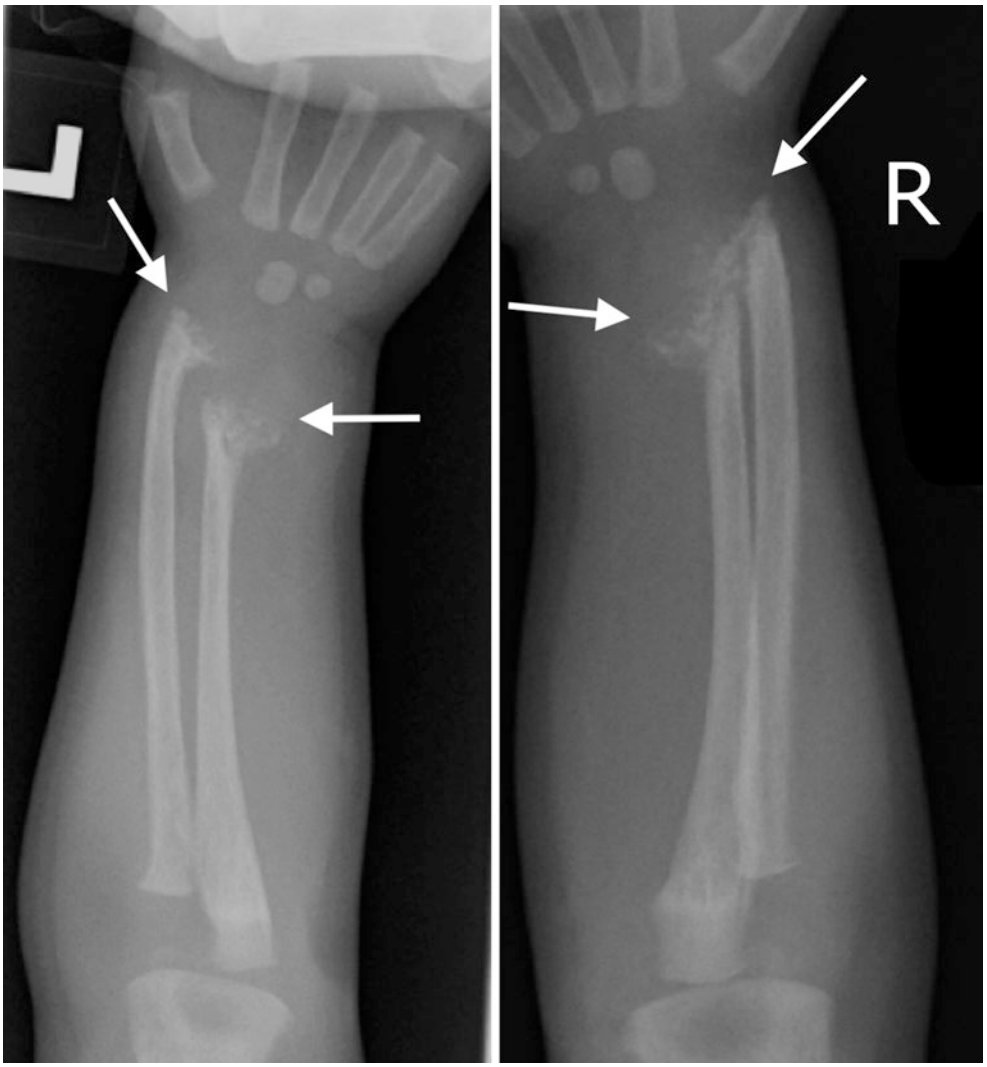


Fig. 32.50

Case 51

7-year-old male with worsening, gradual right thigh pain

Imaging findings (Fig. 32.51): Frontal radiograph of the right thigh (**a**) demonstrates a permeative, moth-eaten diaphyseal bone lesion (*arrow*) with poorly defined margins, aggressive appearing periosteal reaction along the lateral cortex (*arrowhead*) and large soft tissue component (∗). No internal matrix is appreciable. Axial, contrast-enhanced MRI (**b**) demonstrates a large surrounding soft tissue mass with robust enhancement (*arrows*)**.**

Diagnosis: Ewing sarcoma.

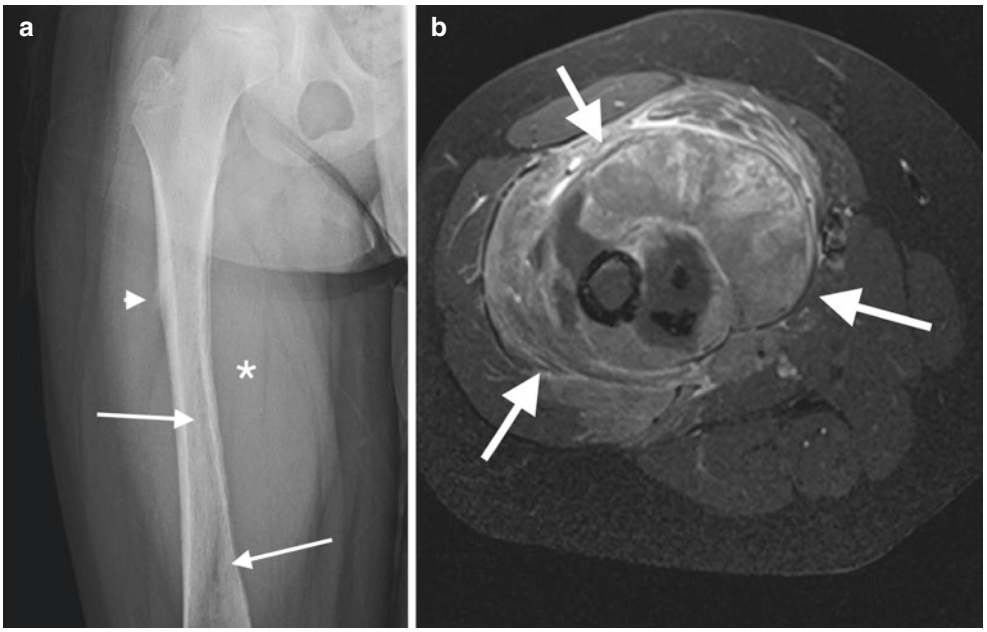


Fig. 32.51

Case 52

8-year-old male with worsening right knee pain and no reported trauma

Imaging findings (Fig. 32.52): Frontal and lateral radiographs of the distal left femur demonstrate an aggressive, permeative lesion with a wide zone of transition between normal and abnormal marrow. There is an aggressive, hair-on-end periosteal reaction along the posteromedial metaphysis of the distal femur (*arrow*), and the periosteum has been lifted from the bone (Codman's triangle, *arrowhead*). Dense, amorphous calcific matrix is present (∗) in the lesion.

Diagnosis: Osteosarcoma.

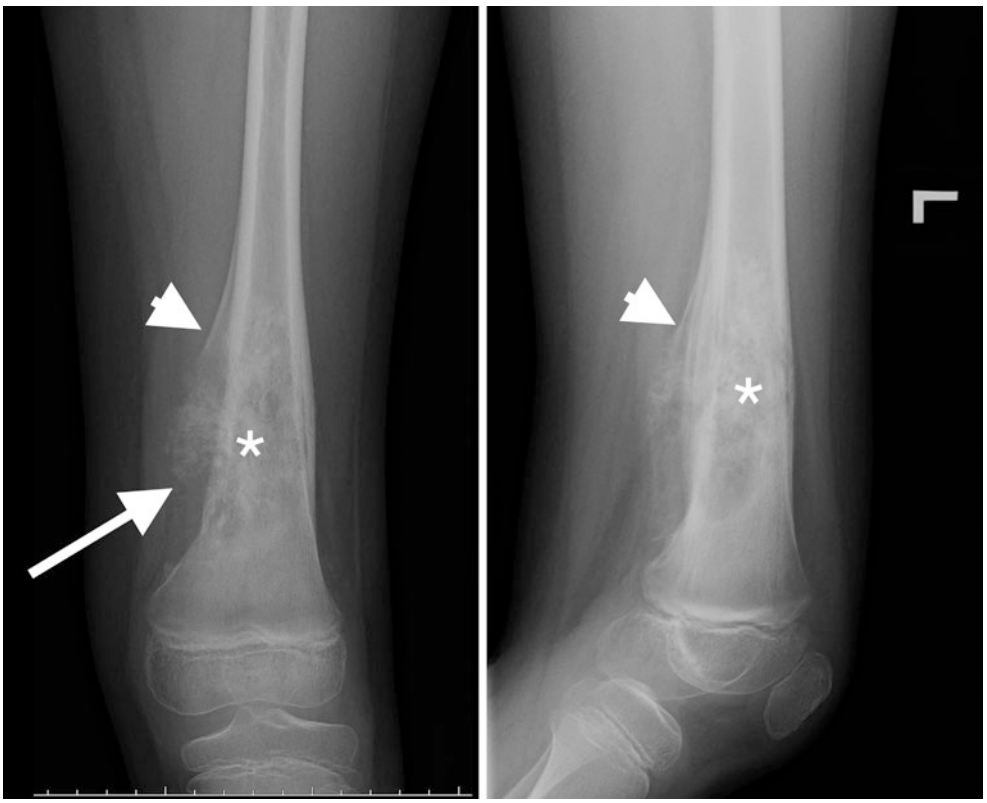


Fig. 32.52

Case 53

11-year-old female with painless, firm, palpable lump of the left lower thigh

Imaging findings (Fig. 32.53): Frontal radiograph of the left knee demonstrates a protuberant bone lesion arising from the medial metaphysis of the distal femur. The lesion is oriented away from the joint space and is in continuity with the bone. There is no soft tissue component or periosteal reaction.

Diagnosis: Osteochondroma.

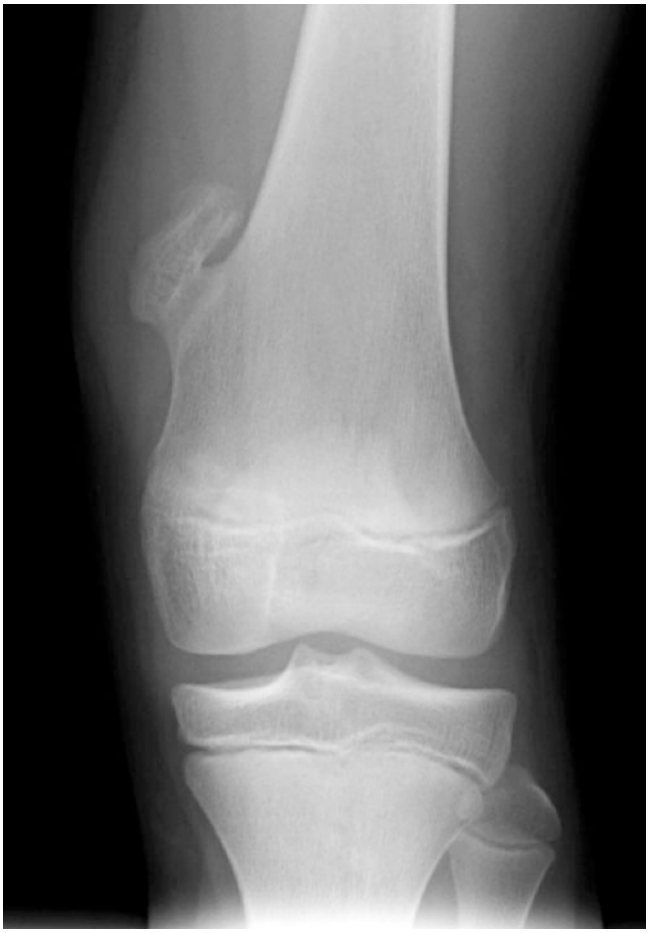


Fig. 32.53

Case 54

17-year-old male with worsening left ankle pain and no antecedent trauma

Imaging findings (Fig. 32.54): Frontal radiograph (**a**) of the left ankle demonstrates an expansile, lucent lesion of the distal fibula (∗). There is a narrow zone of transition proximally (*arrowhead*). No soft tissue component or periosteal reaction is present. Sagittal, fluid sensitive MRI (**b**) of the distal left fibula demonstrates numerous fluid–fluid levels within the lesion (*arrow*).

Diagnosis: Aneurysmal bone cyst.

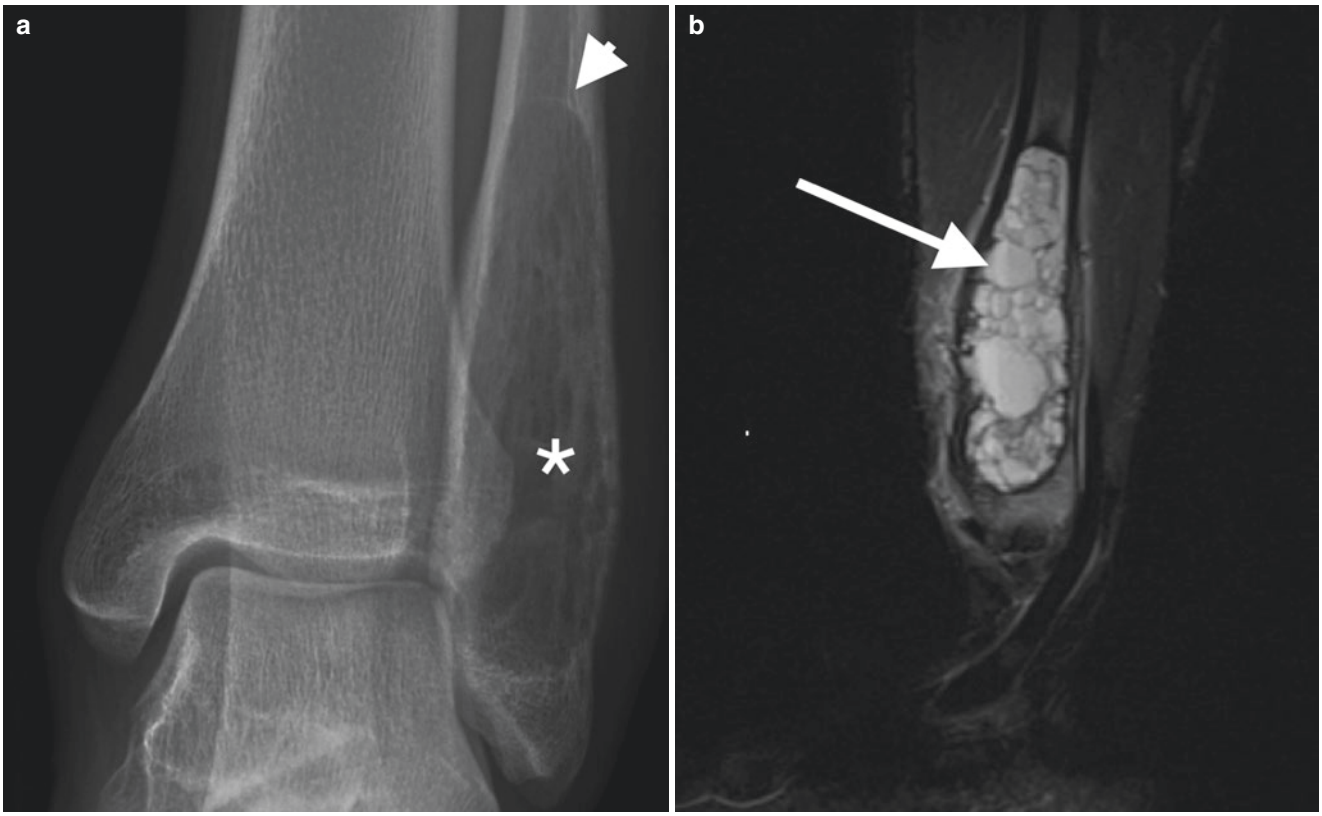


Fig. 32.54

Case 55

4-year-old female with short stature

Imaging findings (Fig. 32.55): Frontal radiograph of the abdomen and pelvis (**a**) demonstrates narrowing rather than widening of the interpeduncular distances of the lower lumbar spine (*arrowheads*). There iliac wings are broad (*arrow*) and the pelvis narrows sharply (∗). Frontal radiograph of the hand (**b**) demonstrates short, broad metacarpals with irregular metaphyses (*arrow*) and splaying of the digits.

Diagnosis: Achondroplasia.

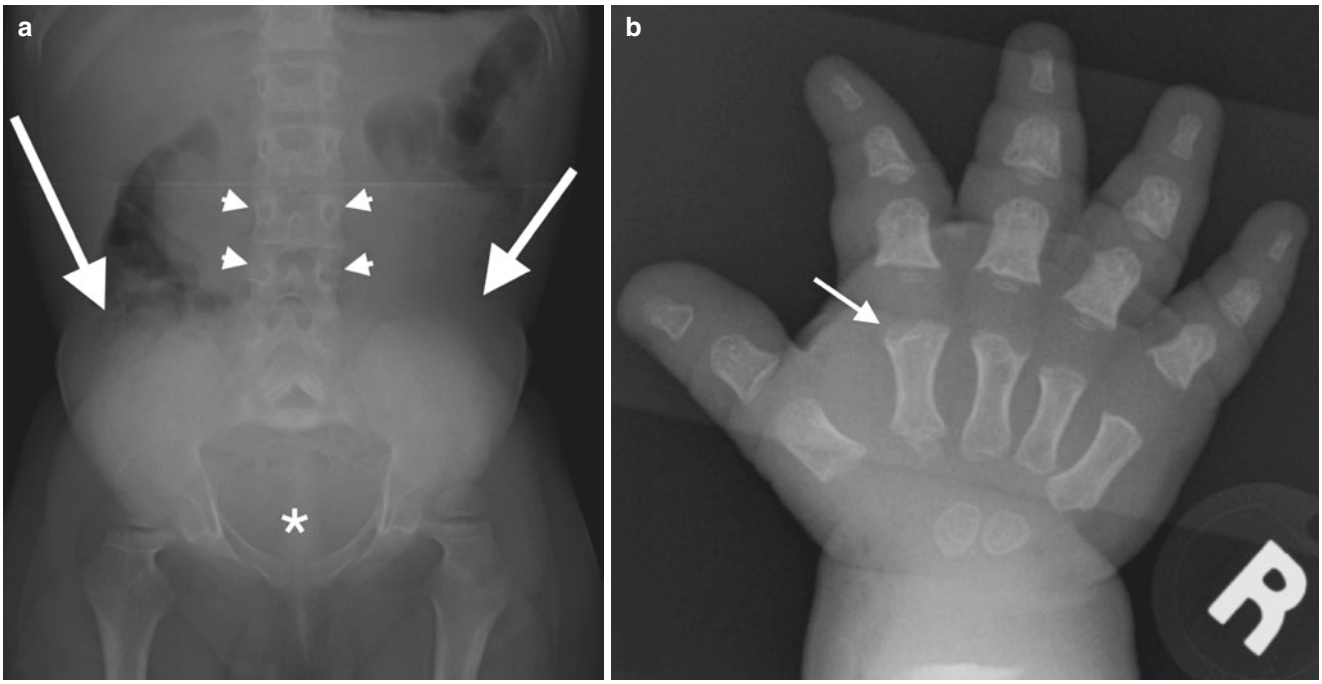


Fig. 32.55

Case 56

8-year-old male with fall on an outstretched hand

Imaging findings (Fig. 32.56): Lateral radiograph of the elbow demonstrates linear lucency through the anterior cortex of the distal humerus (*arrow*). The posterior fat pad is displaced from the olecranon fossa (*arrowhead*), indicative of joint effusion.

Diagnosis: Supracondylar fracture.

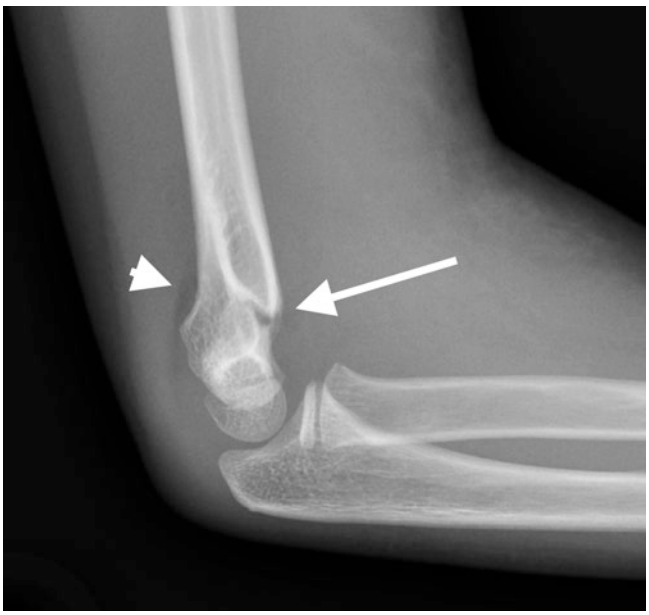


Fig. 32.56

Case 57

11-day-old infant with torticollis to the left

Imaging findings (Fig. 32.57): High frequency gray-scale ultrasound of the right and left neck demonstrates asymmetric enlargement of the right sternocleidomastoid muscle (∗).

Diagnosis: Fibromatosis colli.

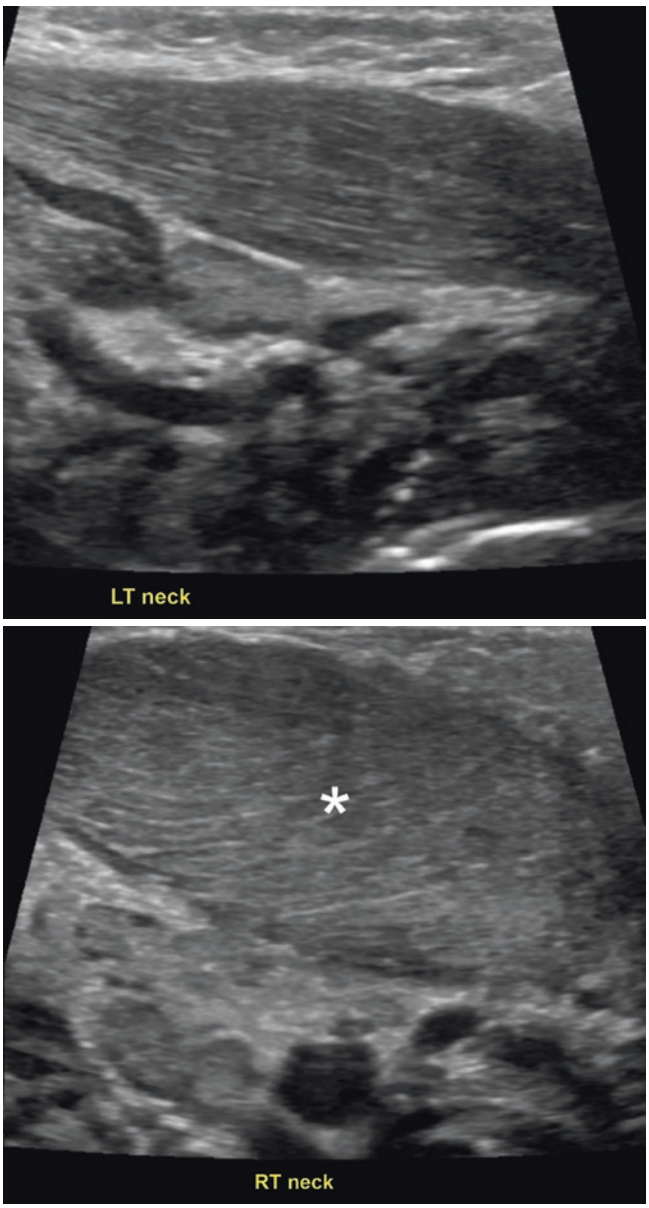


Fig. 32.57

Case 58

9-year-old male with a fall on an outstretched hand

Imaging findings (Fig. 32.58): Frontal radiograph of the elbow demonstrates abnormal medial and inferior positioning of the medial epicondyle (*arrow*). There is subcutaneous edema over the medial aspect of the elbow (∗). The lateral epicondyle (*arrowhead)* is also abnormally laterally positioned.

Diagnosis: Avulsion of the medial and lateral epicondyles of the elbow.

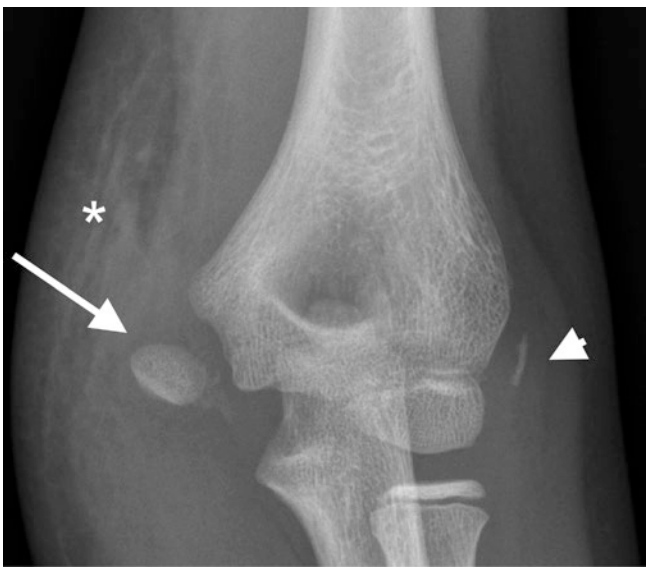


Fig. 32.58

Case 59

16-year-old male who complains of right hip pain after sustaining an injury while playing hockey and is unable to flex the right hip on examination

Imaging findings (Fig. 32.59): Frontal radiograph of the pelvis demonstrates a small fragment adjacent to the right anterior superior iliac spine (*arrow*)**.**

Diagnosis: Apophyseal avulsion fracture of the right anterior superior iliac spine, at the attachment of the sartorius tendon.

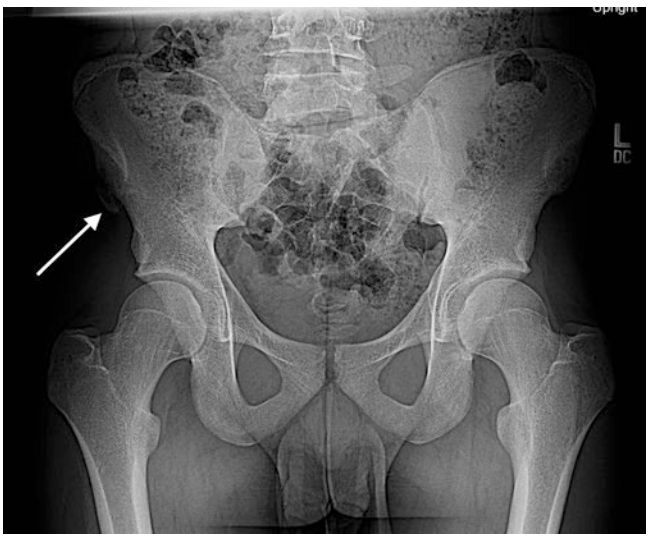


Fig. 32.59

NEURORADIOLOGY

Case 60

1-day-old infant born at 25 weeks gestational age presenting with seizures and drop in hematocrit level

Imaging findings (Fig. 32.60): Anterior fontanel approach coronal gray-scale ultrasound image of the brain demonstrates enlarged lateral and third ventricles, with large volume echogenic material (∗) predominantly within the right lateral ventricle. There is also abnormal echogenicity of the right frontal periventricular white matter (*arrow*), indicative of parenchymal hemorrhage with evolving leukomalacia. Notice also the diffusely echogenic ependymal lining, suggestive of chemical ventriculitis.

Diagnosis: Grade IV intraventricular hemorrhage.

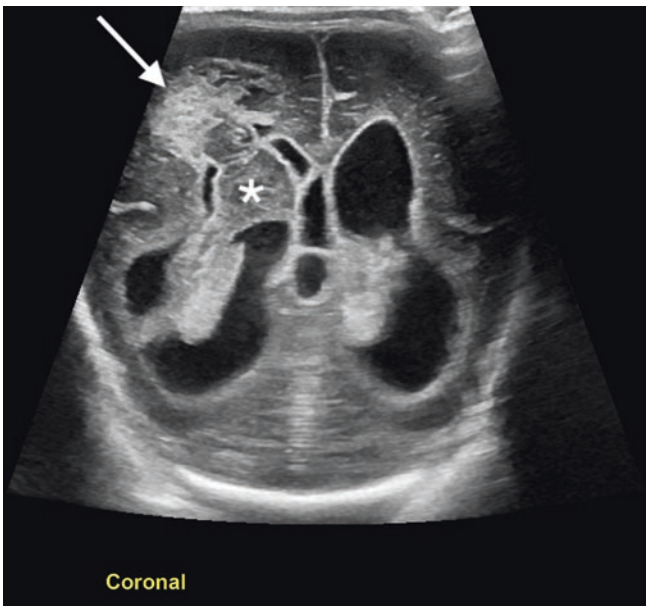


Fig. 32.60

Case 61

Newborn infant with a sacral dimple on exam

Imaging findings (Fig. 32.61): Sagittal ultrasound image of the spine **(a)** demonstrates a low-lying conus medullaris terminating at the sacral level with thickened and echogenic appearance of the filum terminale (*arrow*). Sagittal T2-weighted MRI of the spine (**b**) better demonstrates a soft tissue mass with fat signal (*arrow*) between the low-lying conus and the terminus of the thecal sac.

Diagnosis: Tethered cord with a terminal lipoma.

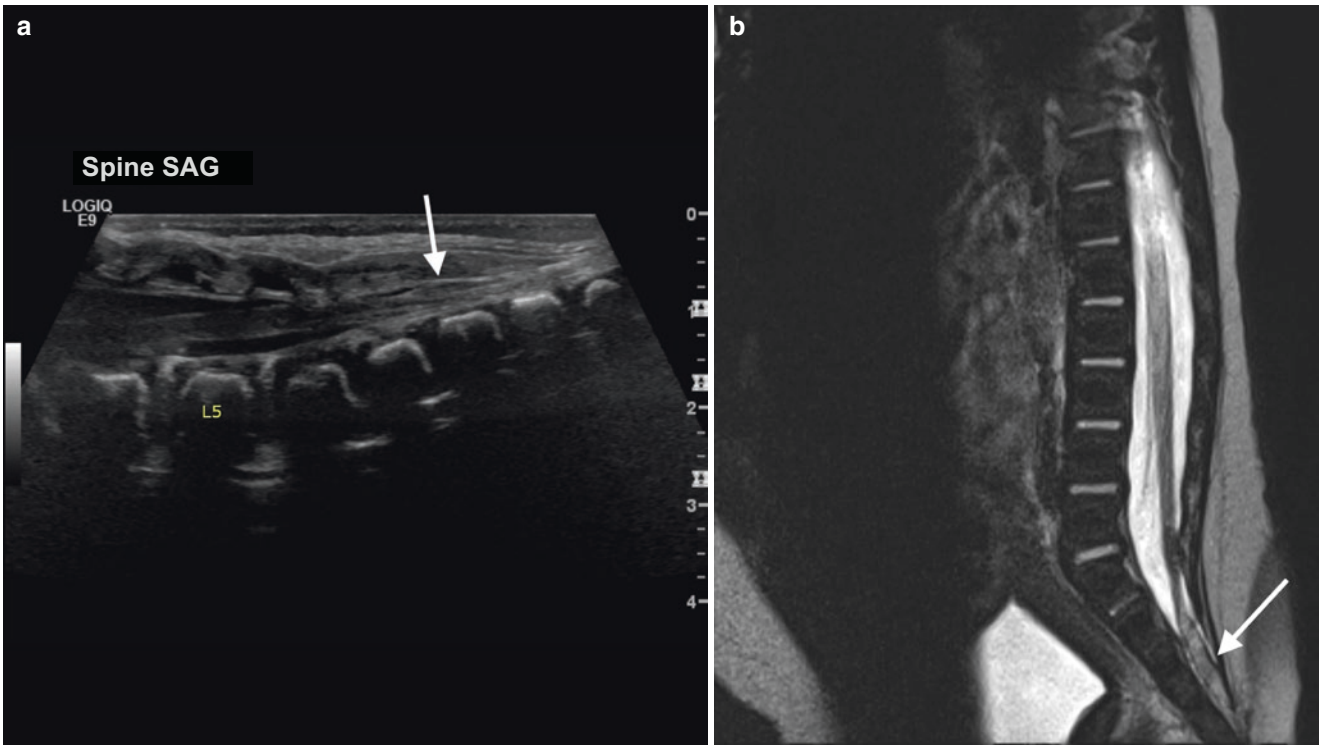


Fig. 32.61

Case 62

5-year-old male presenting with neck pain, stiffness, fever, and difficulty swallowing

Imaging findings (Fig. 32.62): Lateral radiograph of the neck (**a**) demonstrates abnormal thickening of the retropharyngeal soft tissues (∗), larger than the width of a cervical vertebral body. There is also adenoid enlargement causing narrowing of the nasopharynx (*arrow*). This prompted a contrast-enhanced CT of the neck (**b**), which shows a peripherally enhancing, low density collection extending along the retropharyngeal soft tissues (∗).

Diagnosis: Retropharyngeal abscess.

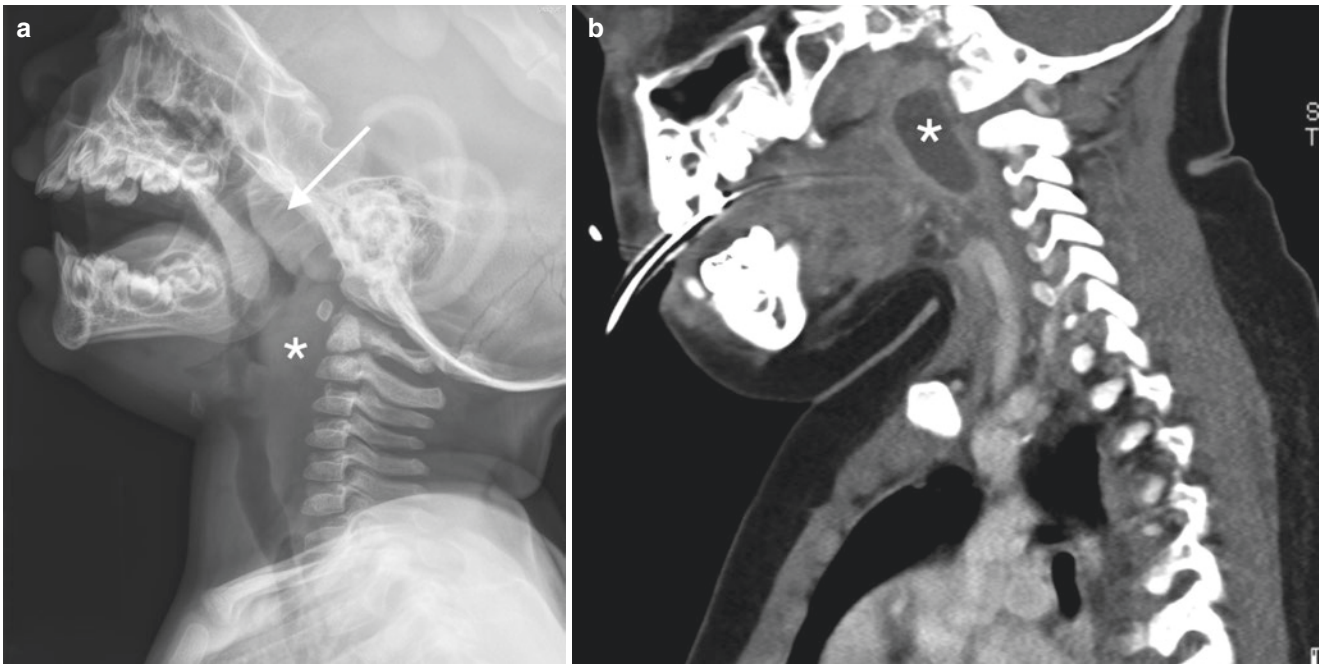


Fig. 32.62

Case 63

5-year-old male with multiple cutaneous neurofibromas and café-au-lait spots presenting with arm weakness and palpable left neck mass

Imaging findings (Fig. 32.63): Coronal MRI of the cervical spine demonstrates multiple lobular hyperintense lesions extending from the neural foramina along the nerve roots bilaterally, larger on the left side.

Diagnosis: Bilateral cervical and brachial plexus plexiform neurofibromas in the setting of neurofibromatosis type 1.

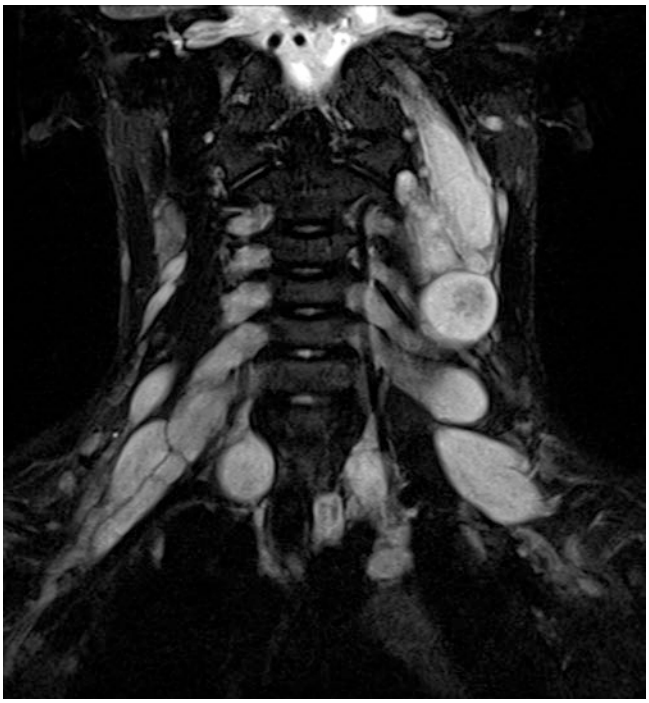


Fig. 32.63

Case 64

9-month-old male with facial port wine stain and intractable seizures

Imaging findings (Fig. 32.64): Axial CT of the brain (**a**) shows cortical and subcortical mineralization in the bilateral posterior parietal and occipital lobes (*arrows*). Axial T2-weighted MRI (**b**) demonstrates associated parenchymal volume loss. Axial susceptibility weighted MRI (**c**) better shows the distribution of predominantly subcortical mineralization.

Diagnosis: Sturge–Weber syndrome.

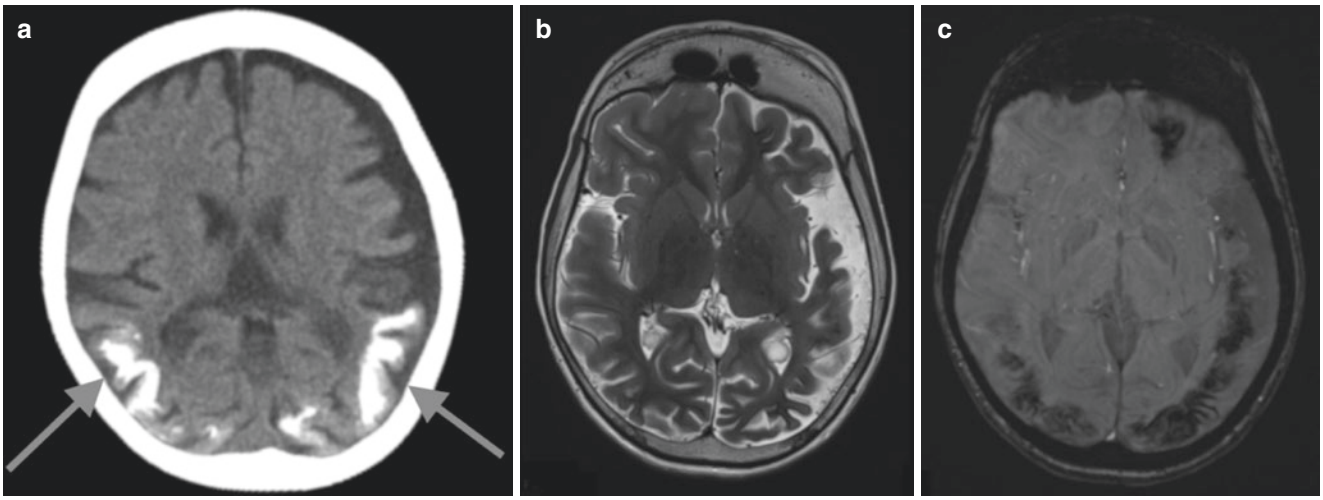


Fig. 32.64

Case 65

5-day-old infant with prenatal history of multiple cardiac and brain lesions

Imaging findings (Fig. 32.65): Axial T1-weighted inversion recovery MRI of the brain shows multiple hyperintense subependymal nodules along the bilateral lateral ventricles (*arrows*). There are also multiple areas of cortical and subcortical thickening and hyperintensity, indicative of cortical tubers (∗).

Diagnosis: Tuberous sclerosis complex.

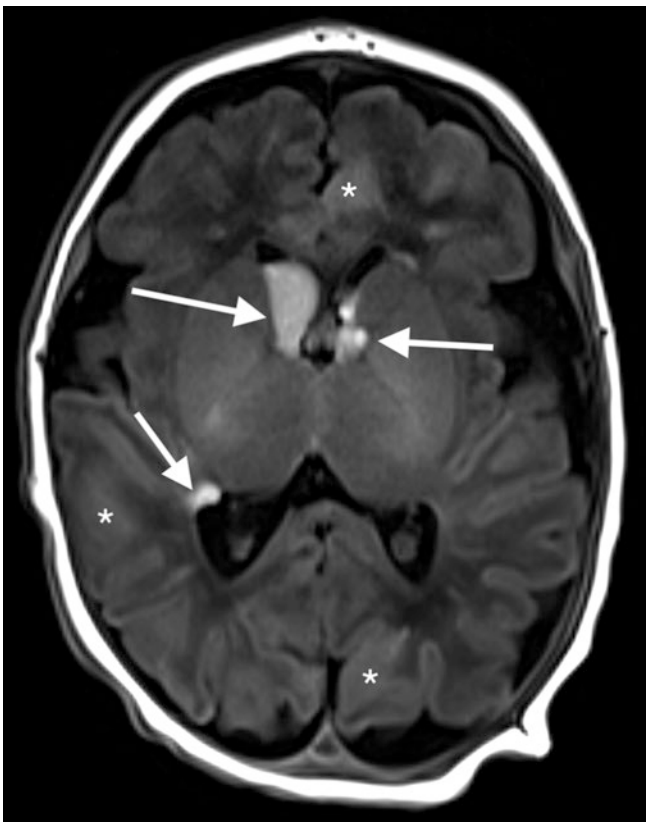


Fig. 32.65

Case 66

Newborn infant with congenital hydrocephalus and macrocephaly

Imaging findings (Fig. 32.66): Axial and sagittal MRI of the brain (**a, b)** demonstrates severe hydrocephalus with marked dilatation of the lateral and third ventricles (∗). The cerebral aqueduct is not patent (*arrow*). Note is also made of dysgenesis of the corpus callosum, a Z-shaped configuration of the brainstem, and inferior vermian hypoplasia.

Diagnosis: Non-communicated hydrocephalus due to aqueductal stenosis, in the setting of Walker–Warburg syndrome.

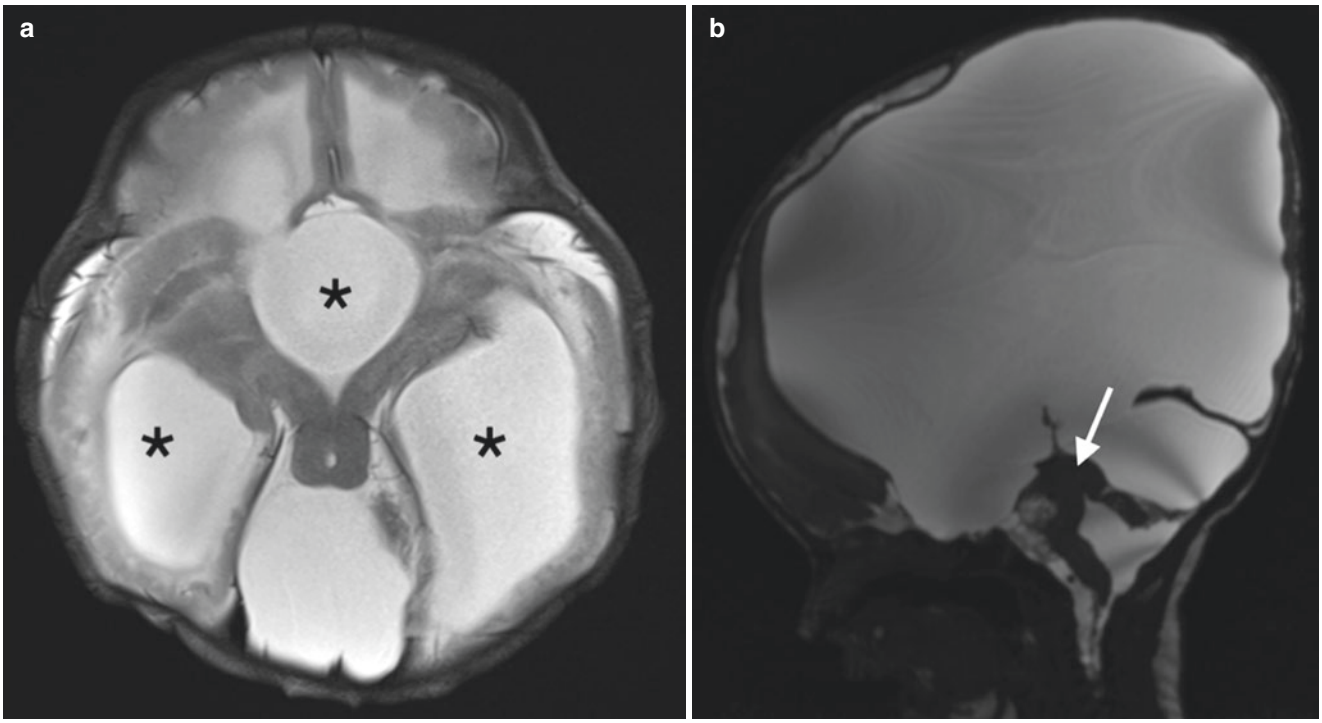


Fig. 32.66

Case 67

15-year-old male who sustained an asphyxiation/strangulation event and subsequent cardiac arrest

Imaging findings (Fig. 32.67): Axial and sagittal CT of the brain (**a, b)** demonstrates profound cerebral and cerebellar swelling with uncal, transtentorial, and tonsillar herniation. Note the loss of gray white matter differentiation, loss of extra-axial spaces, and also the more pronounced focal low-attenuation in the deep gray nuclei (*arrows*). Axial diffusion-weighted MRI of the brain (**c**) demonstrates symmetrically decreased diffusivity involving the cortex, caudate, basal ganglia, and thalami, indicating diffuse ischemic change.

Diagnosis: Global hypoxic ischemic injury.

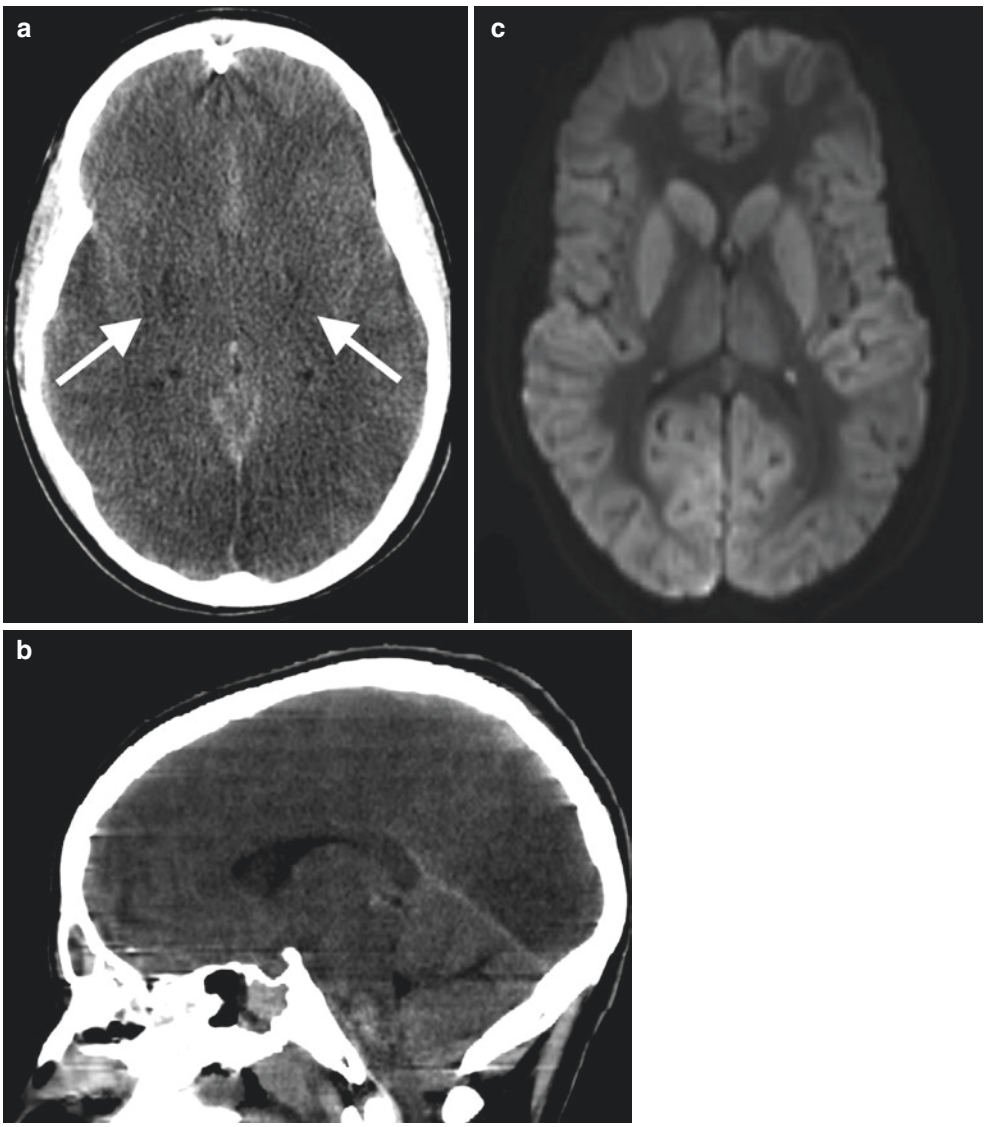


Fig. 32.67

Case 68

5-year-old child who fell off his bike and hit his head

Imaging findings (Fig. 32.68): Axial CT of the brain in bone (**a**) and soft tissue (**b**) windows demonstrate a non-displaced right parietal bone fracture (*arrow*) with an overlying scalp hematoma. There is a subjacent biconvex hyperdense collection (∗) causing mild mass effect on the brain with slight midline shift toward the left.

Diagnosis: Skull fracture with an epidural hematoma.

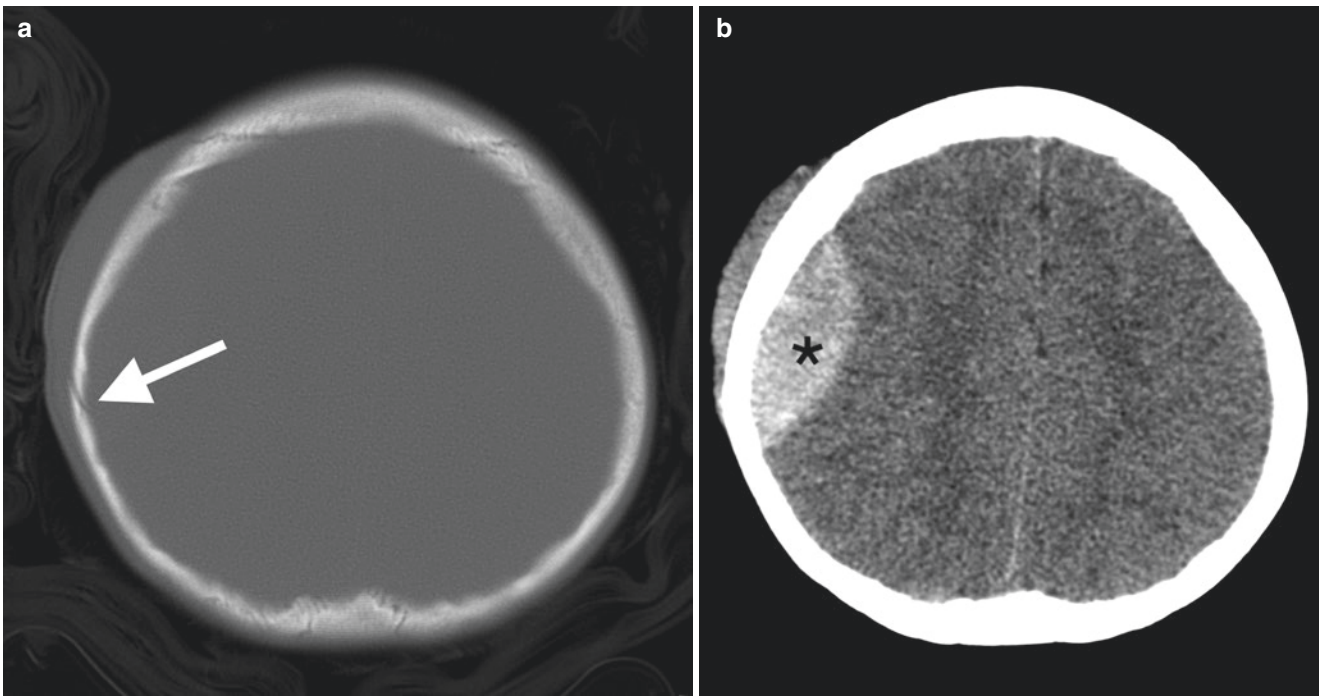


Fig. 32.68

Case 69

4-year-old female presenting with several weeks of headaches and gait instability

Imaging findings (Fig. 32.69): Axial CT of the brain (**a**) demonstrates a large mass lesion centered within the left cerebellar hemisphere and crossing the midline (*arrows*). There is resultant acute obstructive supratentorial hydrocephalus with transependymal edema (∗). Post-contrast axial MRI (**b**) shows the cystic and solid components of the tumor in the posterior fossa.

Diagnosis: Juvenile pilocytic astrocytoma.

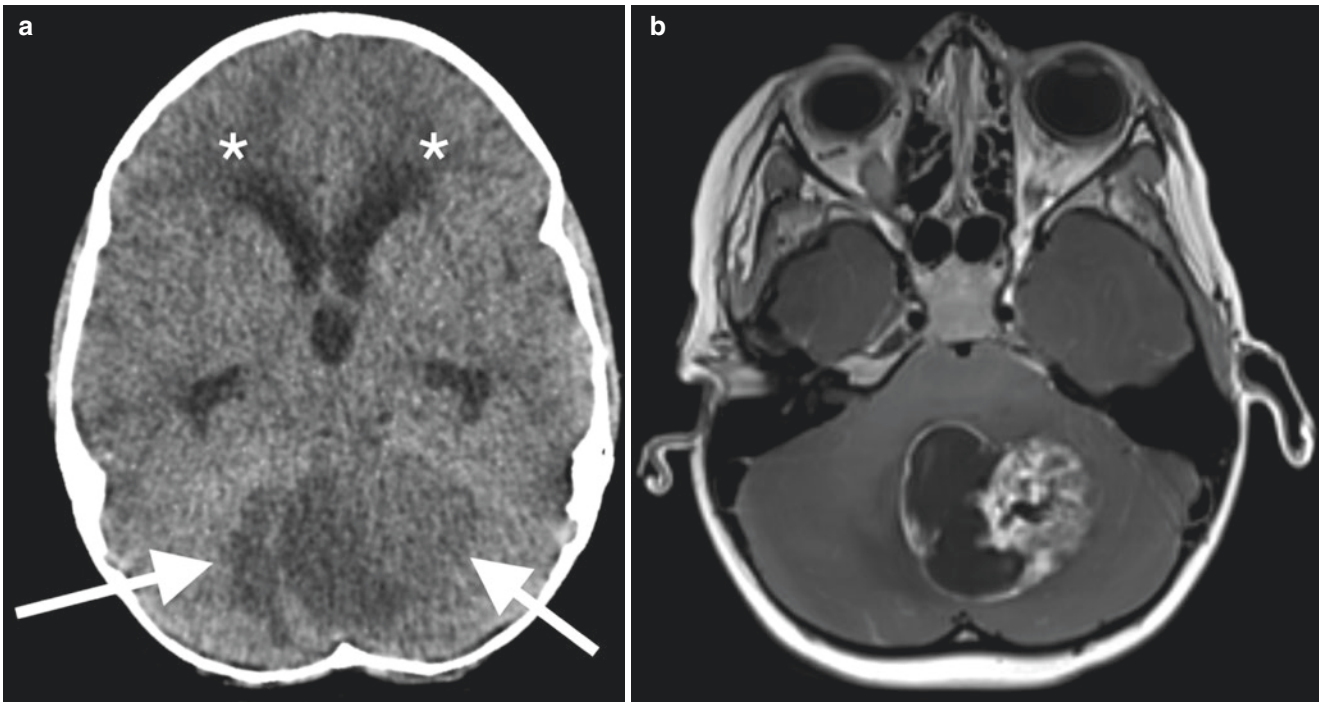


Fig. 32.69

Case 70

17-year-old male presenting with headache and bitemporal visual field defect

Imaging findings (Fig. 32.70): Sagittal contrast-enhanced MRI of the brain demonstrates a mildly enhancing, solid, sellar mass (∗) expanding the sella (*arrow*) and extending into the suprasellar cistern, exerting mass effect upon the optic chiasm.

Diagnosis: Pituitary adenoma.

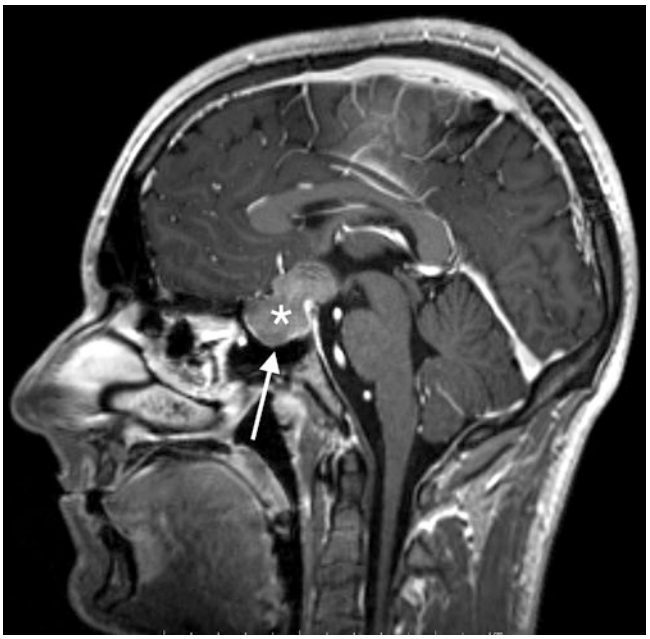


Fig. 32.70

Case 71

1-day-old infant born via spontaneous vaginal delivery presenting with apneic episodes

Imaging findings (Fig. 32.71): Axial diffusion-weighted MRI of the brain shows geographic diffusion restriction of the entire left middle cerebral artery (MCA) territory, including the thalamus, lentiform nucleus, and internal capsule.

Diagnosis: Acute left MCA territory infarction.

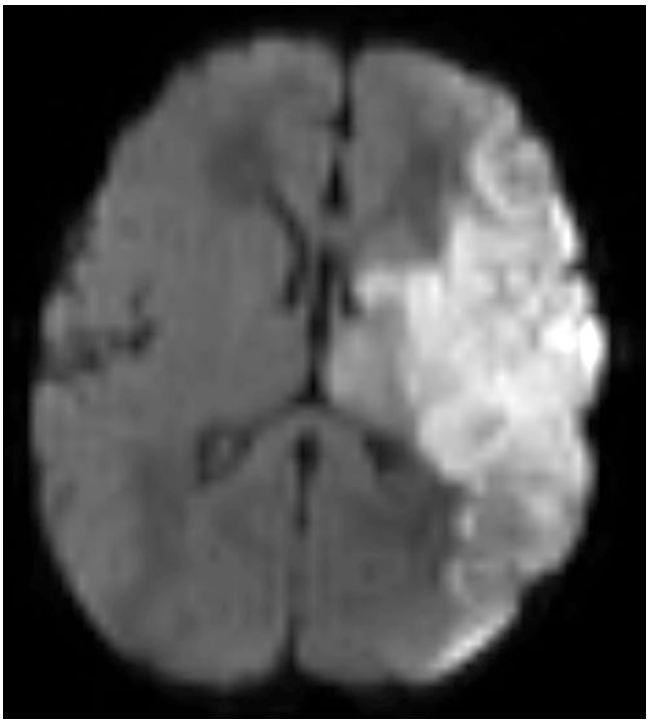


Fig. 32.71

Case 72

Newborn infant presenting with high output congestive heart failure and cranial bruit

Imaging findings (Fig. 32.72): Sagittal ultrasound images (**a**) and post-contrast sagittal MRI (**b**) of the brain demonstrate aneurysmal dilatation of the median prosencephalic vein (*arrows*), which drains into enlarged dural venous sinuses (∗). There are multiple feeding vessels from the pericallosal and anterior choroidal arteries (*arrowhead*). Note the yin-yang appearance of turbulent vascular flow on color Doppler ultrasound imaging.

Diagnosis: Vein of Galen malformation.

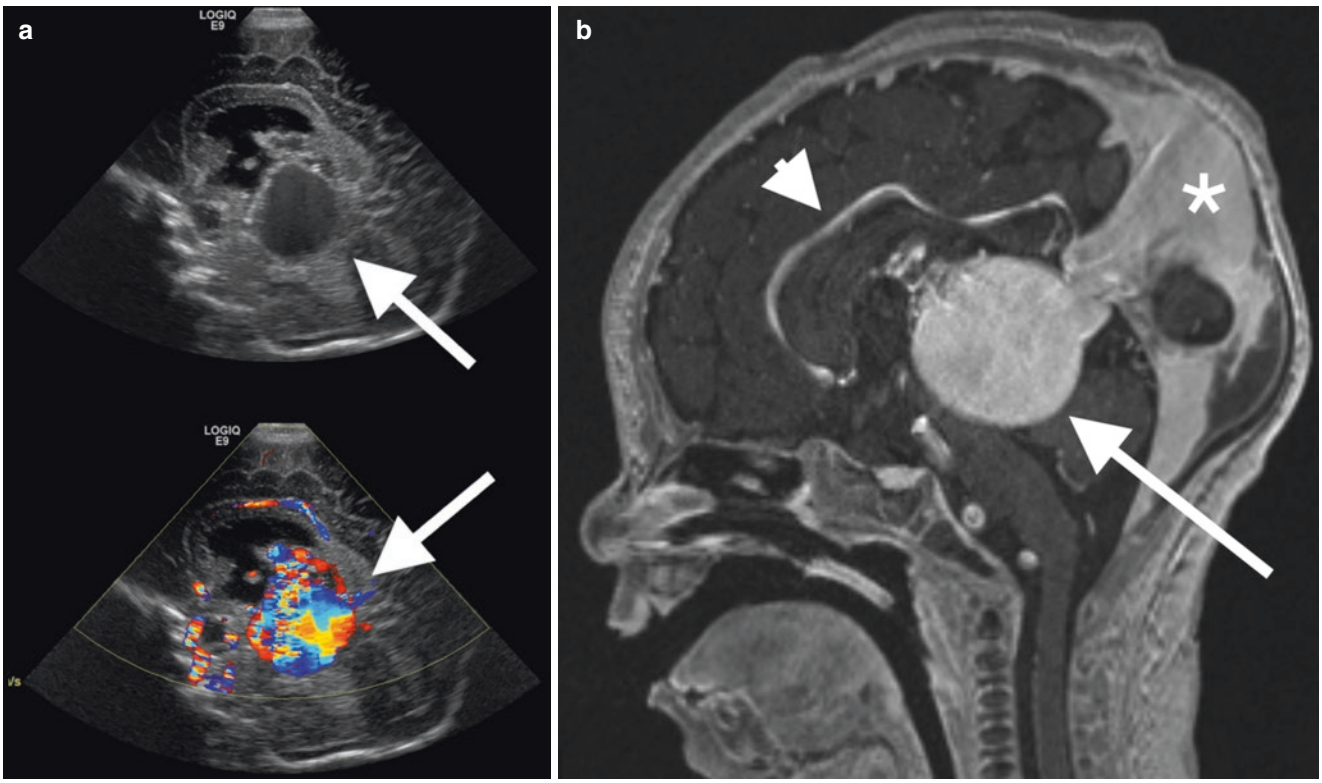


Fig. 32.72

Case 73

14-year-old female presenting with headache and 2 months of lower extremity paresthesia and acute-onset bilateral upper extremity paresthesia and facial numbness

Imaging findings (Fig. 32.73): Axial T2 fluid-suppressed MRI of the brain demonstrates numerous ovoid T2 hyperintense lesions within the juxtacortical and periventricular white matter of the supratentorial brain, particularly along the callosal-septal junction. Additional lesions were present in the posterior fossa, upper cervical cord, and upper thoracic cord.

Diagnosis: Multiple sclerosis.

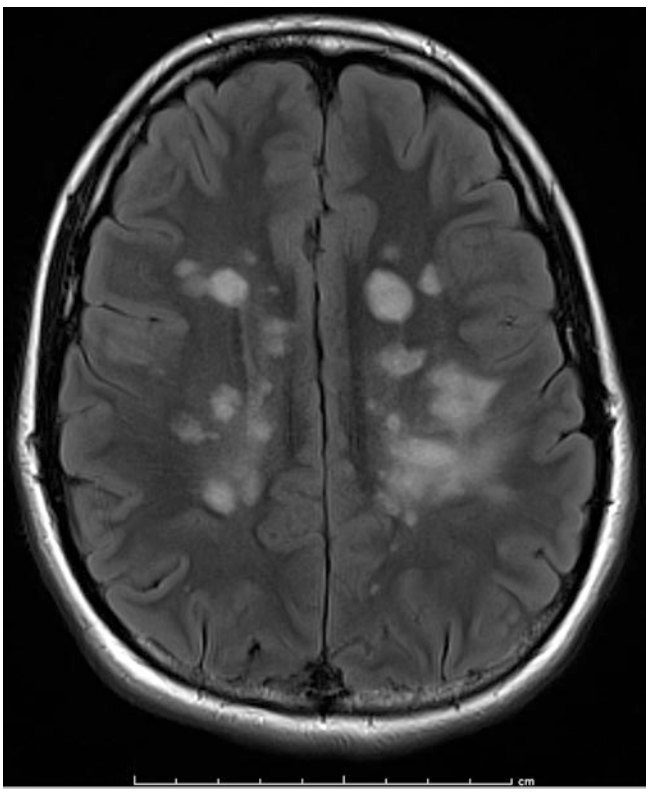


Fig. 32.73

Case 74

2-month-old female with a history of birth trauma presenting with a hard palpable lump on the head

Imaging findings (Fig. 32.74): Radiograph of the skull demonstrates fusiform elevation of the left parietal subperiosteum with a thin rim of calcification (*arrow*).

Diagnosis: Left parietal calcified cephalohematoma.

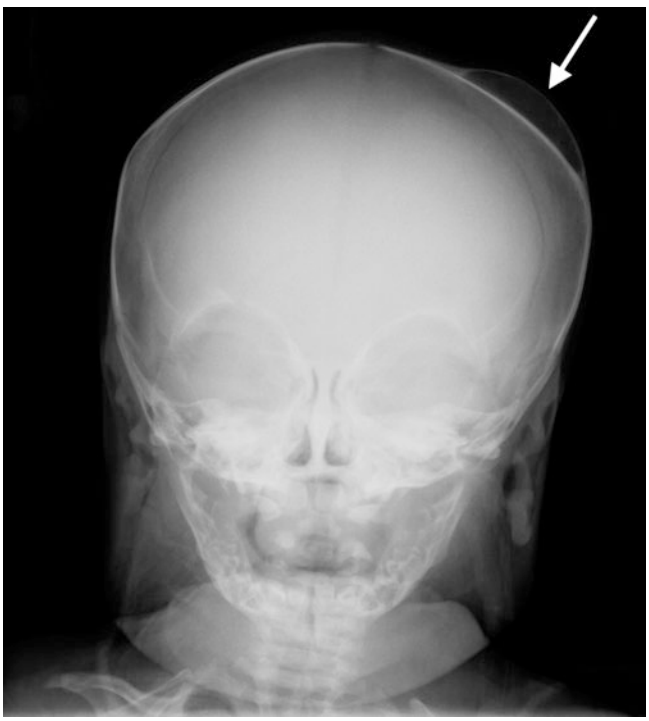


Fig. 32.74

Case 75

15-year-old male presenting with progressive right eye pain, swelling, and fever

Imaging findings (Fig. 32.75): Axial (**a**) and coronal (**b**) contrast-enhanced CT of the orbits demonstrates diffuse sinonasal opacification on the right with a medial right orbital subperiosteal abscess (∗), intraconal fat stranding (*gray arrow*), and asymmetric thickening of the medial rectus and superior oblique muscles (*arrowheads*). There is proptosis of the right orbit (*white arrow*).

Diagnosis: Postseptal orbital cellulitis complicated by a subperiosteal abscess and myositis of the medial rectus and superior oblique muscles.

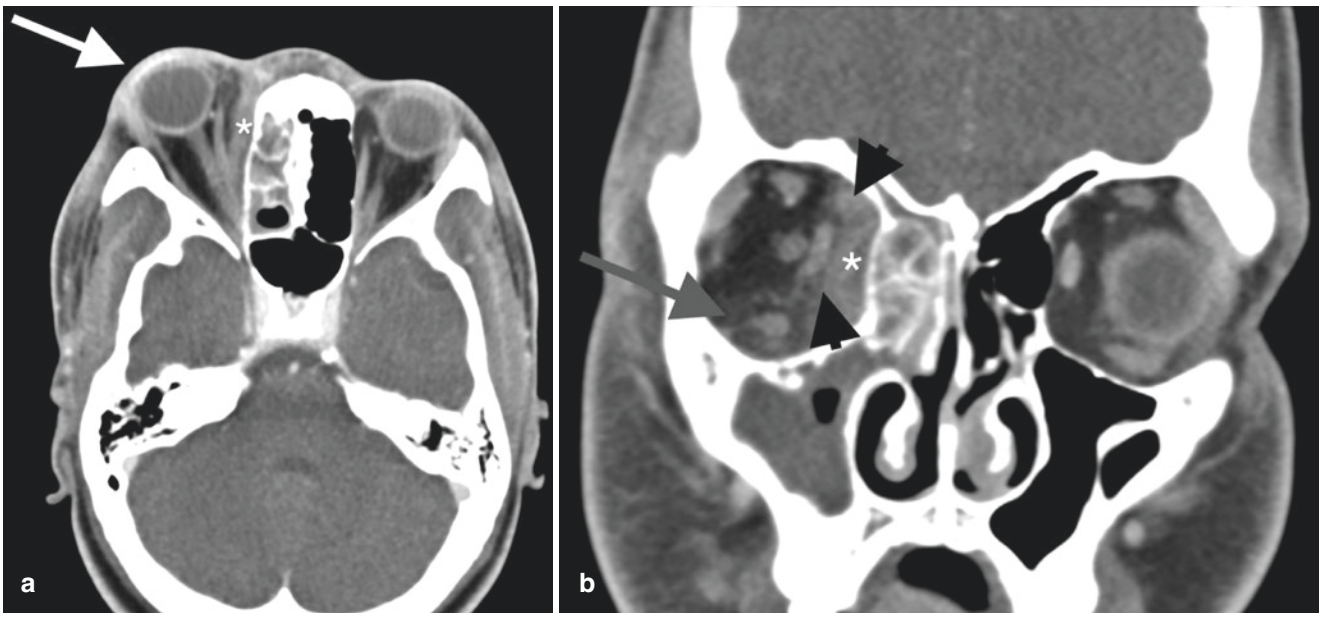


Fig. 32.75

Case 76

7-year-old male with recurrent ear infections, presenting with left ear pain, posterior auricular swelling, and fluctuance

Imaging findings (Fig. 32.76): Axial CT of the temporal bones (**a**) demonstrates opacification and coalescence of the left mastoid air cells. There is osseous erosion of the lateral mastoid cortex (white *arrow*). Axial post-contrast MRI (**b**) demonstrates a subperiosteal abscess in the left postauricular region, with intracranial extension (gray *arrow*).

Diagnosis: Coalescent mastoiditis complicated by intracranial and subperiosteal abscesses.

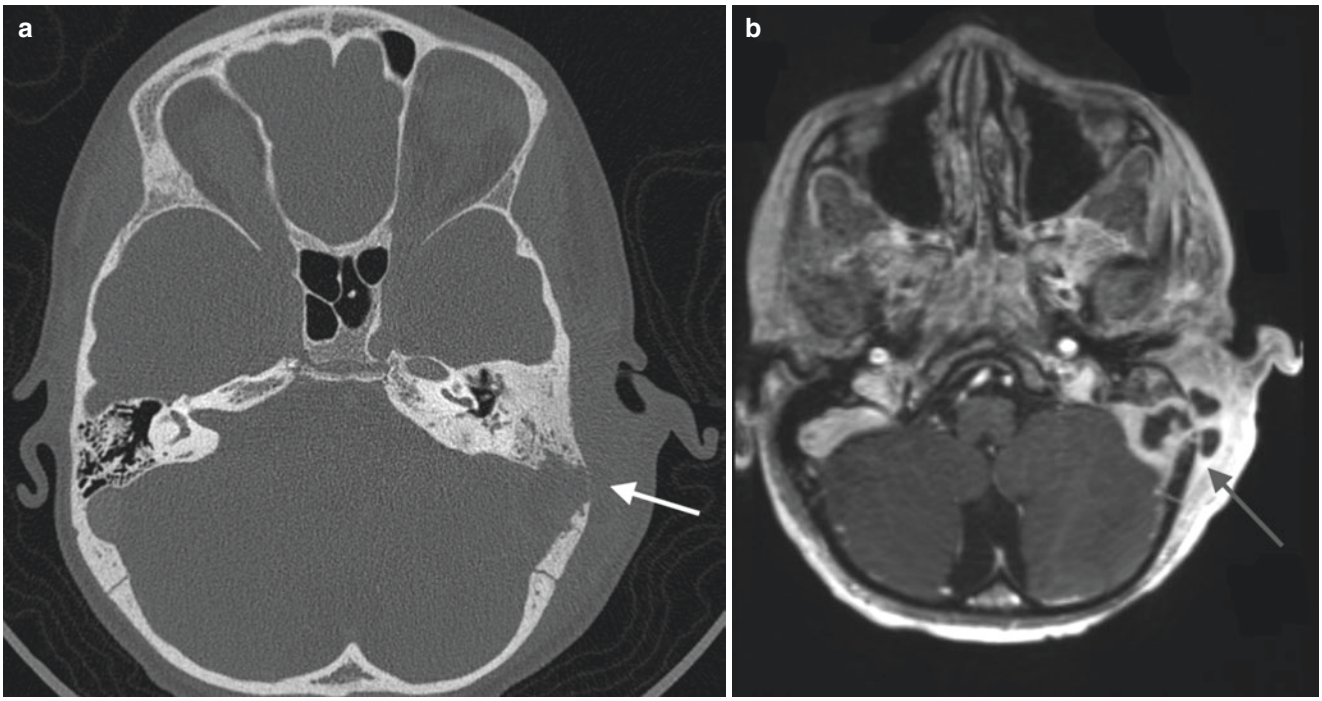


Fig. 32.76

Case 77

12-year-old patient with a midline anterior neck mass that moves with swallowing and tongue protrusion, with an ultrasound initially performed, prompting further evaluation with CT

Imaging findings (Fig. 32.77): Axial (**a**) and sagittal (**b**) contrast-enhanced CT of the neck demonstrates a cystic structure along the anterior midline infrahyoid neck (*arrows*), embedded within the strap muscles. There is a thin enhancing wall and no adjacent fat stranding to indicate active inflammation.

Diagnosis: Thyroglossal duct cyst.

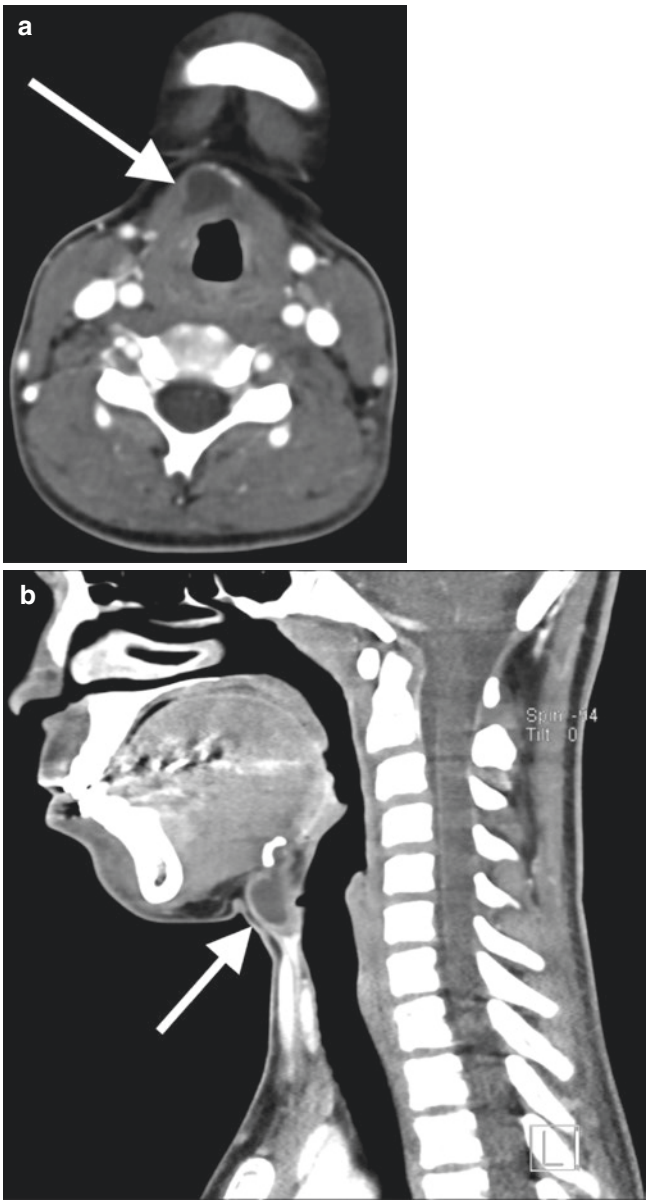


Fig. 32.77

Case 78

9-year-old male presenting with growth arrest and worsening vision

Imaging findings (Fig. 32.78): Sagittal postcontrast MRI of the brain demonstrates a heterogeneously enhancing, suprasellar mass (∗) centered within the pituitary fossa and that extends into the suprasellar cistern. Punctate areas of hypointensity within the mass are indicative of calcifications.

Diagnosis: Craniopharyngioma.

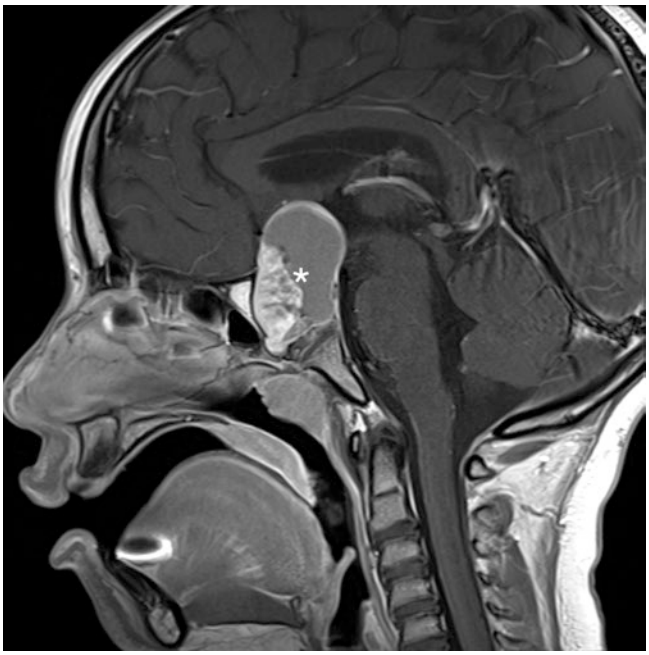


Fig. 32.78

Case 79

10-month-old male with abnormal head shape, worsening over several months

Imaging findings (Fig. 32.79): Surface rendered CT images of the skull demonstrate premature closure of the sagittal suture (*arrow*) with associated dolichocephaly.

Diagnosis: Isolated sagittal craniosynostosis.

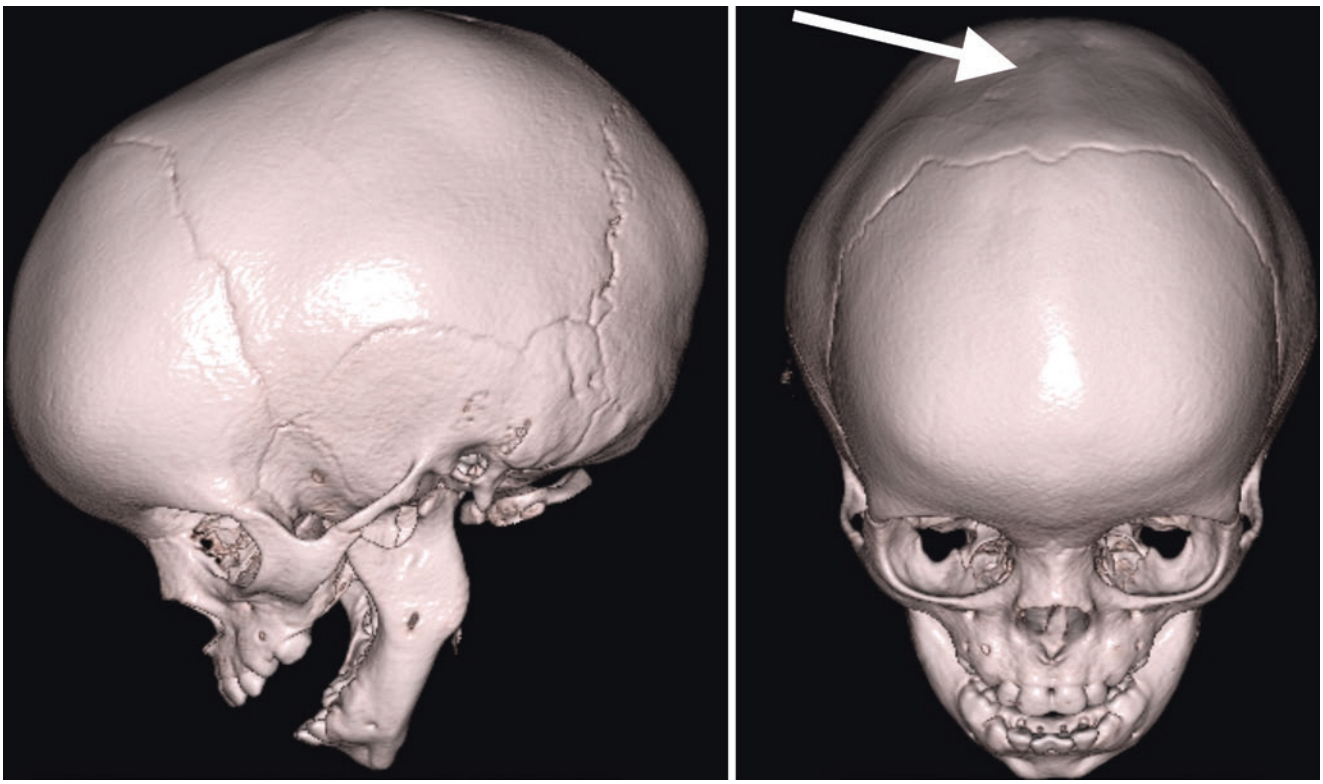


Fig. 32.79

Case 80

2-month-old male presenting after fall and change in mental status

Imaging findings (Fig. 32.80): Coronal CT of the brain (**a**) demonstrates multiple thin hyperdense crescentic collections along the cerebral convexities and within the interhemispheric fissure (*arrows*). Surface-rendered CT of the skull (**b**) demonstrates a depressed right parietal skull fracture (∗).

Diagnosis: Depressed skull fracture with traumatic subdural hemorrhages.

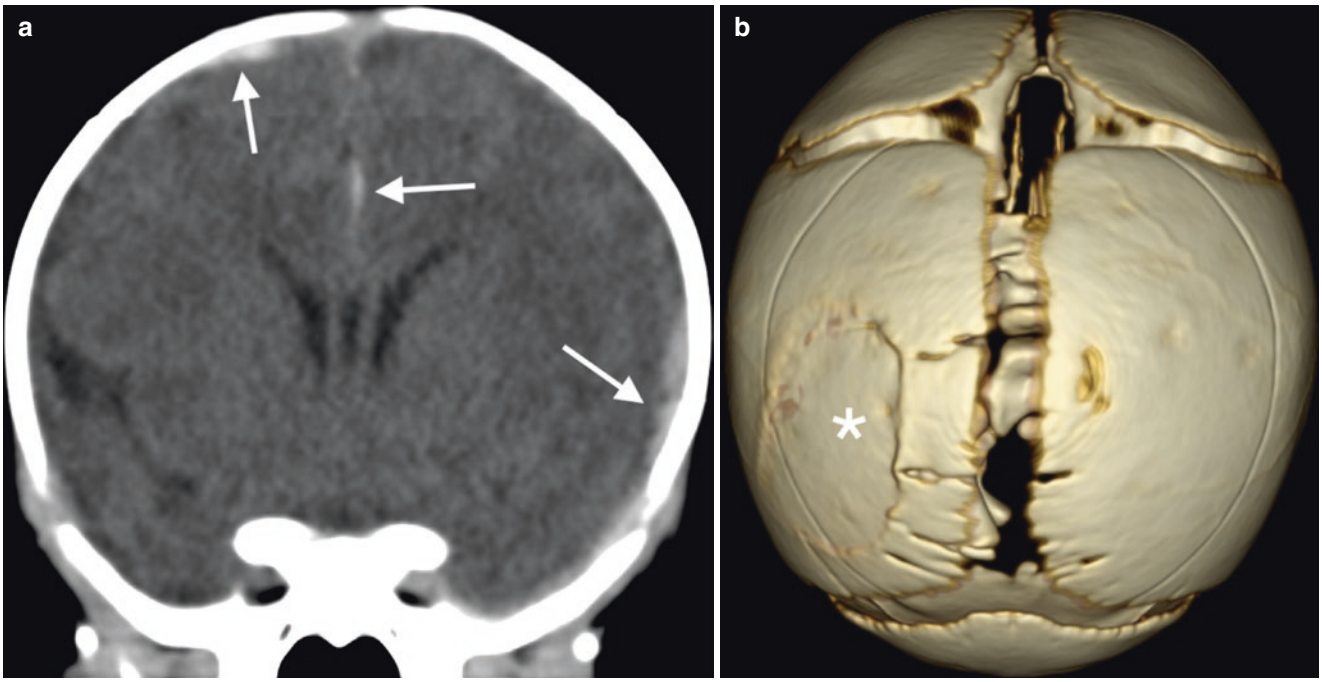


Fig. 32.80

Suggested Reading

American College of Radiology. ACR Appropriateness Criteria®. n.d. Available at https://acsearch.acr.org/list. Accessed 11 Nov 2018.

Donnelly L. Fundamentals of pediatric imaging. 2nd ed. Philadelphia: Elsevier; 2016.

Walters M, Robertson R. Pediatric radiology: The requisites. 4th ed. Philadelphia: Elsevier; 2017.

Last-Minute Review

33

Osama I. Naga

O. I. Naga (✉)
Department of Pediatrics, Paul L. Foster School of Medicine,
Texas Tech University Health Sciences Center, El Paso, TX, USA
e-mail: osama.naga@ttuhsc.edu

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_33

GENERAL PEDIATRICS

Osama I. Naga

Last-Minute Review—General Pediatrics	Most Likely Answer
Which growth charts should be used for children between 0 and 2 years?	World Health Organization (WHO) chart
Which growth charts should be used for children > 2 years?	CDC growth charts
Birth weight of newborn usually regained at what age?	10–14 days
Birth weight doubles at what age?	5–6 months
Birth weight triples at what age?	1 year
Normal weight gain after 2 years of age per year	2–3 kg/year approximately
Body mass index (BMI) should be used starting at what age?	2 years
How is BMI calculated?	Weight (kg)/[height (m)]^2
What is the most common cause of failure to thrive?	Inadequate caloric intake
How much is birth length increased by 1 year of age?	50%
Birth length doubles at what age?	3–4 years
What is the average growth length (growth velocity) per year after 2 years of age (later childhood)?	5 cm/year approximately
What is the approximate range of pubertal peak growth velocities in boys and girls?	7–12 cm/year in boys 6–10.5 cm/year in girls
How much does the head circumference increase per month in the 1st year?	1 cm/month
When does the head grow the fastest?	First 60 days of life (0.5 cm/week)
Head circumference should be measured routinely in each well visit until what age?	2 years
What is the risk for a premature infant with an enlarged head circumference?	Hydrocephalus
What is the study of choice for an infant who presents with macrocephaly?	Head ultrasound (US)
What is the study of choice for an infant who presents with absolute microcephaly?	Brain MRI
Child with enlarged head > 98th percentile, similar to the father, no symptoms and normal cognitive function, head imaging study showed prominent subarachnoid space especially in the frontal region	Benign familial macrocephaly
Anterior displacement of the occiput on one side and the frontal region on the ipsilateral side and the ear is more anterior on the side of occipital flattening (parallelogram)	Positional plagiocephaly
Anterior displacement of the occiput on one side and frontal bossing on the contralateral side and the ear is displaced more posteriorly (trapezoid)	Posterior plagiocephaly (craniosynostosis)

Last-Minute Review—General Pediatrics	Most Likely Answer
The most common type of craniosynostosis	Long narrow head (scaphocephaly), which is an early closure of the sagittal sutures
A 6-month-old with progressive head enlargement and crossing percentiles from 25th percentile at 2 months to 98th percentile at 6 months well visits. The head is elongated in the anterior–posterior diameter and shortened in the biparietal diameter. Ridging of the sagittal suture is palpable	Scaphocephaly (craniosynostosis)
What is the next best step in a child with suspected craniosynostosis?	Refer to a pediatric neurosurgeon (imaging studies are not required to make the diagnosis in typical cases)
What is the only vaccine that can be given at birth?	Hepatitis B
Infant born to HBsAg positive mom what should be given?	Hepatitis B and HepB immunoglobulin in the first 12 h
What is the maximum age you can give DTaP?	DTaP is only for children younger than 7 years old
Encephalopathy within 7 days of administration is an absolute contraindication in which vaccine?	DTaP
When can Tdap or Td be given?	7 years and older
Rotavirus, measles, mumps, rubella (MMR), oral poliovirus vaccine (OPV), and varicella are	Live attenuated virus vaccines
How are MMR, varicella, and inactivated polio (IPV) given?	Subcutaneously (IPV can be given either IM or SC)
Can you give MMR vaccine and perform a purified protein derivative (PPD) test at the same time?	Yes
If you give only MMR vaccine, how long should you wait to do PPD test?	4–6 weeks
Which vaccines are contraindicated to be given to immunocompromised children?	Live vaccines, e.g., MMR, varicella, and rotavirus
Anaphylaxis reaction to neomycin or gelatin is an absolute contraindication to which vaccine?	MMR
The child who received MMR vaccine 2 weeks ago is now having pain in the hip joints. Which component of the vaccine is responsible for this reaction?	Rubella
When does *Haemophilus influenzae* type b vaccination not need to be given to healthy children?	5 years or older
When does pneumococcal (PCV13) vaccination not need to be given to healthy children?	5 years or older
For which conditions can you give *Haemophilus influenzae* type b vaccination at 5 years of age or older?	One dose for unimmunized persons with functional or anatomical asplenia and HIV infection. 3 doses after hematopoietic stem cell transplant (HSCT) regardless of the history of HIB immunization

Last-Minute Review—General Pediatrics	Most Likely Answer
Which pneumococcal vaccines should be given to high-risk children 2 years and older, e.g., HIV, sickle cell disease, asplenia, cochlear implant?	PCV13, and PPSV23 (PPSV23 is given at least 8 weeks after any prior PCV13)
An 11-year-old female is here for HPV vaccination; how many doses are recommended?	2 doses 6–12 months apart
A 15-year-old female is here for HPV vaccination; how many doses are recommended?	3 doses 0, 1–2 months, and 6 months are recommended
Children younger than 9 years of age, never been vaccinated for influenza before; how many doses should they receive during the first instance of influenza vaccination?	2 doses 1 month apart
Child has a severe egg allergy (anaphylaxis). Can he or she receive the MMR vaccine?	Yes
Child is allergic to eggs (only hives). Can he or she receive the influenza vaccine today?	Yes
Child has a severe egg allergy (anaphylaxis). Can he or she receive the influenza vaccine?	Yes. Under the supervision of a health care provider who can recognize and manage severe allergic conditions
Child with a previous severe allergic reaction (anaphylaxis) to the flu vaccine. Can he or she receive the influenza vaccine?	No
A 4-year-old boy has 104 °F fever and ear infection; can he be vaccinated today?	Yes
An unimmunized 4-month-old child came for catch-up vaccination. Can he or she receive the rotavirus vaccine?	No
A 9-month-old boy came for catch-up vaccination, and he had only one dose of rotavirus vaccine at 2 months well visit. Can he receive the rotavirus vaccine?	No
If a household member is immunocompromised, e.g., HIV, leukemia, or severe combined immunodeficiency (SCID), can you give the 4-month-old who is living in the same house oral poliovirus vaccine (OPV)	No
A 2-month-old child with complement component deficiency. What are the vaccines that should be given at the 2-months well visit?	Routine 2 months vaccines plus meningococcal vaccine
A mother declined vaccination of her child. What is the next best step?	Explore any misconceptions about the safety and efficacy of vaccines
Visual acuity for a newborn is	20/400
At what age is a social smile seen?	1–2 months
An infant is able to track an object to 180°	2 months
Moro reflex disappears by what age?	3–6 months
An infant is able to roll from front to back and has no head lag	4 months

Last-Minute Review—General Pediatrics	Most Likely Answer
An infant is able to roll from back to front, supports weight with legs and bounces, able to transfer objects from hand to hand, knows familiar faces, knows own name, and begins to have separation anxiety	6 months
An infant should be able to sit without support	7 months
An infant pulls to stand, says "mama/dada" nonspecifically, and imitates sounds	9 months
An infant is able to stand and take steps, says "mama/dada" specifically, has a mature pincer grasp	12 months
Child is able to say 3–5 words, turns pages of a book, builds a tower of 3 blocks	15 months
Child is able to say 10–25 words, throws a ball overhand, builds 4 blocks towers, uses a spoon, and knows 3 body parts	18 months
At what age are most toddlers able to use a cup well?	15–18 months
Child says 50 words, 2-word sentences, throws overhand, goes upstairs both feet on each step, engages in parallel play	24 months
Child copies a circle, three-word sentences, alternates feet on stairs, knows 2 colors, 75% intelligible speech	36 months (3 years)
Child copies a square, 5-word sentences, identifies gender, knows 5 colors, 100% intelligible speech	48 months (4 years)
Child copies a triangle, uses scissors, and can count to ten	60 months (5 years)
At what age are most children able to copy a diamond?	6–7 years
Inability to hold the head steady is a red flag for abnormal motor development at what age?	4 months
Inability to sit alone and lack of rolling are a red flag for abnormal motor development at what age?	9 months
Inability to walk independently is a red flag for abnormal motor development at what age?	18 months
A 1-year-old boy is unable to stand or crawl, unable to point and is not speaking a single word	Motor, cognitive, and language delay
An 18-month-old with only 3 words, lack of joint attention, not sharing the interest in an object	Screen for autism spectrum disorder and developmental delay with 2 separate tools, e.g., M-CHAT and ASQ
A 2-year-old uses only 5 words. What is the best test to order?	Hearing test
The American Academy of Pediatrics (AAP) recommends that universal hearing screening of all infants occur by what age?	All infants with significant congenital hearing loss should be identified by **3** months of age, and necessary intervention initiated by **6** months of age

Last-Minute Review—General Pediatrics	Most Likely Answer
AAP recommends universal screening for anemia with determination of Hb concentration at what age?	1 year of age
AAP recommends lead screening at what age?	All Medicaid-eligible children and those whose families receive any governmental assistance must be screened at ages 1 and 2 years
What is the non-hematologic consequence of iron deficiency anemia?	Neurocognitive changes
AAP recommends autism screening at what age?	18 months and 24 months
AAP recommends discussing tobacco, alcohol, or drug use with children at what age?	11 years
The US Preventive Services Task Force (USPSTF) recommended age to begin screening all adolescents for HIV	Once between 15 and 18 years (younger if increased risk, e.g., male-to-male sexual contact)
Screening for depression should be done annually starting at what age?	Starting at 12 years
Screening for dyslipidemia should be done at what ages?	Between 9 and 11 years and again between 17 and 21 years, or if there are risk factors (obesity, diabetes, etc.)
A 7-year-old boy has a parent with total cholesterol of 300 mg/dL. What is the next best step?	Order fasting lipid profile, then repeat after 2 weeks to 3 months
Infant is exclusively breastfed. At what age should you recommend daily vitamin D supplementation (400 IU)?	First few days of life
Infant is feeding more than 1 liter of formula per day in addition to breastfeeding; does he or she need vitamin D supplementation?	No (1 liter of formula has 406 IU of vitamin D)
Infant is exclusively breastfed. At what age should you recommend daily iron (1 mg/kg/day)?	4 months
At what age should you recommend starting solid foods in infants?	4–6 months
What is the reason for starting solid foods between 4 and 6 months of age?	May decrease the risk of allergy to that specific food
A 4-week-old infant has been exclusively breastfeeding, and the mother is scheduled for MRI with contrast	Continue breastfeeding
A 4-week-old infant has been exclusively breastfeeding, and the mother has mastitis	Continue breastfeeding (can continue on the other side if breast abscess or cellulitis with direct contact with infant's mouth)
A 4-week-old infant has been exclusively breastfeeding, and the mother recently diagnosed with active tuberculosis. No treatment yet	Discontinue breastfeeding until effective maternal treatment for the initial 2 weeks or the infant is receiving isoniazid)
Newborn with a mother who is HIV positive	Breastfeeding is contraindicated (except in resource-limited settings)
What is the age when infants can drink cow's milk?	12 months

Last-Minute Review—General Pediatrics	Most Likely Answer
At what age can a child be given low-fat milk?	> 2 years
AAP recommends the initial visit to the dentist at what age?	12 months of age
What usually are the first teeth to erupt?	Lower anterior incisors
What is the latest age for first tooth eruption?	18 months (after that, dental consult)
Child with white lines and spots at the bases of several teeth	Referral to a dentist (sign of dental caries)
A 5-year-old boy hit his head and knocked out his 2 primary central incisors 5 min ago. What is the next best step?	Reassurance (re-implantation of the primary tooth may damage the developing permanent tooth)
A 10-year-old boy hit his head and knocked out his 2 permanent central incisors 5 min ago. What is the next best step?	Re-implant the teeth immediately (best prognosis if avulsed tooth re-implanted within 15–30 min)
If a tooth has been knocked out, it should be placed back into its socket until the child can see the dentist, should that prove impossible, what is the best solution in which to keep it?	Cold milk
When should the knocked-out tooth be implanted?	Immediate treatment is essential
At what temperature should you set the water heater at home?	120 °F or less
Child with a capillary lead level of > 5 μg/dL. What is the next best step?	Obtain venous sample
What is the safe blood lead level (BLL)?	There is no safe BLL, and any detectable lead level must be managed
Children should be secured with a rear-facing seat?	Birth to 2–4 years, as long as possible, or until they reach the highest weight or height allowed
Children who have outgrown their rear-facing seat should use?	Forward-facing car seat until they reach the highest weight or height allowed or at least 5 years of age
Children who have outgrown their forward seating and are less than 57 in. (4 ft 9 in.) tall should use?	Booster seat
Children who have outgrown their booster (57 in., or 4 ft 9 in. tall) seat should use?	Seatbelt; if the seat belts fit properly when the lap belt lays across the upper thighs (not the stomach), and the shoulder belt lays across the chest (not the neck)
What is the recommended preventative measure to help prevent drowning?	Enclosing the pool with a 4-ft fence
What is the recommended measure to prevent accidental gun injuries?	Gun and bullets stored in locked and separate locations
AAP does not recommend the use of repellents for children at what age?	Children younger than 2 months
Treatment of a large local reaction after a mosquito bite	Antihistamine, ice, and topical hydrocortisone cream
What is the significant risk of sunburns?	Increases risk of melanoma at all ages
What are the long-term complications of artificial ultraviolet rays (e.g., skin tanning)	Cataracts, skin aging, and cancer

NEONATOLOGY

Mamta Fuloria

Last-Minute Review—Neonatology	Most Likely Answer
Birth weight less than the 10th percentile	Small for age (SGA)
Birth weight more than the 90th percentile	Large for gestational age (LGA)
Birth weight less than 2500 g	Low birth weight
Birth weight less than 1500 g	Very low birth weight (VLBW)
Birth weight less than 1000 g	Extremely low birth weight (ELBW)
Gestational age of screening for group B *Streptococcus* (GBS)	35–37 weeks gestation
What is the drug of choice for GBS prophylaxis?	Penicillin G
Mother currently GBS negative, but the previous infant had GBS disease. Is GBS prophylaxis recommended?	Yes
Which group has the highest infant mortality rate in the USA?	African American infants
Most common cause of infant deaths in the USA	Congenital malformations
What is the clinical significance of a single umbilical artery?	Associated fetal anomalies (20% or more)
The third trimester presents with ***H***emolysis, ***E***levated ***L***iver enzymes, ***L***ow ***P***latelet count	HELLP syndrome (complication of preeclampsia)
What is the definitive treatment for preeclampsia/HELLP syndrome?	Delivery
The best course of action if fetal scalp pH < 7.20	Immediate delivery
Fetal heart rate > 160 beats/min	Fetal tachycardia
Fetal heart rate < 110 beats/min	Fetal bradycardia
Fetal head compression is often associated with which type of deceleration?	Early deceleration (increased vagal tone)—benign tracing
Compression of the umbilical cord is associated with which type of deceleration?	Variable decelerations
Fetal heart monitoring shows: Fetal heart dropped during the peak uterine contraction and recovered after the contraction had ended; the time from the onset of deceleration to the lowest point of deceleration is 30 s	Late deceleration; associated with placental insufficiency
What are the common causes of late deceleration?	Placental insufficiency for any reason
Uteroplacental insufficiency is associated with what type of deceleration?	Late deceleration—potentially ominous
The best course of action in cases of late deceleration	Fetal pH measurement
Newborn at 1 min: Heart rate is 90/min, weak irregular respiration, grimace, some flexion, blue body and limbs, APGAR score is:	4
Newborn infant is just delivered. The infant is apneic and has a heart rate < 100. What is the next best step?	Positive pressure ventilation (PPV) for 30 s, then reassess

Last-Minute Review—Neonatology	Most Likely Answer
In the previous example, the infant's heart rate is < 60 bpm despite adequate ventilation for 30 s. What is the next step?	Chest compressions and PPV using 100% oxygen
In the previous example, the PPV is ineffective, and chest compressions are being performed. What is the next step?	Intubation
In the previous example, the infant's heart rate remains < 60 bpm despite adequate ventilation and chest compressions. What is the next step?	Intravenous administration of epinephrine
Newborn infant with lanugo on the shoulders, creases on the entire foot, scant vernix, both testicles in the inguinal canal with good rugae has an approximate gestational age of?	39 weeks—be familiar with Ballard scoring
Newborn with one side of the body pink and the other side pale, with a sharp line in-between, no other symptoms	Harlequin color change
A neonate is born with severely thickened skin with large, shiny plates of hyperkeratotic scales. Deep, erythematous fissures separate the scales and contraction abnormalities of the eyes (severe ectropion), ears, mouth, and appendages	Harlequin ichthyosis (autosomal recessive)
Newborn with a sharply demarcated ulcerated area of absent skin is?	Aplasia cutis congenita
What is the most common association with aplasia cutis congenita?	Benign isolated defect (less commonly associated with other physical anomalies or malformation syndromes, e.g., trisomy 13)
Newborn infant with head swelling crossing the suture lines; delivery was assisted with the use of a vacuum?	Caput succedaneum
Newborn infant with head swelling that does not cross the suture lines?	Cephalohematoma
A type of hemorrhage in which bleeding is significant and often presents with swelling in the posterior aspect of the head?	Subgaleal hemorrhage
A 7-day-old, 28-week premature infant should be screened for which type of hemorrhage and with which modality?	Intraventricular hemorrhage—with a head US
Maternal fever > 100.4 °F, fetal heart rate more than 160–180 beats/min, maternal tachycardia, purulent foul-smelling amniotic fluid, maternal leukocytosis, and uterine tenderness	Chorioamnionitis
A neonate is born to a mother with chorioamnionitis. The neonate is alert with good tone, no respiratory distress, and vital signs are normal. What is the next best step?	Obtain blood culture, complete blood cell count, and start ampicillin and gentamicin

Last-Minute Review—Neonatology	Most Likely Answer
An infant develops cyanosis when feeding, which disappears when crying	Bilateral choanal atresia
Term infant 1 h after birth develops tachypnea, hypoxia, grunting. Chest radiograph showed fluid in the fissures, flattening of the diaphragm, and prominent pulmonary vasculature	Transient tachypnea of the newborn (self-limited, resolves spontaneously, and requires supportive care)
Newborn initially diagnosed with transient tachypnea of the newborn is requiring more oxygen and is much worse after several days	Consider another diagnosis
A preterm newborn with tachypnea, grunting, nasal flaring, subcostal, and intercostal retractions. Chest radiograph shows ground glass appearance. He continues to require more oxygen	Respiratory distress syndrome
What is the best treatment in the previous case of respiratory distress syndrome?	Surfactant therapy followed by rapid extubation to nasal continuous positive airway pressure (CPAP)
When is surfactant recommended to be used prophylactically after resuscitation in extremely premature neonates to protect the immature lungs?	< 27 weeks gestation (some institutions give surfactant as rescue therapy)
The name of cells that produce lung surfactant	Type 2 alveolar cells
An 8-week-old who was born at 27 weeks was intubated for several weeks and now has chronic hypoxemia, tachypnea, wheezing, along with longstanding respiratory insufficiency. Chest radiograph showed: Decreased lung volumes, areas of atelectasis, hyperinflation, and pulmonary edema	Bronchopulmonary dysplasia
Newborn infant with respiratory distress, bowel sounds in the chest, scaphoid abdomen. Bag-mask PPV after delivery made the infant worse. Chest radiograph shows: loops of bowel in the chest, a mediastinal shift, a paucity of bowel gas in the abdomen, and the presence of the tip of a nasogastric tube in the thoracic stomach	Diaphragmatic hernia
What is the next best step in the newborn with the diaphragmatic hernia in the previous example?	Intubate immediately after delivery, insert a nasogastric tube to decompress the stomach (avoid bag-mask ventilation)
Full-term infant presents with tachypnea, cyanosis only in the lower body, loud second heart sound. Chest radiograph shows clear lungs and decreased vascular markings	Persistent pulmonary hypertension of the newborn
A post-term newborn has respiratory distress. The amniotic fluid was stained with meconium, and the point of maximal cardiac impulse is displaced	Pneumothorax
A common complication from excessive bagging during resuscitation?	Pneumothorax

Last-Minute Review—Neonatology	Most Likely Answer
Meconium-stained amniotic fluid is noted at delivery, and the infant is apneic. What is the next best step?	PPV
Meconium ileus in a newborn	Cystic fibrosis should be ruled out
A 2-week-old preterm infant born at 26 weeks gestation started having more gastric residuals, abdominal distension, blood in stool, abdominal wall erythema. KUB shows pneumatosis intestinalis and gas in the portal vein	Necrotizing enterocolitis
Newborn with bilious vomiting, abdominal distension, and lethargy	Volvulus should be ruled out
Newborn with Down syndrome and bilious vomiting. KUB shows double bubble sign	Duodenal atresia
Differential diagnosis of white pupillary reflex	Cataract, retinoblastoma
Anhidrosis, ptosis, miosis, and enophthalmos	Horner syndrome
Newborn is not moving arm, and the arm is internally rotated in waiter's tip position	Erb's palsy (C5–6)
Newborn is not moving arm and hand, and the hand is held in a claw-like position	Klumpke paralysis (C8-T1)
A diagnostic test to assess associated findings with brachial plexus palsies (BPP)	Chest radiograph can rule out phrenic nerve injury and clavicular fracture
A 2-month-old infant has irritability and poor feeding, swelling, and bone lesions, elevated ESR, and alkaline phosphatase levels. Radiographs show layers of periosteal new bone formation, with cortical thickening of the long bones, mandible, and clavicle. Soft-tissue swelling is evident as well	Infantile cortical hyperostosis (Caffey disease)
A 5-day-old female with vaginal bleeding	Reassurance (maternal hormone withdrawal)
A well-appearing term neonate with bluish discoloration in hands and feet	Reassurance (peripheral cyanosis or acrocyanosis is common and benign)
A neonate has new-onset seizure activity but appears otherwise healthy	Refer to the emergency department immediately
Large for gestational age, lethargy, tremors, seizures, and cyanosis	Hypoglycemia
Neonate with hypoglycemia diagnosed with glucose oxidase test strip; test strip glucose is 30 mg/dL. What is the next best step?	Order plasma glucose level (most accurate); feed infant immediately
Newborn with a micropenis that is less than 2.5 cm when stretched will require?	Endocrine evaluation
Newborn is very quiet, cries very little, and has prolonged jaundice and umbilical hernia	Hypothyroidism
Jaundice, hypocalcemia, and hypoglycemia are usually associated with	Polycythemia
What is the treatment of polycythemia?	Hydration (IV fluids); if symptomatic or significant polycythemia, will need an exchange transfusion

Last-Minute Review—Neonatology	Most Likely Answer
Is jaundice in the first 24 h physiologic?	No
A condition specific for the infant of diabetic mother	Small left colon syndrome
An abdominal wall defect with uncovered abdominal contents noted right of the umbilicus is	Gastroschisis—not associated with genetic abnormalities
An abdominal wall defect covered with a membrane that is often associated with genetic syndromes is	Omphalocele—associated with genetic abnormalities, e.g., trisomies 13, 18, and 21 and Beckwith–Wiedemann syndrome
Syndrome characterized by absent abdominal wall musculature as well as cryptorchidism is	Prune belly syndrome
A full-term newborn with missing right index, middle, and ring fingers	Amniotic band syndrome
Newborn with jitteriness, irritability, tremulousness, limb defect, leukomalacia, and intracranial hemorrhage	Cocaine abuse during pregnancy
Very small for gestational age (SGA) infant, mother with multiple drug abuse during pregnancy, including alcohol, cigarette smoking, cocaine, marijuana. Which substance is most responsible for SGA?	Cocaine
The most common effect of cigarette smoking during pregnancy on newborn	Low birth weight
Excessive exposure to hot water or hyperthermia during the first trimester of pregnancy increases the risk of	Miscarriage, neural tube defect
A virus that can cause fetal hydrops	Parvovirus B19
Newborn with microphthalmia, cataracts, blueberry muffin spots on the skin, hepatosplenomegaly, and patent ductus arteriosus	Congenital rubella syndrome
Newborn with microcephaly, and periventricular calcifications	Congenital cytomegalovirus infection
Newborn with chorioretinitis, hydrocephalus, and intracranial calcifications	Congenital toxoplasmosis
Newborn with snuffles, continuous nasal secretions, anemia, thrombocytopenia, hepatomegaly, and periostitis	Congenital syphilis
SGA newborn with short palpebral fissures, epicanthal folds, micrognathia, smooth philtrum, thin upper lip, and microcephaly	Fetal alcohol syndrome
Lithium use during pregnancy is associated with	Ebstein anomaly
Infant born to an opiate dependent mother presents with increased irritability, fussiness, poor feeding, and sweating	Neonatal abstinence syndrome
Which maternal medication during pregnancy results in a newborn with growth restriction, renal dysgenesis, oligohydramnios, skull ossification defects?	ACE inhibitors

Last-Minute Review—Neonatology	Most Likely Answer
Which anticonvulsant is associated with fetal hydantoin syndrome?	Phenytoin
Valproic acid intake during pregnancy increases the risk of	Neural tube defect, cleft lip and palate, cardiovascular abnormalities, genitourinary defects, developmental delay, endocrine disorders, limb defects, and autism
The most common congenital defect associated with carbamazepine and valproic acid	Neural tube defect
Newborn with isolated congenital deafness	Referral to a geneticist (genetic causes probably account for the majority of cases in developed countries)
A 3-day-old infant presents with bilateral hip clunks. What is the next best step?	US of the hips
An infant is delivered to HBsAg positive mother; what is the next step?	Administer both hepatitis B vaccine and HBIG within 12 h of birth
Critical congenital heart defects screening before discharge from the newborn nursery requirements in most states in the USA	Oxygen saturations should be > 95%, with no more than a 3% difference between pre-ductal and post-ductal oxygen saturations
A mother who delivers a full-term newborn has negative routine maternal labs. The infant is born by vaginal delivery and is stooling, voiding, feeding well. Tc bilirubin is normal on the 25th percentile. What is the recommended discharge time from newborn nursery and follow-up-care?	48 h after birth and follow-up in 2–3 days
What is the current recommendation for umbilical cord care in infants born in developed countries?	To keep it dry (use of isopropyl alcohol is no longer routine cord care)

ADOLESCENT MEDICINE

Hina J. Talib

Last-Minute Review—Adolescent Medicine	Most Likely Answer
Adolescent male twin, whose female twin sibling is taller than he is, is worried about his height	Reassurance (growth spurt occurs at sexual maturity rating [SMR] II-III for girls, whereas at SMR IV for boys)
The first sign of sexual development in boys	Testicular enlargement
The first sign of sexual development in girls	Breast development
Adolescent female is concerned about one breast being slightly larger than the other	Reassurance
A 15-year-old obese male with a sometimes painful breast that is larger than the other, with an otherwise normal exam	Reassurance (benign gynecomastia)
Adolescent female is worried about painful masses noted in both breasts; the pain improves after her menstrual cycle	Reassurance (fibrocystic changes)

Last-Minute Review—Adolescent Medicine	Most Likely Answer
Adolescent female is concerned about a painless rubbery mass located in the upper outer quadrant that does not change in size throughout her cycle; a well-circumscribed, smooth, mobile lesion	Reassurance (fibroadenoma)
The most common cause of breast mass in adolescent girls	Fibroadenoma
The most common cause of mastitis in adolescent girls	*Staphylococcus aureus*
When does a girl usually get her first period?	2–3 years after breast development (12.5 years is mean age)
The drug of choice for treatment of dysmenorrhea in adolescent females	NSAID (cyclooxygenase inhibitors)
The most common cause of secondary amenorrhea in adolescents	Pregnancy
The most common reason for hospitalization in adolescents	Pregnancy
Adolescent with amenorrhea, headaches, blurring of vision, galactorrhea	Prolactinoma
A concerned parent brings her 12-year-old female due to irregular periods; menarche was 6 months ago	Reassurance (likely due to an immature hypothalamic-pituitary-ovarian [HPO] axis)
Adolescent girl with irregular menstrual periods, body mass index at the 98th percentile, acne, acanthosis nigricans, hirsutism, male pattern baldness/alopecia, elevated total and free testosterone	Polycystic ovary syndrome (PCOS)
A female adolescent presenting with abrupt onset of severe, constant, unilateral pain located in the pelvis, associated with recurrent nonbilious vomiting; she has no fever, urinalysis is normal, and pregnancy test is negative	Ovarian torsion
What is the best way to encourage adolescents to disclose information to their pediatrician?	Interview the adolescent alone and in a confidential manner when discussing drugs, contraception, STDs, suicidal ideation
A 16-year-old adolescent girl presents to your clinic to discuss birth control options without parental consent. She is sexually active. You live in a state that allows minor consent for contraceptive services	She can receive birth control pills without parental consent at her current age
The 3 most common causes of death in adolescents	Unintentional injuries, suicide, homicide
What are the consequences of e-cigarette use among adolescents?	May lead to cigarette smoking as well as nicotine addiction
What are the new alternative tobacco products (ATPs) most commonly used by high school students?	E-cigarettes (most common), hookahs, e-hookahs, and smokeless products such as snus (moist powder tobacco)
What are the negative health impacts of ATPs?	May be equal to or even worse than those associated with cigarettes

Last-Minute Review—Adolescent Medicine	Most Likely Answer
What is the best approach to adolescents who are smoking cigarettes or using ATPs?	Provide an accurate and judgment-free education addressing the dangers of e-nicotine delivery systems
The risk of accidental consumption by young children, who may be drawn to brightly colored and flavored e-cigarette liquids	Severe toxicity and death upon consumption
What is the strongest predictor of serious problems with substance use disorder?	Early age drug abuse (the younger the child, the higher the risk)
Adolescent male presents to the ER with respiratory depression, euphoria, and pinpoint pupils	Opiates drug abuse, e.g., codeine
Adolescent who lost his financial support presents with excessive yawning, tearing, dilated pupil, insomnia, nausea, diarrhea, gooseflesh, and cramping	Opiate withdrawal syndrome
Treatment of choice to treat opiate overdose	Naloxone
Adolescent presents with conjunctival injection, gynecomastia, worsening school grades	Marijuana
Adolescent male with new-onset aggression, palpitations, confusion, and disorientation	Synthetic marijuana intoxication
Adolescent male presents with hypertension, hyperthermia, decreased appetite and difficulty sleeping	Amphetamine intoxication
Adolescent presents with drowsiness, dry mouth, flushing, mydriasis, hallucination, delusions, illusions, and body image distortion	Lysergic acid diethylamide (LSD) toxicity
Adolescent with recent schizophrenic thoughts, depression, aggressive language, ataxia, and nystagmus	Phencyclidine (PCP) toxicity
Adolescent inhales toluene, xylene, presents with chest pain and loss of consciousness	Myocardial infarction/cardiac arrhythmia
What is the significant risk of inhalant abuse, including those experimenting with inhalant abuse for the first time?	Sudden sniffing death syndrome (cardiac arrest)
Adolescent presents with euphoria, violent excitement, pulmonary hypertension, restrictive lung defect, peripheral neuropathy, rhabdomyolysis, and hematuria	Gasoline inhalation
Adolescent always absent from school presents with chest pain and myocardial infarction	Cocaine abuse
Adolescent with aggressive behavior, rage, anger, acne, hirsutism, testicular atrophy, gynecomastia, and libido alteration	Anabolic steroids
Adolescent presents with euphoria, increased emotional energy, nausea, jaw clenching, teeth grinding, blurred vision, anxiety, and psychosis	MDMA (ecstasy, methylenedioxymethamphetamine)

Last-Minute Review—Adolescent Medicine	Most Likely Answer
The following sexually transmitted infections need to be reported	HIV, chlamydia, gonorrhea, and syphilis
Annual screening is indicated for sexually active females for which STD?	*Chlamydia trachomatis*
Adolescent male presents with severe dysuria, profuse, purulent discharge	Gonococcal urethritis
What is the best diagnostic test in cases of suspected gonorrhea or chlamydia in sexually active adolescents?	Urine nucleic acid amplification testing for gonorrhea and chlamydia
Adolescent male presents with dysuria, purulent discharge, a petechial rash, as well as new-onset knee pain	Disseminated gonorrhea Treatment: IV ceftriaxone
Adolescent male, sexually active, urethral discharge, Gram stain shows WBCs and no organism	*Chlamydia trachomatis*
Adolescent with profuse, frothy, malodorous yellow-green vaginal discharge, vulvar irritation, and strawberry cervix, vaginal pH < 4.5	*Trichomonas vaginalis* infection Treatment: metronidazole or tinidazole
Adolescent with a fishy odor, homogenous white vaginal discharge, epithelial cells with a ragged border on microscopic examination, vaginal pH > 4.5	Bacterial vaginosis Treatment: metronidazole (not considered STDs)
The most common cause of epididymitis in adolescents	*Chlamydia trachomatis*
Adolescent girl was sexually assaulted a few hours ago	Empiric treatment for chlamydia, gonorrhea, and *Trichomonas*
Adolescent female with lower abdominal pain, fever, chills, dysuria, cervical motion tenderness, and adnexal tenderness	Pelvic inflammatory disease
A 17-year-old female is hospitalized for pelvic inflammatory disease (PID) and has severe allergy to cephalosporin. What is the best choice of antibiotics?	Clindamycin and gentamicin
A sexually active female presents with right upper abdominal pain, fever, and vaginal discharge	Perihepatitis (Fitz–Hugh–Curtis syndrome)
A sexually active adolescent with large, painless, and expanding suppurative ulcers that are beefy and easily bleed on the coronal sulcus and balanopreputial region	Granuloma inguinale (caused by *Klebsiella granulomatis*)
A sexually active adolescent with painful genital ulcer and unilateral inguinal lymphadenopathy	Chancroid (*Haemophilus ducreyi*)
A sexually active adolescent with a painless ulcer on the dorsal penis, punched out, clean appearing, sharp, firm, slightly elevated borders, and bilateral, regional lymphadenopathy	Chancre (primary syphilis)
A sexually active female presents to the clinic due to a rash noted on the palms and soles, along with flu-like symptoms, and malaise	Secondary syphilis

Last-Minute Review—Adolescent Medicine	Most Likely Answer
A sexually active adolescent presents with several days' history of hearing loss, altered mental status, and decreased sensation in both legs	Neurosyphilis
A pregnant adolescent with secondary syphilis has anaphylaxis to penicillin. What is the drug of choice?	Penicillin (desensitization)
Adolescent female, sexually active, presents with painful, itchy vesicular lesion on the vulvar area, low-grade fever, cervical motion tenderness, thin, white vaginal discharge	Herpes simplex infection
Two adolescents are ready to give birth; one has an active herpes genital lesion, and the other has genital wart. Which one should deliver by C-section?	Herpes simplex (genital warts are not an indication of C-section)
Adolescent boy discloses that on most days over the past month, he has been feeling irritable and sad, has decreased pleasure in activities, weight loss, lack of sleep, fatigue, and poor concentration. What is the drug of choice?	Fluoxetine
A 15-year-old gymnast female presents with thin body habitus, bradycardia, lanugo hair, amenorrhea. What do you suspect?	Anorexia nervosa
What are the most common electrolyte abnormalities in refeeding syndrome?	Hypophosphatemia, hypokalemia, and hypomagnesemia
Adolescent girl who has a BMI in the 93rd percentile with bilateral parotid enlargement, erosions of the lingual surface of the teeth, loss of enamel, dental caries?	Bulimia nervosa
SSRIs are more effective in treating which eating disorder?	Bulimia nervosa
Adolescent girl with migraine headaches wants birth control pill. What condition do you need to rule out?	Migraine with aura is an absolute contraindication to the use of combined oral contraceptive pills
What is the most highly effective birth control option available to an adolescent girl?	Long acting reversible contraceptives, including intrauterine devices and subdermal implants
The percentile of BMI that is considered childhood obesity	$\geq$ 95th percentile for age and sex
The percentile of BMI that is considered overweight in children	Between the 85th and 95th percentiles for age and sex
Adolescent male with right breast enlargement that is tender to touch, < 4 cm in size	Reassurance (most cases of pubertal gynecomastia < 4 cm resolve within 3 years)
A 13-year-old girl with left-sided thoracic scoliosis on exam with a scoliometer showing 8°. What is your next step?	Radiograph, and if Cobb angle $\geq$ 20°, refer to orthopedics
A 13-year-old adolescent presents for her third HPV vaccination	CDC now recommends that 11- to 12-year-old receive 2 doses of HPV vaccine instead of 3 doses ($\geq$ 15 years of age require 3 doses)

GENETIC DISORDERS

Golder N. Wilson

Last-Minute Review—Genetic Disorders	Most Likely Answer
Both sexes are equally affected, both sexes transmit to offspring, no skipped generation, every child has a parent with disorder except new or spontaneous mutation	Autosomal dominant (AD)
Both sexes are equally affected, both sexes can transmit a copy of mutated gene, and their risk to have affected child is 25%, the disorder may be seen in one or more sibling, not all generations are affected	Autosomal recessive (AR)
No male-to-male transmission, only females transmit the disease to their sons, daughters are obligate carriers	X-linked recessive
Maternal transmission from egg to zygote; both males and females are affected	Mitochondrial inheritance
Hypotonia, upslanted palpebral fissures, epicanthal folds, systolic murmur, single transverse creases in hands, brachydactyly, broad space between the first and second toe	Down syndrome (trisomy 21)
Screening for hypothyroidism in cases of Down syndrome is at what age?	Newborn screening after birth, at 6 and 12 months, then annually if normal
Acute myeloid leukemia (AML) is a higher risk in the patient with Down syndrome at what age?	< 1 year
Acute lymphocytic leukemia (ALL) is a higher risk in the patient with Down syndrome at what age?	> 1 year
Newborn with Down syndrome with no murmur on physical examination	Echocardiography (50% of children with Down syndrome have a cardiac defect)
The most common cardiac defects associated with Down syndrome	AV canal defects, ventricular septal defect, atrial septal defect, and tetralogy of Fallot
The most common gastrointestinal defects associated with Down syndrome	Duodenal atresia, Hirschsprung disease
Newborn with clenched fist with overriding fingers, rocker bottom feet, small head, eyes, and mouth with low-set malformed ears, micrognathia, prenatal and postnatal growth deficiency, hypotonia, and ventricular septal defect	Trisomy 18 (Edward syndrome)
Newborn with cleft lip, cleft palate, microcephaly, microphthalmia, cutis aplasia, and postaxial polydactyly	Trisomy 13 (Patau syndrome)
A 5-year-old boy with intellectual disability, large hands and feet, long face with large ears, large testicles, and hyperextensible joints	Fragile X syndrome

Last-Minute Review—Genetic Disorders	Most Likely Answer
Newborn girl with microcephaly, ocular hypertelorism, prominent glabella, frontal bossing (Greek helmet face), beaked nose, hypotonia, and seizures	Wolf–Hirschhorn syndrome (4p-deletion)
Newborn with a cat-like cry, hypotonia, microcephaly, moon face, widely-spaced eyes, down-slanting palpebral fissures, high-arched palate, and wide-flat nasal bridge	*Cri du chat* syndrome (5p-deletion)
Newborn with microcephaly, atresia of the ear canal, deep-set eyes, depressed mid-face, protruded mandible, legs are flexed, externally rotated, and in hyperabduction (frog-like position)	De Grouchy syndrome
Newborn with profound hypotonia, small for gestational age, feeding problems, failure to thrive, bitemporal narrowing, thin upper lip, almond-shaped eyes, hypogonadism, bilateral cryptorchidism, and small penis	Prader–Willi syndrome (PWS) (paternally derived deletion 15q11–13)
Child with hypotonia, jerky ataxic movement, fair hair, large chin and mandible, inappropriate bouts of laughter, and severe intellectual disability	Angelman syndrome (maternally derived deletion 15q11–13)
Child with an intellectual disability, supravalvar aortic stenosis, hypercalcemia, friendly "cocktail party" personality, and strabismus	Williams syndrome
The most common cause of hypercalcemia in a child with Williams syndrome	Idiopathic
Wilms tumor, **A**niridia, **G**enitourinary malformation, **R**etardation (intellectual disability), long face, upward-slanting palpebral fissures, ptosis, and a beaked nose, due to the absence of PAX6 and WT1 (Wilms tumor) genes	WAGR syndrome
Newborn with **C**oloboma, Congenital **H**eart defects, choanal **A**tresia, growth and **R**etardation (intellectual disability), GU anomalies (hypogonadism), and **E**ar anomalies	CHARGE syndrome (gene defect CHD7 on chromosome 8q)
Vertebral defects, **A**nal atresia, **C**ardiac defects, **T**racheoesophageal fistula, and/or **E**sophageal atresia, **R**enal anomalies, and **L**imb defects	VACTERL/VATER association
The most common association with VATER/VACTERL syndrome	Congenital heart defects
Jaundice, bile duct paucity with cholestasis, peripheral pulmonary stenosis, butterfly vertebrae, triangular face with a pointed chin, long nose with broad mid-nose, and posterior embryotoxon	Alagille syndrome (20p12)
Cleft palate, absent thymus, hypocalcemia, tetralogy of Fallot, interrupted aortic arch, recurrent infection, short stature, and behavioral problem	DiGeorge syndrome (22q11.2)

Last-Minute Review—Genetic Disorders	Most Likely Answer
Cleft palate, micrognathia, glossoptosis, respiratory distress (airway obstruction caused by backward displacement of the tongue base), and feeding difficulties	Pierre–Robin sequence
Pierre–Robin sequence (cleft palate, glossoptosis, and micrognathia or retrognathia); severe myopia or other ocular abnormalities; sensorineural hearing loss; or skeletal abnormalities including hypermobility, scoliosis, or early arthritis	Stickler syndrome
Newborn with a disruptive cleft on the face and amputated digits	Amniotic band sequence
Preauricular pits, preauricular tags, microtia, hypoplastic cochlea, hearing loss, branchial fistula, and renal dysplasia or aplasia	Branchio-oto-renal syndrome
Newborn with underdeveloped mandibular and zygomatic bones, microtia, stenosis of the external ear canal, down-slanting palpebral fissures, coloboma, and conductive hearing loss	Treacher-Collins syndrome (mandibulofacial dysostosis type 1)
Short stature below third percentile, short length of the proximal segment of upper arms and legs (rhizomelic shortening), trident hands, stenosis of the foramen magnum, macrocephaly, flat nasal bridge and mid-face	Achondroplasia
The most common cause of death in children younger than 4 years with achondroplasia	Brain stem compression
Child, with multiple bruises, blue sclera, recurrent fractures, hyperextensible joints, and had delayed closure of fontanelle	Osteogenesis imperfecta (type I is the most common)
Adolescent, tall, the lens is dislocated upward, high-arched palate, pectus carinatum, aortic dilatation, and lumbosacral ectasia	Marfan syndrome
Adolescent with hyperextensible skin, hypermobile joints, kyphoscoliosis, easy bruising, skin scarring, mitral valve prolapse, and abnormal capillary fragility test	Ehler–Danlos syndrome
Eight *café-au-lait* spots, freckling of the axilla, Lisch nodules, optic glioma, and pseudarthrosis of the fibula	Neurofibromatosis type I
An 18-year-old boy with a family history of eighth cranial nerve masses presents with hearing loss, tinnitus, loss of balance, blurring of vision, and posterior subcapsular lens opacities on eye examination	Neurofibromatosis type II
Adolescent presents with facial acne that is not responding to treatment, has ash leaf (hypopigmented macules), facial angiomas (adenoma sebaceum), nail fibroma, pitting of dental enamel, and renal angiomyolipomas	Tuberous sclerosis

Last-Minute Review—Genetic Disorders	Most Likely Answer
Infantile spasm is commonly associated with	Tuberous sclerosis
Helpful sign to assist in early diagnosis of tuberous sclerosis	Ash leaf spots (hypopigmented macules)
Most common cardiac finding in infants with tuberous sclerosis	Cardiac rhabdomyomas
Newborn with long eyelashes, hirsutism, low hairline, downward-turned mouth, intrauterine growth restriction (IUGR), thin upper lip, micromelia, and syndactyly	Cornelia De Lange syndrome
Child with partial albinism, white forelock, premature gray hair, iris heterochromia, cleft lip, and cochlear deafness	Waardenburg syndrome
Child with a history of hypoglycemia and omphalocele at birth, coarse facial features, large tongue, earlobe creases, posterior auricular pits, Wilms tumor, and cryptorchidism	Beckwith–Wiedemann syndrome
Infant with macrodactyly, hemihypertrophy, lipoma, hemangioma, soft-tissue hypertrophy, and accelerated growth	Proteus syndrome
Newborn large for gestational age, macrocephaly, prominent forehead, hypertelorism, intellectual disability, large hands and feet	Soto syndrome
Brachycephaly, frontal bossing, wormian bones, hypoplastic or absent clavicles, delayed eruption of deciduous teeth, and joint laxity	Cleidocranial dysostosis
Early fusion of sagittal suture, and the head is long and narrow	Scaphocephaly (the most common type of craniosynostosis)
Newborn with craniosynostosis, brachycephaly, strabismus, hypertelorism maxillary hypoplasia, beaked nose, proptosis, syndactyly, single nail, broad thumb	Apert syndrome
Craniosynostosis, short stature, deviated nasal septum, malocclusion, malposed teeth, no limb defects	Crouzon syndrome
Craniosynostosis, broad thumb and toes	Pfeiffer syndrome
Tower or clover-leaf skull due to multiple fused sutures, preaxial polydactyly, obesity	Carpenter syndrome
Genetic counseling requires	A specific diagnosis with known inheritance mechanism
Indications for obtaining a karyotype: examples	Unusual appearance, multiple congenital anomalies, and/or possible mental disability
Child has a routine karyotype that reveals 47, XX+21. Appropriate counseling for the parents is	To explain that their child has Down syndrome due to aneuploidy and that they do not need to have their chromosomes checked
Cytogenetic nomenclature for embryonic germ cells from a female fetus with the trisomy form of Down syndrome would be	47, XX+21

Last-Minute Review—Genetic Disorders	Most Likely Answer
A couple desires prenatal diagnosis because the woman is 39 years old. They want the safest and most reliable form of prenatal testing	Amniocentesis
Child has obesity, compulsive overeating, and underdeveloped genitalia, which make you suspect Prader–Willi syndrome. You recall that FISH testing for a chromosome 15 submicroscopic deletion may be diagnostic. The best approach for obtaining a laboratory diagnosis	Obtain a green-top (heparinized) tube for the harvest of white cells with the indication of routine karyotype, including FISH for microdeletion 15
Chorionic villus sampling is performed at which weeks of pregnancy?	10–12 weeks of pregnancy
Amniocentesis is performed at which weeks of pregnancy?	12–16 weeks of pregnancy
Male with tall stature, speech and language delay, learning disabilities, cystic acne in adolescence, no facial dysmorphology, normal intelligence	47, XYY syndrome
Female with tall stature; speech/language delay; learning disabilities; normal intelligence, sexual development, and fertility	47, XXX syndrome "triple X syndrome"
Male infant with short webbed neck, low posterior hairline, edema of hands and feet, mild intellectual disability mutation of *PTPN11* gene	Noonan syndrome
A 10-year-old boy with progressive motor disability, cognitive decline, and psychiatric disturbances; his father had the same condition at age 40 years, died at age of 60	Juvenile Huntington disease (because of CAG trinucleotide repeat expansion, clinical onset can occur in childhood) AD

METABOLIC DISORDERS

Golder N. Wilson

Last-Minute Review—Metabolic Disorders	Most Likely Answer
Newborn with a high ammonia level, normal anion gap, and respiratory alkalosis. What metabolic disorder category is this likely to be?	Urea cycle defect (UCD)
Newborn with poor feeding, vomiting, elevated ammonia levels, and respiratory alkalosis and elevated citrulline levels	Citrullinemia-UCD
Child presents with ammonia level 2000 μmol/L, low BUN, with respiratory alkalosis without ketoacidosis and high levels of orotic acid	Ornithine transcarbamylase deficiency (OTC)-UCD
What are the initial steps of urea cycle defect (UCD) management?	Reduce protein intake, correct respiratory alkalosis
Normal to high ammonia level with a high-anion gap acidosis. What metabolic category is this likely to be?	Organic acidemia

Last-Minute Review—Metabolic Disorders	Most Likely Answer
A neonate with severe ketoacidemia with or without elevated ammonia level, and long-term complication is associated with cardiomyopathy	Propionic acidemia
Which metabolic disease can cause encephalopathy and is associated with an odor of sweaty feet?	Isovaleric acidemia
Which metabolic disease presents with retinal hemorrhage and intracranial bleeding and can be mistaken for child abuse?	Glutaric aciduria type I
A 1-week-old presents with severe metabolic acidosis, poor feeding, opisthotonos, absent Moro reflex, seizures, and urine with a "caramel-like odor"	Maple urine syrup disease Treatment: restrict leucine intake
What is the category of these amino acids: valine, leucine, and isoleucine?	Three branched-chain amino acids
A 6-month-old has alopecia, encephalopathy; skin rash looks like acrodermatitis enteropathica	Biotinidase deficiency or holocarboxylase synthetase deficiency
A 2-year-old girl presents with seizures, tachypnea, and drowsiness; she has been having diarrhea, vomiting, and loss of appetite for the last few days. Her labs showed hypoglycemia, low ketones, and hyperammonemia	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (due to fatty acid oxidation defect, she is unable to increase ketone body production after glucose consumption during fasting or metabolic stress due to illness)
Child presents with a musty odor, eczema, fair skin and hair, and intellectual disability	Phenylketonuria (PKU)
Newborn with positive PKU on newborn screening. What is the next best step?	Start low-protein diet and a phenylalanine-free medical formula as soon as possible. Then confirm with genetic testing
What is the major consequence of delaying dietary restriction in children with PKU?	Irreversible intellectual disability in most children
Black pigments in the diapers, unusually dark urine few days after birth; when older, develops blue discolorations in the ear cartilage and palpable calcifications in the discolored areas, arthritic symptoms in the spine, hip and knee	Alkaptonuria
Child with an intellectual disability, normal aorta, pectus excavatum, increased risk of clotting, along with *downward dislocation of the lens* (ectopia lentis)	Homocystinuria (in Marfan syndrome the lens is dislocated upward and no intellectual disability)
Infant with failure to thrive, hepatomegaly; renal tubular acidosis may be associated with hepatoblastoma	Tyrosinemia type I (hepatorenal)
Type of tyrosinemia associated with intellectual disability, corneal ulcers, and painful skin lesions on the palms and soles	Tyrosinemia type II (oculocutaneous tyrosinemia)
A 4-week-old infant presents with vomiting, seizure, jaundice, poor weight gain, hepatosplenomegaly, cataracts, and reduced substance in the urine	Galactosemia (galactose 1-phosphate uridyltransferase deficiency)

Last-Minute Review—Metabolic Disorders	Most Likely Answer
Infant had sepsis before the diagnosis of galactosemia. What was the most likely cause?	*Escherichia coli (E. coli)*
Healthy infant presents with cataracts only. What is the most likely cause?	Galactokinase deficiency
A 4-month-old, doll-like face with prominent cheeks, short stature, thin extremities, protuberant abdomen, hepatomegaly, hypoglycemia, seizures, lactic acidosis, hyperuricemia, and hyperlipidemia	Type I glycogen storage disease (von Gierke disease)
What is the best management of infants with von Gierke disease?	Continuous feeding at night with nasogastric tube
Cramps with exercise, burgundy-colored urine after exercise, elevated creatine phosphokinase (CPK), and ammonia levels after exercise	McArdle disease (type V glycogen storage disease)
A 6-week-old infant previously normal presents with muscle weakness, hypotonia, large tongue, hepatomegaly, hypertrophic cardiomyopathy, congestive heart failure, elevated CPK, transaminases, and LDH; muscle biopsy shows vacuoles full of glycogen	Pompe disease (type II glycogen storage disease)
A previously healthy 7-month-old infant with new-onset seizures, vomiting, and lethargy that started after fruit juice was introduced	Fructokinase 1,6, diphosphatase deficiency
An 18-month-old with inguinal and umbilical hernias, now presents with progressive developmental delay, coarse facial features, macroglossia, macrocephaly > 95%, hepatosplenomegaly, corneal clouding, retinal disease, and deafness	Hurler syndrome Mucopolysaccharide (MPS) type I
An 18-month-old boy, previously healthy, presents with progressive developmental delay, coarse facial features, macroglossia, macrocephaly > 95%, hepatosplenomegaly, no corneal clouding	Hunter syndrome MPS type II (X-linked recessive)
Child previously normal presents with a progressive intellectual decline, temper tantrums, hyperactivity, destructive and aggressive behavior, pica and sleep disturbances, now becomes immobile and unresponsive	Sanfilippo syndrome MPS type III
Acroparesthesia or episodes of extremities with burning pain, anhidrosis, fever, proteinuria, hypertension, angiokeratomas (painless papules on the skin), and clouding of the cornea	Fabry disease (X-linked recessive)
A 3-year-old of Ashkenazi Jewish presents with severe splenomegaly, lytic bone lesions, and decreased glucocerebrosidase levels	Gaucher disease type I

Last-Minute Review—Metabolic Disorders	Most Likely Answer
A 2-month-old infant startles easily to any noise, does not diminish with repeated stimuli, hypotonia, progressive muscle weakness, extremity hypertonia, large head, noises trigger seizures, macular cherry-red spot, and no organomegaly	Tay–Sachs disease
A 4-year-old child, dysphagia, abnormal eye movement, ataxia, hepatosplenomegaly, cataplexy when scared, and narcolepsy	Niemann–Pick disease
Infant with a history of developmental delay, **M**yopathy, **E**ncephalopathy, **L**actic Acidosis, and **S**troke	(MELAS) syndrome
Ptosis, ophthalmoplegia, ragged-red fiber myopathy	Mitochondrial DNA (mtDNA) mutation
An 18-year-old develops ophthalmoplegia, night blindness, ataxia, heart block, muscle weakness, proximal myopathy, short stature, and hypogonadism	Kearns–Sayre syndrome
A 12-year-old, ataxia, hypoactive or absent deep tendon reflexes, impaired vibratory and proprioceptive functions, hypertrophic cardiomyopathy, and diabetes mellitus	Friedreich ataxia
Boy, biting his lips, and fingers; normal at birth, had difficulty gaining weight in the 1st year of life, uric acid level is elevated	Lesch–Nyhan disease
What is the enzyme deficiency in patients with Lesch–Nyhan disease?	Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)
How is Lesch–Nyhan disease transmitted?	X-linked recessive
Loss of developmental milestones; failure to thrive; truncal hypotonia; abnormal kinky hair, eyebrows, and eyelashes	Menkes disease or kinky hair disease
How is Menkes disease transmitted?	X-linked; causes an impaired copper intake
Child with cholesterol 650 mg/dL, tendon xanthoma, father died at age 23 with a heart attack	Familial hypercholesterolemia

MENTAL AND BEHAVIORAL HEALTH

Osama I. Naga

Last-Minute Review—Mental and Behavioral Health	Most Likely Answer
A 3-year-old boy is frequently reaching for his genitalia; his face becomes flushed; he is sweating and starts to breathe irregularly, stops when parents distract him	Masturbation (distract the child to stop)

Last-Minute Review—Mental and Behavioral Health	Most Likely Answer
A 2-year-old girl frequently postures her lower extremities and keeps crossing her legs in a repetitive movement; she stops when her mother is distracting her; the mother is concerned about her having a seizure	Masturbation (seizure will not stop with distraction)
What is the best management of masturbation in children?	Guide the child to limit the behavior. Otherwise, it is a normal behavior
A 2-year-old boy is sucking his thumb mostly when he is tired, hungry, or sad. What is the best recommendation?	Reassurance (most children will outgrow the habit by 4 years of age)
A 6-year-old boy with thumb sucking behavior. He is bullied and teased in school. He has dental malocclusion. What is the best recommendation?	Positive reinforcement, aversive techniques, competitive responses, and orthodontic devices (intervention if > 4 years of age)
A 6-year-old boy wakes up in the middle of the night scared; he remembers a giant dinosaur was trying to eat him	Nightmares—reassurance (television viewing should be avoided for about 2 h prior to bedtime)
The parents of a 4-year-old girl have noted episodes of screaming, intense fear, with difficulty of arousal that occur several times per week; she does not remember the episodes	Night terrors—reassurance (preemptive awakening before the episodes and safety precautions)
Adolescent female presents with numbness and difficulty moving her legs. All lab results and imaging studies are normal. The patient has been feeling stressed as a result of school	Conversion disorder
A 7-year-old boy exposed to a horrific car accident; father died in the accident. Boy has difficulty sleeping, a flashback of the event, recurrent distressing dreams for 3 weeks after the accident	Acute stress disorder 3 days to 1 month after exposure
A 7-year-old boy exposed to a horrific car accident; father died in the accident. Boy has difficulty sleeping, a flashback of the event, recurrent distressing dreams for 6 months after the accident	Post-traumatic stress disorder (6 months after exposure)
Two siblings are jealous of each other and are always fighting each other in front of their parents. "Sibling rivalry." What is the best approach?	Focus on individual needs of each child, giving each the time and attention needed, to feel loved and secured
Exposure to which substances during the prenatal period is associated with aggressive behaviors in children?	Cocaine, alcohol, and tobacco
Two siblings are fighting and hurting each other physically	They should be separated, and told violence is not allowed

Last-Minute Review—Mental and Behavioral Health	Most Likely Answer
What is the best way to discipline a 3-year-old boy who is misbehaving?	Time out—1 min for each year of age
	Ensuring that the reward is developmentally appropriate
	Corporal punishment is NOT recommended as a method of discipline
What is the best method of discipline recommended for an adolescent?	Limit privileges and establish boundaries
A 2-year-old boy is crying hysterically and banging his head while the mother and father are in a restaurant	Acknowledge his frustration, take him in safe place letting him ride out the tantrum
Mother is worried about autism in the above instance because of headbanging and frequent outbursts	Headbanging in isolation with a tantrum is not a red flag of autism
A 4-year-old boy is frightened of dogs	Show him pictures of dogs, then videos, then toy dog, then finally a real dog
Child is adaptable to new situations, regular sleeping, and eating patterns, less demanding, and cheerful	Easy temperament
Child with intense emotional reactions adapts poorly to new situations, unpredictable, lower sensory threshold, moody and negative	Difficult temperament
Child initially withdraws from new situations, observes hesitantly before entering a new activity, moderate negative response, and gradually warms up to the new situations	Slow to warm temperament
What is the best management of temperaments?	Reassurance (will learn to moderate their own temperamental reactions as they grow older)
Adolescent with 2 weeks of depressed or irritable mood, decreased pleasure, still going to school and doing homework, no suicidal thoughts. What is the best initial treatment?	Cognitive behavioral therapy (CBT)
Adolescent with 2 weeks of depressed, irritable mood, decreased pleasure, lack of interest in activities, and suicidal thoughts. What is the best initial treatment?	Cognitive behavioral therapy (CBT) and medication
What are the SSRI medications approved by the US Food and Drug Administration (FDA) for the treatment of depression in adolescents?	Fluoxetine and escitalopram
What does CBT aim to achieve?	To reframe present negative thoughts into healthier thoughts, resulting in more positive feelings and behaviors
A 6-year-old boy with significant receptive and expressive language problems; he is in special education classes, has difficulty with changes and sensory sensitivity. He bites his hands frequently and avoids eye contact. What is the most likely underlying condition?	Fragile X syndrome

Last-Minute Review—Mental and Behavioral Health	Most Likely Answer
At what age are the dysmorphic features of fragile X syndrome, such as a long face, prominent jaw, and macroorchidism, usually seen?	Around the time of puberty
What is the most common cause of inherited intellectual disability?	Fragile X syndrome
What is the most likely cognitive deficit in boys with a full mutation (> 200 CGG repeats) in cases of fragile X syndrome?	Moderate ID (average IQ ~41), girls are more mildly affected
What is the best test to confirm the diagnosis of fragile X syndrome	Fragile X DNA analysis
Mother is concerned about possible speech delay in her 2-year-old, who is currently exposed to 2 languages at home	No significant difference between 1 and 2 languages exposure in speech development
Mother is concerned because her 6-year-old has a problem with certain speech sounds, but the child's speech is 100% intelligible to strangers	Reassurance (certain speech sounds may not be well articulated until 8 years of age)
Child with speech and language delay. What is the next best step?	Formal audiology evaluation
A 2-year-old boy presents with speech delay, no eye contact, does not share any activities with other children. Physical examination is normal. What is the next best step?	Refer the child to early intervention (EI) for evaluation of autism spectrum
A 3-year-old boy presents with speech delay, no eye contact, does not share any activities with other children. Physical examination is normal. What is the next best step?	Refer to the school district for evaluation of autism spectrum
What is the mainstay of autism spectrum disorder treatment?	Applied behavioral analysis (ABA), speech and occupational therapies
What is the etiologic workup in classic cases of autism spectrum disorders?	None; it is a clinical diagnosis
What is the etiologic workup in cases of autism spectrum disorders associated with intellectual disability or global developmental delay?	DNA analysis for fragile X syndrome and a chromosome microarray analysis
Adolescent with several antisocial behaviors, defiance, rule-breaking, vandalism, and aggression. What is the best management?	Cognitive behavioral therapy, family therapy, and behavior management training
An 8-year-old boy is struggling academically, no specific learning disability has been identified by the school. What is the next best step?	Summer school, after school programs, tutoring, and early reading programs
What is the disadvantage of grade retention in students who are struggling academically?	High risk of dropping out of high school, and ultimately employment problems
A 10-year-old girl is struggling in school; parents are concerned because of her poor grades. What is the next best step?	Psychoeducational evaluation request in writing from parents to her school

Last-Minute Review—Mental and Behavioral Health	Most Likely Answer
What is the role of pediatricians in children with learning disabilities upon diagnosis?	Review the initial psychoeducational evaluation and child's report card with the family.
	Make sure that the child is receiving remediation, accommodations, modifications, and therapies.
	Investigate for related disorders, such as attention deficit hyperactivity disorder (ADHD), adjustment disorder, or anxiety disorder.
An example of a child who may benefit from the 504 plans	Child with ADHD. Section 504 (Accommodation) of the US *Rehabilitation Act of 1973* covers kids with disabilities who do not require specialized instruction (504 school accommodations for peanut allergy is another example)
Examples of accommodations in school under 504 for children with ADHD	Preferential seating, extended time for testing, modifications in classroom assignments
Which child may benefit from the US *Individuals with Disabilities Education Act (IDEA)*, providing qualified children with an Individualized Education Program (IEP)?	Specific learning disability, e.g., dyslexia, dysgraphia, dyscalculia Others, e.g., autism, deafness, vision impairment, intellectual disability
Can a child with ADHD qualify for IEP?	Yes, if he or she requires specialized instructions
The first-line treatment of ADHD	Stimulant medications, e.g., methylphenidate
Indications of non-stimulant medications (e.g., atomoxetine, guanfacine, clonidine) in the treatment of ADHD	Preference of parents
	Poor response or significant side effects with stimulant medications
	Concerns about substance/stimulant abuse or significant tics
What is the significance of IQ test scores greater than 2 SD below the mean (< 70) in both cognitive and adaptive measures?	Intellectually disabled range
An 8-year-old girl underwent psychoeducational testing, and her aptitude test score in IQ was within normal range, her academic achievement scores were within normal in reading, and writing, but in math her score was < 70	Specific learning disability in math
The girl in the previous example qualifies for which of the following: 504 plan or IEP?	IEP special education program
Participation of children with and without disabilities in the same educational settings	Educational inclusion
What are the benefits of educational inclusion?	Promotes tolerance, empathy, and collaboration among students
Independent in personal care and activities of daily living with minimal support, education level *up to sixth grade*, independent employment with a possible need for minimal support or supervision	Mild intellectual disability (ID)

Last-Minute Review—Mental and Behavioral Health	Most Likely Answer
Can care for personal needs and activities with limited support, education level *up to third grade*; difficulty understanding time and money, supportive living such as in a group home, supported, or supervised job, unskilled or semi-skilled work	Moderate ID

EMERGENCY MEDICINE

Jennifer McConnell and Kenneth Yen

Last-Minute Review—Emergency Medicine	Most Likely Answer
A 27-day-old with fever 103 °F for 1 day, feeding well, no cough, no vomiting, no diarrhea. Physical examination is normal. What is the next best step?	Full sepsis evaluation (blood, urine and CSF testing) and empiric IV antibiotics
An 8-week-old with fever 103 °F for 2 days, feeding well, no cough, no vomiting, no diarrhea. Physical examination is normal. What is the next best step?	Complete blood count (CBC), urinalysis and urine culture (infants < 90 days of age with a temperature > 38 °C should be promptly evaluated)
A 15-month-old with fever 103 °F for 2 days, feeding well, fussy when fever is high, playful for brief periods after receiving antipyretics, no cough, no vomiting, no diarrhea. Physical examination is normal. What is the next best step?	Reassurance (most likely viral syndrome, advise close follow-up)
Non-toxic, fully vaccinated toddler with nasal congestion has a barky cough, inspiratory stridor when agitated, but no resting stridor. What is the next best step?	Oral dexamethasone (viral croup)
A well-appearing, 12-month-old with upper respiratory infection (URI) symptoms and fever presents with diffuse wheezing on lung auscultation. What is the next best step?	Clearance of nasal secretions and reassurance (acute viral bronchiolitis)
Child with asthma, presenting with chest pain, chest tightness and diffuse bilateral expiratory wheezing in the setting of URI symptoms. What is the next best step?	Albuterol and ipratropium nebulizer treatments with oral steroids
Distressed, vaccinated toddler, with sudden onset of cough and inspiratory stridor while eating peanuts. What is the next best step?	Attention to ABCs (airway, breathing, circulation) and emergent subspecialty evaluation for a suspected foreign body in airway
An unvaccinated child with inspiratory stridor at rest, toxic appearing, leaning forward and drooling. Next best step?	Attention to ABCs (airway, breathing, circulation) and emergent subspecialty evaluation for suspected epiglottitis
Child with peanut allergy presents with diffuse hives and flushed skin after ingestion of peanuts, noted to have hypotension on initial vital signs. What is the definitive treatment for the underlying diagnosis?	IM epinephrine for anaphylaxis
Child presents to the emergency department (ED) with a dog bite. What is the next best step?	Wound cleaning with adequate pressure irrigation

Last-Minute Review—Emergency Medicine	Most Likely Answer
After cleaning the wound of dog or cat bite, what is the most appropriate prophylactic antibiotic?	Amoxicillin/clavulanate, cover both aerobes and anaerobes, especially *Pasteurella*
Dog or cat bite and allergy to penicillin	Clindamycin plus trimethoprim-sulfamethoxazole
Teenage patient punches another student in the teeth during an altercation at school and sustains puncture lacerations to knuckles; what is the most appropriate prophylactic antibiotic?	Amoxicillin/clavulanate, cover both aerobes and anaerobes, especially *Eikenella*
A fully vaccinated child with a bite from a stray dog that was not captured. The child was admitted on NPO status due to multiple puncture lacerations requiring surgical repair. What is the next best treatment?	Rabies prophylaxis (rabies vaccine and rabies immunoglobulin) and intravenous ampicillin-sulbactam
Adolescent with pain, redness, and tenderness in the foot after stepping on a rusty nail that punctured the foot. There is no fever and the rest of the exam is normal. Last tetanus vaccine was 7 years ago. What is the best treatment?	Tdap vaccine and oral ciprofloxacin *Pseudomonas aeruginosa* infection
Child with a sudden stinging sensation in the right foot after playing in the basement, within a few hours develops severe pain and enlarging erythema in the right foot, which 2 days later becomes a hemorrhagic blister surrounded by an erythematous halo and dark eschar. What is the most likely cause?	Brown recluse spider bite (local pain, necrosis, and less systemic manifestations)
Child presents with sudden pinching sensation in the foot after playing in the basement, within 8 h develops muscle cramping in the right leg, which progresses to the back and abdomen. O/E: elevated blood pressure, tachycardia, tender abdomen, target-like appearance redness in the foot. What is the most likely cause?	Black widow spider bite (initial pinch or pinprick sensation, or unnoticed bite followed by significant systemic manifestations, muscle cramping, tachycardia, and hypertension)
Child stung on the left arm by a wasp, having pain, itching, erythema, and mild swelling in the left arm without any signs of systemic illness. What is the best treatment?	Removal of the stinger, application of cool compresses or ice packs, and mild oral analgesics and oral antihistamines to help alleviate pruritus
A 1-year-old falls < 3 ft height, no loss of consciousness, no headache, no vomiting. Physical examination is normal except mild swelling in the forehead. What is the next best step?	Reassurance (very low risk of clinically significant traumatic brain injury [height of fall in **< 2** years of age **> 3 ft** is a high risk])
A 3-year-old falls < 5 ft height, no loss of consciousness, no headache, no vomiting. Physical examination is normal except mild swelling in the forehead. What is the next best step?	Reassurance (very low risk of clinically significant traumatic brain injury [height of fall in **> 2** years of age **> 5 ft** is a high risk])
A 6-year-old boy fell and hit his head while running, loss of consciousness for 30 s, one-time vomiting, headache that has slightly improved in the last 30 min. Physical examination is normal except mild swelling in the forehead. What is the next best step?	Observation period 4–6 h in ED

Last-Minute Review—Emergency Medicine	Most Likely Answer
Child brought to the ED after severe head trauma, continues to have persistent vomiting and altered level of consciousness. What is the next best step?	Attention to ABCs (airway, breathing, and circulation)—the child needs CT head but first requires stabilization
A 6-year-old boy fell and hit his head, loss of consciousness for 2 min, progressive headache, persistent vomiting. Physical examination is normal except mild swelling in the forehead. What is the next best diagnostic test?	Head CT scan without contrast
A 6-year-old boy fell and hit his head, loss of consciousness, headache, vomiting, improvement for few hours (lucid interval) followed by deterioration of symptoms and loss of consciousness. CT head shows hyperdense lenticular-shaped mass situated between the brain and the skull. Most likely diagnosis?	Epidural hematoma—convex toward the brain and restricted by suture lines in CT scan
Head trauma, severe headache, and drowsiness. Head CT scan showed hyperdense (white), crescent-shaped mass between the inner table of the skull and the surface of the cerebral hemisphere. Most likely diagnosis?	Subdural hematoma—concave toward the brain and unlimited by suture lines in CT scan
Head trauma, bleeding from the ear, hearing loss, and facial paralysis. Most likely injury?	Temporal bone fracture
Head trauma, ecchymosis behind the ear (battle sign), periorbital ecchymosis (raccoon eyes), abducens nerve paralysis. Most likely injury?	Basilar skull fracture
Glasgow Coma Scale (GCS) of a child after head trauma who opens eyes only to sound, makes a few unintelligible sounds but does not say words, and localizes to pain	GCS = 10 (3 E/2 V/5 M)
Effect of clonidine, cholinergic, opiates, organophosphates, phencyclidine, phenothiazine, pilocarpine, and barbiturates (sedatives) on the pupil	Miosis
Effect of atropine, antihistamines, antidepressants, amphetamine, and cocaine on the pupil	Mydriasis
Ingestion of which agents can cause seizures, hyperthermia, agitation, decreased urine output, anhidrosis, flushing, and mydriasis?	Anticholinergic agents (e.g., amitriptyline, diphenhydramine, jimson weed, or deadly nightshade)
Ingestion of which agent can cause pinpoint pupils, unresponsiveness, and respiratory depression?	Opiate intoxication
What is the treatment of choice for opiate poisoning?	Naloxone
Child presents with neck spasms, oculogyric crisis, and tongue thrusting after accidental ingestion of promethazine (anti-nausea medication). What is the drug of choice to treat these symptoms?	Diphenhydramine; the patient has an acute dystonic reaction
Child ingests a large amount of a grandparent's medicine, presents with hyperventilation, metabolic acidosis, high-anion gap, tinnitus, and confusion. Likely ingestion?	Aspirin

Last-Minute Review—Emergency Medicine	Most Likely Answer
Healthy child ingests caretaker's medicine, presents with altered mental status, seizure, drowsiness, lethargy, sinus tachycardia, widened QRS, prolonged QT interval. Likely ingestion?	Tricyclic antidepressants (TCA) toxicity
Adolescent currently on SSRI treatment for depression presents with confusion, sweating, and myoclonus admits to trying ecstasy at a party. Likely cause of symptoms?	Serotonin syndrome—hallmark is myoclonus Occurs with: monoamine oxidase inhibitor (MAOI) and linezolid
Child is brought to the ED after ingesting numerous pills of metformin. Possible laboratory finding?	Lactic acidosis
Child presents with nausea, vomiting, abdominal pain 6 h after accidental ingestion of pills, felt better for a short period, then 24 h later presents with metabolic acidosis, shock, hepatic failure, and 6 weeks later develops pyloric and gastrointestinal scarring. What is the most likely ingested substance?	Iron
Child reaches the toxic level of acetaminophen 4 h after accidental ingestion. What is the antidote?	N-acetylcysteine (NAC)
Toddler ingests a small amount of windshield wiper fluid about 30 min before the presentation, is asymptomatic. Caretaker calls primary care office for advice. What is the next best step?	Immediate referral to the ED for further laboratory testing (toxic alcohol ingestion→ methanol)
Adolescent presents with slurred speech, tachypnea, cyanosis, pulmonary edema, renal failure, calcium oxalate crystals in the urine, high-anion gap metabolic acidosis. Likely ingestion?	Ethylene glycol
Adolescent presents with visual disturbance, abdominal pain, and high-anion gap metabolic acidosis. Likely ingestion?	Methanol
Child accidentally ingests window cleaner, presents with sore throat, dysphagia, and drooling. Next best step?	Caustic ingestion, immediate subspecialty consultation for endoscopy
Child complains of a headache, weakness, fatigue, and nausea for 2–3 weeks since the start of winter, caretaker reports self and 2 other siblings are feeling the same. Most likely exposure?	Carbon monoxide poisoning (measurement of carboxyhemoglobin on blood gas)
Child at a party ate some cookies then starts vomiting, swelling of the lips, and trouble breathing, should be treated with which medication	IM epinephrine at 0.01 mg/kg
Toddler presents with right arm pain and decreased arm mobility after being lifted up by the right arm during play. No falls or trauma reported. Most likely diagnosis?	Nursemaid's elbow (annular ligament displacement)
Child tripped and fell on an outstretched hand presents with tenderness to distal humerus. No obvious fracture on elbow radiograph, although there is a posterior fat pad sign on the lateral view. Most likely diagnosis?	Occult supracondylar fracture

Last-Minute Review—Emergency Medicine	Most Likely Answer
Term neonate delivered vaginally had difficulty with vacuum extraction presents with "bump" over left clavicle 2 weeks after birth. Most likely diagnosis?	Clavicular fracture with healing callus from a traumatic birth
Chest radiograph performed on a healthy infant for evaluation of chronic cough reveals many callus formations to the posterior ribs bilaterally. Most likely diagnosis?	Non-accidental trauma/child abuse
Toddler presents with left leg pain and limps after going down a slide and getting the left foot stuck and twisted on the edge of the slide. Radiograph of lower leg reveals a non-displaced spiral fracture of the lower third of the tibia. Most likely diagnosis?	Toddler's fracture
Which type of burn is associated with mild pain, swelling, and redness that blanches with pressure?	Superficial burn (formerly 1st-degree burn)
Which type of burn is associated with severe pain, blebs, and blisters?	Partial thickness burn (formerly 2nd-degree burn)
Which type of burn is painless with a dry and leathery appearance?	Full-thickness burn (formerly 3rd-degree burn)
Child has electrical burns to the mouth after chewing on an electrical cord. Next best step?	Refer to burn surgeon—concern for labial artery bleeding
Child who weighs 20 kg has burns on 5% of the body surface area. What IV fluids should be given and how much?	Parkland formula: 4 ml/kg/% of the burn area of lactated Ringer's Total: 400 mL with 200 mL (50% of total) given in the first 8 h and 200 mL over the next 16 h
A toddler who presents with scald burns over legs in a stocking distribution (clearly demarcated) needs what further evaluation	Evaluation for intentional injury/abuse
Toddler presents with sudden onset vomiting and lethargy, bedside point-of-care glucose and venous blood gas are normal with a non-focal neurologic exam, soft abdomen, and no concern for ingestion. Next best test?	Ileocolic US to rule out intussusception
Toddler presents with intermittent screaming episodes followed by periods of normalcy; caretaker reports a pink "jelly"-like stool. Most likely location of the intussusception?	Ileocolic
Adolescent female with acute onset of severe left lower pelvic pain, nausea, and vomiting; exam reveals severe tenderness and guarding in the left lower quadrant. Next best test?	Pelvic US to rule out acute ovarian torsion
Adolescent male with acute onset of severe right testicular pain with nausea and vomiting; exam reveals high riding testicle with absent cremasteric reflex. Next best test?	Testicular US to rule out acute testicular torsion
Child with 1 day of nonbilious emesis and diarrhea, fever, periumbilical abdominal pain, and tenderness that is radiating to the right lower quadrant. Most likely diagnosis?	Acute appendicitis
What is the initial imaging study of choice in cases of suspected acute appendicitis?	Abdominal US

Last-Minute Review—Emergency Medicine	Most Likely Answer
A 4-week-old with 10 days of worsening projectile vomiting and 1 day of intermittent apneic spells, found on ultrasound to have hypertrophic pyloric stenosis. Most likely laboratory finding?	Hypokalemic, hypochloremic metabolic alkalosis
A healthy infant with 1 day of intermittent bilious emesis. Stable vital signs on arrival. Next best test?	Upper GI series to rule out malrotation

CRITICAL CARE

Manpreet K. Virk and M. Hossein Tcharmtchi

Last-Minute Review—Critical Care	Most Likely Answer
Child sustained blunt trauma to the abdomen, all vital signs are normal, and the abdominal ultrasound (US) is positive for splenic rupture. What is the best management?	For hemodynamically stable grades I–III, conservative management with monitoring of vital signs, surgical consult, serial hemoglobin, and hematocrit measurements
Child sustained blunt trauma to the abdomen, low blood pressure, tachycardia, cold, clammy skin, and abdominal US is positive for splenic rupture. What is the best management?	Abdominal exploration
Child presents with nausea, vomiting, and malaise. O/E: the liver is slightly enlarged. Laboratory findings include elevated liver enzymes, high direct bilirubin, hypoglycemia, and prolonged prothrombin time. What is the most likely diagnosis?	Acute hepatic failure
Child presents to the ED with rapid breathing, low blood pressure, and normal oxygen saturation. O/E: tachypnea, tachycardia, clear lungs, and muffled heart sounds and widened pulse pressure. What is the most likely diagnosis?	Cardiac tamponade
A 12-year-old girl was transferred to the ED after a car accident. She is complaining of chest pain on the left side and difficulty breathing. O/E: vital signs are normal; however, she has fast and shallow breathing, a segment of the left chest moves inward upon inspiration and outward upon expiration. What is the most likely diagnosis?	Flail chest
What is the next best step in the previous case of flail chest?	Pain control, pulmonary toilet. Ensure adequate ventilation and oxygenation

Last-Minute Review—Critical Care	Most Likely Answer
A 5-year-old boy with 2 days history of severe vomiting and diarrhea. He is lethargic and not able to drink by mouth. O/E: awake but minimally interactive, low-grade fever, tachypnea, tachycardia, low blood pressure, delayed capillary refill time, cold skin, dry mucous membranes, skin tenting, and diminished peripheral pulses. What is the most likely diagnosis?	Hypovolemic shock (low intravascular volume)
What is the next step in the previous case?	Aggressive fluid resuscitation: 20 ml/kg bolus of normal saline or Ringer's lactate over 5–10 min, additional boluses may be required based on clinical assessment and ongoing losses
A 2-month-old with a history of congenital heart disease presents with hepatomegaly, and cardiomegaly, 20 ml/kg of normal saline leads to new crackles, worsening hypotension, and tachycardia. What type of shock is this?	Cardiogenic shock
Type of shock that is associated with bradycardia, hypotension, and is often associated with spinal cord injury?	Neurogenic shock
A 5-year-old boy with high fever 104 °F for 2 days. He is lethargic and not able to drink by mouth. O/E: awake but minimally interactive, temperature 104.9 °F, ill-looking, tachypnea, tachycardia, low blood pressure, delayed capillary refill time, diminished peripheral pulses. WBC count is 29,000. What is the most likely diagnosis?	Septic shock (cold shock)
The patient in the previous example continues to have low blood pressure, refractory to fluid resuscitation and antibiotics in the first 15 min. What is the next best step?	Start epinephrine infusion
A 5-year-old boy stung by a bee rapidly developed hives, pruritus, facial swelling, wheezing, difficulty breathing. His blood pressure is low. What is the next best step?	Epinephrine IM immediately
A 3-year-old girl arrived in PICU with prolonged cardiac arrest after choking on a hot dog. Her pupils are dilated and fixed, absent gag reflex, absence of spontaneous eye movements during oculovestibular and oculocephalic testing. No spontaneous movement. Lack of any respiratory effort without ventilatory support. What is the next best step to confirm brain death?	Neurological exam followed by apnea test (after 24 h of supportive care)

Last-Minute Review—Critical Care	Most Likely Answer
Child presents with no pulse; the EKG shows ventricular tachycardia. What would be the next step in the management of the arrhythmia?	Defibrillate 2 J/kg
Child presents with tachycardia, hypercarbia, generalized muscle rigidity, and hyperthermia immediately after surgery. What is the diagnosis and treatment?	Malignant hyperthermia IV dantrolene
What is the most important poor prognostic factor in near drowning?	Submersion time > 5 min
Child was found submerged in the pool, is unconscious and not breathing; what is the next best step?	Call for help and begin chest compressions
What is the best way to confirm successful ETT placement?	Colorimetric capnography
What is the depth of CPR compression for infants through puberty?	One-third the depth of the chest
What is the ratio of chest compressions to breaths in single rescuer CPR?	30:2
What is the ratio of chest compressions to breaths in 2-rescuer CPR?	15:2
What is the age range in which pediatric defibrillator pads should be used?	1–8 years
A 6-year-old boy is in cardiac arrest, a pediatric defibrillator is not available, but an adult AED is present. What should be done?	Use the adult defibrillator/adult pads
A 15-year-old male presents after an ATV accident. He is bradycardic, GCS is 7, and the right pupil is dilated and unresponsive. What are the next steps in management?	Neuroprotective measures, including emergent endotracheal intubation
Neurosurgery places an intracranial monitoring device in the previous case. What would be the target cerebral perfusion pressure (CPP) for this age?	More than 50 mmHg (less than 5 years of age > 40 mmHg, 6–17 years of age > 50 mmHg)
What is the size of the ETT for a 4-year-old child?	5 mm uncuffed 4–4.5 mm cuffed
What is the recommended sequence of CPR per PALS guidelines?	C-A-B-D: Circulation—Airway—Breathing—Defibrillate
For which type of cerebral edema is dexamethasone indicated?	Vasogenic

Last-Minute Review—Critical Care	Most Likely Answer
A patient with persistent intracranial hypertension now has unilateral third nerve palsy and unilateral fixed dilated pupils deviating downward and laterally. What is the type of herniation?	Uncal herniation
In the above scenario, what would be the likely location of this constellation of symptoms in the brain?	Midbrain

INFECTIOUS DISEASES

Matthew B. Laurens

Last-Minute Review—Infectious Diseases	Most Likely Answer
Diarrhea and turtle at home	Nontyphoidal *Salmonella*
Childcare center, fever, vomiting, bloody diarrhea, new-onset seizure, leukocytosis, bandemia, and rectal prolapse	*Shigella*
Diarrhea, high BUN/creatinine, thrombocytopenia, and hemolytic anemia	Hemolytic uremic syndrome *E. coli* O157: H7
Child with his family to the Bahamas on a cruise ship, all of them have diarrhea, and a large number of people on the ship have the same	Norovirus outbreak
Child had rice in a restaurant, presents with vomiting and diarrhea	*Bacillus cereus*
Child ate potato salad 3 h ago, presents with sudden onset of nausea, vomiting, severe abdominal cramps and diarrhea	*Staphylococcus aureus* (preformed enterotoxin)
Adolescent recently had grilled rare pork meat presents with acute right lower quadrant (RLQ) abdominal pain, normal appendix on abdominal US	*Yersinia enterocolitica*
Child living in a farm and has been drinking unpasteurized cow milk, presenting with fever, bloody diarrhea, and vomiting. What is the most likely cause?	*Campylobacter jejuni*
Campylobacter is associated with which of the following neurological conditions?	Guillain–Barré syndrome
A 6-month-old infant presents with constipation, and poor feeding (mother tried honey for the first time)	Botulism
What is the best test to confirm the diagnosis in the previous case with suspected botulism?	Detection of botulism toxins or spores in stool
Community outbreak of diarrhea, news reports that the drinking water has been contaminated with acid-fast protozoa	*Cryptosporidium*

Last-Minute Review—Infectious Diseases	Most Likely Answer
What are the common pathogens causing recreational water-associated outbreaks of acute gastroenteritis	*Cryptosporidium*, *Shigella, Giardia,* norovirus, and *E. coli* O157: H7
Traveled to Mexico; foul smelling diarrhea, with burping and flatulence	Giardiasis
Traveled to Mexico; bloody diarrhea, tenesmus, and without fever	Amebiasis (*Entamoeba histolytica*)
Patient with bloody diarrhea with mucus, fever, abdominal pain, liver abscess and recent travel to Mexico	*Entamoeba histolytica* Treatment: metronidazole plus paromomycin
What is the best diagnostic test in cases with suspected invasive amebiasis?	Serum antibodies to *Entamoeba histolytica*
Unimmunized and buccal cellulitis	*Haemophilus influenzae* type b (Hib)
Adolescent presents with, pneumonia, diarrhea, headache, and confusion	*Legionella pneumophila*
Adolescent presents with, cough, low-grade fever, headache, wheezing, and negative cold agglutinins	*Chlamydia pneumoniae*
A 3-day-old newborn, copious purulent eye discharge, and eyelid edema	Gonococcal conjunctivitis
Erythromycin ointment is considered the best regimen for prophylaxis against neonatal conjunctivitis because of its efficacy against	Gonococcal, and nongonococcal non-chlamydial pathogens (does not prevent *Chlamydia trachomatis* transmission from mother to infant)
A 6-week-old, staccato cough, and eye discharge	*Chlamydia trachomatis*
A 3-month-old presents with a staccato cough, no fever, and chest radiograph positive for pneumonia	*Chlamydia trachomatis*
A 16-year-old with fever, recurrent non-productive cough, and malaise; patient was exposed to exotic birds in South America	*Chlamydia psittaci*
Breeds turkey, high fever, pneumonia, muscle pain, and splenomegaly	*Chlamydia psittaci*
Fever of unknown origin with elevated liver enzymes, lives on a farm, the most likely cause	*Brucella*, blood culture is the best test and treat with doxycycline + rifampin
Tick bite, fever, rash, myalgia, headache, pancytopenia, elevated liver enzymes, and hyponatremia	Ehrlichiosis
Tick bite, fever, rash on palms and soles, headache, joint pain, low platelet, and hyponatremia	Rocky Mountain spotted fever (RMSF) *Rickettsia rickettsii*
A 4-year-old with RMSF. What is the drug of choice?	Doxycycline
Connecticut, target skin lesion (erythema migrans), next step	Treat (Lyme disease); do not order serology
Child was camping in a park in New York, developed Bell's palsy, no rash, no other symptoms	Order Lyme serology and treat if positive
A mother found a tick attached to her child's thigh	Ticks should be removed by using forceps or tweezers without twisting or crushing

Last-Minute Review—Infectious Diseases	Most Likely Answer
Child visited Oklahoma with family, they hunted and skinned rabbits, the child presented with a large lymph node in the groin, and fever	Tularemia (*Francisella tularensis*)
Neonate, peripherally inserted central catheter (PICC) line is positive for *Candida albicans*	Remove the catheter and start IV antifungal
Most common electrolyte disturbances associated with amphotericin B therapy	Hypokalemia Hypomagnesemia
Infant presents with 3 days of high fever, febrile seizure, develops a rash when fever resolves	Human herpesvirus 6 infection (roseola infantum)
Fever, headache, runny nose, rash on the cheeks (looks like slapped), lacy rash on both arms	Erythema infectiosum (parvovirus B19)
Very high fever, cough, coryza, conjunctivitis, bluish-gray specks on the buccal mucosa, the maculopapular rash spreading from the head down, splenomegaly, and lymphadenopathy	Measles
Child with mumps. For how long should children with mumps be excluded from school?	5 days from onset of parotid gland swelling
During school outbreak of mumps. For how long unimmunized children should be excluded from school?	At least 26 days after the onset of parotitis in the last person with mumps in the affected school
Posterior auricular and suboccipital lymphadenopathy, headache, eye pain, sore throat, maculopapular rash, low-grade fever, and chills	German measles (rubella)
Newborn with microcephaly, chorioretinitis, periventricular calcification and a major cause of sensorineural hearing loss	Cytomegalovirus (CMV)
Newborn with microcephaly, subcortical intracranial calcifications, eye anomalies, and hyperreflexia. Mother immigrated from Brazil 2 months before giving birth in the USA. She recalls having a fever in the first trimester	Congenital Zika syndrome
A fully immunized 6-year-old presented with malaise, low-grade fever, and a mild vesicular rash that resembles “dew drops on a rose petal”	Varicella zoster—may have mild episode even if vaccinated
Child is born to a mother who is diagnosed with varicella. When should the varicella zoster immunoglobulin (VZIG) be given?	If the mother is diagnosed from 5 days before birth to 2 days after birth
A 5-year-old male with sudden onset of high fever during the month of March; he has body aches, chills, sore throat, and generalized fatigue	Influenza
A 20-month-old boy with sudden onset of high fever 105 °F during the month of January. He has a runny nose, cough, and malaise. O/E: he has nasal flaring and retractions, bilateral rhonchi. Rapid influenza and respiratory syncytial virus (RSV) tests are negative. What is the next best step?	Start oseltamivir and order influenza molecular assays (no need to wait for the result in high-risk children before starting the medicine)

Last-Minute Review—Infectious Diseases	Most Likely Answer
Who is at risk of hospitalization and development of complications caused by influenza infection?	Children younger than 2 years or who have underlying medical conditions
What is the sensitivity of rapid diagnostic influenza assays test?	Ranges from 10% to 70% (negative test result does not rule out influenza)
What is the sensitivity of influenza molecular assay?	Ranges from 86% to 100%
A 3-year-old male never vaccinated against influenza should receive how many doses?	From 6 months to 8 years, if never received a previous influenza vaccine, 2 doses separated by 1 month are needed, then annually afterward
What is the most common cause of croup in children?	Parainfluenza virus
A 4-month-old unvaccinated child with profuse foul-smelling diarrhea, dehydration, and electrolyte abnormalities	Rotavirus
An 8-year-old female with recurrent cold sore on her lower lip	Herpes labialis (HSV-1)
A 16-year-old sexually active male is complaining of painful vesicles noted on the penis	HSV-1 or HSV-2
A 14-year-old with a history of severe eczema presents with diffuse clusters and vesicles noted on the affected area	Eczema herpeticum Treatment: acyclovir
A 16-year-old sexually active female presents with cauliflower-like lesions in the genital region	HPV—strains 6 and 11 are commonly associated with anogenital warts
Which strains of HPV are more commonly associated with cervical cancer?	HPV—strains 16 and 18
Adolescent male present with mumps (parents are asking about the possible complications)	Epididymo orchitis, arthritis, encephalitis
Chickenpox rash is infectious for how long?	1–2 days before the rash, and until all lesions are crusted over
Limping, after stepping on a nail with a shoe on	*Pseudomonas aeruginosa*
Kitten at home, large axillary and cervical lymph nodes	*Bartonella henselae* (cat scratch disease)
What is the best laboratory test to establish the diagnosis of cat scratch disease	Serologic test (indirect immunofluorescent assay)
Dog bite, 12 h later presents with swelling of the hand, tenderness, and erythema	*Pasteurella* species
Dog bite, 5 days later presents with swelling of the hand, tenderness, and erythema	*S. aureus*
Dog, cat, and human bite drug of choice	Amoxicillin/clavulanate
Dog bite with severe complications, the patient is hospitalized	Ampicillin/sulbactam IV
Dog bite and allergic to penicillin	Clindamycin and TMP-SMX
Bitten by a fox	Give rabies vaccine and immunoglobulin
Dead bat found in the same room as the patient	Give rabies vaccine and immunoglobulin
Bitten by a domestic dog during aggressive play	Give amoxicillin/clavulanate

Last-Minute Review—Infectious Diseases	Most Likely Answer
The most common organism that causes infection in cat bite	*Pasteurella multocida*
Cochlear implants are associated with an increased risk of which bacterial infection?	*Streptococcus pneumoniae*
Child with perianal painful rash and rectal pain for 3 days. O.E: bright red, sharply demarcated rash around the anal area	Perianal bacterial dermatitis (caused by *Streptococcus pyogenes* or *S. aureus*),
What is the best empiric treatment in cases of perianal bacterial dermatitis?	Oral cephalexin or another antistaphylococcal antibiotic depends on the local pattern of antibiotic resistance and sensitivity
A 5-year-old, fever, headache, pharyngeal erythema, palatal petechiae, abdominal pain, nausea	*S. pyogenes* (group A streptococcus)
A 5-year-old presents with fever, headache, pharyngeal exudates, and diffuse sandpaper-like rash. Gram-positive beta-hemolytic streptococci isolated from throat culture	Scarlet fever
A 2-year-old child presents with low-grade fever, thick nasal discharge, and anterior cervical lymphadenopathy	Streptococcosis (*Streptococcus*)
A 3-year-old, fever, runny nose, hoarse voice, cough, and pharyngeal exudates	Viral pharyngitis
A 12-year-old, throat pain with exudates, fever, headache, large cervical lymph node, and splenomegaly	Epstein–Barr virus (EBV) infectious mononucleosis
Best screening test for suspected EBV infection in ≥ 5-year-old	Monospot test
A football player is diagnosed with EBV without splenomegaly. How soon can he return to contact sports?	No contact sports for at least 4–6 weeks—increased risk of splenic rupture
Abrupt onset of pharyngitis, palpebral conjunctivitis, fever, a moderate degree of illness, and preauricular lymphadenopathy, mild cough, and nasal congestion, rhinorrhea, abdominal pain	Adenovirus infection (pharyngoconjunctival fever)
Prodromal high fever and irritability, followed by painful vesicles that ulcerate on the anterior palate, tongue, and buccal mucosa, with intensely inflamed gingivae	Primary herpetic gingivostomatitis
A 6-year-old child with fever, headache, throat pain and abdominal pain. O/E: pharyngeal erythema, palatal petechiae, and positive cervical lymphadenopathy. What is the next best step?	Rapid antigen *Streptococcus* testing (RAST). If RAST is negative, obtain a throat culture. Prescribing antibiotics for presumed group A *Streptococcus* (GAS) without testing is not appropriate

Last-Minute Review—Infectious Diseases	Most Likely Answer
Poor feeding, drooling, tiny vesicles, and erythematous ulcers occur on the posterior pharynx, involving the soft palate, uvula, and tonsillar pillars, and resolve spontaneously within 1 week. With or without fever	Herpangina (enteroviral stomatitis)
A painful 1- to 3-mm vesicles on an erythematous base involving the buccal mucosa, palate, tongue, uvula, and anterior tonsillar pillars. A gray-white vesicle surrounded by erythema primarily on the palms and soles, also on the buttocks and distal extremities	Hand-foot-mouth disease (enteroviral stomatitis with exanthem)
Throat pain, fever, grayish-white membrane on the pharynx; the child is not immunized and looks toxic	Diphtheria
Child with a persistent tooth abscess developed multiple sinuses drainage on the cheeks with sulfur granules seen in the exudates	Actinomycosis
A 12-year-old boy with a history of swimming in freshwater lagoons, developed headaches, myalgia, and fever; 7 days later he became jaundiced, with elevated creatinine level, high bilirubin level, mild elevation of AST and ALT	Leptospirosis
Unimmunized, dirty wound, and fracture of the femur	Tetanus vaccine and tetanus immunoglobulin (TIG)
Immunizations up to date, last tetanus vaccine was 3 years ago, dirty wounds, and multiple compound fractures in a car accident	No tetanus vaccine nor TIG
A 12-year-old boy stepped on a dirty rusty nail, the last DTaP immunization was 8 years ago (received 5 doses of DTaP by the age 4 years of age)	Tdap immunization
A 12-year-old boy stepped on a clean object at home, presents with a minor, clean wound (received 5 doses of DTaP by the age 4 years of age)	Needs booster dose for pertussis component at 11–12 years (Tdap). Tetanus booster required every 10 years
Young adolescent works on an animal farm developed skin papule on the arm that eventually ulcerates and forms black eschar with non-pitting, painless induration and swelling	Anthrax
Unimmunized, presents with fever, muscle weakness and paralysis involving the proximal muscles first. History of foreign travel	Poliomyelitis
A 2-month-old developed bronchiolitis and negative RSV	Human metapneumovirus

Last-Minute Review—Infectious Diseases	Most Likely Answer
Child sustained significant burn a few days ago, starts having a fever, tachypnea, tachycardia and new discoloration of wound edges. What is the next best step?	Start IV antibiotics
Central line, methicillin-resistant *S. aureus* (MRSA) infection. What is the drug of choice?	Vancomycin
IV vancomycin, suddenly develop a rash, itchiness, flushing, and tachycardia	Red man syndrome (reduce IV infusion rate)
Recently traveled to Africa, seizure, decreased level of consciousness, retinal hemorrhage, and hypoglycemia. What is the most likely cause?	*Plasmodium falciparum* (cerebral malaria)
For travel to Africa, the prophylactic antimicrobial therapy of choice for malaria is	Atovaquone-proguanil or doxycycline (mefloquine has black box warning)
A 3-year-old developed osteomyelitis, culture is negative, not responding to vancomycin. What is the most likely cause?	*Kingella kingae* (aerobic CO_2 enhanced culture)
Neonate presents with fever, and blood culture grows *Citrobacter*. What is the most common complication?	Brain abscess
The best study for neonates presenting with fever and *Citrobacter* bacteremia	Brain CT or MRI
Late-onset (7 days to 3 months of life) group B streptococcal infection presents with	Bacteremia (more common), meningitis, or osteomyelitis
Stiff neck, fever, CSF WBC < 1000, 80% neutrophil, negative CSF gram stain. What is the best CSF study?	Enterovirus PCR
Empiric antibiotic therapy in a newborn with presumed bacterial meningitis	Ampicillin plus aminoglycoside or ampicillin plus cefotaxime
Empiric antibiotic therapy in infants and children with presumed bacterial meningitis	Vancomycin plus ceftriaxone or cefotaxime
What is the duration of therapy in most of the cases of meningitis?	14–21 days
What are the long-term neurologic complications of bacterial meningitis in children?	Developmental delay, intellectual disability, hearing impairment, epilepsy, spasticity, and hemiparesis
Child with tetralogy of Fallot presents with a headache, seizure and brain abscess	*S. aureus*
A 17-year-old female with a history of IV drug abuse presents with fever, dyspnea, cough, chest pain, tender subcutaneous nodules in the distal nail pads, positive blood culture for *S. aureus*	Endocarditis
Adolescent with high-risk behavior and IV drug abuse presents with fever, lymphadenopathy, pharyngitis, muscle and joint pain, mouth and genital ulcers, skin rash including the palms and soles, rapid strep and monospot tests are negative	Acute retroviral (HIV) syndrome

Last-Minute Review—Infectious Diseases	Most Likely Answer
The best initial test for the diagnosis of acute retroviral (HIV) syndrome	HIV DNA PCR Confirm with ELISA/Western blot and HIV RNA PCR (viral load)
Main side effect of zidovudine (ZDV)	Bone marrow suppression
A pregnant adolescent with HIV, her CD4 count is 800	Start anti-HIV therapy immediately
Patient with HIV infection, diarrhea for 3 weeks and not resolving	Cryptosporidium
Child lives with his father who was in jail, developed cough, weight loss, night sweats, chest radiograph shows hilar adenopathy and pneumonia	Tuberculosis
Developed large matted cervical lymph node, persistent for 6 weeks, and not responding to antibiotic; you notice the overlying skin is violaceous. Most likely diagnosis	*Mycobacterium avium*
Child presents with large anterior cervical lymph node measure 7 × 4 cm, matted, painless, PPD is 9 mm induration, not responding to antibiotics for 9 weeks	Surgical removal of the node with complete excision (atypical mycobacteria, including *M. avium*)
First-line treatment for head lice	Pyrethrin and 1% permethrin
When can children with head lice infestation return to school or daycare?	Should be allowed to complete the school day (no exclusion from school or daycare because of head lice or nits in healthy children)
Head lice resistant after the treatment with permethrin	Give malathion (ovicidal)
A 1-month-old with scabies. What is the drug of choice?	Precipitated sulfur 6% in petrolatum
A young girl with malodorous vaginal discharge. She has a vaginal discharge visible at the introitus. Mother denied sexual abuse or trauma. What is the most likely cause?	Retained foreign body
Adolescent girl presents with severe rash and desquamation in the hands and feet, hypotension, and fever. The vaginal examination reveals a tampon	Toxic shock syndrome due to *Staphylococcus* Treatment: IV vancomycin + clindamycin)
A 7-year-old presents with fever, malaise, skin rash with bullae, and positive Nikolsky sign	Staphylococcal scalded skin syndrome
A 2-week-old neonate with a history of a PICC line, with fever, bacteremia, and positive culture showing gram-positive cocci	*Enterococcus faecium*—resistant to vancomycin (VRE) and cephalosporins Treatment: linezolid
A 13-year-old presents with bloody diarrhea, abdominal pain and cramps; patient recently treated with clindamycin	*Clostridium difficile*—initial treatment choice for first, and a non-severe episode is oral metronidazole
Patient does not respond to metronidazole and is diagnosed with another episode of *C. difficile.* What antibiotic should be used?	Oral vancomycin

Last-Minute Review—Infectious Diseases	Most Likely Answer
Child with a fever, cervical lymphadenopathy. Child ingested undercooked meat. CT scan shows ring enhanced lesion	Toxoplasmosis

HEMATOLOGY/ONCOLOGY

Nora E. Rahmani and Arpan A. Sinha

Last-Minute Review—Hematology/Oncology	Most Likely Answer
Low hemoglobin, low mean corpuscular volume (MCV), low iron, low transferrin saturation, low ferritin, high red cell distribution width (RDW), Mentzer index (MCV/RBCs) > 13 and high total iron-binding capacity (TIBC)	Iron deficiency anemia
Low hemoglobin, low iron, low/normal TIBC, normal/high ferritin level	Anemia of chronic disease
Mild anemia, low MCV, normal iron, normal TIBC, normal ferritin, normal RDW, Mentzer index < 13	Thalassemia trait
Mild anemia, low MCV, normal iron, normal TIBC, normal ferritin, normal RDW, Mentzer index < 13, and normal electrophoresis (no elevated Hgb A2)	Alpha thalassemia trait
A 12-month-old boy adopted from China with delayed growth, hepatosplenomegaly, jaundice, and "chipmunk facies"	Beta thalassemia major. (Alpha thalassemia major leads to severe anemia and hydrops fetalis in utero, typically incompatible with life without treatment)
Electrophoresis result showed: Hb A > 98% with a small amount of Hb A_2 visible	Normal electrophoresis
Electrophoresis of a 3-year-old child, result showed: Hb A is decreased to 94%, Hb A_2 is increased at 5%, and Hb F is 1%	Beta thalassemia minor
After birth, hemoglobin electrophoresis result showed: No Hb A, Hb A_2 of 4%, Hb F of 96%. No other abnormal hemoglobins seen	Beta thalassemia major
A 2-month-old premature infant has a Hgb 9.0 with normal MCV	Anemia of prematurity
How much will 10 mL/kg of packed RBCs raise the hemoglobin?	~2 g/dL
Excessive cow milk consumption (> 16 oz/day) and microcytic anemia	Iron deficiency anemia
What are the best initial laboratory tests in cases with suspected iron deficiency anemia?	CBC and reticulocyte count
What is the best indicator of response to iron therapy?	An increase in hemoglobin, reticulocyte count, and MCV within 1–4 weeks
How long should iron therapy continue in cases of iron deficiency anemia?	At least 1–2 months after anemia has been corrected to replete iron stores

Last-Minute Review—Hematology/Oncology	Most Likely Answer
What is the classic dose of iron in cases of iron deficiency anemia?	3–6 mg/kg/day of "elemental iron"
A 2-year-old infant with a hemoglobin of 4 g/dL, normal MCV, low reticulocyte count, normal ADA (adenosine deaminase activity), negative direct Coombs test and no signs of hemolysis	Transient erythroblastopenia of childhood
A 7-year-old child presents with pancytopenia, on exam also noted to have hypoplastic thumb and radius, hyperpigmentation, and abnormal facies	Fanconi anemia
A 4-month-old infant with severe anemia, high MCV (macrocytic), elevated ADA, and exam shows triphalangeal thumb	Diamond–Blackfan anemia
Macrocytic anemia, neutropenia, thrombocytopenia, exocrine pancreatic insufficiency, ring sideroblasts in the bone marrow	Pearson marrow-pancreas syndrome
Short stature, imperforate anus, hypoplastic teeth, frequent infections, macrocytic anemia, neutropenia, thrombocytopenia, and exocrine pancreatic insufficiency	Shwachman–Diamond syndrome
Child who consumes goat's milk and has macrocytic anemia	Folic acid deficiency
Child whose family is strictly vegan and has macrocytic anemia	Suspect B12 deficiency. Supplement with B12
Child with macrocytic anemia, glossitis, abdominal pain, gait instability with positive anti-IF antibodies	Pernicious anemia (B12 deficiency due to IF antibodies)
Child with pallor, increased jaundice, splenomegaly, reticulocytosis, and normocytic hemolytic anemia. Peripheral smear shows RBCs without central pallor	Hereditary spherocytosis
An African-American boy recently started on Bactrim for UTI with sudden onset of dark urine, jaundice, and pallor. Splenomegaly on the exam. Labs are notable for anemia, reticulocytosis, indirect hyperbilirubinemia, low haptoglobin, and normal G6PD enzyme activity (during the episode). Peripheral smear is positive for Heinz bodies	G6PD deficiency. Enzyme activity test is usually normal (false negative) during active hemolysis due to the destruction of older erythrocytes (that are G6PD deficient) and presence of younger erythrocytes and reticulocytes (that have normal/near-normal enzyme activity). The test should be repeated during remission, not during active hemolysis
Fava beans, primaquine, sulfa drugs, and nitrofurantoin are known to exacerbate which condition?	G6PD deficiency
Sickle cell anemia, swollen hands and feet, severe pain in hands and feet	Dactylitis
The most common cause of sepsis in patients with sickle cell disease	*Streptococcus pneumoniae*
Child with sickle cell disease presents with severe anemia, reticulocytosis, thrombocytopenia, and rapidly enlarging spleen	Splenic sequestration Next best step → transfusion of packed RBCs (monitor hemoglobin, expect additional rise in Hgb from auto-transfusion from spleen)

Last-Minute Review—Hematology/Oncology	Most Likely Answer
Child with sickle cell disease, fever, malaise, rash, severe anemia, and reticulocytopenia	Aplastic crisis → treatment packed RBCs transfusion as needed
Which virus is the most common cause of aplastic crisis?	Parvovirus B19
Common causes of morbidity and mortality in children with sickle cell disease	Infection, acute chest syndrome, stroke
Child with sickle cell anemia presents with fever, chest pain, tachypnea, shortness of breath, and new pulmonary infiltrate on imaging. Management?	Acute chest syndrome—start ceftriaxone + macrolide (to cover for atypical organisms). Avoid overhydration
Sickle cell patients are at higher risk of which type of organisms?	Encapsulated organisms—due to functional asplenia. Make sure vaccines are up to date
What is the most common reason for hospitalization in the child with sickle cell anemia? Management?	Vaso-occlusive pain crisis Treatment: IV hydration, NSAIDs, and opioids
Adolescent male with a painful erection that has lasted for several hours. Management?	Prolonged priapism—needs emergent evaluation and treatment. Ask patient to come to the ER, aspiration +/− irrigation, phenylephrine, pain control, possible surgical management
What is the most common cause of osteomyelitis in a child with sickle cell disease?	*Salmonella*
What is the next best step in a child with sickle cell disease and suspected osteomyelitis?	Imaging studies (MRI), blood culture, antibiotics (cover *Salmonella* and other Gram-negative bacilli, as well as *S. aureus*), consider biopsy for culture
Adolescent with sudden onset of fatigue, pallor, scleral icterus, and tachycardia, high reticulocyte count, positive direct antibody test. What is the most likely diagnosis?	Autoimmune hemolytic anemia (AIHA)
What is the next best step in the previous life-threatening case of autoimmune hemolytic anemia (AIHA)?	Start steroids. Supportive care may include transfusion of the least incompatible packed RBC unit(s)
Fever and absolute neutrophil count (ANC) < 500. What is the next best step?	Admit to the hospital, blood culture, IV antibiotics
Neutropenia for 1 week every 3 weeks, associated with gingivitis, pharyngitis, skin infections during nadir	Cyclic neutropenia
How to establish the diagnosis of cyclic neutropenia?	CBC 2–3 times per week for 6–8 weeks
What is the best management of cyclic neutropenia?	Prophylactic granulocyte-colony stimulating factor (G-CSF). Immediate attention with fevers
Severe neutropenia from birth, oral ulcers, gingivitis, recurrent infections, ANC is low all the time	Kostmann syndrome
Persistent neck lymphadenopathy more than 1 cm, fever, weight loss, night sweats, lack of response to oral antibiotics	Referral to a pediatric oncologist (lymph node biopsy)

Last-Minute Review—Hematology/Oncology	Most Likely Answer
Child with a supraclavicular lymph node for 2 weeks. No other symptoms	Referral to a pediatric oncologist (must be biopsied or investigated)
Most common malignancy in infants	Neuroblastoma
Most common malignancy in childhood	Acute lymphocytic leukemia
Most common CNS tumor in children	Astrocytoma
Most common benign tumor of the liver in children	Infantile hemangioendothelioma (most commonly occurs in the first 6 months of life, rarely seen in children > 3 years of age)
Toddler with an abdominal mass, ecchymosis, raccoon eye, myoclonic jerking, and random eye movements. The abdominal US is positive for a large suprarenal mass. Urine catecholamines are elevated (HVA and VMA)	Neuroblastoma
Child presents with gingivitis, hepatosplenomegaly, orbital chloromas, WBC > 100,000. Peripheral smear shows Auer rods in blasts	Acute myelogenous leukemia
Chronic myelogenous leukemia is associated with which chromosome translocation?	Philadelphia chromosome t(9:22)
A 1-year-old with very large spleen, moderate leukocytosis (increased monocytes), xanthoma, eczema, and *café-au-lait* spots	Juvenile myelomonocytic leukemia (JMML). JMML has an association with NF1 and Noonan syndrome
Child with an abdominal mass presents with abdominal pain, weakness, lethargy, oliguria, edema, elevated lactate dehydrogenase (LDH) and uric acid, hyperkalemia, elevated phosphate, and low calcium	Burkitt lymphoma (tumor lysis syndrome)
What is the next best step in the previous case of tumor lysis syndrome?	Transfer immediately to oncology unit or PICU for supportive care, including hydration, correction of electrolytes—hyperkalemia, hyperphosphatemia, hyperuricemia, renal dysfunction. May even require hemodialysis
Microscopic picture of Hodgkin lymphoma	Reed-Sternberg cell
The most common type of lymphoma in children	Non-Hodgkin lymphoma
Most common malignant tumor of the kidney in children	Wilms tumor
Child with macroglossia and Wilms tumor	Beckwith–Wiedemann syndrome
Most common soft-tissue tumor in children	Rhabdomyosarcoma
Long-term complications of radiotherapy	Growth retardation, hypothyroidism, early onset coronary artery disease, pulmonary fibrosis, secondary malignancy
Complication of doxorubicin therapy	Cardiomyopathy
Complication of vincristine therapy	Neuropathy
This antineoplastic drug can cause renal impairment and ototoxicity	Cisplatin
Complication of methotrexate therapy	Renal and liver toxicity
Complication of cyclophosphamide therapy	Hemorrhagic cystitis

Last-Minute Review—Hematology/Oncology	Most Likely Answer
Common electrolyte abnormalities in tumor lysis syndrome?	Hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia
A 12-year-old boy with pain and swelling above the knee, pain is worse at night; radiograph shows a bone lesion with Codman's triangle and sunburst pattern	Osteosarcoma
A 16-year-old girl with back pain and limp, fever, weight loss, radiograph shows a mass on the iliac bone with a lytic lesion, onion-skin appearance	Ewing sarcoma
The translocation is commonly seen in patients with Ewing sarcoma	t (11;22)
Child with a painless, bony mass on the knee, radiograph shows broad base projection	Osteochondroma
Child with persistent pain in the lower part of the right femur, radiograph shows metaphyseal lucency surrounded by sclerotic bone, NSAIDs relieve the pain	Osteoid osteoma
Hemangioblastoma, pheochromocytoma, renal cell carcinoma, pancreatic cyst, and *café-a- lait* spots	Von–Hippel–Lindau disease
Impaired upward gaze, mid-dilated pupil, nystagmus, and lid retraction	Parinaud syndrome
New-onset head tilt or torticollis, early morning vomiting, headache, and gait disturbance	Posterior fossa brain tumor, e.g., medulloblastoma
Most common malignant CNS tumor in children	Medulloblastoma
Most common CNS tumor	Low-grade glioma (pilocytic astrocytoma is the most common LGG)
Brain tumor with the best survival rate in children	Pilocytic astrocytoma
Child with recurrent headaches, growth failure, polydipsia, double vision	Craniopharyngioma
A 6-month-old child with strabismus, absent red reflex, and leukocoria	Retinoblastoma
The liver tumor that is associated with prematurity	Hepatoblastoma
The tumor that is associated with cryptorchidism	Gonadoblastoma
An infant with intracranial hemorrhage, prothrombin time (PT), partial thromboplastin time (PTT), and platelet count, fibrinogen and vWD panel is within normal limits	Factor XIII deficiency
Child with normal PT, very prolonged PTT, has no history of excessive bleeding even after injuries	Factor XII deficiency
A 5-year-old with upper respiratory tract infection 2 weeks ago, presents with a bloody nose, petechial rash all over the body and oral mucosa. CBC is normal except platelet count is 12,000, peripheral smear shows very few large platelets	Idiopathic thrombocytopenic purpura (ITP)
What is the treatment in the previous case of ITP?	Observation if no signs of bleeding; if signs of bleeding, then treat with IVIG or steroids

Last-Minute Review—Hematology/Oncology	Most Likely Answer
A 2-year-old boy with recurrent infections, eczema, severe thrombocytopenia, and small platelets	Wiskott–Aldrich syndrome
Newborn with severe thrombocytopenia, maternal history of ITP or other autoimmune disorder	Neonatal ITP → give IVIG
Newborn with severe thrombocytopenia, maternal history of prior children with neonatal thrombocytopenia and no maternal history of autoimmunity	Neonatal alloimmune thrombocytopenia → transfuse maternal platelets (gold standard); however, difficult to obtain. The alternative option is donor platelets +/− IVIG, steroids
Unusual bleeding since birth, recurrent bruising, recurrent mucosal bleeding, low to normal platelet count, normal PT and PTT, normal fibrinogen, normal von Willebrand antigen and activity	Platelet function disorders, e.g., Bernard–Soulier syndrome, Glanzmann thrombasthenia
A 10-year-old with recurrent epistaxis, easy bruising, gingival bleeding, normal count and morphology of platelets, platelets agglutinate to ristocetin, poor platelet aggregation with adenosine diphosphate (ADP), epinephrine, and collagen	Glanzmann thrombasthenia (normal platelet count and size)
A 10-year-old with a suspected bleeding disorder, workup shows mild thrombocytopenia, with large abnormal platelets, platelets do not agglutinate to ristocetin but agglutinate to ADP, epinephrine, and collagen	Bernard–Soulier syndrome (large platelets, can have low platelet count)
Most appropriate management for life-threatening bleeding in a child with a known or suspected platelet function disorder	Infusion of platelets with normal function
A 48-h-old newborn presents with prolonged bleeding after circumcision, CBC shows severe thrombocytopenia. On exam no radii in both forearms but with normal thumbs	Thrombocytopenia with absent radii (TAR syndrome)
Male newborn with prolonged bleeding after circumcision, and prolonged PTT	Factor VIII or IX deficiency, or hemophilia A or B
A 15-year-old girl with excessive menstrual bleeding every month since menarche, normal PT and PTT, decrease in biological activity of ristocetin cofactor assay (rCoF)	Von Willebrand disease
A 4-year-old child with a recent history of vomiting and bloody diarrhea found to have thrombocytopenia, elevated BUN and creatinine, schistocytes on peripheral smear	Hemolytic uremic syndrome—occurs in infants and children after prodromal diarrhea, associated with bacteria particularly *E. coli* O157: H7, and *Shigella dysenteriae*
Child currently hospitalized in the PICU with prolonged PT, PTT, elevated D-dimer, thrombocytopenia, and decreased fibrinogen	Disseminated intravascular coagulation (DIC) Treatment: treat the underlying cause (e.g., antibiotics for sepsis). Supportive care with blood products—FFP +/− cryoprecipitate
A 17-year-old Caucasian boy with recurrent episodes of DVT along with a strong family history of DVT	Factor V Leiden mutation—resistance to activated protein C

Last-Minute Review—Hematology/Oncology	Most Likely Answer
A 2-year-old boy with oral ulcers, cradle cap-like rash, and gingivitis, with radiograph showing lytic lesions in the skull	Langerhans cell histiocytosis—Birbeck granules on electron microscopy
A 1-year-old sick-appearing child with fever, hepatosplenomegaly, pancytopenia, hypertriglyceridemia, and very elevated ferritin; presence of hemophagocytosis in bone marrow	Hemophagocytic lymphohistiocytosis (HLH)

ALLERGY AND IMMUNOLOGY

Maria I. Garcia Lloret and Caroline Y. Kuo

Last-Minute Review—Allergy and Immunology	Most Likely Answer
Antibody that has a major role in allergic conditions, e.g., anaphylaxis, atopy, asthma, allergic rhinitis, food allergies	IgE
Antibody that mediates type I hypersensitivity reaction	IgE
First antibody produced in an infection	IgM
An antibody found in body mucosal secretions	IgA
What is the prevalence of atopic disorders in children with one affected parent?	Up to 60%
What is the prevalence of atopic disorders in children with 2 affected parents?	Up to 80% (family history is critical in all atopic disorders)
What are atopic disorders?	Atopic dermatitis, asthma, allergic rhinitis, and food allergies
What are the indications of allergy testing?	Significant allergies, e.g., asthma, anaphylaxis, food or drug allergies, difficult to treat allergies or requirement for specific treatment
An infant with severe eczema and/or severe egg allergy	Evaluate for peanut reactivity with either skin-prick testing and/or serum IgE levels, and if necessary, oral food challenge
Which allergy test is preferred in cases of dermatographism, generalized dermatitis, or a clinical history of severe anaphylactic reactions to a given food?	Radioallergosorbent test (RAST) (allergen-specific IgE antibody)
Which allergy test is associated with a high false positive rate?	Both skin-prick testing and serum IgE levels
Child currently on diphenhydramine for allergies is scheduled for skin allergy testing. When should diphenhydramine be stopped?	At least 5 days prior to testing
Child currently on cetirizine for allergies is scheduled for skin allergy testing. When should cetirizine be stopped?	At least 7 days prior to testing

Last-Minute Review—Allergy and Immunology	Most Likely Answer
Child currently on amitriptyline for migraine headache prophylaxis is scheduled for skin allergy testing. When should amitriptyline be stopped?	At least 2 weeks prior to testing
What is the first step that should be taken in the management of allergic rhinitis?	Avoidance or reduction of allergen exposures
The first-line pharmacologic treatment of allergic rhinitis	Intranasal steroids and/or second-generation oral antihistamines
Common complications of untreated allergic rhinitis	Recurrent acute otitis media, sinusitis, chronic cough, and asthma
Complications of prolonged use of nasal adrenergic drops	Rhinitis medicamentosa
An 8-year-old male presents with congestion, itchy nose, and watery eyes. Symptoms are exacerbated when playing with the pet cat. He loves his cat. What is the most effective treatment?	Avoid the trigger (e.g., by keeping the cat at least outside the bedroom or the house all the time; HEPA filters can help)
Child with a history of pollen allergy develops rapid onset of itching, swelling of the lips, mouth, and throat when eating raw fruits and vegetables. What is the most likely cause?	Oral allergy syndrome (OAS) (cross-reactivity with pollen)
What is the best treatment for OAS?	Avoid offending foods
How long do the allergies to peanuts, tree nuts, seafood, and fish last?	Lifelong allergies
How long do the allergies to milk, eggs, and soy last?	Most children outgrow by 5 years of age
A 2-month-old exclusively breastfed infant is seen for bloody stools; weight gain is appropriate, and physical exam is normal	Reassurance (counsel mother to avoid dairy, soy, eggs for 2 weeks, then re-evaluate)
Induration reaction to TB testing after 72 h is an example of	Type IV: cell-mediated hypersensitivity
Allergy to contrast media is an example of	Non-IgE mediated
Child with a history of severe allergic reaction to radiographic contrast media is going for CT scan with IV contrast	Administer prednisone and diphenhydramine before injection or choose other alternative imaging tests
Child with a history of severe allergic reaction to seafood is going for an abdominal CT scan with oral and IV contrast. Does he or she need a pretreatment with prednisone and diphenhydramine?	No (iodine allergy is not a risk factor for allergic-type contrast reactions)
A 16-year-old male with a new watch notices an area of erythema located on the wrist where the watch was worn. No other lesions	Type 4—contact dermatitis, a delayed hypersensitivity reaction
What is the best treatment in cases of contact dermatitis?	Avoid offending agents
Child received penicillin 10 days ago for the first time, presents with fever, nausea, vomiting, pruritic skin rash (urticaria), angioedema, joint pain, lymphadenopathy, myalgia, and proteinuria	Serum sickness

Last-Minute Review—Allergy and Immunology	Most Likely Answer
A common trigger of allergic reactions in a patient with spina bifida or congenital urogenital problems	Latex
What is the most common specific autoimmune association with chronic urticaria?	Autoimmune thyroid disease (laboratory evaluation should include thyroid-stimulating hormone (TSH) level and thyroid antibodies)
Sudden onset of lip swelling, abdominal pain, swelling of both feet, non-pruritic erythematous skin rash; one family member has the same condition	Hereditary angioedema
What is the cause of hereditary angioedema (HAE)?	Low levels or decreased function of plasma protein C1 inhibitor (C1-INH). (Autosomal dominant)
Initial screening test for a patient with suspected hereditary angioedema	C4 level most reliable and cost-effective screening test for HAE
The test that can differentiate between various types of hereditary angioedema	C1-INH functional assay
A 6-year-old male with yellow-tan macules located on the upper extremities. Parents notice localized erythema following scratching of the lesions and after taking a hot shower	Mastocytosis—Darier sign: urticaria after stroking lesions
Common diagnostic lab for mastocytosis	Elevated tryptase levels
A 15-year-old male presents with several erythematous, pruritic circumscribed lesions that occur with exercise	Exercise-induced urticaria
Child presents a few minutes after eating peanut butter with urticaria, skin flushing, pruritus, angioedema, rhinorrhea, wheezing, shortness of breath, abdominal pain, vomiting, diarrhea, light-headedness. What is the next best step?	IM epinephrine to administer as quickly as possible
Child with a history of life-threatening reaction to a bee sting is coming to your office for a follow-up after he was discharged from the ER with EpiPen prescription. What is the next best step?	Referral to an allergist for immunotherapy
A 4-year-old male scheduled for a well child check; he was recently treated with a 5-day course of oral steroids for asthma exacerbation. Which vaccines can be given?	All vaccines including MMR and varicella
A 4-year-old male scheduled for a well child check; he has been treated with high dose steroids for 4 weeks. Should the MMR and varicella vaccines be given?	No—patients receiving high steroids for greater than 2 weeks should be off steroids for at least 1 month
Child is being treated with intranasal steroids for allergic rhinitis. Should the MMR and varicella vaccines be given?	Yes
What is the best initial test for any child with suspected immunodeficiency?	Complete blood count (CBC)

Last-Minute Review—Allergy and Immunology	Most Likely Answer
Patient with recurrent meningococcal meningitis	The defect in terminal complement C5–C9 deficiency
Initial screening test for a patient with suspected complement deficiency, e.g., recurrent (*Neisseria meningitidis*) meningitis	(CH50) test
Complement deficiency that increases the risk of systemic lupus erythematosus	C2 deficiency
What is the best screening test for cell-mediated immunity associated with T-cell defects?	T-cell phenotyping (CD4/CD8, memory vs. naïve T cells) and T-cell proliferative responses
What is the best initial test for an infant with suspected humoral immune deficiency?	Immunoglobulin levels
An 8-week-old boy presents with diarrhea, pneumonia, persistent oral thrush, eczematous-like skin lesions, sepsis, lymphopenia, and failure to thrive	Severe combined immunodeficiency (SCID)
The enzyme deficiency that is found in SCID?	Adenosine deaminase deficiency
A 9-month-old boy, previously healthy, presents with recurrent otitis media, 2 episodes of pneumonia in the last 2 months, persistent giardiasis. O/E: the lymph nodes, the tonsils are absent	X-linked agammaglobulinemia (usually starts after first 6 months of life)
Adolescent presents with recurrent sinus and pulmonary infections due to encapsulated bacteria, malabsorption, hepatosplenomegaly, and low level of immunoglobulins (IgG, IgM, and IgA)	Common variable immunodeficiency
The best treatment for a child with asymptomatic transient hypogammaglobulinemia of infancy	Observation (no treatment is necessary)
An 8-year-old boy presents with eczema, recurrent *Staphylococcus aureus* skin infections without inflammatory response "cold abscess," pneumatoceles, coarse facial features, eosinophilia, and IgE level is 80,000 IU	Job syndrome (autosomal dominant hyper-IgE syndrome)
A 5-month-old presents with *Pneumocystis jiroveci* pneumonia, mouth ulcers, severe neutropenia, recurrent sinusitis, otitis media, chronic diarrhea, failure to thrive, and negative HIV	X-linked hyper IgM syndrome
A 4-year-old boy with recurrent skin abscesses, spleen and liver abscesses, and osteomyelitis	Chronic granulomatous disease (X-linked)
Test of choice in a patient with a suspected chronic granulomatous disease	DHR oxidation is preferred, NBT reduction can be used
Severe progressive infectious mononucleosis and Epstein–Barr virus (EBV) fulminant hepatitis	X-linked lymphoproliferative syndrome (Duncan syndrome)
Highly elevated WBC in a 10-week-old infant who still has an umbilical cord	Leukocyte adhesion defect type I
Test of choice in a patient with suspected leukocyte adhesion defect	Flow cytometry beta 2 integrin CD11b/CD18 on leukocytes

Last-Minute Review—Allergy and Immunology	Most Likely Answer
Newborn with hypocalcemia, tetralogy of Fallot, interrupted aortic arch, and abnormal facial features	DiGeorge anomaly (deletion of chromosome 22q11.2)
Recurrent ear infections, eczema, profuse bleeding during a circumcision procedure, thrombocytopenia, and small platelets	Wiskott–Aldrich syndrome
Persistent thrush, nail dystrophy, and endocrinopathies	Chronic mucocutaneous candidiasis
Short stature, fine hair, and severe varicella infection	Cartilage-hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infections, and easy bruising	Chédiak–Higashi syndrome
Candidiasis with raw egg ingestion	Biotin-dependent carboxylases deficiency
A 4-year-old with short stature, micrognathia, telangiectasia, immunodeficiency, learning disability, deficiency of DNA ligase I	Bloom syndrome
An 8-year-old boy presents with recurrent ear and sinus infections, ataxia, oculocutaneous telangiectasia, and elevated α1-fetoprotein	Ataxia–telangiectasia (autosomal recessive)

ENDOCRINOLOGY

Amr Morsi

Last-Minute Review—Endocrinology	Most Likely Answer
What is the first sign of puberty in a boy?	Testicular enlargement
What is the first sign of puberty in a girl?	Breast budding
The height acceleration peaks in girls is at which sexual maturation rating (SMR) stage?	Between stage 2 and 3 SMR
The height acceleration peaks in boys is at which SMR stage?	Between stage 4 and 5 SMR
How many years after breast development does menarche start?	2.5 years (approximately)
A 5-year-old female, pubic hair, adult odor, no breast development, bone age is equal to chronological age, slightly increased dehydroepiandrosterone (DHEA) level, normal growth pattern for age	Premature adrenarche
A 2-year-old female with bilateral breast buds, unchanged for 1 year, no growth acceleration	Benign premature thelarche
A 4-year-old female with new-onset bilateral breast enlargement, advanced bone age, and elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	Central precocious puberty is very likely

Last-Minute Review—Endocrinology	Most Likely Answer
A 4-year-old boy presents with an adult-size phallus, pubic and axillary hair, acne, well-defined muscle tone, **pre**pubertal size testicles	Peripheral precocious puberty
A 4-year-old boy presents with an adult-size phallus, pubic and axillary hair, acne, well-defined muscle tone, **p**ubertal size testicles, advanced bone age	Central precocious puberty
A 4-year old boy with new-onset adult body odor, recent growth acceleration, pubic and axillary hair, thinning of the scrotum, enlargement of both testicles. Elevated LH and FSH. What is the best study to establish the diagnosis?	Brain MRI
A 5-year-old girl with pubic hair, mild hyperpigmentation of skin folds, slightly enlarged clitoris	Simple virilizing CAH-21 OH deficiency
Second newborn screen positive for high 17-hydroxyprogesterone. What is the next best step?	Repeat 17-hydroxyprogesterone test
Newborn with proximal hypospadias (e.g., penoscrotal) and cryptorchidism	Ultrasonography for internal genitalia, karyotype, and serum electrolytes to screen for congenital adrenal hyperplasia
What is the best treatment of congenital adrenal hyperplasia?	Hydrocortisone and fludrocortisone
What is the treatment for a patient with congenital adrenal hyperplasia who presents with vomiting and low blood pressure?	IV hydrocortisone and IV fluid hydration
A 2-week-old male with failure to thrive, persistent vomiting, dehydration, acidosis	CAH 21-OH deficiency (pyloric stenosis is associated with metabolic alkalosis)
Ambiguous genitalia, nephropathy, Wilms tumor, renal failure by 3 years of age	Denys–Drash syndrome
Female phenotype at birth with undifferentiated streak gonads, presence of vagina/fallopian tubes, at puberty no breast development/menstruation, development of gonadoblastoma is the highest risk	Swyer syndrome (XY pure gonadal dysgenesis)
Newborn with a small penis, bifid scrotum, urogenital sinus, blind vaginal pouch, testes are in the inguinal canal, raised as a female, virilization occurs at the time of puberty, enlargement of penis and scrotum, sperm formation, and normal adult height	5-alpha reductase deficiency (autosomal recessive)
Infant phenotypically female at birth, raised as female, vagina ends in a blind pouch, no uterus, no fallopian tubes, intra-abdominal testes, normal breast development, no menses, normal male adult height, testosterone level is normal	Androgen insensitivity syndrome; 46, XY (X-linked recessive disorder)

Last-Minute Review—Endocrinology	Most Likely Answer
XY normal male phenotype, inguinal hernia, undescended testis, Müllerian structures found incidentally (uterus and fallopian tubes)	Persistent Müllerian duct syndrome
A 4-year-old with precocious puberty, large *café-au-lait* spots, skeletal fibrous dysplasia, and vaginal bleeding are associated with	McCune–Albright syndrome
A slow growth rate in the first 2 years of life (< third percentile), growth velocity afterward is 5.5 cm/year, delayed bone age, delayed puberty, father was a late bloomer	Constitutional growth delay
Short child, growth velocity is 5 cm/year. Bone age is consistent with chronological age, father and mother are short	Genetic/familial short stature
A 4-year-old, height < 3rd percentile, growth velocity is less than 5 cm/year, microphallus	Growth hormone deficiency
Common hormone deficiency associated with single maxillary central incisors, septo-optic dysplasia, cleft lip, cleft palate, and microphallus	Growth hormone deficiency
Normal length and weight by birth initially that drops by 1-year, conjugated hyperbilirubinemia, hypoglycemia, broad facies, and microphallus	Congenital growth hormone deficiency
Decreased levels of IGF-1 and IGF-BP3 are seen in which hormone deficiency?	Growth hormone deficiency
Normal growth hormone levels, height < 2.25 SD below mean for age, otherwise normal healthy child	Idiopathic short stature
How do you calculate the mid-parental height for a male?	[Mother height + Father height +13 cm]/2
How do you calculate the mid-parental height for a female?	[Mother height + Father height—13 cm]/2
Pseudotumor cerebri, slipped capital femoral epiphysis, and gynecomastia are the possible side effects of which hormonal therapy	Growth hormone
A 7-year-old boy with a progressive headache, vomiting without nausea, bitemporal hemianopsia, short stature, weight gain, and fatigue. What is the next best step?	Brain MRI (craniopharyngioma)
A 7-year-old boy, at birth, was large for gestational age, macrocephaly, a rapid growth rate in the first 3 years of life; now presenting with cognitive deficiency, autistic behavior, attention deficit hyperactivity disorder (ADHD), large and protruded head, large hands and feet, hypotonia, clumsiness, advanced bone age	Cerebral gigantism (Soto syndrome)

Last-Minute Review—Endocrinology	Most Likely Answer
Boy with hypoplasia of optic nerves, nystagmus, an absence of septum pellucidum, schizencephaly, seizures, hypopituitarism, presented with hypoglycemia, jaundice, and micropenis at birth	Septo-optic dysplasia (De Morsier syndrome)
A 17-year-old female, amenorrhea, headache, galactorrhea, visual field defect; the pregnancy test is negative, and serum prolactin is > 200 mg/dL. MRI showed a pituitary mass of 15 mm with encroachment on the optic chiasm	Prolactinoma (macroadenoma)
A 17-year-old boy, no signs of puberty, penis, and testicles are prepubertal, and anosmia	Kallmann syndrome (hypogonadotropic hypogonadism)
A 17-year-old male presents for a well visit. He has academic difficulty, gynecomastia, small firm testicles (< 10 mL). He is tall with disproportionately long legs and arms	Klinefelter syndrome 47, XXY karyotype
A 16-year-old female, short stature (< third percentile), no breast development, amenorrhea, low hairline, shield-shaped chest, spooning of her fingernails, cubitus valgus, and sensorineural hearing loss	Turner syndrome; 45, X karyotype
The most common cardiac defect associated with Turner syndrome	Bicuspid aortic valve
Newborn girl had cystic hygroma on fetal ultrasound, lymphedema of the feet, webbed neck, heart murmur, and horseshoe kidney	Turner syndrome; 45, X karyotype
A 5-year-old male, lymphedema of the feet at birth, short stature, webbed neck, strabismus, hearing loss, joint laxity, pulmonary stenosis, intellectual disability, normal karyotype	Noonan syndrome (mutations in the RAS-MAPK pathway)
Newborn screen of a 6-day-old boy showed abnormal thyroid-stimulating hormone (TSH) level of 230 mIU/L (elevated TSH > 40 mIU/L). Physical examination is unremarkable. What is the next best step?	Obtain confirmatory TSH and free thyroxine now but initiate the treatment immediately, before the results of the confirmatory tests are available
What is the optimal care of neonates with congenital hypothyroidism?	Early diagnosis before age 10–13 days and normalization of thyroid hormone blood levels by age 3 weeks
The most common cause of congenital hypothyroidism	Thyroid dysgenesis
What is the treatment of congenital hypothyroidism and how should the treatment be given?	Levothyroxine tablet (initial dose is 10–15 mcg/kg/day) should be crushed and mixed with breast milk or formula (cannot be mixed with soy formula)
Low free T4, elevated TSH	Primary hypothyroidism
Low free T4, normal or low TSH	Central hypothyroidism
High free T4 and T3, low TSH	Hyperthyroidism (most common)

Last-Minute Review—Endocrinology	Most Likely Answer
Normal or low free T4, high T3, low TSH	Hyperthyroidism (less common)
Normal T4, low T3, normal/low TSH, the patient has pneumonia	Euthyroid sick syndrome
Low total T4, normal free T4, normal TSH	Thyroxine-binding globulin deficiency (TBG), hypoproteinemia, e.g., malnutrition and nephrotic syndrome
A 11-year-old female with no growth for 2 years, tired, constipated and "yellowish" skin	Hypothyroidism (likely Hashimoto)
Adolescent with thyroid enlargement, no symptoms, TSH and free T4 are within the reference range, positive antithyroid peroxidase (TPO)	Hashimoto thyroiditis
A 14-year-old girl, school troubles, getting in fights, appears to be on drugs because of red bulgy eyes and irritability	Graves disease (hyperthyroidism)
What is the best test to confirm the diagnosis of Graves disease?	Thyrotropin receptor-stimulating immunoglobulin (TSI)
A painful thyroid gland that started after viral infection associated with elevated ESR with an eventual return to normal thyroid function	De Quervain thyroiditis—initial hyperthyroid phase, then hypothyroid phase with eventual recovery
Newborn child with tachycardia, irritability, hypertension, mother with a history of Graves disease?	Neonatal thyrotoxicosis
The most common symptom of hyperthyroidism or Graves disease	Weakness/fatigue
The most common side effect of antithyroid drugs (e.g., methimazole)	Transient urticarial rash
The best diagnostic test for solitary thyroid nodule	Fine needle aspiration biopsy; US-guided
The most common thyroid cancer in pediatric patients	Well-differentiated thyroid (follicular/papillary) carcinoma
Medullary thyroid cancer, hyperparathyroidism, pheochromocytoma	Multiple endocrine neoplasia (MEN)-2A
Medullary thyroid cancer, pheochromocytoma, mucosal neuroma	MEN-2B
Calcitonin is elevated in which type of thyroid cancer?	Medullary thyroid cancer
Low to normal serum Ca, low serum phosphate, high alkaline phosphatase, low 25-(OH) vitamin D, high parathyroid hormone (PTH)	Vitamin D deficiency (rickets)
Normal serum Ca, low serum phosphate, very high alkaline phosphatase, normal vitamin D, failure to thrive, hypotonia, delayed dentition	Hypophosphatemic rickets or X-linked hypophosphatemic rickets
What is the mode of inheritance of hypophosphatemic rickets?	X-linked dominant

Last-Minute Review—Endocrinology	Most Likely Answer
High serum PTH, low serum Ca, high phosphate, short stature, stocky habitus, soft-tissue calcifications/ossifications, short fourth and fifth metacarpal bones	Albright hereditary osteodystrophy (pseudohypoparathyroidism type 1A)
Short stature with stocky body habitus, soft-tissue calcification/ossifications, short fourth and fifth metacarpals with normal PTH, normal calcium, and normal phosphate	Pseudopseudohypoparathyroidism—due to paternal mutation
Normal serum Ca, low serum phosphate, very high alkaline phosphatase, non-anion gap metabolic acidosis, developmental delay, cataracts, glaucoma	Oculocerebrorenal dystrophy (Lowe syndrome)
A 7-year-old with obesity, hyperphagia, small hands and feet, small penis, cryptorchidism, and cognitive deficiency	Prader–Willi syndrome
What is the chromosomal deletion of Prader–Willi syndrome?	Paternal chromosome 15q11-q13 deletion
Obesity, retinitis pigmentosa, hypogonadism, intellectual disability	Bardet–Biedl syndrome or Laurence–Moon–Biedl syndrome
Adolescent female, obesity, acanthosis nigricans, HBA1c 6.9%, elevated testosterone and LH, hirsutism, no ovarian cysts noticed on ultrasonography	Polycystic ovary syndrome
Failure to thrive, microcephaly, intellectual disability, ptosis, strabismus, syndactyly, pyloric stenosis, and low-plasma cholesterol	Smith–Lemli–Opitz syndrome (autosomal recessive)
Polydipsia, hypernatremia, serum osmolarity > 300 mOSm/kg, urine osmolarity < 300 mOSm/kg	Diabetes insipidus (DI)
Patient with meningitis on IV fluids, hyponatremia, hypo-osmolality, elevated blood pressure, inappropriately concentrated urine, and high urine sodium level	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
What is the best initial treatment for the patient with SIADH in the previous example?	Reduce IV fluid rate (fluid restriction)
A patient underwent neurosurgery for a brain tumor, develops dehydration, hyponatremia, high urine output, hypovolemia, low blood pressure, high urine Na	Cerebral salt wasting
Cerebral salt wasting is associated with which hormone is being elevated?	Atrial natriuretic peptide
What is the best treatment for a patient with cerebral salt wasting dehydration?	Isotonic fluid hydration
Patient with diabetes insipidus comes in for water deprivation test, after administration of DDAVP (desmopressin) the urine becomes concentrated	Central diabetes insipidus

Last-Minute Review—Endocrinology	Most Likely Answer
Patient with diabetes insipidus comes in for water deprivation test, after administration of DDAVP there is no effect on urine concentration	Nephrogenic diabetes insipidus
Child with obesity, height < 3rd percentile, blood pressure > 95th percentile for age	Cushing syndrome
A 7-year-old boy with a history of severe asthma, presents with a 3-day history of worsening nausea, abdominal pain, and vomiting, he was on a high dose of inhaled steroids for 1 year. Lately, the child is not compliant with medications. What is the most likely cause of his symptoms?	Adrenal insufficiency
Child is presents with fatigue, nausea, weight loss, hypotension, volume depletion, and diffuse hyperpigmentation	Addison disease
Child with type 1 diabetes mellitus, well controlled, suddenly develops hypotension and shock	Addison disease
Best initial treatment for a patient with diabetic ketoacidosis within the first hour who presents with volume depletion, e.g., tachycardia, prolonged capillary refill time, and elevated blood urea nitrogen and creatinine	IV hydration: 10 mL/kg of intravenous normal saline over 1 h
The most common cause of death in children who have type 1 diabetes	Diabetic ketoacidosis (DKA)
What is the most common cause of recurrent DKA?	Insulin omission
The most common cause of death related to DKA in children	Cerebral edema
Adolescent female presents with recurrent vaginal candidiasis, BMI > 97th percentile, hypertension, acanthosis nigricans. What is the next best step?	Fasting blood glucose level
Adolescent female presents with polyuria, polydipsia, BMI > 97th percentile, hypertension, acanthosis nigricans; her blood glucose level is 200 mg/dL, A1C is 7%. What is the best treatment?	Metformin
Adolescent female presents with polyuria, polydipsia, BMI > 97th percentile, hypertension, acanthosis nigricans; her blood glucose level is 350 mg/dL, A1C is 10%. What is the best initial treatment?	Insulin Blood glucose level ≥ 250 mg/dL, A1C ≥ 8.5% insulin is the best initial treatment
What is the A1C goal recommended by the American Diabetes Association for all pediatric age-groups with type 1 diabetes mellitus?	A1C target < 7.5% should be considered but individualized
A 3-day-old infant, 10 lbs at birth, jittery	Infant of a diabetic mother with hypocalcemia

Last-Minute Review—Endocrinology	Most Likely Answer
A 9-year-old male with sweating, jitteriness, and tachycardia with sudden onset of symptoms	Hypoglycemic episode Treatment: 15 g of carbohydrate
A 9-year-old male who has altered mental status glucose is noted to be 45 mg/dl. Best treatment?	IM glucagon
An infant with a history of tetralogy of Fallot presents with jitteriness and muscle twitching that has been worsening over the past few days. Blood glucose level is 85 mg/dL, and the calcium level is 7 mg/dL. What is the most likely cause?	Hypoparathyroidism
A 5-day-old infant, small jaw, broad nose, tetralogy of Fallot, seizure	DiGeorge/velocardiofacial (VCF)
A 3-month-old male with elfin facies, supravalvular aortic stenosis, now with serum Ca of 12.2	Williams syndrome
A 4-day-old male with hypoglycemia, omphalocele, hemihypertrophy	Beckwith–Wiedemann syndrome
Which childhood tumor is associated with Beckwith–Wiedemann syndrome?	Wilms tumor
A 10 lb plethoric neonate, requiring 15 mg/kg/min dextrose infusion. The mother without gestational diabetes mellitus (DM)	Congenital hyperinsulinism
A 5-year-old male previously healthy with throat pain and loss of appetite for 2 days, suddenly starts feeling dizzy, jittery, becomes unconscious in ER; the glucose level is 37 mg/dL, high level of serum and urine ketone, undetectable serum insulin, elevated serum cortisol, and growth hormone. What is the most likely cause?	Ketotic hypoglycemia (treatment is IV dextrose)
An 18-month-old thin boy with mild fever overnight presents with loss of consciousness and hypoglycemia	Ketotic hypoglycemia (diagnosis of exclusion)
A 5-day-old male with a small phallus, jaundice, now with glucose of 45 mg/dl and ketones in urine after 4 h of fasting	Hypopituitarism (adrenocorticotropic hormone (ACTH), growth hormone (GH) deficiency)
A 6-year-old with nighttime headaches, height has fallen from 25th percentile to 5th percentile over 1 year. Enuresis	Intracranial tumor in the region of the pituitary
An 18-month-old male, length, and weight "stalled" for 9 months. Stools remarkably odorous	Celiac/malabsorption
What are the components of metabolic syndrome?	Impaired glucose Low HDL High triglycerides Elevated blood pressure Central obesity

ORTHOPEDICS

Amr Abdelgawad

Last-Minute Review—Orthopedics	Most Likely Answer
First newborn female, breech presentation, positive Barlow	Developmental dysplasia of the hip (DDH)
What is the imaging modality of choice in a 2-month-old girl with concern for DDH?	Ultrasound (US) of the hips (< 6 months)
What is the imaging modality of choice in a 7-month-old girl with concern for DDH?	Pelvis radiograph (> 6 months)
What is the earliest time for US screening for DDH?	6 weeks of age (before 6 weeks, overly sensitive and can result in overtreatment)
A 1-month-old is diagnosed with DDH. What is the preferred treatment?	Pavlik harness
An 8-year-old boy presents with limping, pain in the right hip and knee, plain radiograph shows ossified and collapsed femoral epiphysis	Legg–Calve–Perthes disease
Adolescent with obesity presents with limping, pain in the right hip and knee, plain radiograph shows displacement of the femoral epiphysis	Slipped capital femoral epiphysis
A 5-year-old boy with upper respiratory symptoms, complaining of left leg pain and difficulty walking, decreases movement of the left hip. ESR and CRP are within normal ranges	Transient synovitis
A 5-year-old boy presents with left hip pain, fever and limping; he appears ill, grimaces with any left hip movement, limited range of motion, ESR and CRP are significantly elevated, hip US shows left hip effusion	Septic hip (pyogenic arthritis)
What is the next best step in cases of pyogenic arthritis?	Antimicrobial to cover against *Staphylococcus aureus* and streptococcal species, and in young children, *Kingella kingae* should also be covered Urgent orthopedic consultation
A 12-year-old male presents with left knee redness, pain, and swelling. There is a decreased range of motion along with elevated WBC, CRP, and ESR	Distal femur osteomyelitis
What is the most sensitive imaging modality to check for osteomyelitis?	MRI
Short umbilical cord, oligohydramnios, pulmonary hypoplasia, joint contractures, micrognathia, absent skin creases	Arthrogryposis
Indications for radiographic evaluation of bow leg "genu varum"	> 2 years of age, unilateral, progressive after 1 year, thigh leg angle > 20°, suspected rickets or associated deformities
A 3-year-old African-American girl with obesity has severe progressive genu varum; plain radiograph shows proximal metaphyseal beaking	Blount disease

Last-Minute Review—Orthopedics	Most Likely Answer
Basketball player presents with left knee pain, recurrent effusion, quadriceps atrophy, and pain with range of motion; plain radiograph shows subchondral fragment with a lucent line separating it from the condyle	Osteochondritis dissecans
A 13-year-old female with right knee pain; she feels that her knee cap is unstable, parapatellar tenderness, plain radiograph sunrise view shows lateral tilt of patella	Recurrent patellar subluxation and dislocation
A 5-year-old has cystic mass in the back of the left knee for 3 months, it is painless, with no tenderness, normal range of motion	Popliteal cyst (Baker cyst)
The best management of Baker cyst	Observation for 12 months
Knee pain with prolonged sitting, activity, and climbing or descending stairs, feeling of knee instability. Tenderness over the medial patellar facet, pain with patellar compression, and mild swelling	Patellofemoral pain syndrome (PFPS)
The best management of patellofemoral pain syndrome	Ice, rest, NSAID, quadriceps and hamstring strengthening
The most common cause of intoeing in children > 3 years	Femoral torsion
A 7-year-old girl, patellae are looking inward (kissing patellae), running like an egg-beater, always sitting in W position, internal rotation of the hip is more than external rotation	Femoral anteversion
Management of femoral anteversion	Reassurance (spontaneous resolution in more than 80% of the cases)
Are shoe wedges, twister cables, night splint, or discouraging W-sitting effective in cases of femoral anteversion?	Showed to be ineffective
The most common cause of intoeing in children between 18 months and 3 years	Tibial torsion
A 2-year-old with both feet pointing medially, especially when running, patellae in both legs are pointing anteriorly. The child trips frequently	Internal tibial torsion
Management of internal tibial torsion	Reassurance (almost all cases resolve spontaneously)
A 4-month-old with a curved foot; by drawing an imaginary line bisecting the foot, it passes laterally to the fourth toe	Metatarsus adductus
The best management of metatarsus adductus	Observation (if persists beyond 6 months and deformity is rigid, a referral is necessary)
Newborn with a deformed foot; the foot can be everted and dorsiflexed (the foot touches the anterior tibia)	Postural or positional (calcaneovalgus foot) this is not a clubfoot

Last-Minute Review—Orthopedics	Most Likely Answer
The best management of calcaneovalgus foot	Observation—condition due to the intrauterine position
Newborn male infant with turned inward right foot. The right foot can be passively stretched almost to the midline. The ankle is in equinus (downward), the foot is supinated (varus) and adducted, dorsiflexion beyond 90° is not possible	Clubfoot or congenital talipes equinovarus (TEV)
Best management of clubfoot	Serial casting (requires an immediate referral)
The most common neurological conditions associated with clubfoot	Myelomeningocele and cerebral palsy
The most common condition associated with cavus foot	Charcot–Marie–Tooth syndrome
A mother is concerned that her 6-month-old has a flat foot	Reassurance (medial arch of the foot does not develop until 4 years of age and reaches adult value by 8 years)
A 3-year-old child with tiptoe walking, normal neurological examination, the best course of action	Physical therapy for 6 months for Achilles tendon stretching; if no improvement, orthopedic referral
A 15-year-old presents with progressive back deformity, plain radiographs of the thoracic spine shows 3 adjacent wedged vertebral bodies of at least 5°	Scheuermann kyphosis
A 12-year-old female has spinal scoliosis detected by school nurse; the scoliometer measures 7°	Adolescent idiopathic scoliosis (AIS)
Cases with AIS should be referred to orthopedic if	Scoliometer 7° or more, Cobb angle > 20°
Management of female adolescent with AIS and Cobb angle > 25°	Bracing (if skeletal growth remaining)
Management of female adolescent with AIS and Cobb angle > 50°	Usually, surgery is required
The indication for MRI in cases with scoliosis	Pain, left thoracic curve, abnormal neurological exam, infantile and juvenile types
Adolescent with low-back pain for a few months. The pain is worse after physical activity or prolonged sitting. O/E: pain is exaggerated with lumbar flexion and bilateral rotation. Tenderness to palpation along the lumbar paraspinal muscles; tightness of the hamstring and calf muscles. Normal neurologic examination. No other symptoms. Normal spine radiograph	Mechanical low-back pain
What is the best management in the previous case?	Physical therapy (lumbar/core strength and stability exercises)
A 10-year-old female does gymnastics; presents with low-back pain that increases with the extension of the spine, plain radiograph shows defect in pars interarticularis, oblique view shows Scotty dog collar sign	Spondylolysis

Last-Minute Review—Orthopedics	Most Likely Answer
A 10-year-old female does gymnastics; presents with low-back pain that increases with the extension of the spine, plain radiograph shows forward slippage in L5 over S1	Spondylolisthesis
Best initial management of spondylolysis	NSAID and rest
Management of spondylolisthesis	Referral to orthopedics
A 15-year-old boxer complaining of dull pain in radial aspect of the right wrist that is exacerbated by clenching, and tenderness in the anatomic snuffbox; plain radiograph on the right wrist is negative	Possible scaphoid fracture. (Radiograph is usually negative in the first 2 weeks). Treat if highly suspected
The best management of scaphoid fracture	Thumb spica splint and repeat radiograph in 2 weeks
The motor manifestation of posterior interosseous nerve injury	Finger drop (inability to extend the fingers at the metacarpophalangeal joint)
The motor manifestation of radial nerve injury	Wrist drop and finger drop
The motor manifestation of ulnar nerve injury	Partial claw hand
The motor manifestation of median nerve injury	Inability to flex the index finger
The most common sports injury in the knee, e.g., female playing soccer	Anterior cruciate ligament (ACL) injury
A 14-year-old complains of right shoulder pain after a fall, arm held in abduction, and externally rotated, the shoulder is boxlike. Patient resists adduction and internal rotation, plain radiograph shows a subcoracoid position of the humeral head in the AP view and humeral head lies anterior to the "Y" in an axillary view	Anterior shoulder dislocation
A 14-year-old complains of right shoulder pain after an electric shock, the arm is held in adduction and internal rotation, patient resists external rotation and abduction. Plain AP radiograph shows a humeral head that resembles an ice cream cone. The scapular "Y" view reveals the humeral head behind the glenoid (the center of the "Y")	Posterior shoulder dislocation
Child with anterior shoulder dislocation loses the pinprick sensation in the deltoid	Axillary nerve injury (check axillary nerve sensation before and after reduction)
Right shoulder pain after a fall during basketball practice, prominent clavicle with loss of the normal contour of the shoulder, shoulder radiographs show separation between the clavicle and acromion	Acromioclavicular joint disruption
Right shoulder pain after a fall during basketball practice directly onto the lateral aspect of the right shoulder, pain when adducting the arm across the chest, there is mild swelling and tenderness at the distal end of the clavicle, shoulder radiographs are normal	Acromioclavicular joint sprain

Last-Minute Review—Orthopedics	Most Likely Answer
The most common ligaments affected in ankle sprain	Lateral ligaments of the ankle (*anterior talofibular most common*, calcaneofibular, and posterior talofibular ligaments)
When can a patient with an ankle sprain go back to sports?	If no pain and painless range of motion
The best way to differentiate between an ankle sprain and fracture	Bony tenderness is usually a fracture
A 2-year-old boy fell 2 h ago; now he is refusing to walk. He appears to have tenderness over the distal third of the left tibia. Radiographs of lower extremities are normal. What is the next best step?	Apply a cast on the left lower extremity and repeat radiography in 2 weeks (possible toddler fracture)
A 12-year-old boy had a fracture of right tibia, fixed with an above-knee cast. He continues to have pain afterward, the pain keeps getting worse despite the maximum dose of prescribed pain medicine, any movement of the toes causes him excruciating pain, also he has numbness between the first 2 toes	Compartment syndrome. Presence of pain despite fracture immobilization and pain medication is a red flag for compartment syndrome
What is the next best step in the previous case of compartment syndrome?	Report immediately to the nearest ER (immediate removal of cast and orthopedic consultation)
The most common orthopedic complication of snake bite in the extremities	Compartment syndrome
A 12-year-old with right knee trauma. Knee radiograph showed no fracture but incidentally found a small, well-defined radiolucent cortical lesion with a surrounding rim of sclerosis in the upper tibia. The longitudinal axis of the lesion is parallel to the axis of the tibia	Fibrous cortical defect (non-ossifying fibromas), Most cases are accidentally discovered in radiographs taken for other reasons. No treatment is required in most cases
A 12-year-old with severe pain in the upper part of the right tibia at night improved dramatically with ibuprofen; radiograph showed 1.5 cm sharp round lesion (nidus) surrounded by a rim of radiodensity	Osteoid osteoma
A 2-year-old child suddenly stops moving his right arm after his brother forcibly pulled his hand	Nursemaid elbow
Short, webbed neck decreased the range of motion in the cervical spine, low hairline. Fusion of cervical vertebrae on radiograph	Klippel–Feil syndrome
Common associations with Klippel–Feil syndrome	Sprengel's deformity (elevation of the scapula), thoracolumbar anomalies, renal and cardiac anomalies

SPORTS MEDICINE

Daniel Murphy

Last-Minute Review—Sports Medicine	Most Likely Answer
Adolescent plays football, presents with pain in the right knee, swollen tender tibial tubercle; plain radiograph shows ossification of the tibial tubercle with fragmentation	Osgood–Schlatter disease
What is the best treatment of Osgood–Schlatter disease?	Icing, muscle stretching, and strengthening decrease activities triggering the pain, NSAIDs, knee brace
An 8-year-old boy recently starts playing basketball for 2 h every day, he is complaining of pain in both heels, the pain is worse when jumping and with exercise. The exam is positive for tenderness at both heels and and with dorsiflexion of both feet	Sever disease
What is the best treatment of Sever disease?	Icing, stretching of Achilles tendon, NSAIDs, heel cups, avoid activities triggering the pain, e.g., jumping
Adolescent girl is complaining of right hip pain that developed during track practice. She felt a pop in the front of her right hip and had immediate onset of pain. There is tenderness over anterior inferior iliac spine, pain and weakness with resisted hip flexion, and pain with passive extension of the hip. What is the most likely diagnosis?	Anterior inferior iliac spine (AIIS) apophyseal avulsion injury (due to strong muscle contraction and skeletal immaturity and relatively weak apophysis)
Healthcare providers should educate athletes at high risk for ACL tear about neuromuscular training programs that reduce the risk of injury. What are the components of neuromuscular training?	Strengthening, balance, and plyometric (jump) training, proper knee position and technique
What are the highest rates of dental injuries among high school sports in boys?	Basketball, baseball, wrestling, and soccer
What are the highest rates of dental injuries among high school sports in girls?	Field hockey, softball, basketball, and lacrosse
What is the best protective gear during sports that decreases oral injuries, including tooth avulsions, tooth fractures, and lacerations?	Mouthguard
Adolescent with a history of 3 concussions is suffering from forgetfulness and difficulty concentrating since last concussion, which was 2 months ago. What is the best diagnostic test to identify impaired cognitive function?	Neuropsychological testing

Last-Minute Review—Sports Medicine	Most Likely Answer
Adolescent with a history of scoliosis is in your office for sports clearance. Physical examination is significant for pectus excavatum, hypermobility of the wrist and finger joints, long and thin fingers, arm span–to–height ratio that is greater than 1.05	Echocardiography (Marfan syndrome is a high risk of aortic root rupture and aortic dissection)
What is the next best step?	
What is the best treatment of apophyseal avulsion injuries?	Rest and protected weight-bearing; surgery is rarely indicated
Adolescent boy presents to your office for preparticipation evaluation before football season. He has a history of 2 episodes of syncope. What is the most important finding that warrants a through cardiology evaluation?	Syncope during exercise
What is the best drink for sports activities lasting 1 h or less?	Water is enough for hydration
What is the best drink for sports activities lasting longer than 1 h?	Sports drinks (contain electrolyte and sugar; may encourage for hydration with longer activities)
A father is asking about energy drinks for his children during sports	Not recommended for young children and adolescents (due to high caffeine level in energy drinks)
An athlete has been doing strenuous exercise for a prolonged period in hot weather, excessively sweating, dizziness, thirst, weakness, headache, malaise, tachycardia, and the temperature is 103 °F	Heat exhaustion
An athlete has been doing strenuous exercise for a prolonged period in hot weather, presents with dry and hot skin, feeling dizzy, weak, altered mental status, low blood pressure, and tachycardia, and the temperature is 105 °F	Heat stroke
What is the next best step in an athlete with suspected heat stroke?	Rapid and immediate cooling (ice water bath) at the scene then transfer to the ED
An athlete is complaining of headaches, dizziness, poor concentration after a head concussion while playing volleyball. What is the next best step?	Remove from sports. Neurocognitive rest
Adolescent boy is presenting with a large swelling in the left thigh after hitting another player during the game, radiograph on the left femur is normal. What is the most likely diagnosis?	Soft-tissue hematoma
A 17-year-old boy is interested in building muscles, the mother is concerned about his acne, aggressive behavior. Gonads are small for age. What is the most likely underlying cause?	Anabolic steroids intake

RHEUMATOLOGY

Dawn M. Wahezi

Last-Minute Review—Rheumatology	Most Likely Answer
A 7-year-old with morning stiffness, knee and ankle swelling for 2 months, ESR is normal, antinuclear antibody (ANA) 1:160	Oligoarticular juvenile idiopathic arthritis (JIA)
A 2-year-old female with recently diagnosed oligo JIA and positive ANA requires frequent screening for this comorbidity	Chronic anterior uveitis
Fatigue, weight loss, arthritis in multiple joints for > 6 weeks, positive RF, anti-cyclic citrullinated peptide antibodies present and ANA is negative	Polyarticular JIA
Fatigue, weight loss, no fever, arthritis in multiple joints, negative RF, ANA is positive	Polyarticular JIA with an increased risk of uveitis
A 5-year-old girl recently diagnosed with JIA, her ANA is positive; how frequently does she need screening for uveitis?	Every 3–4 months (JIA, < 7 years and positive ANA is the highest risk of uveitis)
A 9-year-old girl recently diagnosed with JIA, her ANA is positive, how frequently does she need screening for uveitis?	Every 6 months (JIA, > 7 years and positive ANA)
An 8-year-old with knee pain for 6 weeks, noted to have pain, swelling, decreased range of motion, difficulty bearing weight, synovial fluid shows decreased viscosity and WBC 15,000	Inflammatory arthritis
Fever, salmon-colored rash with fever and hot showers, arthritis in major joints, hepatosplenomegaly, leukocytosis, thrombocytosis, anemia of chronic disease, elevated ESR, negative RF, and negative ANA	Systemic JIA
Side effects include immunosuppression, adrenal suppression, weight gain, cushingoid facies, diabetes and acne	Corticosteroids
Child with systemic JIA presents with elevated liver enzymes, prolonged PTT, positive D-dimer, thrombocytopenia, hyperferritinemia, and low ESR	Macrophage activation syndrome
Malar rash, arthritis, proteinuria, leucopenia, thrombocytopenia, positive ANA, and anti-dsDNA	Systemic lupus erythematosus (SLE)
An African-American girl with pericarditis, pleurisy, recurrent oral ulcers, hemolytic anemia, and RBC casts in urine	SLE
This test is very sensitive but not specific for SLE	Antinuclear antibody (ANA)
Autoantibodies associated with arterial/venous thrombosis or recurrent miscarriage (in patients with or without SLE)	Antiphospholipid antibodies

Last-Minute Review—Rheumatology	Most Likely Answer
The most severe type of lupus nephritis resulting in hematuria, proteinuria, elevated blood pressure and can lead to end-stage renal disease	Diffuse lupus nephritis (membranoproliferative, class IV)
Neonate born with heart block, annular erythematous plaques, anemia, thrombocytopenia, and elevated liver enzymes, positive SSA (Ro) and SSB (La) antibodies	Neonatal lupus
Recurrent parotitis, xerophthalmia, conjunctivitis, xerostomia, positive ANA, RF, and anti-Ro	Sjögren syndrome
A 7-year-old female, with proximal muscle weakness in both sides, arthralgia, heliotrope rash, elevated creatine phosphokinase (CPK) and LDH	Juvenile dermatomyositis
A 6-year-old female with difficulty climbing stairs and voice change, Gottron papules and abnormal nailfolds, and telangiectasias	Juvenile dermatomyositis
A 15-year-old had diarrhea positive for *Yersinia* 2 weeks ago, now is having conjunctivitis, urethritis, arthritis of the hip and knee	Reactive arthritis
Adolescent with inflammatory bowel disease (IBD) has arthritis	Arthritis-related to IBD
An 8-year-old, pain in the sacroiliac joint, tenderness, stiffness and joint pain in the morning that improves with activity, and positive HLA-B27	Enthesitis-related arthropathies
Child with nail pitting, psoriasis, arthritis, positive ANA	Juvenile psoriatic arthritis
Adolescent with recurrent oral and genital ulcers, positive pathergy test	Behçet disease
Adolescent girl with chronic left foot pain, minimal touch aggravates the pain, foot is swollen, warm to touch, and mottled skin	Complex regional pain syndrome or reflex sympathetic dystrophy (RSD)
A 7-year-old boy with pain in both legs, worse in the evening, sometimes awakens him from sleep, no fever, no limping, joints are normal on exam, pain responds to ibuprofen and heat massage	Growing pain
Adolescent, 1 year with fatigue, multiple areas of pain, tenderness, no signs of inflammation, and labs are normal	Fibromyalgia
A 5-year-old boy with acute onset palpable purpura on lower extremities, joint swelling and abdominal pain, labs reveal normal CBC, PT and PTT, positive proteinuria	Henoch-Schönlein purpura (HSP)
An 18-month-old with fever for 6 days, rash, conjunctivitis, strawberry tongue, and erythema of the palms and soles	Kawasaki disease
The primary treatment for Kawasaki disease, ideally given between day 5 and 10 of illness	IVIG, aspirin

Last-Minute Review—Rheumatology	Most Likely Answer
A 15-year-old female with fatigue, weight loss, recurrent sinusitis, and joint pain. Labs reveal hematuria, proteinuria, and positive cANCA	Granulomatous polyangiitis (GPA, formerly Wegener granulomatosis)
Pain, numbness, and discoloration of fingers (white then blue then red) that is triggered by cold weather	Raynaud's disease
A 12-year-old female with a linear hyperpigmented lesion on her leg that appears white and sclerotic in the center and has an erythematous border	Localized scleroderma
A 14-year-old female with severe Raynaud disease with ulceration on her fingertip, tightening of her skin, sclerodactyly, positive ANA, positive anti-Scl-70	Systemic sclerosis
A chest radiograph with pulmonary infiltrates and hilar adenopathy, biopsy with non-caseating granulomas, elevated ACE	Sarcoidosis
Recurrent knee arthritis in an otherwise well child with a prior history of camping in the woods	Lyme arthritis
Newborn infant presents a few hours after birth with hypotonia, facial muscle weakness, ptosis, weak cry, respiratory distress, the mother has a history of muscle weakness	Neonatal myasthenia gravis
Adolescent with muscle weakness, worsens with repetitive movement and at the end of the day, difficulty breathing, abnormal ocular movement	Juvenile myasthenia gravis
A 3-year-old child from the Middle East, recurrent fever and abdominal pain, during the episode the ESR and CRP are elevated, WBC 25,000	Familial Mediterranean fever
Child with fever for 3–5 days every month associated with mouth ulcers, throat pain, cervical lymphadenitis. The patient is well in- between episodes	PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis)

NEUROLOGY

Ivet HartonianJong W. Yoo, and Jason T. Lerner

Last-Minute Review—Neurology	Most Likely Answer
An 18-month-old turns cyanotic associated with a brief loss of consciousness that occurred during a temper tantrum	Reassurance (cyanotic breath-holding spell)
An 18-month-old turns pale with limp jerking and brief loss of consciousness that occurred after the child was scared by his sibling	Reassurance (pallid breath-holding spell)

Last-Minute Review—Neurology	Most Likely Answer
A 4-month-old infant is having episodes of tonic neck extension and dystonic posturing of trunk associated only with feedings. Has a normal neurologic exam	Sandifer syndrome
A premature infant has brief jerking of the right upper extremity that cannot be suppressed	Neonatal seizure
A previously healthy 16-month-old boy has 60 s generalized seizure in the setting of febrile illness (not involving the CNS) and is now acting normal	Simple febrile seizure
A previously healthy 16-month-old boy has had 2 febrile seizures in the last 24 h, and the infant is now acting normal	Complex febrile seizures
What is the recurrence risk after the first simple febrile seizure?	Approximately 30%
What is the risk of developing epilepsy in children with simple febrile seizures?	Approximately 2%
An 8-year-old boy is having multiple brief daily episodes of behavioral arrest and eye fluttering with an EEG showing 3 Hz/s spike-and-wave discharges	Absence seizure (*petit mal* seizure)
The first-line treatment for absence seizures	Ethosuximide
Antiseizure medication that should be avoided in women of child-bearing age due to teratogenicity	Valproic acid
A 6-month-old infant having episodes of tonic flexion of trunk, head, and extremities, occurring in clusters	Infantile spasms
Triad of infantile spasms, hypsarrhythmia on EEG, developmental regression	West syndrome
A 3-year-old boy with a prior history of infantile spasms who now has intellectual disability, multiple seizure types, EEG showing slow spike-wave activity	Lennox–Gastaut syndrome
An 16-year-old girl who is an excellent student has a generalized tonic-clonic seizure after a sleepover party with her friends. She also reports having jerking movements of her arms in the mornings	Juvenile myoclonic epilepsy
A 5-year-old with nighttime seizures involving the face and focal centrotemporal spikes in sleep	Rolandic epilepsy with centrotemporal spikes
A 3-year-old with language regression and continuous spike-wave discharges in slow wave sleep	Landau–Kleffner syndrome
A 9-year-old previously healthy girl with intractable focal seizures as well as hemiparesis and cognitive decline. MRI of the brain shows atrophy of one hemisphere	Rasmussen encephalitis

Last-Minute Review—Neurology	Most Likely Answer
An infant with rapid head growth, full fontanel, irritability, vomiting	Hydrocephalus
The most common cause of macrocephaly	Benign familial macrocephaly
An infant with failure to thrive, developmental delay, intractable seizures with an MRI showing a "smooth brain"	Lissencephaly
Elevated maternal alpha-fetoprotein, an infant born with a large cranial defect, abnormalities of the face and eyes, without a cortex but an intact brainstem	Anencephaly
Global intellectual disability, brain MRI showing bilateral clefts within the cerebral hemisphere	Schizencephaly
An infant with a sacral tuft of hair and normal neurologic exam	Spina bifida occulta
MRI showing downward displacement of the cerebellar tonsils through the foramen magnum	Arnold–Chiari malformation
Cystic expansion of the fourth ventricle in the posterior fossa, associated with hydrocephalus, cerebellar ataxia, and associated with corpus callosum agenesis	Dandy–Walker syndrome
Newborn with a skull defect, a sac-like protrusion containing brain material	Encephalocele
Infant born with a short neck, very low hairline in the back of the head, and limited range of motion in the neck	Klippel–Feil syndrome
Child with a stroke-like event has MRI with the appearance of a "puff of smoke"	Moyamoya disease
Adolescent girl presents with ptosis and double vision and is also complaining that she feels weaker by the end of the day	Juvenile myasthenia gravis
Preschool age boy has a history of toe walking, frequent falls, and enlarged calves. O/E: he has significant proximal muscle weakness, positive Gower sign, and laboratory evaluation shows elevated CPK (creatine phosphokinase)	Duchenne muscular dystrophy
A 10-year-old boy presents frequent falls, and weakness for 3 months. O/E: he has mild proximal muscle weakness, and calf pseudohypertrophy and his echocardiogram shows cardiomyopathy, laboratory shows elevated serum CPK	Becker muscular dystrophy—older onset and milder form
Newborn infant presents with hypotonia, respiratory distress, and facial muscle weakness. The genetic test is positive for CTG trinucleotide repeat	Congenital myotonic dystrophy

Last-Minute Review—Neurology	Most Likely Answer
Group of disorders characterized by decreased deep tendon reflexes, decreased proprioception, and a vibratory sense that is caused by defective peripheral nerve demyelination	Charcot–Marie–Tooth syndrome
A 12-year-old girl previously healthy over few months presents with progressive clumsiness, gait and limb ataxia, recurrent falls, rapid, jerky movements of both eyes, areflexia, lower extremity weakness, dysarthria, and dysphagia. Positive frataxin gene sequencing, associated with cardiomyopathy and increased risk of diabetes mellitus	Friedreich ataxia—GAA trinucleotide repeat (autosomal recessive and presents in older children)
A 3-year-old girl presents with recurrent respiratory infections, clumsiness, gait and limb ataxia, recurrent falls, oculomotor apraxia, choreoathetosis, dysarthria, and ocular telangiectasias, and serum α-fetoprotein is elevated	Ataxia–telangiectasia (autosomal recessive and presents in young children)—mutation of the *ATM* gene
Adolescent with a history of herpes zoster presents with peripheral nerve paralysis, facial pain, and deafness	Ramsay Hunt syndrome
History of diarrhea followed by progressing ascending weakness and loss of deep tendon reflexes with CSF showing elevated protein	Guillain–Barré syndrome
A 4-month-old infant with severe hypotonia and feeding difficulty. O/E: the infant is in frog-leg position and has tongue fasciculations	Spinal muscular atrophy
Progressive weakness in legs with focal back pain, bowel and bladder dysfunction and sensory level on the exam. Eventually develops into spastic diplegia	Transverse myelitis
A 6-month-old consistently reaches for toys with the right hand. What is the most likely underlying cause?	Central or peripheral neurologic abnormality of the opposite side, including hemiparesis
An 18-month-old boy with a history of prematurity, including bilateral intraventricular hemorrhages, who is brought in for evaluation because he is not walking and has increased tone in his legs. Scissoring of the legs is noted when he is held in a vertical position	Spastic diplegic cerebral palsy
Child with dyskinetic cerebral palsy and a history of elevated bilirubin	Kernicterus
A school-age child develops abnormal limb movements a few weeks after a group A beta-hemolytic strep infection	Sydenham chorea

Last-Minute Review—Neurology	Most Likely Answer
An 18-month-old girl with acquired microcephaly, language regression, repetitive hand-wringing movements, loss of purposeful hand use. Genetic testing reveals a mutation in the *MECP2* gene	Rett syndrome
Adolescent girl is complaining of right frontal pulsating headache with photophobia and nausea. She reports that during the headache episodes, she prefers to be in a dark, quiet room. Her father and paternal grandmother also get headaches	Migraine headache
Adolescent complaining of a mild headache described as "band-like" around the head. Headache is responsive to over-the-counter analgesics	Tension headache
Adolescent girl with a BMI more than 98th % presenting with headaches, nausea, vomiting, double vision, papilledema, and inability to abduct her left eye. What is the most likely underlying cause?	Idiopathic intracranial hypertension (pseudotumor cerebri)
A 1-year-old girl presents with an increasing number of *café-au-lait* spots all over her body. She has more than 6 macules, each macule measuring more than 5 mm. The rest of the exam is normal. No family history of neurofibromatosis. What is the next best step?	Referral to a pediatric ophthalmologist to check for Lisch nodules annually
The child in the previous example is positive for Lisch nodules. What are the recommendations?	Genetic consultation, annual pediatric ophthalmology evaluation, regular developmental assessment, and regular blood pressure monitoring
Multiple *café-au-lait* spots, Lisch nodules on ophthalmology exam, and presence of multiple neurofibromas	Neurofibromatosis type 1 Autosomal dominant
Presents with ringing in the ears; imaging shows bilateral vestibular schwannomas	Neurofibromatosis type 2 Autosomal dominant
A 10-month-old infant presents with infantile spasms and is noted to have multiple hypomelanotic macules (ash leaf spots). MRI brain shows cortical tubers	Tuberous sclerosis complex
History of port-wine stain, seizures, and glaucoma	Sturge–Weber syndrome
Child presenting with chronic back pain, lower extremity weakness, leg length discrepancy, foot deformities, scoliosis, neurogenic bladder, and recurrent urinary tract infections. There is no acral hair or skin abnormalities in the lower back	Tethered cord syndrome
Toddler refusing to walk or stand, with back tenderness and elevated ESR	Diskitis

Last-Minute Review—Neurology	Most Likely Answer
The child with a ventriculoperitoneal (V/P) shunt with a triad of high fever, focal neurologic deficits, and headache	Shunt infection—possible brain abscess
Child with recurrent throat clearing, facial grimacing, and grunting, but otherwise acting normal	Tic disorder (Tourette syndrome if symptoms > 12 months)
What is the first-line therapy for tic disorder with no other complications?	Behavioral modification
An infant with nystagmus, titubation, and torticollis	Spasmus nutans
A teenager with excessive daytime sleepiness, sudden episodes of loss of muscle tone and hallucinations when going to sleep	Narcolepsy
A 9-year-old has a sudden onset of severe abdominal pain, becomes pale, feels dizzy, and her vision slowly goes black followed by loss of consciousness for a few seconds and quick return to baseline	Vasovagal syncope
The reflex that appears around 8–9 months in preparation for a child to stand and walk	Parachute reflex

OPHTHALMOLOGY

Violeta Radenovich

Last-Minute Review—Ophthalmology	Most Likely Answer
A 5-day-old infant with severe bilateral purulent conjunctivitis and severe conjunctival chemosis. What is the most likely organism?	*Neisseria gonorrhoeae* conjunctivitis
A 5-day-old newborn presents with severe bilateral purulent conjunctivitis, severe conjunctival chemosis. What is the best treatment?	IM or IV 3rd generation cephalosporin, topical erythromycin, ophthalmology consultation
A 10-day-old infant with mild to moderate purulent discharge also associated with a cough and congestion. What is the most likely organism?	*Chlamydia* conjunctivitis
A 14-day-old infant presents with mucoid discharge from both eyes and eyelid swelling. What is the best treatment?	Oral erythromycin. Erythromycin ophthalmic ointment 4 times a day for 1 week
Excessive tearing, photophobia, frequent spasms of the eyelid, corneal clouding and enlargement of the eye	Congenital glaucoma (immediate referral to pediatric ophthalmology)
A newborn is being evaluated in the office for leukocoria. The reflexes are absent in both eyes. What is the next best step?	Immediate referral to ophthalmology—concern for cataract or retinoblastoma

Last-Minute Review—Ophthalmology	Most Likely Answer
An 8-week-old male infant with right eye more watery than the left. There is a golden-colored crust on his eyelashes, more prevalent in the morning. No redness	Nasolacrimal duct obstruction (topical antibiotic if suspected bacterial infection)
What is the best initial treatment of nasolacrimal duct obstruction?	Lacrimal sac massage 2–3 times daily
Most of the cases of nasolacrimal duct obstruction spontaneously resolve at what age?	6 months to 1 year with no need for probing or surgery
A 2-month-old baby boy presents with alternating deviations in both eyes, no other symptoms	Strabismus—if both eyes are alternating, monitor till 3 months of age (refer if persists)
A 2-month-old infant presents with left eye deviated inward with no other symptoms	Strabismus—if only one eye is deviating, refer to ophthalmology to exclude underlying pathology
The infant in the previous example continued to have left eye deviation at 4 months well visit	Referral to a pediatric ophthalmologist
How long can a newborn be monitored for poor tracking, lack of fixation, head tilt, nystagmus, or squinting?	If persist beyond 3 months of age must be referred to a pediatric ophthalmologist
A 9-month-old boy with crossed eyes. O/E: corneal light reflex is centered in both pupils equally; cover test shows no ocular deviation	Reassurance (pseudostrabismus)
A 9-month-old boy with crossed eyes. O/E: corneal light reflex is asymmetric; the cover test shows ocular deviation	Referral to a pediatric ophthalmologist
Red reflex is asymmetric, absent, dull, or opaque; dark spots in the red reflex; or leukocoria (white reflex). What is the next step?	Referral to ophthalmologist
What is the major consequence of delaying the treatment of strabismus or cataract in pediatric patients?	Amblyopia (lazy eye)
A 6-month-old infant presents with nystagmus, head nodding, and torticollis. The nystagmus is disconjugate, high frequency, small amplitude, pendular, and intermittent	Spasmus nutans (often disappears after a few years)—brain MRI on spasmus nutans patients to rule out optic nerve glioma that can present exactly like spasmus nutans
Child presents with swelling in the eyelid, hyperemia, normal vision, no pain with eye movement, no decrease in eye movement. What is the most likely diagnosis?	Periorbital cellulitis (may be treated with an oral antibiotic as an outpatient)
Child with a fever, malaise, proptosis, decreased vision, pain with eye movement, orbital pain and tenderness, decreased eye movement, dark red discoloration of the eyelids, chemosis, hyperemia of the conjunctiva. What is the most likely diagnosis?	Orbital cellulitis (admit for IV antibiotics and ophthalmology consultation)
Child is presenting with a painful, warm, swollen, red lump on the eyelid. What is the best treatment?	Warm compresses and massages, topical antibiotic if the lesion is draining

Last-Minute Review—Ophthalmology	Most Likely Answer
Child is presenting with a painless nodule on the left upper eyelid for 5 months not responding to conservative measures (warm compresses and lid hygiene). What is the next best step?	Referral to a pediatric ophthalmologist
A 5-year-old boy presents with eye pain, foreign body sensation, and tearing after self-inflicted eye injury with a sharp pencil. What is the next best step?	Examine the eye with fluorescein stain (corneal abrasion)
Management of corneal abrasion	Topical antibiotic, an oral analgesic, refer to an ophthalmologist if no improvement in 24 h
Child is presenting with sudden onset of right eye discomfort and blurring of vision after exposure to flying debris of broken glass. What is the next best step?	Ophthalmology consult to rule out corneal laceration and intraocular foreign bodies
A 7-year-old is noted to have blood in the anterior chamber of the eye after blunt trauma and pain with extra-ocular movements	Hyphema—emergent ophthalmology consult Sickle cell screening if African-American
Management of hyphema	Ophthalmology consult, 45° bed elevation, bed rest, eye shield, analgesia, sedation, topical cycloplegic, and topical steroids
Child is complaining of significant pain, bruising, and swelling in the periorbital area after eye trauma; "sunken" appearance to the eye on the affected side; decreased sensation to the cheek, upper lip, and upper gingiva on the affected side; and limitation of upward gaze on the affected side	Orbital floor fractures (due to inferior rectus muscle entrapment)
Adolescent girl with obesity is complaining of pounding headache, double vision, nausea, and vomiting; the headache is worse when she is leaning forward. Her vital signs are normal, but she is unable to abduct her right eye. What is the most likely finding in her eye exam?	Papilledema (untreated pseudotumor cerebri can result in permanent vision loss)
Child with pink eye, fever, cloudy rhinorrhea, cough, headache, pharyngeal redness with scant exudates, a palpable right preauricular lymph node, profuse tearing, and edematous nasal mucosa. The right eye conjunctiva is hyperemic, and tiny follicles are present on the inner lower lid. What is the best treatment?	Reassurance (pharyngoconjunctival fever commonly caused by adenovirus) Treatment: cold compresses to the eyes, analgesics, rest, and fluids
A 7-year-old girl is noted to have a large bloody blotch under the conjunctiva, no history of trauma; she has a runny nose and congestion	Reassurance (viral subconjunctival hemorrhage [enterovirus, or adenovirus infection])
A 7-year-old is noted to have a small area of unilateral eye redness in the sclera. The redness was noticed after a forceful sneeze	Reassurance (subconjunctival hemorrhage)

Last-Minute Review—Ophthalmology	Most Likely Answer
Child with watery, itchy eyes bilaterally, mild eyelid edema, along with conjunctival erythema. No mucoid or purulent discharge	Allergic conjunctivitis
Child is being treated for allergic conjunctivitis for 2 weeks with oral and topical antihistamine eye drops with no improvement. What is the next best step?	Referral to an ophthalmologist (topical ophthalmic steroids require monitoring of eye pressure)
A 3-year-old boy presents with different stage skin bruises; fundus examination shows bilateral multilayered flame shaped retinal hemorrhages. What is the most likely cause?	Child abuse
Night blindness, flashes of light, visual loss. O/E: optic nerve waxy pallor, mid-peripheral retinal hyperpigmentation, retinal arteriolar attenuation	Retinitis pigmentosa
Pigmentary retinopathy, polydactyly, truncal obesity, kidney dysfunction, short stature	Bardet–Biedl syndrome
Syndromes associated with retinitis pigmentosa and hearing loss	Alport syndrome, Waardenburg syndrome, Refsum disease, Usher syndrome
A 9-year-old girl with a history of short stature, vision 20/40, her eye exam is significant for optic nerve atrophy. What is the next best step?	Brain MRI (optic nerve atrophy can be associated with a brain tumor)
Risk factors commonly associated with retinopathy of prematurity (ROP)	Birth before 30 weeks gestation, or low birth weight < 1500 g
Who should screen preterm infants at risk for ROP?	Pediatric ophthalmologist with experience in ROP
Do preterm infants at risk of ROP should be followed by an ROP experienced ophthalmologist after discharge from the NICU	Yes. Within 4–6 months after discharge because of risk of developing strabismus, amblyopia, high refractive errors, cataracts, and glaucoma

EAR, NOSE, AND THROAT

Kara D. Meister and Anna H. Messner

Last-Minute Review—Ear, Nose, and Throat	Most Likely Answer
Newborn with isolated preauricular skin tags	Renal US is not indicated if no other congenital anomalies or risk factors
What is the risk of permanent hearing impairment in a newborn with isolated preauricular skin tags or pits?	5-fold higher compared to the general population
Prior to discharge, newborn hearing screen refers to the right (i.e., did not pass the hearing test in the right ear). Repeat testing also refers to the right. What is the next best step?	Refer for acute brainstem response (ABR) testing
Which antibiotic often used to treat newborn sepsis that may cause ototoxicity?	Gentamicin

Last-Minute Review—Ear, Nose, and Throat	Most Likely Answer
Child with acute otitis media or externa and perforation of tympanic membrane—which topical antibiotic drops should be avoided to prevent ototoxicity?	Aminoglycosides
A 12-month-old child with severe bilateral sensorineural hearing loss. What is the best treatment?	Cochlear implant
What is the best audiometric test for an infant 6–9 months or for older children with developmental delay?	Visual reinforcement/behavioral audiometry
What is the best audiometric test for a child as young as 2.5 years	Play audiometry
What is the best audiometric test for children > 4 year, and adolescents?	Conventional audiometry: pure-tone, speech
What is the hallmark sign of otitis externa?	Tenderness of the tragus or pinna
Child with persistent purulent otorrhea for more than 2 weeks despite treatment with oral and topical antibiotics	Referral to otolaryngologist
Child with persistent otorrhea for more than 6 weeks and not responding to oral and topical antibiotics. What is the most frequent cause?	Cholesteatoma (collection of squamous epithelial cells and keratin within the middle ear)
Child presents with persistent ear discharge more than 3 months despite the treatment with multiple courses of topical and systemic antibiotics. What is the most common bacteria associated with chronic suppurative otitis media (CSOM)?	Methicillin-resistant *Staphylococcus aureus* (MRSA) is most common isolate, *Pseudomonas* is also a common cause
Adolescent is complaining of nasal obstruction, pain, and rhinorrhea after nasal trauma. O/E: intranasal cavity reveals a tense red mass on each side of the nasal septum. What is the next best step?	Prompt drainage of nasal septal hematoma to prevent nasal cartilage ischemia, necrosis, and deformity
Adolescent wrestler with blue swelling and redness in the right ear pinna, occurred during a school match	Auricular (ear pinna) hematoma—urgent aspiration of the hematoma and pressure dressing
A 7-year-old child had tympanostomy tubes placed 4 years ago because of acute otitis media with effusion and conductive hearing loss. O/E: you clearly visualize a white tympanostomy tube in the right tympanic membrane. What is the next best step?	Referral to ENT for surgical removal (tympanostomy tubes that remain in place for longer than 3 years should be surgically removed)
How long is a tympanostomy tube expected to remain in place?	12–18 months
Child has otitis media with effusion (OME) less than 3 months	Tympanostomy tube insertion is not indicated
Child has OME lasting 3 months with conductive hearing loss	Tympanostomy tube insertion is indicated

Last-Minute Review—Ear, Nose, and Throat	Most Likely Answer
Child has recurrent acute otitis media with OME at the time of presentation	Tympanostomy tube insertion is indicated
Child with bilateral or unilateral OME lasting at least 3 months together with risk factors for speech, language, or learning problems (e.g., neurodevelopmental disabilities, craniofacial anomalies)	Tympanostomy tube insertion is indicated
A 5-year-old with nasal discharge, congestion, and cough for 10 days without improvement	Acute bacterial sinusitis (duration of symptoms)
A 5-year-old with temperature 101.3 °F with purulent rhinorrhea for 3 days	Acute bacterial sinusitis (severity of symptoms)
A 5-year-old with worsening of nasal congestion or rhinorrhea, cough, and fever after a 3- to 4-day period of improved symptoms	Acute bacterial sinusitis (worsening of symptoms)
Child presents with a 1-week history of fever of 102 °F, cough, bilateral purulent nasal discharge, and frontal sinus tenderness	Acute sinusitis First-line treatment: amoxicillin clavulanate for 10–14 days
Child presents with nasal congestion, post nasal drip, altered sense of smell, as well as facial pressure for over 3 months	Chronic sinusitis
Child with an isolated fracture in the paranasal sinus. What is the best treatment?	1-week course of oral antibiotics and oral analgesics, referral in 1 week to ENT or a surgeon specialized in facial trauma
What are the sinus precautions in cases of paranasal sinus fractures?	To avoid swimming, blowing the nose, playing wind instruments, and use of drinking straws
A 6-year-old boy presents with throat pain, fever, headache, and abdominal pain. Rapid antigen detection test for group A *Streptococcus* is positive. What is the best treatment?	10-day course of oral penicillin V
A 6-year-old boy presents with the third episode of streptococcal pharyngitis in the last 3 months. Rapid antigen detection test for group A *Streptococcus is* positive. He was treated previously with penicillin V and amoxicillin. What is the next best treatment?	Clindamycin for 10 days
A 6-year-old boy presents with throat pain, fever, headache, and abdominal pain. Rapid antigen detection test for group A *Streptococcus* is positive. He had an anaphylactic reaction to penicillin. What is the best treatment?	Clindamycin for 10 days
A 6-year-old boy presents with throat pain, fever, headache, and abdominal pain. Rapid antigen detection test for group A *Streptococcus* is positive. He had a non-anaphylactic reaction to penicillin. What is the best treatment?	Oral cephalosporin for 10 days

Last-Minute Review—Ear, Nose, and Throat	Most Likely Answer
A 5-year-old boy presents with the insidious onset of fever, sore throat, neck stiffness, tachypnea, drooling, and stridor. Lateral neck radiograph shows thickened prevertebral soft tissues	Retropharyngeal abscess
What is the next best step in the previous case with retropharyngeal abscess?	Airway management, IV fluids, IV antibiotics, emergent ENT consultation
Adolescent female presents with fever, sore throat, difficulty opening her mouth, muffled voice, and dysphagia. She has tender anterior cervical lymphadenopathy. Her right tonsil is erythematous and enlarged, pushing her uvula to the left	Peritonsillar abscesses
What is the next best step in the previous case with peritonsillar abscess?	Needle aspiration of her right tonsil (diagnostic and therapeutic)
A 9-month-old presents with fever, ear tugging, and runny nose. Both tympanic membranes are bulging; this is the first ear infection. What is the first-line treatment?	Amoxicillin 90 mg/kg/day for 10 days
The same child presents to the office 3 weeks later with the same symptoms. Which antibiotic should be used?	Amoxicillin/clavulanate—due to treatment failure within the last 30 days
A 2-year-old child presents with fever and purulent conjunctivitis. Physical exam shows bulging of the tympanic membrane. Which antibiotic should be used?	Amoxicillin/clavulanate—likely due to non-typeable *Haemophilus influenzae* with concurrent bacterial conjunctivitis
Child presents with fever, tenderness, and edema in the postauricular region. Child was diagnosed with otitis media recently, but the parent was not compliant with therapy	Mastoiditis—needs ENT consult and IV antibiotics
Newborn child with severe cyanosis that improves with crying. Nurse attempts to pass a 6 French catheter and is not successful	Bilateral choanal atresia—requires immediate airway, can also be unilateral (less severe) and associated with CHARGE
Child with chronic nasal congestion, mucoid rhinorrhea, and noisy breathing for several months. No history of recurrent serious bacterial infections and normal weight for age. On examining the nasal passages, you note glistening, bluish-gray, grape-like masses bilaterally. What is the next best test?	Sweat chloride test
Children with nasal polyps should be screened for	Cystic fibrosis
The most common cause of epistaxis in a child	Trauma secondary to digital manipulation
A 2-year-old with unilateral rhinorrhea and foul smell from the left nostril. The child is otherwise acting normal?	Foreign body in the nose
Child presents with runny nose, congestion, itchy eyes, sneezing, and darkened skin around the eyes	Allergic rhinitis (under eye circles are called allergic shiners)
What is the most conservative method to control allergic rhinitis symptoms?	To avoid allergic triggers such as pets

Last-Minute Review—Ear, Nose, and Throat	Most Likely Answer
Child has a painless blue mass noted on the right lower lip. The child is otherwise healthy, but the mother is concerned	Reassurance unless bothersome, then can consider excision (mucocele)
A 4-year-old girl presents with unilateral cervical lymphadenopathy, mild fevers; she was scratched by her new kitten several weeks ago	Cat scratch fever—*Bartonella henselae*
What is the most common complication of an adenoidectomy?	Hypernasal speech secondary undiagnosed predisposition to velopharyngeal insufficiency (such as submucosal cleft palate)

CARDIOLOGY

Grace KungAllison Hill, and Jennifer Su

Last-Minute Review—Cardiology	Most Likely Answer
Newborn with cyanosis, pulse oximetry changed from 60% to 64% only on 100% oxygen	Cardiac (most likely)
Newborn with cyanosis, pulse oximetry changed from 60% to 88% on 100% O_2	Pulmonary (most likely)
What is the reason that left to right shunt lesions may not present until 1 month of age?	The pulmonary vascular resistance drops to normal levels at that time
A 1-day-old infant with a history of maternal diabetes, cyanosis, and tachypnea, poor response to supplemental oxygen, loud single second heart sound, no murmur, chest radiograph shows narrow mediastinum with small heart tipped on side, increased pulmonary vascularity	Transposition of great vessels
What is the next best step in a newborn with suspected transposition of the great vessels?	Prostaglandin E1 to keep the patent ductus arteriosus (PDA) open, followed by +/− balloon atrial septostomy and surgery
The most common cause of cyanotic heart disease presenting a few days after birth	Transposition of the great vessels
Newborn presents with cyanosis in the lower extremities, tachycardia, respiratory distress, and loud single S2 sound	Persistent pulmonary hypertension (R→L shunting across the PDA)
A 1-day-old newborn presents with cyanosis, single first and second heart sounds, chest radiograph, shows decreased lung markings, and electrocardiogram shows left axis deviation	Tricuspid atresia with pulmonary atresia
Newborn presents with cyanosis (mother was on a medicine for severe bipolar disorder), chest radiograph shows cardiomegaly and right atrial enlargement	Ebstein anomaly

Last-Minute Review—Cardiology	Most Likely Answer
Newborn presents with severe cyanosis, systolic ejection murmur, and a single second heart sound, chest radiograph shows decreased pulmonary vascular markings	Severe pulmonary stenosis
Newborn presents with intense cyanosis and respiratory distress, chest radiograph shows a "snowman" shaped heart	Supracardiac total anomalous pulmonary venous return
An 8-week-old boy presents with feeding difficulties, poor weight gain, episodes of bluish discoloration of the skin while feeding and crying, a harsh systolic ejection murmur (SEM) is heard over the pulmonic area and left sternal border; chest radiograph shows diminished vascularity in the lungs and diminished prominence of the pulmonary arteries, a boot-shaped heart (*cœur en sabot*)	Tetralogy of Fallot
A 2-year-old with a history of tetralogy of Fallot has progressive agitation, increasing cyanosis, and increased fussiness	Hypercyanotic spell (Tet spell)—next step is the knee-chest position
During the first 48 h of life, a newborn rapidly develops cyanosis, tachypnea, respiratory distress, pallor, lethargy, metabolic acidosis, oliguria, weak pulses in all extremities, hepatosplenomegaly, and no murmur	Hypoplastic left heart (as PDA closes)
What is the next best step for the newborn in the previous case with suspected hypoplastic left heart?	Prostaglandin E1
A 2-week-old boy develops congestive heart failure, severe metabolic acidosis, and poor perfusion of the lower extremities	Coarctation of the aorta
Newborn presents with shock; the echocardiogram shows coarctation of the aorta. What is the drug of choice?	Prostaglandin E1
A 12-year-old presents with hypertension, occasional headache, leg cramps, weak and delayed femoral pulse, and blood pressure in the upper limb is higher than the lower limb, chest radiograph shows rib notching and scalloping on the undersurface of posterior ribs	Coarctation of the aorta
A girl with Turner syndrome presents with hypertension, weak and delayed femoral pulse	Coarctation of the aorta
Newborn infant presents with a soft, harsh systolic ejection murmur, best heard at the axillae, and precordium and no symptoms	Peripheral pulmonary stenosis (PPS)
The most common cardiac lesion associated with trisomy 21 (Down syndrome)	Endocardial cushion defect

Last-Minute Review—Cardiology	Most Likely Answer
The most common cardiac lesion associated with trisomy 18	Ventricular septal defect (VSD)
The most common cardiac lesion associated with Turner syndrome	Bicuspid aortic valve
The most common cardiac lesion associated with Williams syndrome	Supravalvar aortic stenosis
The most common cardiac lesion associated with Alagille syndrome	Branch pulmonary stenosis
The most common cardiac lesion associated with Noonan syndrome	Pulmonary stenosis
The most common cardiac lesion associated with DiGeorge syndrome	Tetralogy of Fallot
The most common cardiac lesion associated with *cri du chat* syndrome	VSD
The most common cardiac lesion associated with Holt–Oram syndrome	Atrial septal defect (ASD)
The most common cardiac lesion in fetal alcohol syndrome	VSD, ASD
The most common cardiac lesion associated with lithium teratogen	Ebstein anomaly
The most common cardiac lesion associated with supraventricular tachycardia	Ebstein anomaly
The most common cardiac lesion associated with the infant of a diabetic mother	Ventricular hypertrophy
The most common cardiac lesion associated with tuberous sclerosis	Cardiac rhabdomyoma
The most common valvular lesion associated with acute rheumatic fever	Mitral regurgitation
The most common cardiac lesion associated with Marfan syndrome	Aortic root dilation (risk for dissection)
The most common congenital cardiac lesion overall	VSD
The syndrome that is associated with true interrupted aortic arch	DiGeorge syndrome
Adolescent routine physical exam, apical mid-systolic non-ejection click, and late systolic murmur; the murmur is louder when goes from a supine to a standing position, and the murmur becomes softer when squatting	Mitral valve prolapse
Child routine physical exam, systolic murmur with a vibratory character, best heard in the lower sternal border, varies with changes in respiration and position	Still's murmur
A 6-year-old with a continuous murmur, low-pitched sound, best heard in the infraclavicular region, disappears when supine and with gentle pressure on the jugular vein	Venous hum

Last-Minute Review—Cardiology	Most Likely Answer
While having her hair brushed, a 15-year-old girl develops cold sweats, pallor, and palpitations and loses consciousness for 10 s	Vasovagal syncope
While running, a 15-year-old girl lost consciousness	Thorough cardiac evaluation and referral to a cardiologist
A 15-year-old girl faints while running and has a positive family history of deafness and sudden death	Long QT syndrome
The most common cause of sudden cardiac death in an athlete	Hypertrophic cardiomyopathy
Newborn fails hearing screen; EKG shows a very prolonged QT interval	Jervell and Lange-Nielsen syndrome
A 5-year-old, heart rate is 230 beats/min, chest discomfort; the heart rate decreases to 80 beats/min after ice is applied to the face	Supraventricular tachycardia (SVT)
What is the definitive treatment for SVT?	Radiofrequency ablation
Child presents with a history of intermittent tachycardia; EKG shows a short PR interval, slurred and slow rise of the initial upstroke of QRS (delta wave), widened QRS complex	Wolff–Parkinson–White syndrome (WPW)
Child presents with chest pain, fever, friction rub; EKG shows diffuse ST-segment elevation, had upper respiratory infection 10 days before	Pericarditis
Adolescent diagnosed with influenza presents with fever, tachycardia, edema, and gallop; chest radiograph shows pulmonary edema, cardiomegaly, low-voltage EKG	Myocarditis
An athlete presents with dyspnea while playing; systolic ejection crescendo-decrescendo murmur best heard at the apex and left sternal border, and radiates to the suprasternal notch; the murmur is louder while standing and with Valsalva maneuver	Hypertrophic cardiomyopathy
A football player presents with chest pain with exertion and several near syncope episodes during his football game. Next best step?	Restrict from sports then EKG and echocardiogram
EKG in a 12-day-old shows negative T wave in V6	Left ventricular hypertrophy
A 15-year-old boy with a history of recurrent chest pain during exercise faints and dies while playing basketball; hypertrophic cardiomyopathy ruled out as a cause of death. What is the next likely cause?	Anomalous left coronary artery is most likely
What is the most common organism responsible for infective endocarditis in pediatric patients with or without congenital heart disease?	*Staphylococcus aureus*
History of repaired VSD with a small residual VSD next to the VSD patch, going in for dental work. Is subacute bacterial endocarditis (SBE) prophylaxis indicated?	Antibiotic prophylaxis

Last-Minute Review—Cardiology	Most Likely Answer
Child with prosthetic mitral valve going for surgery; is SBE prophylaxis indicated?	Antibiotic prophylaxis
Child with mitral regurgitation and VSD, going in for dental work. Is SBE prophylaxis indicated?	No antibiotic prophylaxis
A mildly desaturated child with tetralogy of Fallot going in for dental work; is SBE prophylaxis indicated?	Antibiotic prophylaxis
Child with a previous history of endocarditis; is SBE prophylaxis indicated?	Antibiotic prophylaxis
Tall, peaked T waves in precordial leads indicates	Hyperkalemia
An infant of diabetic mother presents a few hours after birth with jitteriness, hypoglycemia, cyanosis; EKG shows prolonged QT interval	Hypocalcemia
EKG shows sinus tachycardia, widened QRS complex with an interval greater than 100 ms, in a child who presents with altered mental status after accidentally ingesting grandmother's medication	Tricyclic antidepressant (TCA) toxicity
EKG shows progressive prolongation of PR interval followed by a drop in QRS	Type I second degree AV block (Mobitz I or Wenckebach)
EKG shows normal PR intervals and periodic drop in QRS	Type II second degree AV block (Mobitz II)
An asymptomatic adolescent with blood pressure 137/87, all labs normal, renal US and chest radiograph normal. What is the next best step?	Salt restriction in diet
A late complication of an untreated ASD or VSD that results in desaturation	Eisenmenger syndrome—shunt becomes a right to left shunt
A 6-month-old infant with failure to thrive, diaphoresis, and hepatomegaly. Echocardiogram shows a large VSD. Next best step?	Surgical correction
A 4-year-old boy with physical examination significant for widely split and fixed S_2 and crescendo-decrescendo systolic ejection murmur heard in the second intercostal space at the upper left sternal border. EKG shows a RSR1 pattern in V1. What is the most likely diagnosis?	Atrial septal defect
A premature infant with a continuous machine-like murmur and bounding pulses	PDA
Which medication is used to close a PDA in a premature infant?	Indomethacin
What are some common side effects of indomethacin?	Thrombocytopenia GI bleeding Necrotizing enterocolitis Renal failure
Systolic murmur most commonly heard at the right upper sternal border radiates to the neck and is associated with an ejection click	Aortic stenosis

Last-Minute Review—Cardiology	Most Likely Answer
Most common valve abnormality associated with aortic stenosis	Bicuspid aortic valve
What is the most likely etiology of an early high-pitched diastolic murmur associated with bounding pulses in a patient with Marfan syndrome?	Aortic regurgitation
High-pitched holosystolic blowing murmur heard loudest at the apex and radiates to the axilla	Mitral valve regurgitation
Late crescendo systolic murmur associated with a mid-systolic click, may be seen in adolescents	Mitral valve prolapse
Late diastolic rumbling murmur with an opening snap heard at the apex	Mitral valve stenosis
What is the most feared complication of Kawasaki disease?	Coronary artery aneurysm
An 8-year-old presents with sharp stabbing non-specific chest pain at rest that resolves shortly. There are no other symptoms and no past medical history	Reassurance (precordial catch syndrome)
A 10-year-old male presents with sharp chest pain; the pain is reproducible on physical exam	Costochondritis
At what ages is lipid screening universally recommended in the pediatric population?	Once between 9 and 11 and again between 17 and 21
What is the initial management for an obese adolescent with elevated cholesterol levels?	Diet and lifestyle modifications, and if cholesterol is still elevated after 6 months, then start statin

PULMONOLOGY

Osama I. Naga

Last-Minute Review—Pulmonology	Most Likely Answer
Newborn with inspiratory stridor and noisy breathing; stridor improves in the prone position with head elevated and worsens in the supine position	Laryngomalacia (usually benign, self-limiting and improves as the child reaches age 1–2 years)
What is the treatment for laryngomalacia?	Reassurance (careful observation and growth monitoring)
Newborn with a hoarse voice, weak cry, and biphasic stridor that is louder when awake. Improves when positioned to be lying down on one side	Unilateral vocal cord paralysis
An infant with bulging anterior fontanelle, high-pitched biphasic stridor, respiratory distress, and recurrent pneumonia	Bilateral vocal cord paralysis

Last-Minute Review—Pulmonology	Most Likely Answer
Adolescent male present with shortness of breath, choking sensation within a few minutes after starting track training; there is a voice change during exercise. He was treated for exercise-induced asthma with no improvement in his symptoms. What is the next best step?	Vocal cord evaluation. Most likely diagnosis is paradoxical vocal cord dysfunction
Child with a history of chin hemangioma, worsening inspiratory stridor	Subglottic hemangioma
Newborn with intermittent cyanosis that disappears when crying but prominent during feeding; nasogastric tube unable to pass through the nostrils	Choanal atresia
An infant with cyanosis, the mother is mixing the formula with well water; normal cardiac and pulmonary examination, normal pulse oximetry. Chocolate-colored blood noticed when collecting the blood for testing	Methemoglobinemia
Boy with unilateral persistent offensive smelling nasal discharge	Nasal foreign body
Recurrent pneumonia and nasal polyps	Cystic fibrosis
Failure to thrive, rectal prolapse, persistent cough	Cystic fibrosis
Sinusitis, bronchiectasis, situs inversus, reduced male fertility	Kartagener syndrome
A 4-year-old boy is suffering from recurrent sinusitis, chronic otitis media; during the neonatal period he had respiratory distress, daily nasal congestion, and wet cough. What is the most likely diagnosis?	Primary ciliary dyskinesia
Child with no known health problem woke up suddenly coughing blood. What is the most likely cause?	Epistaxis
Child with a 1-day history of low-grade fever, malaise, congestion, and very thick, very green nasal discharge	Viral upper respiratory tract infection
Child with 2 weeks of clear nasal discharge and a cough that is worse at night and while lying down supine. Not responding to nasal allergy medications	Acute bacterial sinusitis
A 7-year-old with fever, runny nose, throat pain; the pharynx is erythematous and shows white exudate	Viral pharyngitis
A 7-year-old with abrupt onset of fever, headache, stomach pain, mild throat pain; the pharynx is erythematous, with petechiae, no white exudates	Strep throat (*Streptococcus pyogenes*)
A 15-month-old boy presents with poor feeding, high fever, thick, purulent profuse nasal discharge, crust and irritation around the nostrils	Streptococcal fever or streptococcosis

Last-Minute Review—Pulmonology	Most Likely Answer
When can a child with streptococcal infection go back to school after taking an antibiotic (become noninfectious)?	Next day if improved (typically 24 h after the antibiotic)
Toddler with a barking cough, fever, inspiratory stridor, suprasternal retractions, and neck radiograph is normal	Croup
What is the mainstay treatment of croup?	Dexamethasone and racemic epinephrine can be used in moderate/severe cases
A toddler presents with high fever, looks toxic, brassy cough, and stridor. He was sent home on oral antibiotics and ibuprofen, a few hours later he died	Bacterial tracheitis
A 5-year-old, unimmunized, presents with sudden onset of fever, stridor, drooling and throat pain, leaning forward and crying	Epiglottitis
Preschool child has been having recurrent attacks of barking cough and croup over the last few nights, and no symptoms of cough in-between the attacks	Spasmodic croup or due to GI reflux
A 3-month-old with fever, cough, runny nose, tachypnea and retractions. O/E: wheezing, and crackles in both lung fields; pulse oximetry is 92%	Acute bronchiolitis
What is the first-line treatment for bronchiolitis?	Nasal suctioning and supportive care
A preterm boy with chronic lung disease is receiving palivizumab prophylaxis, recovered from RSV bronchiolitis a few days ago. Can he take his next due dose of palivizumab?	No (discontinue palivizumab for the season)
A 1-month-old infant who was born at 35 weeks during winter has been having nasal congestion for the last 2 days; stopped breathing for a few seconds and turned blue, positive RSV	Apnea secondary to RSV viral infection
A 3-week-old with pneumonia; chest radiograph shows bilateral infiltrates	*Chlamydia trachomatis*
Adolescent with fever, cough, chest pain, shortness of breath, tachypnea, and pleural friction rub	*Streptococcus pneumoniae*
Adolescent had influenza A infection, now is having a very high fever, looks toxic; tachypnea, respiratory distress, and tachycardia; chest radiograph is positive for infiltration, cavities, and pleural effusion	*Staphylococcus aureus* pneumonia
A 7-year-old boy has a cough, on and off fever, and headache for 2 weeks, on the exam he has diffuse expiratory wheezing and crackles in both lung fields with no retractions or tachypnea. Pulse oximetry is normal. The wheezing is not fully responsive to nebulized albuterol treatment. What is the most likely cause?	*Mycoplasma pneumoniae*

Last-Minute Review—Pulmonology	Most Likely Answer
What is the most helpful diagnostic test in cases of atypical pneumonia possibly due to *Mycoplasma pneumoniae*	Polymerase chain reaction (PCR) from nasal washing for *Mycoplasma* antigen
What is the antibiotic of choice for older children with atypical pneumonia who are ill enough to require hospitalization?	Macrolide antibiotic to shorten the course of illness
Mississippi and Ohio river valleys, chickens, caves, low-grade fever, cough, hilar lymphadenopathy	Histoplasmosis
Adolescent living in Arkansas presents with flu-like symptoms; fever, chills, headache, myalgia, and cough; 2 weeks later developed hemoptysis, chest pain, shortness of breath, weight loss, extreme fatigue, and skin lesions. Chest radiograph shows a focal mass with well-defined margins about 6 cm in size in the right upper lobe and few other focal segmental opacities	Blastomycosis
Child visited California's San Joaquin Valley 3 weeks ago, now has a fever, chills, cough, weight loss, chest pain, and erythema nodosum. Chest radiograph is normal	Coccidioidomycosis
What is the most sensitive serologic test in cases with suspected coccidioidomycosis?	*Coccidioides* immunoglobulin M (IgM)
History of asthma, recurrent attacks of fever, fatigue, coughing mucus plugs, hemoptysis, eosinophilia, high IgE	Allergic bronchopulmonary aspergillosis
A sore throat with hoarseness; 3 weeks later develops pneumonia	*Chlamydophila pneumoniae*
Toddler with a history of choking 2 weeks ago; he has had a cough since then, wheezing, diminished breath sounds on the right; normal chest radiograph	Foreign body aspiration
Chest radiograph views that may help in the diagnosis of cases with suspected foreign body aspiration	Inspiratory and expiratory or bilateral decubitus views to see asymmetric hyperinflation on the side with foreign body due to ball-valve effect
Child with progressive dyspnea, fatigue, recurrent cough, new-onset hemoptysis; sputum shows hemosiderosis-laden alveolar macrophages, and CBC is consistent with iron deficiency anemia	Pulmonary hemosiderosis
African-American with shortness of breath, blurring of vision, erythema nodosum, hypercalcemia, elevated ACE level. Chest radiograph shows bilateral hilar lymphadenopathy	Sarcoidosis
Child with recurrent episodes of left lower lobe pneumonia; chest radiographs demonstrated focal consolidation in the same location in all events; between episodes the child is well, active, and playful	Pulmonary sequestration

Last-Minute Review—Pulmonology	Most Likely Answer
Child with fever, chest pain, and productive cough; chest radiograph shows cyst-like lesion close to the mediastinum	Bronchogenic cyst
An infant has difficulty with feeding, stridor, recurrent wheezing, history of recurrent pneumonia. Barium esophagography showed posterior compressions. What is the most likely diagnosis?	Vascular ring
Asthma > 1 night/week, throughout the day, extreme limitation of activity, FEV1: < 60%	Severe persistent
Asthma 3–4 nights/month, daily, some limitation of activity, FEV1 60–80%	Moderate persistent
Asthma 1–2 nights/month, 3–6 days/week, minor limitation of activity, FEV1 > 80%	Mild persistent
Asthma ≤ 2 days/week, 0 nights/month, no limitation of activity, FEV1 > 80%	Intermittent
Step 1 management of intermittent asthma	Short-acting beta agonists (SABA) as needed
Step 2 management of mild persistent asthma	Low-dose inhaled corticosteroids (ICS)
Step 3 management of moderate persistent asthma	Medium-dose ICS, and consider short course oral corticosteroids (OCS)
Step 4 management of severe persistent asthma	Medium-dose ICS + LABA and consider a short course of OCS
What is the most effective primary controller treatment for asthma of any severity?	ICS
A 10-year-old boy has shortness of breath and cough every time he runs or exercises; positive family history of asthma; on physical exam the lung is clear, the pulmonary function test is normal. What is the next best step?	Exercise-induced asthma—use albuterol (bronchodilator) inhaler 15 min before exercise. Warm up prior to strenuous activity
Child with nighttime snoring, enlarged tonsils, and difficulty concentrating in school	Obstructive sleep apnea

NUTRITION

Susan S. Baker

Last-Minute Review—Nutrition	Most Likely Answer
Xerophthalmia, corneal opacity, bitot spots, night blindness, growth failure, and recurrent infection	Vitamin A deficiency
Gingival bleeding, anemia, corkscrew-coiled hairs, anorexia, and irritability	Vitamin C deficiency
Breastfed children should be supplemented with which vitamin from birth?	Vitamin D

Last-Minute Review—Nutrition	Most Likely Answer
Child with a history of cystic fibrosis presents with ataxic gait, diminished deep tendon reflexes in the lower extremities, as well as generalized weakness in the lower extremities	Vitamin E deficiency
Vitamin that affects prothrombin, factor VII, factor IX, factor X	Vitamin K
Child is receiving a prophylactic antibiotic for the last few months. Prothrombin time (PT) and partial thromboplastin time (PTT) are mildly prolonged	Vitamin K deficiency
Foot and wrist drop, ataxia, ophthalmoplegia, confusion, abnormal sensation, heart failure, dyspnea, and edema	Vitamin B1 deficiency (thiamine)
Redness and fissuring of lips (cheilitis), soreness of tongue, anemia, fatigue	Vitamin B2 deficiency (riboflavin)
Diarrhea, dementia, dermatitis, and death in severe cases	Vitamin B3 deficiency (niacin)
Which vitamin is needed to supplement a child on a strict vegan diet?	Vitamin B12 (other supplements to consider: iron, zinc, and calcium)
The site of vitamin B12 absorption	Ileum
Infant drinks goat's milk, looks pale, CBC shows macrocytic anemia	Folic acid deficiency
Acute illness with diarrhea, fever, and vomiting for 2 days, followed by persistent diarrhea for 3 weeks, 6–9 episodes of liquid stools without visible blood or mucus, associated with generalized abdominal pain, distended and flatulent since the acute illness. A positive reducing substance in the stool. What is the best management?	Lactose-free diet and lactase supplement (lactose intolerance)
Taste and smell impairment, night blindness, and depressed immunity	Zinc deficiency
Deficiency associated with recurrent diarrhea, alopecia, and rash (acrodermatitis enteropathica)	Zinc deficiency
Child previously healthy is living with stepfather, generalized loss of muscle mass, and no subcutaneous fat	Marasmus and possible calorie deprivation
Child lives in a shelter, poor nutrition, failure to thrive, weakness, edema, moon facies, a swollen abdomen (potbelly), dark, dry skin, with pale areas between the cracks, depigmentation of hair, and fatty liver	Kwashiorkor (protein-energy malnutrition)

GASTROENTEROLOGY

Robert D. Baker

Last-Minute Review—Gastroenterology	Most Likely Answer
An exclusively breastfed infant has not stooled for 5 days with no other symptoms. The stool is soft with no rectal bleeding. The infant is gaining weight	Reassurance (breastfed infants may go several days or even a week between bowel movements)
A 1-week-old child with frequent spit-ups, otherwise doing well	Reassurance (newborn reflux is normal)
What are the upper GI series useful for?	To rule out anatomic or motility problems. Does not diagnose reflux
A 3-week-old first newborn boy presents with nonbilious projectile vomiting, hypochloremic, hypokalemic metabolic alkalosis, and dehydration	Pyloric stenosis
What is the next best step in cases with suspected pyloric stenosis?	Abdominal US (pylorus)
Weight loss, abdominal pain, nausea, effortless postprandial regurgitation after at least 1 meal daily for 1 month, regurgitated food occasionally reswallowed, rechewed, or spit out	Rumination syndrome
Child with no known health problem woke up suddenly vomiting blood. The child is stable and acting normal. What is the most likely cause?	Epistaxis (nose bleeding is the most common source in healthy children)
Nausea and vomiting every 1–2 months, each episode lasts for few hours, otherwise healthy, no symptoms in-between episodes, positive family history of migraine	Cyclic vomiting syndrome
A 7-year-old healthy child, with periumbilical abdominal pain worse in the morning prior to school, improves during weekends with normal growth parameters	Reassurance (functional abdominal pain)
High achieving adolescent complains of crampy abdominal pain, diarrhea, and at other times, constipation; pain is relieved with stooling	Irritable bowel syndrome
Adolescent presents with recurrent episodes of abdominal pain, diarrhea, and sometimes constipation in the previous 3 months. No weight loss and all labs are normal. What is the best treatment?	Peppermint oil, diet modifications, cognitive behavioral therapy
A mother brought her toddler with a diaper full of undigested food, the child is holding a large bottle of apple juice	Toddler diarrhea
The best management of toddler's diarrhea	Juice restriction and allow normal dietary fat
Child with a low-grade fever, 6 episodes of diarrhea, otherwise reassuring medical exam. What is the treatment of choice?	Oral rehydration therapy (avoid anti-diarrheal agents)

Last-Minute Review—Gastroenterology	Most Likely Answer
What is the major concern of using antimotility drugs such as Loperamide?	May induce ileus
An infant presents with bright red blood stool, poor weight gain, diarrhea, and fussiness; the infant is breastfeeding, supplemented with standard infant formula; stool guaiac test is positive	Cow milk protein intolerance
Child with dysphagia, recurrent food impaction; biopsy shows an increased eosinophil?	Eosinophilic esophagitis
Adolescent with recurrent headaches takes ibuprofen as needed, presents with dysphagia and chest discomfort (does not like to drink water with medicine)	Pill-induced esophagitis
Child accidentally swallowed caustic liquid 6 h ago, presents with dysphagia, oral pain, chest pain, nausea, and vomiting	Endoscopy in 12–24 h after ingestion
Swallowed a coin, no symptoms, and radiograph showed the coin still in the esophagus	Observe for 12–24 h, removal of the coin if it does not pass to the stomach or if the patient became symptomatic
Swallowed a coin, no symptoms, and radiograph showed the coin in the stomach	Checking the stool for passage for 4 weeks, with weekly radiographs, if indicated
4 weeks passed and the coin still in the stomach with no symptoms	If the coin does not pass through the stomach by 4 weeks or if the patient is symptomatic, removal by endoscopy should be considered
Swallowed a coin, excessive drooling, and chest pain, and radiograph showed the coin still in the esophagus	Immediate removal
Swallowed a button battery (BB), and passed to the stomach with symptoms	Immediate removal
Swallowed a BB, and passed to the stomach without symptoms	Urgent removal (if age < 5 and BB ≥ 20 mm) Elective if not moving (checking the stool for passage for 4 weeks, with weekly radiographs)
Swallowed a BB that got stuck in the esophagus	Immediate removal
Swallowed small pieces of magnet metals; the abdominal radiograph showed the pieces in the stomach	Immediate removal
An older child with bloating, constant burping, sharp epigastric pain that awakens the child from sleep	*Helicobacter pylori* infection
The most common cause of chronic gastritis in pediatrics	*H. pylori*
The best and most definitive test for peptic ulcer disease	Endoscopy
What is the treatment of *H. pylori* infection?	Amoxicillin or metronidazole + clarithromycin + PPI for 2 weeks

Last-Minute Review—Gastroenterology	Most Likely Answer
Infant suddenly develops bilious vomiting, abdominal distension, tenderness, and fussiness. What is the diagnostic test of choice?	Upper GI series with follow through
In the infant above, the GI series shows a bird's beak sign of the second portion of the duodenum	Volvulus
Intermittent crampy abdominal pain, lethargy, bilious vomiting, and a palpable mass in the right upper quadrant	Intussusception
What is the best initial diagnostic test of choice in cases of intussusception?	Abdominal US (target sign, reflecting a segment of bowel trapped within a distal segment of bowel)
What is the therapeutic procedure of choice in cases of intussusception?	Air contrast enema (diagnostic and therapeutic)
Down syndrome, bilious vomiting, double bubble sign on KUB	Duodenal atresia
A mother brought her 9-month-old girl with a diaper full of red, maroon stool; the physical exam is normal, and the infant is feeding well and smiling (she is receiving an antibiotic for AOM)	Most likely the medicine, e.g., cefdinir may change the stool color to maroon color (blood-like color)
A 2-year-old boy, frank rectal bleeding, anemia, no pain, no other symptoms	Meckel diverticulum
What are the 2 most common ectopic tissues found in Meckel diverticulum?	Gastric and pancreatic
How is Meckel diverticulum diagnosed?	Technetium 99 scan
Infant, failure to thrive, rectal prolapse	Cystic fibrosis
Most common cause of rectal prolapse in the USA	Constipation
Rectal bleeding, large and hard stool in the diaper	Anal fissure
The most common cause of rectal bleeding in infants	Anal fissures
A 2-year-old boy with chronic constipation, ineffective laxatives, fails to pass meconium in the first 48 h of life, explosive stools on rectal exam, KUB showed very distended colon	Hirschsprung disease
A 48-h old boy did not pass the meconium; the abdomen is slightly distended	Hirschsprung disease
Most accurate diagnostic test for Hirschsprung disease	Full-thickness rectal biopsy performed by surgery
Persistent epigastric abdominal pain, vomiting; the pain is referred to the back, tenderness in the epigastric region, elevated amylase, and lipase enzymes	Acute pancreatitis
Child with Down syndrome, intermittent abdominal pain, and failure to thrive	Celiac disease
Child with type 1 diabetes mellitus and recurrent abdominal pain	Celiac disease

Last-Minute Review—Gastroenterology	Most Likely Answer
Child with a history of recurrent abdominal pain presents with fever, abdominal pain, bloody diarrhea, migratory arthritis, erythema nodosum, ankylosing spondylitis, elevated ESR, positive P-ANCA	Ulcerative colitis
Recurrent aphthous ulcers, abdominal pain, weight loss, perianal lesions, positive anti-*Saccharomyces* antibodies	Crohn's disease
Jaundice, abdominal pain, and fever	Cholangitis
Jaundice, abdominal pain, and a palpable mass in the right upper quadrant	Choledochal cyst
Hydrops of the gallbladder can be seen in	Kawasaki disease
Conditions associated with an increased incidence of cholelithiasis	Sickle cell anemia, chronic total parenteral nutrition (TPN), adolescent pregnant females
What is the most common complication of cholelithiasis?	Pancreatitis
A 3-year-old boy presents with failure to thrive, difficulty walking; the metabolic panel shows elevated aspartate transaminase (AST) and alanine transaminase (ALT). Total bilirubin, prothrombin time, blood glucose, TSH and free T4 are all normal, negative hepatitis viral panel. What is the test of choice in this case?	Creatinine phosphokinase (CK) (muscular dystrophy most likely)
What are the sources of transaminases (ALT and AST)? It is important to consider other sources of transaminases if they are elevated and the liver function is normal	Liver, heart, muscles, kidney, and brain
The best laboratory test for acute hepatitis A	Anti-HAV IgM
A mom is asking about prophylaxis for her 4-month-old child after she was recently diagnosed with hepatitis A?	Administer IG as prophylaxis (< 1 year)
Prophylaxis of a 3-year-old child exposed to a documented case of hepatitis A in a child care center	Hepatitis A vaccine (> 1 year)
All hepatitis viruses are composed of RNA except	Hepatitis B virus is composed of DNA
Which virus infection must have hepatitis B?	Hepatitis D
Child with a family history of lupus disease presents with jaundice, hepatomegaly, weight loss, loss of appetite, positive anti-smooth muscle antibodies	Autoimmune hepatitis
One week with jaundice, hepatomegaly, slightly elevated ALT and AST, prolonged PT that is not responding to IV vitamin K, and recurrent hypoglycemia	Acute hepatic failure

Last-Minute Review—Gastroenterology	Most Likely Answer
An 8-year-old boy has recurrent jaundice, slightly elevated indirect bilirubin; physical examination and all other labs are normal	Gilbert syndrome
A 1-day-old boy with intense jaundice, unconjugated bilirubin is 25 mg/dL, and no conjugated bilirubin; and poor response to phototherapy	Crigler–Najjar syndrome type I (exchange transfusion is warranted)
Mild conjugated hyperbilirubinemia with black liver	Dubin–Johnson syndrome
An infant with jaundice, dark urine, light-colored stool, hepatomegaly, and elevated conjugated bilirubin	Biliary atresia
What is the most valuable study for neonatal biliary atresia?	Percutaneous liver biopsy
If liver biopsy confirmed biliary atresia, what is the next appropriate test?	Intraoperative cholangiography
Adolescent presents with depression, psychosis, and elevated liver enzymes	Wilson disease
Which mineral is affected in Wilson disease?	Copper (excess)
How to establish the diagnosis of Wilson disease	Ceruloplasmin < 20 mg/dL. Hepatic copper > 250 ug/g dry weight. Urine copper > 100 ug/24 h. Presence of Kayser–Fleischer rings
Broadened forehead, jaundice, pulmonary stenosis, and butterfly hemivertebrae	Alagille syndrome
Abdominal mass, elevated liver enzyme, and high serum alpha-fetoprotein	Hepatoblastoma
A 3-month-old, failure to thrive, extreme pruritus, steatorrhea, very high-conjugated bilirubin, hepatosplenomegaly, mutilated skin, elevated serum alkaline phosphatase, and normal gamma-glutamyl transferase (GGT)	Progressive familial intrahepatic cholestasis (PFIC) type 1
Prognosis of all forms of PFIC	Lethal during childhood unless treated early
Hematochezia, intestinal polyp, pigmented penile lesion, large head, *café-au-lait* spots, intellectual disability	Bannayan–Riley–Ruvalcaba syndrome
> 5 juvenile polyps	Juvenile polyposis
What is the next step in children with ≥ 5 juvenile polyps or any number of adenomatous intestinal polyps?	Genetic testing
100 or more adenomatous polyps in the large and/or small intestines	Familial adenomatous polyposis
Intestinal polyps, osteoma of the mandible, papillary carcinoma of thyroid, and hepatoblastoma	Gardner syndrome
Intestinal polyps and brain tumor	Turcot syndrome

Last-Minute Review—Gastroenterology	Most Likely Answer
Intestinal polyps, hematochezia, mucocutaneous freckling, and a family history of polyposis	Peutz–Jeghers syndrome (increases the risk of cancer)
Hamartomas involving many areas of the body, e.g., skin, oral mucosa, thyroid, breast, and colon	Cowden syndrome
Associated risks of Cowden syndrome	Cancer, e.g., thyroid cancer
Hemihypertrophy, very large extremities, epidermal nevus, hamartomatous polyps, intellectual disability	Proteus syndrome
Potential risks of Proteus syndrome	Deep vein thrombosis (DVT) and thromboembolism
The best diagnostic test for lactose intolerance	Hydrogen breath test

NEPHROLOGY

Beatrice Goilav

Last-Minute Review—Nephrology	Most Likely Answer
A 5-year-old hospitalized and receiving penicillin IV for 10 days, developed rash, eosinophilia, eosinophiluria, pyuria (sterile), hematuria, moderate proteinuria (usually < 1 g/day)	Antibiotic-induced allergic interstitial nephritis
A 4-year-old had throat infection 2 weeks ago, tea-colored urine, BP is slightly elevated, RBC casts in urine, low C3 and normal C4	Postinfectious glomerulonephritis
History of impetigo, tea-colored urine, hypertension, periorbital edema, C3 is low, normal C4, azotemia, normal ASO titer, positive anti-DNAse, oliguria, and RBC casts in urine	Postinfectious glomerulonephritis
Low C3 and cola-colored hematuria (RBC casts) 2–3 weeks after upper respiratory tract infection	Postinfectious glomerulonephritis
Normal C3 and episodic gross hematuria (RBC casts) during acute upper respiratory tract infection	IgA nephropathy
The most common cause of gross hematuria in children	IgA nephropathy
Can antibiotics prevent acute postinfectious glomerulonephritis?	No
Can antibiotics prevent acute rheumatic fever?	Yes
After poststreptococcal glomerulonephritis (PSGN) does the C3 level normalize immediately after the illness?	No—at least 6 weeks before C3 levels return to normal
Are steroids indicated in PSGN?	No—only supportive care measures and BP control as needed

Last-Minute Review—Nephrology	Most Likely Answer
Adolescent female with rapidly progressive glomerulonephritis, hypertension, and both C3 and C4 are decreased	Lupus nephritis
A healthy child with proteinuria, morning specimen is negative for proteinuria	Benign orthostatic proteinuria
A 3-year-old, swelling of the face and generalized edema, normal blood pressure, 4+ proteinuria, no hematuria, hyperlipidemia, hypoalbuminemia, normal C3 and C4, urine is negative for protein after 3 weeks of steroid therapy	Nephrotic syndrome due to minimal change disease
Child with nephrotic syndrome not responding to treatment and progressing to chronic kidney disease	Focal segmental glomerulosclerosis
Adolescent with nephrotic syndrome, microscopic hematuria, and hypertension	Focal segmental glomerulosclerosis
Adolescent presents with proteinuria, hematuria, hypertension, persistent low C3, hyperlipidemia, renal failure	Membranoproliferative glomerulonephritis
Child presents with persistent proteinuria, history of hepatitis B virus infection	Membranous glomerulonephritis
Child develops acute kidney injury and within 4 weeks progresses to end-stage renal disease, renal biopsy shows crescents formation in most glomeruli	Rapidly progressive (crescentic) glomerulonephritis
Which serologic marker can be positive in rapidly progressive glomerulonephritis?	P-ANCA
A 5-year-old has blood in urine, urine is positive for hematuria, RBC casts, renal function is normal, no hypertension, positive family history of hematuria with every generation affected	Familial thin basement membrane nephropathy (autosomal dominant)
Microhematuria, proteinuria, absent patella, dystrophic nails, dysplasia of elbows	Nail-patella syndrome (autosomal dominant)
A 7-year-old, failure to thrive, polyuria, polydipsia, anemia, ocular apraxia, retinitis pigmentosa, coloboma, nystagmus, aplasia of the cerebellar vermis, loss of differentiation between cortex and medulla on renal US	Juvenile nephronophthisis
Boy with a sensorineural hearing loss, proteinuria, mother's brother died from renal failure	Alport syndrome (X-linked disease)
Upper respiratory infection a week ago, now with petechiae on the buttocks and lower extremities, abdominal pain, arthralgia, and hematuria	Henoch-Schönlein purpura
Bloody diarrhea, which resolves, but then the child becomes pale and tired and is found to have hemolytic anemia, thrombocytopenia, elevated BUN and creatinine. A stool culture is positive for *Escherichia coli (E. coli)* O157: H7	Hemolytic uremic syndrome

Last-Minute Review—Nephrology	Most Likely Answer
The most common causes of oliguric acute kidney injury requiring dialysis in children	Nephrotoxins and rhabdomyolysis
Child on amphotericin B developed kidney stones, and blood work showed non-anion gap metabolic acidosis. What is the most likely cause?	Renal tubular acidosis (RTA) type 1
Child with polyuria, polydipsia, dehydration, growth failure, non-anion gap metabolic acidosis, hypokalemia, hypophosphatemia, proteinuria, glucosuria	Fanconi syndrome
Type of renal tubular acidosis associated with Fanconi syndrome	RTA type 2
Type of renal tubular acidosis associated with hyperkalemia	RTA type 4
Hemoptysis, hematuria, proteinuria, positive anti-glomerular basement membrane antibodies (anti-GBM)	Goodpasture syndrome
Child on Lasix, presents with oliguria, elevated creatinine; urine osmolality is > 400 mOsm/L, urine Na < 20, FeNa < 1%, urine is positive for hyaline cast	Prerenal acute kidney injury
Child after a car accident and crush injury presents with high BUN/Cr, oliguria, urine osmolality 300 mOsm/L. FeNa > 1%, urine Na > 20, large muddy brown granular cast	Acute tubular necrosis (intrarenal acute kidney injury)
A male infant with posterior urethral valves, born prematurely and is found to have high BUN/Cr, elevated FeNa, normal urine osmolality, elevated urine Na	Postrenal acute kidney injury
Status post-cardiac arrest, BUN and creatinine are elevated, hyperkalemia, hyponatremia, hyperphosphatemia, hypocalcemia, urine shows muddy brown, and granular casts	Acute tubular necrosis secondary to ischemia
Adolescent with severe muscle cramps, numbness, low blood pressure, fatigue, metabolic alkalosis, hypochloremia, hypokalemia, hyponatremia, hypomagnesemia, polyuria, low urine calcium, and high urinary chloride 70 mEq/L. High aldosterone and renin levels	Gitelman syndrome (metabolic alkalosis and high urine chloride, low serum Mg, and low urine Ca)
An infant with failure to thrive, dehydration, low blood pressure, metabolic alkalosis, hypochloremia, hypokalemia, hyponatremia, normal serum magnesium level, polyuria, normal urine calcium, and high urinary chloride 70 mEq/L. High aldosterone and renin levels. High urinary prostaglandin level	Bartter syndrome (metabolic alkalosis and high urine chloride, normal serum Mg, and normal or high urine Ca)

Last-Minute Review—Nephrology	Most Likely Answer
Child with a positive family history of hypertension (parents) presenting with headache, hypertension, hypokalemia, metabolic alkalosis, and high urinary chloride	Liddle syndrome (autosomal dominant)
Adolescent with mild glomerulonephritis, history of allergies/asthma with elevated eosinophil levels on CBC	Churg Strauss syndrome
An older child with a prolonged history of fever, weight loss, hematuria, and hemoptysis. Radiograph shows necrotizing granuloma and C-ANCA positive	Granulomatosis with polyangiitis (formerly Wegner granulomatosis)
A young child with palpable kidneys bilaterally, hypertension, and associated with a history of oligohydramnios	Autosomal recessive polycystic kidney disease
The predominant type of polycystic kidney disease seen in adults	Autosomal dominant polycystic kidney disease
How is hypertension defined in children?	BP > 95th percentile for age, height, and gender on 3 different occasions or greater than 130/90 mmHg in children aged 13 years and older
How is elevated blood pressure defined in children?	BP ≥ 90th (≥ 13 years BP > 120/80 mmHg matching new adult guideline)
Adolescent with severe muscle weakness after exercise, hypophosphatemia, hypokalemia and elevated CPK with myoglobinuria	Rhabdomyolysis—heme positive urine but no RBC
Child with nausea, severe flank pain, and hematuria	Renal stone
The most common type of stones in children	Calcium oxalate
Type of kidney stone associated with staghorn calculi and *Proteus*?	Struvite stones
Type of stone associated with an autosomal recessive pattern	Cystine stones
First-line therapy for children with primary monosymptomatic nocturnal enuresis	Bedwetting alarm and desmopressin (both)
Recommended lifestyle changes in all cases of monosymptomatic nocturnal enuresis	Adequate hydration during the day Limit fluids before bed (≤ 200 mL) Void before bed Regular sleep and wake schedule
Diurnal enuresis after continence	Requires prompt evaluation

FLUIDS AND ELECTROLYTES

Beatrice Goilav

Last-Minute Review—Fluids and Electrolytes	Most Likely Answer
Low urinary fractional excretion of sodium, high urine osmolality, high serum osmolality	Dehydration
High urinary fractional excretion of sodium, low serum sodium, low serum osmolality, inappropriately high urine osmolality	Syndrome of inappropriate ADH secretion (SIADH)
Low urine osmolality, high serum sodium, and serum osmolality (urine osmolality < serum osmolality)	Diabetes insipidus
Low serum and urine osmolality	Primary polydipsia
Child with mild to moderate dehydration because of diarrhea, able to drink with no emesis. What is the best treatment?	Oral rehydration solution (ORS)
What is the mechanism of action of ORS?	Sodium-glucose transporter in the gut (co-transports one sodium with one glucose)
Child with moderate dehydration, no emesis, and low serum potassium (K) level 2.6 mEq/L. No other symptoms. What is the best treatment?	ORS and oral K chloride supplementation (oral replacement is better than IV if tolerating oral intake)
Child with vomiting, weakness, lethargy, moderate-severe dehydration, and low serum potassium (K) level 2.6 mEq/L. What is the best treatment?	IV bolus 20 ml/kg normal saline, then IV fluids and electrolyte replacement
Based on the Holliday-Segar method, what is the maintenance fluid rate for 45 kg child?	First 10 kg × 4 = 40 2nd 10 Kg × 2 = 20 25 kg × 1 = 25 40 + 20 + 25 = 85 ml/h
A 12-month-old girl with 4 days of frequent watery stool; she is listless. O/E: dry mucous membrane, skin is tenting, HR 150, BP 85/45 mmHg. Weight 8.5 kg. Weight before illness 10 kg, serum Na 136 mEq/dL. 200 mL of NS given IV. What is the most appropriate IV fluid and rate for this child?	D5 ½ NS +KCl 40 meq/L to run at 95 mL/h (15% dehydration; fluid deficit is 1500 + 1000 (maintenance—200 (bolus) = 2300/24 h = 95 ml/h)
A 12-month-old girl with 4 days of frequent watery stool, she is listless. O/E: dry mucous membrane, skin is tenting, HR 170, BP 80/40 mmHg. Weight 8 kg. Weight before illness 10 kg, serum Na 136 mEq/dL. 200 mL of NS given IV. What is the most appropriate IV fluid and rate for this child?	D5 ½ NS + KCl 40 meq/L to run at 116 mL/h (20% dehydration; fluid deficit is 2000 + 1000 (maintenance—200 (bolus) = 2800/24 h = 116 ml/h)
A quick calculation in the previous case?	The maintenance rate for a 10 kg child = 40 ml/h → triple the maintenance rate in 20% dehydration → 120 ml/h (close to 116)

Last-Minute Review—Fluids and Electrolytes	Most Likely Answer
A quick calculation of IV fluid rate in 5% dehydration	1½ times the maintenance rate
A quick calculation of IV fluid rate in 10% dehydration	Double the maintenance
A quick calculation of IV fluid rate in 15% dehydration	2 ½ times the maintenance rate
What is the advantage of ORS over other fluid options?	Low carbohydrate, high sodium and potassium (minimizing osmotic loads that drive more diarrhea)
What is a normal anion gap?	$Na^+ - (Cl^- + HCO_3^-) = 10–12$ mEq/L
What are the causes of anion gap metabolic acidosis?	**M**ethanol poisoning, **U**remia, **D**KA, **P**araldehyde, **I**ron toxicity, **I**NH, **L**actic acidosis, **E**thylene glycol, **S**alicylate poisoning (MUD PILES)
What are the causes of non-anion gap metabolic acidosis?	Renal tubular acidosis Diarrhea Chronic total parenteral nutrition (TPN) Acetazolamide (carbonic anhydrase inhibitor)
A 3-week-old boy with projectile vomiting after each feed, dehydration, metabolic alkalosis, hypochloremia, hypokalemia, oliguria, and low urinary chloride (< 20 mEq/L)	Pyloric stenosis (metabolic alkalosis and low urine chloride)
Child with bloody diarrhea, high fever, weakness, edema, oliguria, BUN 80 mg/dL, creatinine 5 mg/dL, K level is 7.5 mg/dL. EKG shows a widening of QRS complexes and an increased PR interval. What is the best management?	Intravenous calcium gluconate, glucose, and insulin, beta agonists, cation exchange resins (sodium polystyrene sulfonate), until dialysis can be initiated
What is the earliest EKG manifestations in cases of mild hyperkalemia?	Tall and peaked T waves
What is the EKG manifestation in cases of moderate hyperkalemia?	Widening of QRS complexes and an increased PR interval
What is the EKG manifestation in cases of severe hyperkalemia?	Broad and low amplitude P waves, a prolonged QT interval, and ST-segment changes (elevation or depression)
What is the EKG manifestation of hyperkalemia > 8 mEq/L?	Gradually widening QRS complexes and absent P waves → ventricular fibrillation or asystole

UROLOGY

Osama I. Naga

Last-Minute Review—Urology	Most likely Answer
Newborn with prenatal ultrasound (US) positive for hydronephrosis (> 10 mm AP diameter of the renal pelvis. What is the next best step?	Renal US after 48 h of life

Last-Minute Review—Urology	Most likely Answer
What is the best test to confirm the diagnosis of urinary tract infection (UTI)	Urine culture
A one-year-old child presents with the first febrile UTI. What is the appropriate imaging study?	Renal-bladder US (RBUS)
What is the gold standard test for the diagnosis of anatomical details of the renal system and degree of reflux?	Voiding cystourethrography (VCUG). It should not be routinely performed in children after a first febrile UTI
What are the indications of VCUG?	Findings on RBUS that suggest the presence of high-grade vesicoureteral reflux or the recurrence of febrile UTIs
What is the main difference between cystitis and acute pyelonephritis?	Presence of fever and urine infection is highly suggestive of pyelonephritis
Prevalent cause of recurrent UTIs in children	Constipation
Child with an indwelling catheter and a urine dipstick analysis negative for nitrites	Enterococcal UTI
Empiric antibiotics in patients suspected of having an enterococcal UTI	Combination of ampicillin or amoxicillin and, third-generation cephalosporin or aminoglycoside
A 4-year-old boy with weak urine stream, failure to thrive, recurrent UTIs, enuresis. The renal US is positive for bilateral hydronephrosis. What is the best test to establish the diagnosis?	VCUG for the possibility of a posterior urethral valve
A 4-year-old female with a history of chronic constipation presenting with vaginal bleeding and urethral mass	Female urethral prolapse
A 6-year-old female with persistently damp underwear (day and night)	Ectopic ureter
A 7-year-old uncircumcised boy with penile pain, swollen foreskin O/E: head of the penis is enlarged and congested with a collar of edematous foreskin. A constricting band of retracted foreskin is noted past the head of the penis. What is the best treatment?	Emergent reduction of the foreskin to its anatomical position. May apply compression, sugar, pin-pricks to decrease the edema
What are the most common anatomical contraindications of circumcision?	Hypospadias with incomplete foreskin, epispadias, ambiguous genitalia
An uncircumcised 3-year-old boy presents with a nonpainful, white, mobile mass just distal to the corona of the boy's penis	Reassurance (normal smegma)
Full-term male newborn presents with right undescended testis. The remainder of the physical examination is unremarkable. What is the next best step?	Referral to a surgeon if the testis remains undescended at 6 months of age
A 15-year-old boy presents with a painless, solid, firm, irregular mass in the left testicle	Testicular cancer until proven otherwise
A 12-year-old boy presents with sudden onset of testicular pain, vomiting, the right testicle is swollen, tender, absent cremasteric reflex	Testicular torsion

Last-Minute Review—Urology	Most likely Answer
Patient presents with testicular torsion	Immediate urology consult (the testicular US should not delay the consultation)
A 12-year-old boy presents with pain, tenderness, and swelling in the upper pole of the right testicle. O/E: bluish dot is visible through the scrotum	Torsion of the testicular appendage
A 12-year-old boy presents with soft non-tender fullness within the left hemiscrotum, homogenous glow without internal shadows on transillumination; testes are palpable posteriorly	Hydrocele
An 18-year-old male presents with a left-sided mass that feels like a bag of worms; the left testicle is smaller than normal; the mass increases in size with Valsalva maneuver	Varicocele
Adolescent male is complaining about a mobile nodule noted above the testis; the mass does not increase with Valsalva	Spermatocele
A sexually active adolescent male presents with testicular pain that improves with testicular elevation; he has dysuria and fever. The cremasteric reflex is intact	Epididymitis
A 10-year-old boy with a sudden onset of right flank colicky abdominal pain, nausea, vomiting, frequent urination. Physical examination is normal. The urine test is positive for 20 RBCs. The renal US shows 3 mm stone in the right ureter	Pain medicine, aggressive hydration (most stones smaller than 5 mm pass spontaneously in children)
A 10-year-old boy presents with blood in urine and difficulty voiding after blunt trauma to the genital area. O/E: there is a drop of blood on the meatus	Urethral injury (best study is retrograde urethrography)

DERMATOLOGY

Megan Craddock and Jennifer Ruth

Last-Minute Review—Dermatology	Most Likely Answer
Pustules of erythema toxicum contain	Eosinophils (reassurance)
Pustules of transient neonatal pustular melanosis contain	Neutrophils (reassurance)
Newborn with white papules on the hard palate	Epstein pearls (reassurance)
Newborn with pinhead white papules on the face	Milia (reassurance)
Newborn with white papules on the upper gums	Bohn nodules (reassurance)
An infant with small papules and pustules on the forehead, nose, and cheeks and an absence of comedones.	Neonatal acne (resolves without treatment)

Last-Minute Review—Dermatology	Most Likely Answer
Newborn with blistering and erosions of the skin. May have mucous membrane and nail involvement. Infection has been ruled out	Epidermolysis bullosa
What is the best diagnostic test for epidermolysis bullosa?	Skin biopsy of an induced blister or genetic testing
Well-defined erythematous plaques on the knees and elbows, covered with silvery scales, bleed when removed, pitting of the nails	Psoriasis
Child with ulcerative colitis presents with bright red, tender nodules on the anterior leg	Erythema nodosum
Erythematous, scaly plaques in periorificial and acral areas, alopecia, and diarrhea	Acrodermatitis enteropathica (zinc deficiency)
A 2-year-old boy with fever, fragile blisters, and denuded skin, predominantly affecting the flexures and perioral skin	Staph scalded skin syndrome (SSSS)
Adolescent boy with a history of cold sores presents with targetoid papules, distributed acrally, and hemorrhagic crusting of the lips	Erythema multiforme
Child is taking penicillin for a dental abscess, developed macules, papules, vesicles, bullae, and ulcerations on 8% of the body surface area. Sloughing, blistering, and ulceration around the lips, eyes, and genitalia are also present	Stevens–Johnson syndrome
Most common virus that triggers erythema multiforme	Herpes simplex virus (HSV)
Poorly defined, hypopigmented rough macules and patches on the cheeks	Pityriasis alba
Adolescent with oval scaly papules and plaques on the trunk that run parallel to skin cleavage lines	Pityriasis rosea
Adolescent boy with hypopigmented scaly lesions on the neck, chest, and back that worsen with sun exposure	Tinea versicolor
What is the cause of tinea versicolor?	*Malassezia furfur*
Child with an itchy rash affecting both feet. Exam shows scaling, fissuring, and maceration in the interdigital spaces. What is the best treatment?	Topical antifungal cream, e.g., terbinafine cream
Child with one bald spot on the scalp with scale and “black-dot” hairs (the remnants of broken hairs within follicles). What is the best treatment?	Oral antifungal
Child with one bald spot on the scalp with no associated scale or redness. What is the best treatment?	Reassurance or topical steroids (alopecia areata)
A young child with diffuse thinning of the hair on the scalp after undergoing major surgery 3 months prior	Telogen effluvium

Last-Minute Review—Dermatology	Most Likely Answer
Condition with pegged-shaped teeth, prominent ears, small chin, frontal bossing, absence of sweating with associated overheating	Hypohidrotic ectodermal dysplasia
Female neonate with blistering and/or hyperpigmentation of the skin in a blaschkoid distribution. May be associated with eye and neurologic abnormalities	Incontinentia pigmenti (X-linked dominant)
Fish-like scaling of the body, sparing flexural areas, with corneal opacities and history of cryptorchidism	X-linked recessive ichthyosis
Extremities are covered with fine, irregular, polygonal scales, hyperlinear palms; worse with dry weather and during winter, family history of "dry skin"	Ichthyosis vulgaris
Erythematous, scaly, itchy plaques in the antecubital and popliteal fossae, older brother with asthma	Atopic dermatitis
A 3-year-old boy was exposed to poison ivy while playing in the garden. He developed itchy linear streaks of vesicles on both arms. What is the best treatment?	Topical steroids (Rhus dermatitis)
What is the most important recommendation for all cases of contact dermatitis?	Avoidance of triggering agents
Folliculocentric papules with central keratinous debris on the upper arms and thighs	Keratosis pilaris
Unilateral, irregular brown to blue-gray pigmentation of the neck, shoulder, supraclavicular, deltoid, and/or upper arm skin. May darken at puberty	Nevus of Ito
Unilateral, irregular, blue-gray discoloration in the periorbital area and sclera (**O**cular)	Nevus of **O**ta
A nevus of Ota involving the sclera requires monitoring by ophthalmology due to increased risk of	Glaucoma > ocular melanoma
Large congenital nevi likely carry an increased risk of what type of cancer?	Melanoma
Child is going to the beach for swimming and parents are concerned about sunburn. How would you counsel the family about sunscreen use?	Apply SPF 30 or greater sunscreen 15–30 min before sun exposure, reapply every 2 h
Large facial port-wine stain involving V1, seizures, and glaucoma	Sturge–Weber syndrome
Posterior fossa malformations (Dandy–Walker), hemangiomas, arterial anomalies, cardiac defects (e.g., coarctation of the aorta), and eye abnormalities	PHACE syndrome

Last-Minute Review—Dermatology	Most Likely Answer
An infant with a large hemangioma on the upper eyelid is at risk for	Amblyopia
What is the best treatment for a hemangioma on the upper eyelid that obstructs the visual axis?	Oral propranolol
Annular plaque without scale not responding to topical antifungals	Granuloma annulare
An infant with orange to brown macules and papules that become red and swollen when stroked	Urticaria pigmentosa (cutaneous mastocytosis)
An infant with a 4-month history of seborrheic dermatitis-like rash on the scalp, behind the ears, and in the diaper area not responsive to topical antifungals or steroid cream	Langerhans cell histiocytosis
A 12-year-old boy with learning disabilities and seizure disorder presents with persistent papules on the face despite acne treatment. He is also found to have hypopigmented skin lesions on the exam	Tuberous sclerosis
A 10-month-old with light brown macules and small patches on the body. How many *café-au-lait* macules should raise concern for neurofibromatosis?	Six
What is the treatment for head lice?	Permethrin 1% liquid; 2 treatments spaced 1 week apart
What is the treatment for scabies?	Permethrin 5% cream; 2 treatments spaced 1 week apart

PSYCHOSOCIAL ISSUES AND CHILD ABUSE

Mohamed Zebda

Last-Minute Review—Psychosocial Issues and Child Abuse	Most Likely Answer
Factors that determine the understanding of death and expression of grief	Chronologic age and levels of cognitive development
What does exposure to high levels of parental conflict lead to?	Predictive of poor emotional adjustment by the child regardless of the parents' marital status
What are the most helpful measures for children in cases of divorce?	Regular schedule with flexibility
	Consistency with structure and routine
	Cooperative co-parenting
Consequences of divorce on a child's emotional adjustment	May affect his/her subsequent intimate relationships
Consequences of adoption on children from institutional or orphanage care	A higher risk of medical and developmental problems than their counterparts who have resided in foster care
Child is being placed in foster care; how soon should this child be evaluated by a provider?	Initial visit should take place within 72 h after placement in the foster care system

Last-Minute Review—Psychosocial Issues and Child Abuse	Most Likely Answer
TV watching is not recommended at what age?	Children younger than 2 years of age
How long should children 2 years and older be allowed to watch TV?	2 h/day or less for all children, including other forms of screen (solitary TV watching is highly discouraged)
Increased aggressive behavior and acceptance of violence, obscuring of the distinction between fantasy and reality, trivialization of sexuality are effects of	Excessive media time
One of the most common causes of school refusal in children	Separation anxiety disorder
A set of clinical features in which unfounded parental anxiety about the health of a child results in disturbances of the parent–child interaction	Vulnerable child syndrome
At what age should discussions start regarding transition of care for adolescents and young adults with chronic medical conditions?	Around 12 years of age
A child tends to have asynchronous developmental patterns, very advanced in one domain area compared to the rest	Gifted child
Maternal depression, substance use/abuse, and physical injuries	May indicate intimate partner violence
A frequent risk factor for child abuse	Intimate partner violence
Consequences of children who are exposed to corporal punishment and intimate partner violence	More likely to exhibit aggressive/violent behaviors than other children
What is the most common form of child abuse?	Neglect
What is the most common presentation in an abused child?	Asymptomatic—just because there are no physical signs does not mean that the child has not been abused
What is the most common cause of head injury in a child less than 1 year of age?	Child abuse
A 3-week-old girl presents to ER with lethargy, poor sucking, and retinal hemorrhages; mother stated the child rolled over and fell from the bed. What is the most likely cause?	Abusive head trauma (shaken baby syndrome)
What are the consequences of child abuse during early development?	Physiologic and anatomic changes in the brain, increased risk of physical and behavioral problems
Parents or guardians who failed to provide adequate medical care for a child, e.g., refused to administer medications for a serious medical condition	Medical neglect
Parents or guardian fail to provide basic needs (nutrition, shelter, clothes) or who abandon the child	Physical neglect

Last-Minute Review—Psychosocial Issues and Child Abuse	Most Likely Answer
Parents or guardian fail to enroll the child in school or provide homeschooling, allow frequent absenteeism, or ignore special education needs	Educational neglect
Parents or guardian isolate the child, withhold emotional support, expose the child to interpersonal violence or substance abuse, e.g., fight or engage in sex in front of the child	Emotional neglect
Parents or guardian leave the child alone or improperly supervised, fail to keep the child from safety hazards, e.g., leaving strong chemicals open and not safely secured in the house	Supervision neglect
Posterior rib fracture, bucket handle fracture, femur fracture in child less than 1 year old, distal humeral physeal fracture, and humeral shaft fracture in child less than 3 years old are high suspicion of	Child abuse
Bucket handle fracture (also known as a classic metaphyseal fracture or metaphyseal corner fracture) in infants	High specificity for child abuse. It may occur with shaking, vigorous pulling or twisting of an infant's extremity
What is the next best step with any suspicion of child abuse in a child less than 2 years of age?	Skeletal survey
Difference between bucket handle fractures and buckle fractures	Fracture of the distal radius (buckle fracture) is common and is not associated with child abuse
A 7-month-old healthy infant with a few bruises on arms and legs	Must be evaluated for child abuse and reported to child protective services
A 7-year-old healthy child with multiple bruises on both tibial shins and elbows	Reassurance
Entire foot is burned, with a well-demarcated line of injury around the leg and absence of splash marks (stocking distribution)	Child abuse (possible forced immersion into hot water)
Entire hand is burned, with a well-demarcated line of injury around the forearm and absence of splash marks (glove distribution)	Child abuse (possible forced immersion into hot water)
What is the most common physical examination finding in a child with sexual abuse?	Normal examination
Physical contact between the victim and the perpetrator, with or without oral, anal, or vaginal penetration	Child sexual abuse
Which gender is less likely to disclose sexual abuse and might be victimized more often than the reported ratio	Boys
A 16-year-old adolescent presents to the ER due to a sexual assault that occurred 1 day ago, what should be done?	SANE exam—should be done by a specialized nurse. The cutoff for exam 72–120 h (within 5 days)

Last-Minute Review—Psychosocial Issues and Child Abuse	Most Likely Answer
What is the SANE exam?	Exam performed by a Sexual Assault Nurse Examiner who examines the victim of sexual assault and collects all forensic evidence
A healthy child with multiple recurrent ER visits; the mother is a healthcare professional who demands tests and imaging with each visit; before discharge patient's blood glucose is 40 mg/dL. Further evaluation shows high serum insulin level and absence of serum C-peptide level	Caregiver-fabricated illness

ETHICS

Mohamed Zebda

Last-Minute Review—Ethics	Most Likely Answer
The ethical principle of referring a child to an expert in the field or providing the best treatment available, considering treatment efficacy and potential to lessen disability	Beneficence (doing good for others or the best interest of the patient)
The ethical principle of not ordering a head CT scan for a well-appearing child with trivial head injury or referring a child with obstructive sleep apnea secondary to enlarged tonsils and adenoids to ENT (weighing the risks and benefits in each case and avoiding possible complications)	Nonmaleficence (do no harm)
The ethical principle of informing an adolescent about their diagnosis	Veracity (truthfulness or truth-telling)
The ethical principle of maintaining the confidentiality of emancipated minor with STD	Fidelity, e.g., maintaining confidentiality or faithfulness
The ethical principle of ideal distribution of risks and benefits, and resolving potential conflict	Justice, e.g., clinical research trials in children
The ethical principle of ensuring access to medical care with federally sponsored child health insurance	Justice
The ethical principle of autonomy of thought, intention, and action when making decisions regarding health care procedures or treatment	Autonomy
Newborn with ambiguous genitalia. What is the best strategy in helping the parents consider the gender in which to rear the child?	A multidisciplinary team should give parents as much information as possible about their child's diagnosis and prognosis

Last-Minute Review—Ethics	Most Likely Answer
Family desires to continue invasive therapy for child with irreversible and devastating neurological damage. The critical care physician and the neurologist strongly believe that there will be neither benefit nor quality of life for the child in continuing life support	Physicians are not obligated to provide futile care
What is the best approach to the family in the previous example?	Physicians must provide families with relevant risks and benefits of available options and to provide specific recommendations
Declaration of brain death requires	*Two* independent examinations, including a physical examination and apnea testing
Following the agreement of parents or guardian for a child to participate in clinical research, at what age is consent of the child also required?	7 years and older (unless cognitively impaired)
A physician is receiving financial incentives for recruiting children to participate in a clinical drug trial	This practice is prohibited because of the potential element of undue influence and coercion
What are the most critical criteria required to conduct a clinical drug trial in children?	Consent of guardians, child ≥ 7 years, the best interests of the child, minimizing harm, safety committees, monitoring, meaningful and measurable outcomes
How should the consent document for the clinical trial or research be written?	Easy to understand (sixth to eighth-grade reading level)
What is the age of a minor to give consent for screening of sexually transmitted infections, consent for contraceptive services, and consent for general medical care?	Laws related to minor consent vary by state
At what age are contraceptive pills (progestin-only emergency contraceptive) available over the counter (OTC) to adolescents in all states in the USA?	17 years of age and older
What is a minor called if the minor is married, in the military, a parent, self-supporting while not living with parents, or a high school graduate?	Emancipated minor (has the right to provide informed consent for medical care). The criteria vary by jurisdiction
A 4-year-old boy involved in a car accident requires a lifesaving blood transfusion. His adult parents refuse based on religious reasons. What should be done?	Transfuse the child (informed consent is *not* required to treat a child with a life-threatening condition)
A 19-year-old involved in a car accident requires a lifesaving blood transfusion. Based on religious reasons he is refusing the blood transfusion. What should be done?	Respect the patient's wishes and do not transfuse (patient is an adult)
The process in which the risks and benefits along with potential alternatives are discussed with the parents before performing any procedure is known as	Informed consent—must be sought from the parents unless there is a life-threatening emergency and unable to contact them

Last-Minute Review—Ethics	Most Likely Answer
A 16-year-old teenager requests confidential STD testing and pregnancy test. The mother comes without her child to demand the results of the pregnancy/STD testing. What should you do?	Do not disclose the results and protect patient confidentiality
A 16-year-old teenager positive for gonorrhea is in the office with her 17-year-old boyfriend, who is waiting outside. She begs you not to tell him about her diagnosis. What should you do?	Do not tell the boyfriend, report her diagnosis to the CDC. Encourage her to inform him herself
In what situation is a breach in confidentiality allowed, and parents or guardian must be notified about an adolescent's medical condition?	Risk of harming self or others
The mother of a 15-year-old female is here to obtain lab results that were ordered for obesity. The patient is unable to be present. What should you do?	Disclose the results to the mother (guardian)
You are seeing a 15-year-old female who says she has had consensual sexual activity with her boyfriend who is 21 years old. What should be done in this situation?	A report should be filed with child protective services—the child is a minor (age may vary by state) and the boyfriend is an adult
At what age is a minor considered developmentally mature and able to understand the consequences of his or her medical decision, and thus should be involved in making decisions about their medical care?	The beginning of 12–13 years of age (mature minor doctrine)
Parents have asked the pediatrician *not* to reveal a diagnosis to their adolescent because of the psychological impact. What is the best approach?	Arrange a meeting with parents and the adolescent to discuss the diagnosis and prognosis and provide psychological support if needed
A 10-year-old girl recently diagnosed with a brain tumor; parents are asking you not to tell the child about her condition. What should be done in this situation?	Discuss the diagnosis and treatment with parents and the child (the child must know)
What are the ethical principles in the previous 2 examples?	Veracity (truthfulness or being honest) and fidelity (faithfulness)
A 15-year-old boy with terminal cancer has been hospitalized for 3 months because of life-threatening complications and recurrent relapses. He decides to discontinue his medical care, and the family desires to continue treatment regardless of outcome. What is the best approach to the end-of life-care?	Medical team meeting with the child and family to elicit his preferences, inform him and his family about end-of-life decisions, improve communication, and increase agreement among all involved parties regarding end-of-life care
A family with a well-known adult-onset genetic disorder (in the fifth to sixth decade) desires genetic testing for their children to know their future risks	No testing until the children reach adulthood (after 18 years of age) when able to make an independent and informed decision

Last-Minute Review—Ethics	Most Likely Answer
Parents are new to your practice and refuse vaccinations to their children	Listen to parents and address all their concerns about vaccines Explain all risks and benefits of the vaccines in question
Parents continue to reject the vaccination to their children	Continue their care. Discuss risks and benefits in each subsequent visit
If parents continue to refuse vaccinations for their child, is the pediatrician obligated to dismiss the child from his or her practice?	No. Pediatrician should continue care unless a strong sense of distrust develops that impacts a child's overall care
Parents brought their unimmunized 7-year-old boy who is bleeding from a raccoon bite. Parents refuse rabies vaccine	Report the family to state welfare agency (medical neglect)

RESEARCH AND STATISTICS

Mohamed Zebda

Last-Minute Review—Research and Statistics	Most Likely Answer
Study best suited to evaluate the risks and benefits of a new treatment, establishes a direct causal relationship between treatment and outcomes	Randomized control trial
Study in which 2 groups are followed prospectively over time to see which exposures/risks cause disease and to provide information about prognosis	Cohort study (type of observational study)
Retrospective study in which people with a disease are compared to those without the disease to evaluate risk factors, useful for rare outcomes	Case-control study (type of observational study)
Type of study used to compare a new diagnostic test to the current gold standard diagnostic test in a given population	Cross-sectional study
Retrospective statistical analysis of several studies on the same topic	Meta-analysis
What is the best way to eliminate confounding variables?	Randomization of study subjects
Type of bias that occurs when an association between an exposure and an outcome is distorted by another variable	Confounding bias
The percent of people with the disease in a given population being studied	Prevalence
The number of new cases of a given disease in a specific period of time	Incidence
The probability of correctly identifying those who truly have the disease	Sensitivity = TP/(TP+FN) SnOUT sensitivity → rules out disease when they're negative

Last-Minute Review—Research and Statistics	Most Likely Answer
The probability of correctly identifying those who truly do not have the disease	Specificity = TN/(TN+FP) SPIN specificity → rules in disease when they're positive
The probability of correctly identifying those who truly have the disease among those whose tests are positive	Positive predictive value = TP/(TP+FP)
The probability of correctly identifying those not having a disease among those whose tests are negative	Negative predictive value = TN/(TN+FN)
The hypothesis of no difference, i.e., daily exercising does not reduce the risk of heart disease	Null hypothesis
The hypothesis of difference, i.e., daily exercising does reduce the risk of heart disease	Alternative hypothesis
Rejecting the null hypothesis when in fact it is true—a difference that was seen when one does not exist	Type 1 error
Failure to reject the null hypothesis when the null hypothesis is false—a difference that was not seen when one does exist	Type 2 error
The probability that a study can detect a treatment effect	Power of a study
A range of values with a specified probability that a given parameter falls in that range	Confidence interval
What is the interpretation of a confidence interval that includes 0 or 1	There is no statistical significance
The total number needed to treat to prevent one bad outcome or adverse events	The number needed to treat NNT = 1/absolute risk reduction
The total number of patients receiving intervention for each patient that is harmed	The number needed to harm NNH = 1/attributable risk

PATIENT SAFETY AND QUALITY IMPROVEMENT

Mohamed Zebda

Last-Minute Review—Patient Safety and Quality Improvement	Most Likely Answer
Wrong plan to achieve a desired aim	Medical error
An error reaches the patient but does not result in harm	Non-intercepted near miss error
Recognized and corrected errors before it reaches the patient	Intercepted near miss error
An unexpected occurrence of death or serious physical or psychological injuries	Sentinel event

Last-Minute Review—Patient Safety and Quality Improvement	Most Likely Answer
A 4-year-old child with leukemia who requires a transfusion receives the wrong type of blood, resulting in a serious transfusion reaction	Sentinel event
When a sentinel event has been identified, an investigation is undertaken immediately to determine the root causes that have led to the event. An action plan is then developed and implemented to monitor the system in order to minimize the risk that such an event will recur in the future	Root cause analysis
A patient who is allergic to penicillin was prescribed amoxicillin and developed a skin rash after drug administration	Preventable medical error
A patient with no history of allergic reaction to penicillin developed a severe allergic reaction to amoxicillin	Non-preventable medical error
Suspected child physical or sexual abuse is an example of	Mandatory reporting
Serious reportable hospital events that should not have occurred, resulting in death or significant disability	Never events
Mistakenly, a surgery was performed on the healthy left knee instead of the right knee with torn ligaments	Surgical never event
Frequent nonclinically relevant alarm alerts result in desensitization to the alarms, and caregiver may miss some signals that should necessitate an intervention	Alarm fatigue (adjust alarm thresholds to reduce nonclinically relevant noises); patients' variability should be considered
What are some ways to prevent dosing and medication errors?	Avoid trailing zeros such as 20.0 mg Use leading zeros such as 0.1 mg Avoid abbreviations such as BID Write out unit
What are some ways to prevent medication administration errors?	Syringes are the preferred dosing device, measuring cups and spoons calibrated and marked in milliliters are acceptable alternatives
Child in your clinic received the wrong immunization; what should be done in this situation?	Provide apology to parents The error should be disclosed to the parents in a clear manner, and the steps that need to be taken to prevent further errors should be discussed
What are the components of a successful quality improvement project?	Plan—what will be changed/what intervention Do—try the change on a small scale Study—analyze results of the change/ intervention Act—implement changes on a larger scale

PHARMACOLOGY AND PAIN MANAGEMENT

Mohamed Zebda

Last-Minute Review—Pharmacology and Pain Management	Most Likely Answer
The time it takes the plasma concentration of a drug to decrease by half	Half-life (t½)
The lowest concentration reached by a drug before the next dose is administered	Trough levels
The highest concentration reached by a drug after the dose is administered	Peak level
Child is taking griseofulvin for tinea capitis. What is the best recommendation to maximize absorption?	To be taken with whole milk or fatty meal
Child is taking oral penicillin for streptococcal infection developed non-pruritic rash, nausea, and vomiting. What is the type of this reaction?	Non-IgE-mediated
Child is taking oral penicillin for streptococcal infection developed pruritic rash, swollen lips and difficulty breathing. What is the type of this reaction?	IgE mediated "anaphylaxis" to penicillin
What is the most common side effects of drugs in general?	Nausea
Anxiolysis with the maintenance of consciousness	Minimal sedation
Controlled depressed consciousness, airway reflexes, and airway patency are maintained; the patient responds appropriately to age-appropriate commands and touch	Moderate sedation (conscious sedation)
Controlled depressed consciousness, airway reflexes and airway patency may not be maintained, ventilatory function may be impaired, patient not easily aroused but responds purposefully following repeated or painful stimulation	Deep sedation
Loss of consciousness occurs; impaired airway reflexes, airway patency, and ventilatory function; not arousable; not responsive to painful stimulation	General anesthesia
In order to decrease the requirements of morphine post-operatively in neonates, infants, and children, what is the best recommendation?	Give an appropriate dose of acetaminophen (oral or rectal) for mild to moderate pain even after major surgeries
Complication of gentamicin therapy, especially in newborns?	Ototoxicity
Which complication is associated with erythromycin in children less than 1 month?	Pyloric stenosis
Complication of tetracyclines in children less than 8 years old	Teeth staining

Last-Minute Review—Pharmacology and Pain Management	Most Likely Answer
Mother is asking if she can give her 5-month-old benzocaine gel for teething	Not recommended; increases the risk of methemoglobinemia
What are the common side effects of ADHD medications?	Weight loss, difficulty sleeping, palpitations
In young children with aspirin use, and concurrent viral infection such as varicella, may cause	Reye syndrome

Correction to: Pediatric Board Study Guide

Osama I. Naga

Correction to: O. I. Naga (ed.), Pediatric Board Study Guide, https://doi.org/10.1007/978-3-030-21267-4

This book was inadvertently published with a couple of incorrect sentences that have been corrected now.

In Chapter 4, p. 115, the sentence 'Cervical flexion-extension radiographs by 3–5 years, when planning to participate in contact sports or if neck pain, torticollis, gait disturbance, or weakness' has now been corrected to 'Sport pre-participation screening for atlanto-axial instability (AAI) symptoms e.g., neck pain, torticollis, gait disturbance, or weakness. Routine neck x-ray for asymptomatic patients with DS is no longer recommended.'

In Chapter 6, the phrase "Dry mouth" has been removed from Table 6.4 (last row, column 4).

In Chapter 14, p. 510, the sentence 'The Special Olympics organization requires radiographic evaluation of the cervical spine before sports participation' has now been corrected to 'Sport pre-participation screening for AAI symptoms. Routine neck x-ray for asymptomatic patients is no longer recommended.'

The updated versions of the chapters can be found at
https://doi.org/10.1007/978-3-030-21267-4_4
https://doi.org/10.1007/978-3-030-21267-4_6
https://doi.org/10.1007/978-3-030-21267-4_14

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4_34

Index

O. I. Naga (ed.), *Pediatric Board Study Guide*, https://doi.org/10.1007/978-3-030-21267-4

E